# Appendix A Literature search summary

*Table 71 Search summary of all searches for this review*

| Database / resource name | Search date | Results |
|---|---|---|
| Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to current date | 15 June 2022 | 2237 |
| CINAHL Complete (EBSCO) | 15 June 2022 | 1080 |
| SciELO | 16 June 2022 | 232 |
| Cochrane Library (John Wiley & Sons) | 16 June 2022 | 430 |
| Epistemonikos | 16 June 2022 | 558 |
| Campbell Collaboration | 16 June 2022 | 0 |
| AHRQ Systematic review data repository | 16 June 2022 | 1 |
| DARE (University of York Centre for Reviews and Dissemination) | 20 June 2022 | 182 |
| DoPHER (EPPI-Centre) | 20 June 2022 | 46 |
| JBI Evidence Synthesis (Joanna Briggs Institute) | 20 June 2022 | 23 |
| International HTA database | 20 June 2022 | 21 |
| Health Systems Evidence (McMaster University) | 20 June 2022 | 16 |
| Social Systems Evidence (McMaster University and Monash University) | 20 June 2022 | 14 |
| Health Evidence (McMaster University) | 20 June 2022 | 93 |
| Google.com 1st 100 results | 20 June 2022 | 67 |
| DuckDuckGo targeted searches | 20 June 2022 | 80 |
| Google Scholar 1st 100 results | 20 June 2022 | 49 |
| Total | | 5,129 |
| **Total after deduplication** | | **4,315** |

*Table 72 Supplemental searches - reference and citation chasing*

| Database / resource name | Search date | Results |
|---|---|---|
| Reference and citation chasing of original 88 included papers and 63 umbrella /scoping /other reviews (after duplication and deduplication against the original results of the primary database search) | 19 October-7 November 2022 | 4,415 |
| **Total** | | **4,106** |

*Table 73 Supplemental searches – updated database search*

| Database / resource name | Search date | Results |
|---|---|---|
| Updated database search (Medline, Cochrane Library and Epistemonikos databases) | 29 November 2022 | 170 |
| **Total** | | **170** |

*Table 74 Supplemental searches – Grey literature search*

| Database / resource name | Search date | Results |
|---|---|---|
| Prospero database | 7 November 2022 | 99 |
| Core.ac.uk | 21 December 2022 | 0 |
| Osf.io | 21 December 2022 | 0 |
| Researchsquare | 21 December 2022 | 1 |
| Medrxiv and Biorxiv | 21 December 2022 | 0 |
| Organisational websites (See Table X1) | 9-15 December 2022 | 4 |
| **Total** | | **104** |

*Table 75 Websites included in supplementary grey literature search*

| Country | Organisation | Website |
|---|---|---|
| Australia | Australia National Health and Medical Research Council (NHMRC) | https://www.nhmrc.gov.au/ |
| Canada | Canadian Dental Association | https://www.cda-adc.ca/en/index.asp |
| | Canadian Institute for Health Information | https://www.cihi.ca/en |
| Ireland | Dental Council | http://www.dentalcouncil.ie |
| | Irish Expert Body on Fluorides and Health | https://www.fluoridesandhealth.ie/ |
| | UCC Oral Health Services Research Centre | https://www.ucc.ie/en/ohsrc/ |
| New Zealand | New Zealand Ministry of Health | https://www.health.govt.nz/ |
| | Environmental Health Intelligence New Zealand (EHINZ) | https://www.ehinz.ac.nz/ |
| UK | NICE | https://www.nice.org.uk/ |
| | Scottish Dental Clinical Effectiveness Programme | https://www.sdcep.org.uk |
| | British Dental Association | https://www.bda.org/ |
| USA | Center for Disease Control (CDC) | https://www.cdc.gov/fluoridation/ |
| | U.S. Department of Health and Human Services | https://www.hhs.gov/about/index.html |
| | American Dental Association (ADA) | https://www.ada.org/ |
| International organisations | European Food Safety Authority | https://www.efsa.europa.eu/en |
| | International Association for Dental Research | https://www.iadr.org/ |
| | International HTA Database | https://database.inahta.org/ |
| | World Health Organization | https://www.who.int/ |

*Table 76 Medline search strategy.*

**Database:** Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to June 14, 2022
**Search date:** 15 June 2022

| # | Searches | Results |
|---|---|---|
| 1 | exp Dental Caries/ or Tooth Demineralization/ | 50718 |
| 2 | Dental Cavity preparation/ or DMF Index/ or Dental Caries Activity tests/ or Dental Caries Susceptibility/ | 20047 |
| 3 | (Caries or carious or cariogenic or cariology or dental fissure*).mp. | 67742 |
| 4 | (karie* or "cariës" or carie).mp. | 3412 |
| 5 | ((decay* or lesion* or cavity or cavities or cavitated or "micro-cavity" or "micro-cavities") and (dent$ or tooth or teeth)).mp. | 69939 |
| 6 | ((proximal or primary or secondary or progressive or progressing or arrested or frank) adj2 (lesion or lesions or defect* or fissure*)).mp. | 27150 |
| 7 | (cavosurface* or cavitated or "non-cavitated" or noncavitated or "microcavitated" or microcavit* or precavitat* or "pre-cavitated").mp. | 4460 |
| 8 | (active lesion* or inactive lesion* or sticky lesion* or defective filling*).mp. | 1940 |
| 9 | ((Dentine or dentin or enamel or root or pulp or cementum) adj2 (lesion* or decay* or cavit* or defect* or fissure*)).mp. | 16974 |
| 10 | ((Molar* or premolar* or incisor* or canine* or distal or mesial or coronal or "lingual-palatinal" or lingual or palatinal or buccal or "labial-buccal" or labial or occlusal or "incisal–occlusal" or incisal or pit or apical or periapical or approximal or proximal or maxillary or axiopulpal or subsurface or root) adj2 (lesion* or decay* or cavit* or fissure*)).mp. | 16672 |
| 11 | (((root or cervical) adj2 (lesion* or decay* or cavit* or fissure*)) and (dent* or tooth or teeth)).mp. | 1789 |
| 12 | ((decalcif* or demineral* or hypomineral*) adj5 (dent* or tooth or teeth)).mp. | 5282 |
| 13 | (dent* and (white spot* or "white-spot" or brown spot*)).mp. | 1050 |
| 14 | (ICDAS or ICDAS-II).af. | 639 |
| 15 | ("Decayed, Missing, and Filled" or "Decayed, Missing, Filled" or "decayed-missing-filled" or DMFT or DMF Index).mp. | 12400 |
| 16 | (lesion severity assessment or lesion activity assessment).mp. | 33 |
| 17 | or/1-16 | 160586 |
| 18 | prevent*.mp. | 2663498 |
| 19 | exp Primary Prevention/ | 172261 |
| 20 | exp Preventive Dentistry/ | 36507 |
| 21 | exp Dental Caries/pc [Prevention & Control] | 14671 |
| 22 | 18 or 19 or 20 or 21 | 2760278 |

| # | Searches | Results |
|---|---|---|
| 23 | (((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw. or exp Review Literature as Topic/ or exp Review/ or Meta-Analysis as Topic/ or Meta-Analysis/ or "systematic review"/ | 3290796 |
| 24 | 17 and 22 and 23 | 4845 |
| 25 | limit 24 to yr="2010 -Current" | 2237 |

*Table 77 CINAHL search strategy*

**Database:** CINAHL Complete (EBSCO)

**Search date:** 15 June 2022

| # | Searches | Results |
|---|---|---|
| S25 | S23 AND S24 | 1,080 |
| S24 | DT 20100101-20221231 | 5,451,250 |
| S23 | S15 AND S19 AND S22 | 1,246 |
| S22 | S20 OR S21 | 274,882 |
| S21 | PT "systematic review" OR "Meta Analysis" OR "Meta Synthesis" | 187,341 |
| S20 | TI (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR AB (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR metasynthe*) OR KW (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR MH ("Literature Review+" OR "Meta Analysis" OR "Meta Synthesis" OR "Cochrane Library")) | 268,276 |
| S19 | S16 OR S17 OR S18 | 1,468,661 |
| S18 | TX (prevent*) | 1,466,998 |
| S17 | (MH "Preventive Dentistry") OR (MH "Dental Prophylaxis") OR (MH "Dental Scaling") | 3,029 |
| S16 | (MH "Preventive Health Care") OR (MH "Pre-Exposure Prophylaxis") | 25,272 |
| S15 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 | 59,834 |
| S14 | TX ("lesion severity assessment" OR "lesion activity assessment") | 15 |

| # | Searches | Results |
|---|---|---|
| S13 | TI ("Decayed, Missing, and Filled" OR "Decayed, Missing, Filled" OR "decayed-missing-filled" OR DMFT OR "DMF Index") OR AB ("Decayed, Missing, and Filled" OR "Decayed, Missing, Filled" OR "decayed-missing-filled" OR DMFT OR "DMF Index") OR KW ("Decayed, Missing, and Filled" OR "Decayed, Missing, Filled" OR "decayed-missing-filled" OR DMFT OR "DMF Index") | 1,858 |
| S12 | TX (ICDAS or "ICDAS-II") | 459 |
| S11 | TX ((dent*) AND ("white spot" OR "white spots" OR "white-spot" OR "brown spot" OR "brown spots")) | 746 |
| S10 | TX ((decalcif* OR demineral* OR hypomineral*) N5 (dent* OR tooth OR teeth)) | 1,808 |
| S9 | TX ((Cervical OR root) N2 (lesion* OR decay* OR cavit*)) AND TX (dent* OR tooth OR teeth) | 1,138 |
| S8 | TX (((Molar* OR premolar* OR incisor* OR canine* OR distal OR mesial OR coronal OR "lingualpalatinal" OR Lingual OR Palatinal OR buccal OR "labial-buccal" OR labial OR occlusal OR "incisal–occlusal" OR incisal OR pit OR apical OR periapical OR approximal OR proximal OR maxillary OR axiopulpal OR subsurface) N2 (lesion* OR decay* OR cavit* OR fissure*))) AND (dent* OR tooth OR teeth OR oral) | 3,256 |
| S7 | TX ((Dentine OR dentin OR enamel OR root OR pulp OR cementum) N2 (lesion* OR decay* OR cavit* OR defect* OR fissure*)) AND TX (dent* OR tooth OR teeth OR oral) | 3,414 |
| S6 | TX ("active lesion" OR "active lesions" OR "inactive lesion" OR "inactive lesions" OR "sticky lesion" OR "sticky lesions" OR "defective filling" OR "defective fillings") AND TX (dent* OR tooth OR teeth OR oral) | 374 |
| S5 | TX (cavosurface* OR Cavitated OR "Non-cavitated" OR Noncavitated OR "Micro-cavitated" OR "Micro-cavity" OR "Micro-cavities" OR Microcavit* OR "Pre-cavitated" OR Precavitat*) | 851 |
| S4 | (TX ((proximal OR primary OR secondary OR progressive OR progressing OR Arrested OR frank) N2 (lesion OR lesions OR defect* OR fissure*))) AND (dent* OR tooth OR teeth OR oral)) | 967 |
| S3 | (TX (decay* OR lesion* OR cavity OR cavities OR cavitated OR "micro-cavity" OR "micro-cavities") N4 (dent* OR tooth OR teeth)) | 11,441 |
| S2 | (TX (Caries OR carious OR cariogenic OR cariology OR karie* OR "cariës" OR carie OR "dental fissure" OR "dental fissures")) | 50,624 |
| S1 | (MH "Dental Caries") OR (MH "Tooth Demineralization+") OR (MH "Dental Caries Activity Tests") | 14,120 |

*Table 78 SciELO database*

**Database:** SciELO
**Search date:** 16 June 2022

| Searches | Results |
|---|---|
| (ab:((caries) AND (review OR systematic OR meta-analysis) )) OR (ti:((caries) AND (review OR systematic OR meta-analysis) )) | 231 |

*Table 79 Cochrane Library search strategy*

**Database:** Cochrane Library (Wiley)
**Search date:** 16 June 2022

| | Searches | Results |
|---|---|---|
| #1 | MeSH descriptor: [Dental Caries] explode all trees | 2871 |
| #2 | MeSH descriptor: [Tooth Demineralization] explode all trees | 3083 |
| #3 | MeSH descriptor: [Dental Cavity Preparation] explode all trees | 639 |
| #4 | MeSH descriptor: [DMF Index] explode all trees | 519 |
| #5 | MeSH descriptor: [Dental Caries Activity Tests] explode all trees | 42 |
| #6 | MeSH descriptor: [Dental Caries Susceptibility] explode all trees | 151 |
| #7 | (Caries or carious or cariogenic or cariology or "dental fissure" or "dental fissures" or cavosurface* or cavitated or "non-cavitated" or noncavitated or "micro-cavitated" or microcavit* or precavitat* or "precavitated" or "active lesion" OR "active lesions" or "inactive lesion" OR "inactive lesions" or "sticky lesion" or "sticky lesions" or "defective filling" or "defective fillings" or "lesion severity assessment" or "lesion activity assessment" or ICDAS or "ICDAS-II" or "Decayed, Missing, and Filled" or "Decayed, Missing, Filled" or "decayed-missing-filled" or DMFT or "DMF Index"):ti,ab,kw (Word variations have been searched) | 9686 |
| #8 | ((decay* or lesion* or cavity or cavities or cavitated or "micro-cavity" or "micro-cavities") and (dent* or tooth or teeth)):ti,ab,kw (Word variations have been searched) | 8030 |
| #9 | ((proximal or primary or secondary or progressive or progressing or arrested or frank or Dentine or dentin or enamel or root or pulp or cementum or Molar* or premolar* or incisor* or canine* or distal or mesial or coronal or "lingual-palatinal" or lingual or palatinal or buccal or "labial-buccal" or labial or occlusal or "incisal–occlusal" or incisal or pit or apical or periapical or approximal or proximal or maxillary or axiopulpal or subsurface or root) NEAR (lesion or lesions or defect* or fissure*)):ti,ab,kw (Word variations have been searched) | 10480 |
| #10 | (((root or cervical) NEAR (lesion* or decay* or cavit* or fissure*)) and (dent* or tooth or teeth)):ti,ab,kw (Word variations have been searched) | 806 |
| #11 | ((decalcif* or demineral* or hypomineral*) NEAR (dent* or tooth or teeth)):ti,ab,kw (Word variations have been searched) | 665 |
| #12 | (dent* and (white spot* or "white-spot" or "brown spot" or "brown spots")):ti,ab,kw (Word variations have been searched) | 339 |

| | Searches | Results |
|---|---|---|
| #13 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 | 21654 |
| #14 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 in Cochrane Reviews | 469 |
| #15 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 with Cochrane Library publication date Between Jan 2010 and Jul 2022, in Cochrane Reviews | 430 |

*Table 80 Epistemonikos search strategy*

**Database:** Epistemonikos

**Search date:** 16 June 2022

| Searches | Results |
|---|---|
| (title:((Caries OR carious OR cariogenic OR cariology OR "dental fissure" OR "dental fissures" OR "dental decay" OR "dental lesion" OR cavity OR cavities OR cavitated OR "micro-cavity" OR "micro-cavities" OR "non-cavitated" OR noncavitated OR "micro-cavitated" OR precavitat* OR "pre-cavitated" OR cavosurface OR "active lesion" OR "active lesions" OR "inactive lesion" OR "inactive lesions" OR "sticky lesion" OR "sticky lesions" OR "defective filling" OR "defective fillings" OR "proximal lesion" OR "primary lesion" OR "secondary lesion" OR "progressive lesion" OR "progressing lesion" OR "arrested lesion" OR "frank lesion") AND (prevent OR prevention OR preventative OR reduce OR reduction)) OR abstract:((Caries OR carious OR cariogenic OR cariology OR "dental fissure" OR "dental fissures" OR "dental decay" OR "dental lesion" OR cavity OR cavities OR cavitated OR "micro-cavity" OR "micro-cavities" OR "non-cavitated" OR noncavitated OR "micro-cavitated" OR precavitat* OR "pre-cavitated" OR cavosurface OR "active lesion" OR "active lesions" OR "inactive lesion" OR "inactive lesions" OR "sticky lesion" OR "sticky lesions" OR "defective filling" OR "defective fillings" OR "proximal lesion" OR "primary lesion" OR "secondary lesion" OR "progressive lesion" OR "progressing lesion" OR "arrested lesion" OR "frank lesion") AND (prevent OR prevention OR preventative OR reduce OR reduction))) | 3,332 |
| Limit to 2010-2022 | 2,021 |
| Limit to Systematic Reviews | 558 |

*Table 81 Campbell search strategy*

**Resource:** Campbell Collaboration
**Search date:** 16 June 2022

| Searches | Results |
|---|---|
| Caries | 0 |
| Carious | 0 |

*Table 82 AHRQ Systematic Review Data Repository*

**Resource:** AHRQ Systematic Review Data Repository
**Search date:** 16 June 2022

| Searches | Results (2010+) |
|---|---|
| Caries | 1 |
| Carious | 0 |

*Table 83 DARE/NHS EED/ HTA search strategy*

**Database:** Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (EED) and HTA.
**Search date:** 20 June 2022

| | Searches | Results |
|---|---|---|
| 1 | MeSH DESCRIPTOR Dental Caries EXPLODE ALL TREES | 164 |
| 2 | ((caries OR carious OR dental cavity OR dental cavities OR cavitated OR cavities OR dental fissure OR dental fissures OR dental decay OR tooth decay OR dental lesion OR dental lesions OR microcavity OR micro-cavity OR micro-cavities OR precavitated OR noncavitated OR non-cavitated )) IN DARE, NHSEED, HTA FROM 2010 TO 2022 | 125 |
| 3 | ((lesion* OR decay* OR defect* OR fissure*) AND (dent* OR teeth OR tooth)) IN DARE, NHSEED, HTA FROM 2010 TO 2022 | 77 |
| 4 | ((Molar* OR premolar* OR incisor* OR canine* OR distal OR mesial OR coronal OR "lingual-palatinal" OR Lingual OR Palatinal OR buccal OR labial-buccal OR labial OR occlusal OR "incisal-occlusal" OR incisal OR pit OR apical OR periapical OR approximal OR proximal OR maxillary OR axiopulpal OR subsurface OR root) AND (lesion* OR decay* OR cavit* OR fissure*) ) IN DARE, NHSEED, HTA FROM 2010 TO 2022 | 60 |
| 5 | #1 OR #2 OR #3 OR #4 | 273 |
| | 2010-2022 | 182 unique results |

*Table 84 DoPHER search strategy*

**Database:** Database of promoting health effectiveness reviews (DoPHER).
**Search date:** 20 June 2022

| Searches | Results |
|---|---|
| Freetext (All but Authors): caries OR carious OR "dental cavity" OR "dental cavities" OR cavitated OR cavities OR "dental fissure" OR "dental fissures" OR "dental decay" OR "tooth decay" OR "dental lesion" OR "dental lesions" OR microcavity OR "micro-cavity" OR "micro-cavities" OR precavitated OR noncavitated OR "non-cavitated" | 78 |
| Freetext (All but Authors):Dental AND<br>Freetext (All but Authors): Molar* OR premolar* OR incisor* OR canine* OR distal OR mesial OR coronal OR "lingual-palatinal" OR Lingual OR Palatinal OR buccal OR labial-buccal OR labial OR occlusal OR "incisal-occlusal" or incisal OR pit OR apical OR periapical OR approximal OR proximal OR maxillary OR axiopulpal OR subsurface OR root | 24 |
| Limited to 2010-2022 | 46 |

*Table 85 JBI Evidence Synthesis search strategy*

**Resource:** JBI Evidence Synthesis
**Date of search:** 20 June 2022

| Searches | Results |
|---|---|
| caries OR carious OR "dental cavity" OR "dental cavities" OR cavitated OR cavities OR "dental fissure" OR "dental fissures" OR "dental decay" OR "tooth decay" OR "dental lesion" OR "dental lesions" OR microcavity OR "micro cavity" OR "micro cavities" OR precavitated OR noncavitated OR "non cavitated" | 27 |
| Limited to 2010-2022 | 23 |

*Table 86 International HTA database search strategy*

**Resource:** International HTA database
**Date of search:** 20 June 2022

| Search term(s) | Results |
|---|---|
| (Dental Caries)[mh] OR (caries OR carious OR "dental cavity" OR "dental cavities" OR cavitated OR cavities OR "dental fissure" OR "dental fissures" OR "dental decay" OR "tooth decay" OR "dental lesion" OR "dental lesions" OR microcavity OR "micro-cavity" OR "micro-cavities" OR precavitated OR noncavitated OR"non-cavitated") | 21 |
| TOTAL | 21 |

*Table 87 Health Evidence search strategy*

**Resource:** Health Evidence

**Date of search:** 20 June 2022

| Search term(s) | Results |
|---|---|
| (caries OR cavit*) | 93 |
| **TOTAL** | **93** |

*Table 88 Social Systems Evidence*

**Resource:** Social Systems Evidence

**Date of search:** 20 June 2022

| Search term(s) | Results | Date range 2010 - 2022 |
|---|---|---|
| caries OR cavities | 14 | 12 |
| **TOTAL** | | **12** |

*Table 89 Health Systems Evidence search strategy*

**Resource:** Health Systems Evidence

**Search date:** 20 June 2022

| Search term(s) | Results | Date range 2010 - 2022 |
|---|---|---|
| Caries OR cavities | 18 | 16 |
| **TOTAL** | | **16** |

# Appendix B PRIOR Checklist

*Table 90 PRIOR checklist*

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as an overview of reviews. | Title page |
| **ABSTRACT** | | | |
| | 2 | Provide a comprehensive and accurate summary of the purpose, methods, and results of the overview of reviews. | Executive summary |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for conducting the overview of reviews in the context of existing knowledge. | Section 1.2 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) addressed by the overview of reviews. | Section 2 |
| **METHODS** | | | |
| Eligibility criteria | 5a | Specify the inclusion and exclusion criteria for the overview of reviews. If supplemental primary studies were included, this should be stated, with a rationale. | Section 3.7 |
| | 5b | Specify the definition of 'systematic review' as used in the inclusion criteria for the overview of reviews. | Section 3.10.2 |
| Information sources | 6 | Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify systematic reviews and supplemental primary studies (if included). Specify the date when each source was last searched or consulted. | Section 3.8 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, such that they could be reproduced. Describe any search filters and limits applied. | Appendix A |
| Selection process | 8a | Describe the methods used to decide whether a systematic review or supplemental primary study (if included) met the inclusion criteria of the overview of reviews. | Section 3.7-3.9 |
| | 8b | Describe how overlap in the populations, interventions, comparators, and/or outcomes of systematic reviews was identified and managed during study selection. | Section 3.6 |
| Data collection process | 9a | Describe the methods used to collect data from reports. | Section 3.11 |

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|---|---|---|---|
| | 9b | If applicable, describe the methods used to identify and manage primary study overlap at the level of the comparison and outcome during data collection. For each outcome, specify the method used to illustrate and/or quantify the degree of primary study overlap across systematic reviews. | Section 3.6 |
| | 9c | If applicable, specify the methods used to manage discrepant data across systematic reviews during data collection. | Sections 3.12, 3.13, 4.2 and 5.4.1 |
| Data items | 10 | List and define all variables and outcomes for which data were sought. Describe any assumptions made and/or measures taken to identify and clarify missing or unclear information. | Section 3.12 and Appendix H |
| Risk of bias assessment | 11a | Describe the methods used to assess risk of bias or methodological quality of the included systematic reviews. | Section 3.13 and Appendix E |
| | 11b | Describe the methods used to collect data on (from the systematic reviews) and/or assess the risk of bias of the primary studies included in the systematic reviews. Provide a justification for instances where flawed, incomplete, or missing assessments are identified but not re-assessed. | Section 3.11 |
| | 11c | Describe the methods used to assess the risk of bias of supplemental primary studies (if included). | n/a |
| Synthesis methods | 12a | Describe the methods used to summarize or synthesize results and provide a rationale for the choice(s). | Section 3.13 |
| | 12b | Describe any methods used to explore possible causes of heterogeneity among results. | Described heterogeneity throughout Section 4 but did not analyse casual factors |
| | 12c | Describe any sensitivity analyses conducted to assess the robustness of the synthesized results. | n/a |
| Reporting bias assessment | 13 | Describe the methods used to collect data on (from the systematic reviews) and/or assess the risk of bias due to missing results in a summary or synthesis (arising from reporting biases at the levels of the systematic reviews, primary studies, and supplemental primary studies, if included). | n/a |

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|---|---|---|---|
| Certainty assessment | 14 | Describe the methods used to collect data on (from the systematic reviews) and/or assess certainty (or confidence) in the body of evidence for an outcome. | Section 3.13 |
| **RESULTS** | | | |
| Systematic review and supplemental primary study selection | 15a | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Section 3.14 |
| | 15b | Provide a list of studies that might appear to meet the inclusion criteria, but were excluded, with the main reason for exclusion. | Appendix C |
| Characteristics of systematic reviews and supplemental primary studies | 16 | Cite each included systematic review and supplemental primary study (if included) and present its characteristics. | Section 4 and Appendix I |
| Primary study overlap | 17 | Describe the extent of primary study overlap across the included systematic reviews. | Section 4 |
| Risk of bias in systematic reviews, primary studies, and supplemental primary studies | 18a | Present assessments of risk of bias or methodological quality for each included systematic review. | Appendix F |
| | 18b | Present assessments (collected from systematic reviews or assessed anew) of the risk of bias of the primary studies included in the systematic reviews. | Appendix H |

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|---|---|---|---|
| | 18c | Present assessments of the risk of bias of supplemental primary studies (if included). | n/a |
| Summary or synthesis of results | 19a | For all outcomes, summarize the evidence from the systematic reviews and supplemental primary studies (if included). If meta-analyses were done, present for each the summary estimate and its precision and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Section 4 |
| | 19b | If meta-analyses were done, present results of all investigations of possible causes of heterogeneity. | n/a |
| | 19c | If meta-analyses were done, present results of all sensitivity analyses conducted to assess the robustness of synthesized results. | n/a |
| Reporting biases | 20 | Present assessments (collected from systematic reviews and/or assessed anew) of the risk of bias due to missing primary studies, analyses, or results in a summary or synthesis (arising from reporting biases at the levels of the systematic reviews, primary studies, and supplemental primary studies, if included) for each summary or synthesis assessed. | n/a |
| Certainty of evidence | 21 | Present assessments (collected or assessed anew) of certainty (or confidence) in the body of evidence for each outcome. | Appendix K |
| **DISCUSSION** | | | |
| Discussion | 22a | Summarize the main findings, including any discrepancies in findings across the included systematic reviews and supplemental primary studies (if included). | Section 5 |
| | 22b | Provide a general interpretation of the results in the context of other evidence. | Section 5 |
| | 22c | Discuss any limitations of the evidence from systematic reviews, their primary studies, and supplemental primary studies (if included) included in the overview of reviews. Discuss any limitations of the overview of reviews methods used. | Section 5 |
| | 22d | Discuss implications for practice, policy, and future research (both systematic reviews and primary research). Consider the relevance of the findings to the end users of the overview of reviews, e.g., healthcare providers, policymakers, patients, among others. | Section 5 |

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|---|---|---|---|
| **OTHER INFORMATION** | | | |
| Registration and protocol | 23a | Provide registration information for the overview of reviews, including register name and registration number, or state that the overview of reviews was not registered. | Section 3.7 |
| | 23b | Indicate where the overview of reviews protocol can be accessed, or state that a protocol was not prepared. | Section 3.7 |
| | 23c | Describe and explain any amendments to information provided at registration or in the protocol. Indicate the stage of the overview of reviews at which amendments were made. | Section 3.15 |
| Support | 24 | Describe sources of financial or non-financial support for the overview of reviews, and the role of the funders or sponsors in the overview of reviews. | n/a |
| Competing interests | 25 | Declare any competing interests of the overview of reviews' authors. | n/a |
| Author information | 26a | Provide contact information for the corresponding author. | n/a |
| | 26b | Describe the contributions of individual authors and identify the guarantor of the overview of reviews. | To be completed when peer review paper is written |
| Availability of data and other materials | 27 | Report which of the following are available, where they can be found, and under which conditions they may be accessed: template data collection forms; data collected from included systematic reviews and supplemental primary studies; analytic code; any other materials used in the overview of reviews. | Appendices D–K |

# Appendix C Excluded papers

## (a) Non-English language papers excluded at any stage of screening

Note: This list includes non-English language papers excluded from the review process at the title and abstract screening stage that may cover topics relevant to the review, indicating the wider body of relevant literature that was beyond the scope of the review but must be acknowledged.

There were 19 languages represented in this group of papers: Chinese, Croatian, Danish, Dutch, French, German, Italian, Japanese, Korean, Norwegian, Pashto, Persian, Polish, Portuguese, Russian, Spanish, Swedish, Turkish, and Ukrainian. These papers originated from a range of countries and were captured using English based databases, suggesting that there is considerable research done on this topic across the globe in many languages other than English. Some of these papers were published with English abstracts or keywords.

*Table 91 Non-English language papers excluded during screening*

| Chinese (n = 9) |
| --- |
| Guo JJ, Qiu LH. [Prevention and treatment of root surface caries]. Zhonghua Kou Qiang Yi Xue Za Zhi Zhonghua Kouqiang Yixue Zazhi Chin J Stomatol 2021;56:27–32. doi:10.3760/cma.j.cn112144-20201106-00554 |
| Huang J, Chen Z, Guo Y. Topical fluoride for the prevention of dental caries in children: a sytematic review. Chin J Evid-Based Med 2012;12:848–54. https://www.ncbi.nlm.nih.gov/books/NBK121513/ (accessed 20 Feb 2023). |
| Xiaotong W, Nanquan R, Jing X, et al. [Remineralization effect of casein phosphopeptide-amorphous calcium phosphate for enamel demineralization: a system review]. Hua Xi Kou Qiang Yi Xue Za Zhi Huaxi Kouqiang Yixue Zazhi West China J Stomatol 2017;35:629–35. doi:10.7518/hxkq.2017.06.013 |
| Xu QA, Fan MW. [Research progress in ecological prevention of dental caries]. Zhonghua Kou Qiang Yi Xue Za Zhi Zhonghua Kouqiang Yixue Zazhi Chin J Stomatol 2022;57:297–301. doi:10.3760/cma.j.cn112144-20210529-00273 |
| Yaling J, Mingye F, Lei C. [Research progress on a nanodrug delivery system for prevention and control of dental caries and periodontal diseases]. Hua Xi Kou Qiang Yi Xue Za Zhi Huaxi Kouqiang Yixue Zazhi West China J Stomatol 2017;35:104–7. doi:10.7518/hxkq.2017.01.017 |
| Zhang J, Xu X. [Research Progress in the Relationship Between Lactobacillus and Dental Caries]. Sichuan Da Xue Xue Bao Yi Xue Ban 2022;53:929–34. doi:10.12182/20220960103 |
| Zong Y-W, Cheng L, Guo Q, et al. [Research progress on the regulation of phenolic compounds of traditional Chinese herbs on oral microbes]. Hua Xi Kou Qiang Yi Xue Za Zhi Huaxi Kouqiang Yixue Zazhi West China J Stomatol 2020;38:319–23. doi:10.7518/hxkq.2020.03.016 |
| 陈奕瞳. Self-Etch Adhesives' Effectiveness in the Performance of Pit and Fissure Sealants. Adv Clin Med 2021;11:5313–21. doi:10.12677/ACM.2021.1111785 |
| 饶宜迅, 郭 晶, 楼菁菁, et al. 益生菌预防儿童龋齿效果的系统评价. Chin Evid-Based Nurs 2022;8:1032–8. doi:10.12102/j.issn.2095-8668.2022.08.006 |
| Croatian (n = 2) |
| Ambarkova V, Goršeta K, Jankolovska M, et al. Učinak fluoridnih gelova i lakova na demineralizaciju/remineralizaciju cakline u usporedbi s kompleksom CPP-ACP. Acta Stomatol Croat Int J Oral Sci Dent Med 2013;47:99–110. doi:10.15644/asc47/2/1 |
| Vodanović M. [Prevention of oral diseases]. Acta Medica Croat Cas Hravatske Akad Med Znan 2013;67:251–4. |

Danish (n = 2)

Nørregaard M-LM, Larsen LS. Caries – kontrol og behandlingsmuligheder i det primære tandsæt. Aktuel Nord Odontol 2020;45:206–24. doi:10.18261/issn.2058-7538-2020-01-17

Røn Larsen K, Johansen JD, Arenholt-Bindslev D, et al. [Dental materials can cause oral allergic reactions]. Ugeskr Laeger 2013;175:1785–9.

Dutch (n = 7)

de Baat C, van der Maarel-Wierink CD. Preventieve tandheelkunde 6. Preventie van cariës bij kwetsbare ouderen. Ned Tijdschr Tandheelkd 2017;124:303–7. http://www.ntvt.nl/tijdschrift/editie/artikel/t/preventieve-tandheelkunde-6-preventie-van-caries-bij-kwetsbare-ouderen.

Huysmans MCDNJM, van Strijp AJP, Kuper NK. Management van wortelcariës. In: Aps JKM, Boxum SC, De Bruyne MAA, et al., eds. Het tandheelkundig Jaar 2018. Houten: Bohn Stafleu van Loghum 2018. 205–19. doi:10.1007/978-90-368-1784-4_14

Merhai M. Cariës in het melkgebit. Bohn Stafleu van Loghum 2021. https://mijn.bsl.nl/caries-in-het-melkgebit/19960666?fulltextView=true&doi=10.1007%2F978-90-368-2739-3_105.

Van Loveren C. Cariëspreventieve strategieën bij 6-jarigen. Een gerandomiseerd, gecontroleerd onderzoek. Ned Tijdschr Tandheelkd 2015;122:200–8. http://www.ntvt.nl/tijdschrift/editie/artikel/t/cariespreventieve-strategieen-bij-6-jarigen-een-gerandomiseerd-gecontroleerd-onderzoek.

Van Loveren C. Preventieve tandheelkunde 1. Fluoridetandpasta's, de hoeksteen van de cariëspreventie. Ned Tijdschr Tandheelkd 2016;123:601–8. http://www.ntvt.nl/tijdschrift/editie/artikel/t/preventieve-tandheelkunde-1-fluoridetandpastas-de-hoeksteen-van-de-cariespreventie.

van Palenstein Helderman WH, Gruythuysen RJM, Bruers JJM, et al. Een omslag in cariësbehandeling bij kinderen: 'Gewoon Gaaf'. Ned Tijdschr Tandheelkd 2015;122:132–8. http://www.ntvt.nl/tijdschrift/editie/artikel/t/een-omslag-in-cariesbehandeling-bij-kinderen-gewoon-gaaf.

Vissink A, Spijkervet FKL, Stegenga B, et al. Geneesmiddelen in de tandheelkundige praktijk. In: Aps JKM, Brand HS, Duyck J, et al., eds. Het tandheelkundig jaar 2014. Houten: Bohn Stafleu van Loghum 2014. 225–50. doi:10.1007/978-90-368-0455-4_17

French (n = 12)

Buxeraud J. Prévention de la carie dentaire. Actual Pharm 2017;56:51–4. doi:10.1016/j.actpha.2017.05.020

Holve S, Braun P, Irvine JD, et al. La carie de la petite enfance dans les communautés autochtones. Paediatr Child Health 2021;26:257–8. doi:10.1093/pch/pxab028

Irvine J, Holve S, Krol D, et al. La carie de la petite enfance dans les communautés autochtones: Un document de principes conjoint avec l'American Academy of Pediatrics. Paediatr Child Health 2011;16:358–64. doi:10.1093/pch/16.6.358

Kengne Talla P, Gagnon M-P, Dramaix M, et al. Hygiène dentaire et caractéristiques prothétiques de la population belge : analyse des données de l'enquête nationale de santé 2004. Prat Organ Soins 2011;42:255–64. doi:10.3917/pos.424.0255

Lacoste-Ferré M-H, Hermabessière S, Jézéquel F, et al. L'écosystème buccal chez le patient âgé. Gériatrie Psychol Neuropsychiatr Vieil 2013;11:144–50. http://dx.doi.org/10.1684/pnv.2013.0401.

Meuric V, Boyer É. Chapitre 2 - Mise en place du microbiote buccal depuis la naissance. In: Alliot-Licht B, Thivichon-Prince B, eds. La Bouche de L'enfant et de L'adolescent. Paris: Elsevier Masson 2019. 25–30. doi:10.1016/B978-2-294-76255-0.00002-0

Muller-Bolla M, Doméjean S. Sucres et santé bucco-dentaire. Cah Nutr Diététique 2018;53:341–6. doi:10.1016/j.cnd.2018.10.003

Muller-Bolla M, Doméjean S. Chapitre 14 - Maladie carieuse. In: Alliot-Licht B, Thivichon-Prince B, eds. La Bouche de L'enfant et de L'adolescent. Paris: Elsevier Masson 2019. 171–93. doi:10.1016/B978-2-294-76255-0.00014-7

Muller-Bolla M, Doméjean S. Dentifrices et vernis fluorés, intérêt dans la prévention des lésions carieuses. Actual Pharm 2019;58:49–53. doi:10.1016/j.actpha.2019.04.009

Picaud J-C. 38 - L'entérocolite ulcéronécrosante: Concepts actuels. Prévention et prise en charge. In: Saliba É, ed. Néonatologie : bases scientifiques. Paris: Elsevier Masson 2017. 499–515. doi:10.1016/B978-2-294-73742-8.00038-8

Roques-Latrille C-F, Hubert J, Lévi Y, et al. Rapport sur les mentions d'étiquetage des eaux conditionnées (Saisine Direction générale de la santé – DGS – du 16 juin 2021). Bull Académie Natl Médecine 2022;206:579–90. doi:10.1016/j.banm.2022.03.003

Rowan-Legg A, Société canadienne de pédiatrie, Comité de la pédiatrie communautaire. Les soins buccodentaires des enfants – un appel à l'action. Paediatr Child Health 2013;18:44–50. doi:10.1093/pch/18.1.44

German (n = 44)

Enax J, Fabritius H-O, Amaechi BT, et al. Hydroxylapatit als biomimetischer Wirkstoff für die Remineralisation von Zahnschmelz und Dentin. ZWR - Dtsch Zahnärztebl 2020;129:277–83. doi:10.1055/a-1167-4888

Epple M, Enax J. Moderne Zahnpflege aus chemischer Sicht. Chem Unserer Zeit 2018;52:218–28. doi:10.1002/ciuz.201800796

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Krause L, Mensink GBM, Hoepfner T, et al. Fluoridanwendungen bei Kindern und Jugendlichen in Deutschland. Oralprophylaxe Kinderzahnheilkd 2022;44:30–40. doi:10.1007/s44190-022-0038-2

Kühnisch J, Heinrich-Weltzien R, Hickel R. SOP Fissuren- und Grübchenversiegelung. Zahnmed Up2date 2021;15:9–12. doi:10.1055/a-1323-0637

Lange M, Figura Y, Böhne C, et al. Management of Enteral Feeding and Application of Probiotics in Very Low Birth Weight Infants – A National Survey in German NICUs. Z Für Geburtshilfe Neonatol 2023;227:51–7. doi:10.1055/a-1936-0826

Mahjoub N. Prävention initialer kariöser Läsionen bei Patienten mit Multibracketapparaturen durch Fluoridgel-Applikation: eine prospektive, randomisierte Doppelblindstudie. Published Online First: 2014. doi:10.17169/refubium-12134

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Meyer F, Enax J. Demografische Entwicklung und häusliche Zahnpflege. ZWR - Dtsch Zahnärztebl 2018;127:98–104. doi:10.1055/s-0044-102283
Mühlhauser I. Vorsorge und Früherkennung - Präventionshandeln zwischen gesellschaftlicher Verpflichtung und individueller Selbstbestimmung. In: Hensen P, Kölzer C, eds. Die gesunde Gesellschaft: Sozioökonomische Perspektiven und sozialethische Herausforderungen. Wiesbaden: VS Verlag für Sozialwissenschaften 2011. 229–47. doi:10.1007/978-3-531-92818-0_12
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Schiffner U. Aktuelle Präventionskonzepte bei Kleinkindern mit erhöhtem Kariesrisiko. Zahnmed Up2date 2019;13:343–52. doi:10.1055/a-0887-0552
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Schiffner U. Fluoridanwendung zur Kariesprävention. Kinder- Jugendmed 2021;21:431–40. doi:10.1055/a-1654-6874
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Schlüter N, Ganß C, Luka B. Biofilmentfernung und Kariesprävention – chemisch oder doch lieber mechanisch? Zahnmed Up2date 2017;11:455–71. doi:10.1055/s-0043-114285
Schmidt P, Fricke O, Schulte AG. Aufsuchende zahnärztliche Versorgung von Kindern und Jugendlichen mit Pflegegrad oder Eingliederungshilfe – eine Auswertung von Abrechnungsdaten der KZBV. Gesundheitswesen 2021;84:952–60. doi:10.1055/a-1388-7203
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Spalek M, Albrecht U, Albrecht K, et al. Pathologien und Funktionseinschränkungen. In: Motzko M, Weinert M, Albrecht U, eds. Kiefergelenk und Kaustörungen: Ein multidisziplinäres Praxisbuch. Berlin, Heidelberg: Springer 2019. 51–94. doi:10.1007/978-3-662-59210-6_4

Splieth C. Zahnärztliche Untersuchung und Prophylaxe. In: Hoffmann GF, Lentze MJ, Spranger J, et al., eds. Pädiatrie: Grundlagen und Praxis. Berlin, Heidelberg: Springer 2014. 138–41. doi:10.1007/978-3-642-41866-2_11

Staehle HJ, Frese C, Wolff D. Neue konservierend-restaurative Optionen in der Gerontostomatologie. Zahnmed Up2date 2017;11:127–51. doi:10.1055/s-0042-116609

Tinnemann P, Stöber Y, Roll S, et al. Zahnmedizinische Indikationen für standardisierte Verfahren der instrumentellen Funktionsanalyse unter Berücksichtigung gesundheitsökonomischer Gesichtspunkte. Deutsche Agentur für Health Technology Assessment & Schriftenreihe Health Technology Assessment 2010. doi:10.3205/hta000084L

Wagner Y. Gesund im Mund – frühkindliche Karies verhindern. Kinder- Jugendmed 2021;21:419–24. doi:10.1055/a-1656-7799

Wierichs RJ, Meyer-Lückel H. Wurzelkaries: Ätiopathogenese und Therapie. Zahnmed Up2date 2020;14:107–22. doi:10.1055/a-1104-2598

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Zimmer S, Su F, Su E. Pilotprojekt zur betrieblichen zahnmedizinischen Prävention. Gesundheitswesen 2020;84:154–9. doi:10.1055/a-1205-1207

Zittermann A. Neuere Erkenntnisse über Vitamin D. Ernähr Med 2018;33:25–8. doi:10.1055/s-0044-101818

Italian (n = 1)

Sparabombe S, Piergallini A, Orsini G, et al. Studio clinico sull'efficacia del polishing nelle sedute di mantenimento. Prev Assist Dent 2011;37:71–9. doi:10.1016/j.pad.2011.04.001

Japanese (n = 2)

Itai K. [Chronic effects of fluoride on human health]. Chudoku Kenkyu Chudoku Kenkyukai Jun Kikanshi Jpn J Toxicol 2012;25:193–9.

洋子阿部, ゆかり篠永, さよ子人見, et al. 某予防歯科センターにおける幼児の齲蝕, フロッシングおよび歯列・咬合に関する実態調査. 小児歯科学雑誌 2018;56:434–40. doi:10.11411/jspd.56.4_434

Korean (n = 2)

Hwang Y-S, Lee H-J. The Various Effects of Xylitol as a Dietary Sugar Substitute on Improving Oral Health. J Food Hyg Saf 2022;37:107–13. doi:10.13103/JFHS.2022.37.2.107

Kim H-N, Jeong M-S, Kim S-Y, et al. Evaluation of release of fluoride from dental varnishes marketed in Korea. J Korean Acad Oral Health 2014;38:131–7. doi:10.11149/jkaoh.2014.38.3.131

Norwegian (n = 5)

Denison E, Lidal IB, Strauman GH. Effects of Dental and Oral Examination in Children Aged 0-5 Years. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH) 2015. http://www.ncbi.nlm.nih.gov/books/NBK390587/ (accessed 3 Feb 2023).

Giertsen E, Bakken TB, Bergesen GH, et al. Alternative søtningsmidler: Egenskaper, bruksområder, sikkerhetsaspekter og helseeffekter – Del 1: Sukkeralkoholene | Den norske tannlegeforenings Tidende. 2021;132:690–700. doi:10.56373/2021-8-4

Preus HR, Scheie AA. Har munnskyllemidler noen plass i dagens tannhelse? Aktuel Nord Odontol 2016;41:18–32. doi:10.18261/ISSN2058-7538-2016-01-03

Rygh SB, Alexandersen TM. Forekomst av dental fluorose i Tromsø og Balsfjord. Basert på material fra Fit-Futures. 2016. https://munin.uit.no/handle/10037/10952 (accessed 20 Feb 2023).

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Pashto (n = 1)

Ghadimi S, Khami M, Razeghi S. Combined effect of laser irradiation and fluoride application in dental caries prevention. J Dent Med Tehran Univ Med Sci 2015;28:76–85. https://www.researchgate.net/publication/318307155_Combined_effect_of_laser_irradiation_and_fluoride_application_in_dental_caries_prevention

Persian (n = 3)

Mansouri M, Maryam K. Application of silver diamine fluoride in dentistry: A review. J Dent Med 2013;26:224–33. http://jdm.tums.ac.ir/article-1-5052-en.html (accessed 20 Feb 2023).

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Safarcherati H, Esmaeili B, Anvari T, et al. Laboratory Evaluation of Fluoride Varnish Effect on Ionomer Glass Color Using a Digital Camera and Spectrophotometer. J Babol Univ Med Sci 2016;18:44–9. https://jbums.org/article-1-6003-fa.html

Polish (n = 3)

Fux-Zalewska K, Szymańska J. Skuteczność antybakteryjna powidonku jodyny w próchnicy wczesnego dzieciństwa. Pediatr Pol 2017;92:173–7. doi:10.1016/j.pepo.2016.08.016

Janczarek M, Bachanek T, Mazur E, et al. The role of probiotics in prevention of oral diseases. Postepy Hig Med Doswiadczalnej 2016;70:850–7. doi:10.5604/17322693.1214381

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## (b) Studies excluded at full-text and extraction screening stages

*Table 92 Studies excluded during extraction and full-text screening stages*

| Domain | Inclusion | Exclusion |
|---|---|---|
| Population | The population of interest is people with some or all teeth that are caries free | Animal studies, in-vitro, and in-situ studies |
| Intervention | The interventions of interest should prevent caries. See Figure 3 | Oral health promotion, behaviour change programmes<br>Community water fluoridation programmes<br>Interventions targeting diet and sugar intake |
| Comparator | Placebo<br>Any relevant alternative treatment<br>No treatment | Studies with no comparator |
| Outcome | Any indicator of caries incidence or new caries presentation on any part of the tooth (e.g. % of new carious lesions, mean number of teeth with new caries, cumulative survival rate of caries free teeth, etc. with no mention of the dentistry-specific indexes)<br>D(E/M)FT*/d(e/m)ft† (or any variation of this index, e.g. DMFT/dmft, DEFT/deft, DFT/dft, DMFRT)<br>D(E/M)FS‡/d(e/m)fs∞ (or any variation of this index, e.g. DMFS/dmfs, DEFS/defs, DFS/dfs, DMFRS)<br>Root caries index (RCI) | |
| Study design | Systematic review of trials and/or prospective longitudinal cohort studies | Systematic reviews that did not include a PICO statement or the four aspects of PICO mentioned in the methods<br>Systematic reviews based on searches of only one bibliographic database<br>Systematic reviews that don't have at least one grey literature search and/or a supplementary search<br>Systematic reviews without a quality assessment/risk of bias assessment of their included studies or reviews that used an inappropriate tool for assessment (e.g., tools such as the Critical Appraisal Skills Programme (CASP) that are study design |

| Domain | Inclusion | Exclusion |
|---|---|---|
| | | checklists, not quality assessment tools)<br>Systematic reviews of case-control studies, retrospective cohort studies, cross-sectional studies, case series studies, or ecological studies<br>Narrative reviews<br>Scoping review<br>Primary studies |
| Date | 2010 – mid-June 2022 | Pre-2010 |
| Language | English | Non-English languages |

## 1. Papers excluded on full-text screening, with reasons (n=380)

*Table 93 Papers excluded on full-text screening, with reasons*

| Excluded on Population (n = 10) |
|---|
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| 4. Cao Y, Mei ML, Li Q-L, et al. Enamel prism-like tissue regeneration using enamel matrix derivative. J Dent 2014;42:1535–42. doi:10.1016/j.jdent.2014.08.014 |
| 5. Delimont Nicole M, Carlson Brandi N. Prevention of dental caries by grape seed extract supplementation: A systematic review. Nutr Health 2020;26:43–52. doi:10.1177/0260106019887890 |
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Exclude on Study Design (n = 141)

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Excluded – Withdrawn or retracted (n = 5) Unique n =3

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## 2. Papers excluded at extraction stage, with reasons (n=27)

*Table 94 Papers excluded at the extraction stage, with reasons*

Exclude on Population (n = 1)

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Exclude on Comparator (n = 3)

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12. Wierichs RJ, Wolf TG, Campus G, *et al.* Efficacy of nano-hydroxyapatite on caries prevention—a systematic review and meta-analysis. *Clin Oral Investig* 2022;**26**:3373–81. doi:10.1007/s00784-022-04390-4

13. Yeung SST, Argáez C. *Silver Diamine Fluoride for the Prevention and Arresting of Dental Caries or Hypersensitivity: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines*. Canadian Agency for Drugs and Technologies in Health 2017. https://www.ncbi.nlm.nih.gov/books/NBK493244/

Exclude on Study Design (n = 5)

1. Kumar S, Tadakamadla J, Johnson NW. Effect of Toothbrushing Frequency on Incidence and Increment of Dental Caries: A Systematic Review and Meta-Analysis. J Dent Res 2016;95:1230–6. doi:10.1177/0022034516655315

2. Lo Y-F, Crispin A, Kessler A, et al. What is an Appropriate Etching Time For Sealant Application on Permanent Molars? Results from a Meta-Analysis. J Adhes Dent 2019;21:487–95. doi:10.3290/j.jad.a43181

3. Mota KR, Silva JVF da, Borges CD, et al. Effectiveness of the use of xylitol chewing gum in prevention of dental caries: A systematic review. J Indian Soc Pedod Prev Dent 2021;39:113. doi:10.4103/JISPPD.JISPPD_330_20

4. Skeie MS, Klock KS. Dental caries prevention strategies among children and adolescents with immigrant - or low socioeconomic backgrounds- do they work? A systematic review. BMC Oral Health 2018;18:20. doi:10.1186/s12903-018-0478-6

5. Twetman S, Dhar V. Evidence of Effectiveness of Current Therapies to Prevent and Treat Early Childhood Caries. Pediatr Dent 2015;37:246–53.

Exclude on Quality Assessment / Risk of Bias (n = 3)

1. Ástvaldsdóttir Á, Naimi-Akbar A, Davidson T, et al. Arginine and Caries Prevention: A Systematic Review. Caries Res 2016;50:383–93. doi:10.1159/000446249

2. Jafarzadeh D, Rezapour R, Abbasi T, et al. The Effectiveness of Fluoride Varnish and Fissure Sealant in Elementary School Children: A Systematic Review and Meta-Analysis. Iran J Public Health 2022;51:266–77. doi:10.18502/ijph.v51i2.8680

3. Mickenautsch S, Yengopal V. Caries-Preventive Effect of High-Viscosity Glass-ionomer and Resin-Based Fissure Sealants on Permanent Teeth: A Systematic Review of Clinical Trials. PLOS ONE 2016;11:e0146512. doi:10.1371/journal.pone.0146512

# Appendix D Included studies

*Table 95 List of included studies*

| Included studies (n = 66) |
| --- |
| 1. Ahovuo-Saloranta A, Forss H, Walsh T, et al. Pit and fissure sealants for preventing dental decay in permanent teeth. *Cochrane Database Syst Rev* 2017;7:CD001830. doi:10.1002/14651858.CD001830.pub5 |
| 2. Akera P, Kennedy SE, Lingam R, et al. Effectiveness of primary school-based interventions in improving oral health of children in low- and middle-income countries: a systematic review and meta-analysis. BMC Oral Health 2022;22:264. doi:10.1186/s12903-022-02291-2 |
| 3. Alharthy H, Elkhodary HM, Nahdreen A, et al. Comparative evaluation of retention and cariostatic effect of hydrophilic and hydrophobic resin-based sealants: A systematic review and meta-analysis. *Niger J Clin Pract* 2022;25:861–84. doi:10.4103/njcp.njcp_1863_21 |
| 4. Alirezaei M, Bagherian A, Sarraf Shirazi A. Glass-ionomer cements as fissure sealing materials: yes or no?: A systematic review and meta-analysis. J Am Dent Assoc 1939 2018;149:640-649.e9. doi:10.1016/j.adaj.2018.02.001 |
| 5. Alsabek L, Al-Hakeem A, Alagha MA, et al. Efficacy of hydrophilic resin-based sealant: A systematic review and meta-analysis. J Dent 2021;114:103816. doi:10.1016/j.jdent.2021.103816 |
| 6. Antonio AG, Pierro VS da S, Maia LC. Caries preventive effects of xylitol-based candies and lozenges: a systematic review. J Public Health Dent 2011;71:117–24. doi:10.1111/j.1752-7325.2010.00208.x |
| 7. CADTH. Dental Sealants and Preventive Resins for Caries Prevention: A Review of the Clinical Effectiveness, Cost-effectiveness and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health 2016. http://www.ncbi.nlm.nih.gov/books/NBK401525/ |
| 8. Cagetti MG, Campus G, Milia E, et al. A systematic review on fluoridated food in caries prevention. Acta Odontol Scand 2013;71:381–7. doi:10.3109/00016357.2012.690447 |
| 9. Carvalho DM, Salazar M, Oliveira BH de, et al. Fluoride varnishes and decrease in caries incidence in preschool children: a systematic review. Rev Bras Epidemiol Braz J Epidemiol 2010;13:139–49. doi:10.1590/s1415-790x2010000100013 |
| 10. Chan AKY, Tamrakar M, Jiang CM, et al. Clinical evidence for professionally applied fluoride therapy to prevent and arrest dental caries in older adults: A systematic review. J Dent 2022;125:104273. doi:10.1016/j.jdent.2022.104273 |
| 11. Chong L-Y, Clarkson JE, Dobbyn-Ross L, et al. Slow-release fluoride devices for the control of dental decay. Cochrane Database Syst Rev Published Online First: 2018. doi:10.1002/14651858.CD005101.pub4 |
| 12. Chou R, Pappas M, Dana T, et al. Screening and Interventions to Prevent Dental Caries in Children Younger Than 5 Years: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2021;326:2179–92. doi:10.1001/jama.2021.15658 |
| 13. de Sousa FS de O, Dos Santos APP, Nadanovsky P, et al. Fluoride Varnish and Dental Caries in Preschoolers: A Systematic Review and Meta-Analysis. Caries Res 2019;53:502–13. doi:10.1159/000499639 |
| 14. dos Santos APP, de Oliveira BH, Nadanovsky P. A systematic review of the effects of supervised toothbrushing on caries incidence in children and adolescents. Int J Paediatr Dent 2018;28:3–11. doi:10.1111/ipd.12334 |
| 15. dos Santos APP, Nadanovsky P, de Oliveira BH. A systematic review and meta-analysis of the effects of fluoride toothpastes on the prevention of dental caries in the primary dentition of preschool children. Community Dent Oral Epidemiol 2013;41:1–12. doi:10.1111/j.1600-0528.2012.00708.x |
| 16. Fee PA, Riley P, Worthington HV, et al. Recall intervals for oral health in primary care patients. Cochrane Database Syst Rev Published Online First: 2020. doi:10.1002/14651858.CD004346.pub5 |

| Included studies (n = 66) |
| --- |
| 17. Figuero E, Nóbrega DF, García-Gargallo M, et al. Mechanical and chemical plaque control in the simultaneous management of gingivitis and caries: a systematic review. J Clin Periodontol 2017;44 Suppl 18:S116–34. doi:10.1111/jcpe.12674 |
| 18. Grandjean M-L, Maccarone NR, McKenna G, et al. Silver Diamine Fluoride (SDF) in the management of root caries in elders: a systematic review and meta-analysis. Swiss Dent J 2021;131:417–24. |
| 19. Gupta A, Sharda S, Nishant, et al. Topical fluoride-antibacterial agent combined therapy versus topical fluoride monotherapy in preventing dental caries: a systematic review and meta-analysis. Eur Arch Paediatr Dent 2020;21:629–46. doi:10.1007/s40368-020-00561-7 |
| 20. Gupta A, Nishant, Sharda S, et al. Comparing the Effectiveness of Topical Fluoride and Povidone Iodine with Topical Fluoride Alone for the Prevention of Dental Caries among Children: A Systematic Review and Meta-analysis. Int J Clin Pediatr Dent 2020;13:559–65. doi:10.5005/jp-journals-10005-1844 |
| 21. Hao S, Wang J, Wang Y. Effectiveness and safety of Bifidobacterium in preventing dental caries: a systematic review and meta-analysis. Acta Odontol Scand 2021;79:613–22. doi:10.1080/00016357.2021.1921259 |
| 22. Hendre AD, Taylor GW, Chávez EM, et al. A systematic review of silver diamine fluoride: Effectiveness and application in older adults. Gerodontology 2017;34:411–9. doi:10.1111/ger.12294 |
| 23. Hujoel PP. Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis. Nutr Rev 2013;71:88–97. doi:10.1111/j.1753-4887.2012.00544.x |
| 24. Hujoel PP, Hujoel MLA, Kotsakis GA. Personal oral hygiene and dental caries: A systematic review of randomised controlled trials. Gerodontology 2018;35:282–9. doi:10.1111/ger.12331 |
| 25. James P, Parnell C, Whelton H. The Caries-Preventive Effect of Chlorhexidine Varnish in Children and Adolescents: A Systematic Review. Caries Res 2010;44:333–40. doi:10.1159/000315346 |
| 26. Jørgensen MR, Castiblanco G, Twetman S, et al. Prevention of caries with probiotic bacteria during early childhood. Promising but inconsistent findings. Am J Dent 2016;29:127–31. |
| 27. Joury E, Bernabe E, Sabbah W, et al. Systematic review and meta-analysis of randomised controlled trials on the effectiveness of school-based dental screening versus no screening on improving oral health in children. J Dent 2017;58:1–10. doi:10.1016/j.jdent.2016.11.008 |
| 28. Kashbour W, Gupta P, Worthington HV, et al. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents. Cochrane Database Syst Rev Published Online First: 2020. doi:10.1002/14651858.CD003067.pub5 |
| 29. Konradsson K, Lingström P, Emilson C-G, et al. Stabilized stannous fluoride dentifrice in relation to dental caries, dental erosion and dentin hypersensitivity: A systematic review. Am J Dent 2020;33:95–105. |
| 30. Lam PPY, Sardana D, Ekambaram M, et al. Effectiveness of Pit and Fissure Sealants for Preventing and Arresting Occlusal Caries in Primary Molars: A Systematic Review and Meta-Analysis. J Evid-Based Dent Pract 2020;20:101404. doi:10.1016/j.jebdp.2020.101404 |
| 31. Li F, Jiang P, Yu F, et al. Comparison between Fissure Sealant and Fluoride Varnish on Caries Prevention for First Permanent Molars: a Systematic Review and Meta-analysis. Sci Rep 2020;10:2578. doi:10.1038/s41598-020-59564-5 |
| 32. Marghalani AA, Guinto E, Phan M, et al. Effectiveness of Xylitol in Reducing Dental Caries in Children. Pediatr Dent 2017;39:103–10. |
| 33. Marinho VC, Chong L-Y, Worthington HV, et al. Fluoride mouthrinses for preventing dental caries in children and adolescents. Cochrane Database Syst Rev Published Online First: 2016. doi:10.1002/14651858.CD002284.pub2 |

| Included studies (n = 66) |
| --- |
| 34. Marinho VC, Worthington HV, Walsh T, et al. Fluoride varnishes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev Published Online First: 2013. doi:10.1002/14651858.CD002279.pub2 |
| 35. Marinho VC, Worthington HV, Walsh T, et al. Fluoride gels for preventing dental caries in children and adolescents. Cochrane Database Syst Rev Published Online First: 2015. doi:10.1002/14651858.CD002280.pub2 |
| 36. Newton JT, Awojobi O, Nasseripour M, et al. A Systematic Review and Meta-Analysis of the Role of Sugar-Free Chewing Gum in Dental Caries. JDR Clin Transl Res 2020;5:214–23. doi:10.1177/2380084419887178 |
| 37. Oliveira BH, Cunha-Cruz J, Rajendra A, et al. Controlling caries in exposed root surfaces with silver diamine fluoride: A systematic review with meta-analysis. J Am Dent Assoc 1939 2018;149:671-679.e1. doi:10.1016/j.adaj.2018.03.028 |
| 38. Oliveira BH, Rajendra A, Veitz-Keenan A, et al. The Effect of Silver Diamine Fluoride in Preventing Caries in the Primary Dentition: A Systematic Review and Meta-Analysis. Caries Res 2019;53:24–32. doi:10.1159/000488686 |
| 39. Pagano S, Lombardo G, Orso M, et al. Lasers to prevent dental caries: a systematic review. BMJ Open 2020;10:e038638. doi:10.1136/bmjopen-2020-038638 |
| 40. Poorni S, Srinivasan MR, Nivedhitha MS. Probiotic Streptococcus strains in caries prevention: A systematic review. J Conserv Dent JCD 2019;22:123–8. doi:10.4103/JCD.JCD_505_18 |
| 41. Ramamurthy P, Rath A, Sidhu P, et al. Sealants for preventing dental caries in primary teeth. Cochrane Database Syst Rev Published Online First: 2022. doi:10.1002/14651858.CD012981.pub2 |
| 42. Rashed T, Alkhalefa N, Adam A, et al. Pit and Fissure Sealant versus Fluoride Varnish for the Prevention of Dental Caries in School Children: A Systematic Review and Meta-Analysis. Int J Clin Pract 2022;2022:e8635254. doi:10.1155/2022/8635254 |
| 43. Rethman MP, Beltran-Aguilar ED, Billings RJ, et al. Non-fluoride caries preventive agents: full report of a systematic review and evidence-based recommendations. Centre for Reviews and Dissemination (UK) 2011. https://www.ncbi.nlm.nih.gov/books/NBK137902/ (accessed 6 Jan 2023). |
| 44. Riggs E, Kilpatrick N, Slack-Smith L, et al. Interventions with pregnant women, new mothers and other primary caregivers for preventing early childhood caries. Cochrane Database Syst Rev Published Online First: 2019. doi:10.1002/14651858.CD012155.pub2 |
| 45. Riley P, Moore D, Ahmed F, et al. Xylitol-containing products for preventing dental caries in children and adults. Cochrane Database Syst Rev Published Online First: 2015. doi:10.1002/14651858.CD010743.pub2 |
| 46. Santos APP, Oliveira BH, Nadanovsky P. Effects of low and standard fluoride toothpastes on caries and fluorosis: systematic review and meta-analysis. Caries Res 2013;47:382–90. doi:10.1159/000348492 |
| 47. Sharda S, Gupta A, Goyal A, et al. Remineralization potential and caries preventive efficacy of CPP-ACP/Xylitol/Ozone/Bioactive glass and topical fluoride combined therapy versus fluoride mono-therapy – a systematic review and meta-analysis. Acta Odontol Scand 2021;79:402–17. doi:10.1080/00016357.2020.1869827 |
| 48. Singal K, Sharda S, Gupta A, et al. Effectiveness-of Calcium Phosphate derivative agents on the prevention and remineralization of caries among children- A systematic review & meta-analysis of randomized controlled trials. J Evid-Based Dent Pract 2022;22:101746. doi:10.1016/j.jebdp.2022.101746 |
| 49. Slot DE, Vaandrager NC, Loveren CV, et al. The Effect of Chlorhexidine Varnish on Root Caries: A Systematic Review. Caries Res 2011;45:162–73. doi:10.1159/000327374 |

| Included studies (n = 66) |
| --- |
| 50. Smith L, Blinkhorn FA, Blinkhorn AS, et al. Prevention of dental caries in Indigenous children from World Health Organization–listed high-income countries: A systematic review. Health Educ J 2018;77:332–48. doi:10.1177/0017896917749264 |
| 51. Subbiah GK, Gopinathan NM. Is Silver Diamine Fluoride Effective in Preventing and Arresting Caries in Elderly Adults? A Systematic Review. J Int Soc Prev Community Dent 2018;8:191–9. doi:10.4103/jispcd.JISPCD_99_18 |
| 52. Takahashi R, Ota E, Hoshi K, et al. Fluoride supplementation (with tablets, drops, lozenges or chewing gum) in pregnant women for preventing dental caries in the primary teeth of their children. Cochrane Database Syst Rev Published Online First: 2017. doi:10.1002/14651858.CD011850.pub2 |
| 53. Tubert-Jeannin S, Auclair C, Amsallem E, et al. Fluoride supplements (tablets, drops, lozenges or chewing gums) for preventing dental caries in children. Cochrane Database Syst Rev Published Online First: 2011. doi:10.1002/14651858.CD007592.pub2 |
| 54. Twetman S, Jørgensen M r. Can probiotic supplements prevent early childhood caries? A systematic review and meta-analysis. Benef Microbes 2021;12:231–8. doi:10.3920/BM2021.0008 |
| 55. Walsh T, Oliveira-Neto JM, Moore D. Chlorhexidine treatment for the prevention of dental caries in children and adolescents. Cochrane Database Syst Rev Published Online First: 2015. doi:10.1002/14651858.CD008457.pub2 |
| 56. Walsh T, Worthington HV, Glenny A-M, et al. Fluoride toothpastes of different concentrations for preventing dental caries. Cochrane Database Syst Rev Published Online First: 2019. doi:10.1002/14651858.CD007868.pub3 |
| 57. Wang Y, Li J, Sun W, et al. Effect of non-fluoride agents on the prevention of dental caries in primary dentition: A systematic review. PloS One 2017;12:e0182221. doi:10.1371/journal.pone.0182221 |
| 58. Wierichs RJ, Wolf TG, Campus G, et al. Efficacy of nano-hydroxyapatite on caries prevention—a systematic review and meta-analysis. Clin Oral Investig 2022;26:3373–81. doi:10.1007/s00784-022-04390-4 |
| 59. Worthington HV, MacDonald L, Pericic TP, et al. Home use of interdental cleaning devices, in addition to toothbrushing, for preventing and controlling periodontal diseases and dental caries. Cochrane Database Syst Rev Published Online First: 2019. doi:10.1002/14651858.CD012018.pub2 |
| 60. Wright JT, Tampi MP, Graham L, et al. Sealants for preventing and arresting pit-and-fissure occlusal caries in primary and permanent molars: A systematic review of randomized controlled trials-a report of the American Dental Association and the American Academy of Pediatric Dentistry. J Am Dent Assoc 1939 2016;147:631-645.e18. doi:10.1016/j.adaj.2016.06.003 |
| 61. Xiao J, Alkhers N, Kopycka-Kedzierawski DT, et al. Prenatal Oral Health Care and Early Childhood Caries Prevention: A Systematic Review and Meta-Analysis. Caries Res 2019;53:411–21. doi:10.1159/000495187 |
| 62. Yeung CA, Chong L-Y, Glenny A-M. Fluoridated milk for preventing dental caries. Cochrane Database Syst Rev Published Online First: 2015. doi:10.1002/14651858.CD003876.pub4 |
| 63. Yu L, Yu X, Li Y, et al. The additional benefit of professional fluoride application for children as an adjunct to regular fluoride toothpaste: a systematic review and meta-analysis. Clin Oral Investig 2021;25:3409–19. doi:10.1007/s00784-021-03909-5 |
| 64. Zhang J, Sardana D, Li KY, et al. Topical Fluoride to Prevent Root Caries: Systematic Review with Network Meta-analysis. J Dent Res 2020;99:506–13. doi:10.1177/0022034520906384 |
| 65. Zhang Y, Wang Y, Chen Y, et al. The clinical effects of laser preparation of tooth surfaces for fissure sealants placement: a systematic review and meta-analysis. BMC Oral Health 2019;19:203. doi:10.1186/s12903-019-0892-4 |

Included studies (n = 66)

66. Zhou N, Wong HM, Wen YF, et al. Efficacy of caries and gingivitis prevention strategies among children and adolescents with intellectual disabilities: a systematic review and meta-analysis. J Intellect Disabil Res JIDR 2019;63:507–18. doi:10.1111/jir.12576

# Appendix E HRB-adapted AMSTAR 2 instrument

## (a) Example critical appraisal tool

- **An asterisk *** following a number denotes a critical factor.
- **Text in red** indicates an exclusion factor.
- **Text in purple** indicates agreed adaptations and interpretation.

*Table 92 HRB-adapted AMSTAR-2 instrument*

| HRB-adapted AMSTAR-2 instrument | | |
|---|---|---|
| 1 | **Did the research questions and inclusion criteria for the review include the components of PICO?**<br><br>**Four of five components must be in the introduction or methods to be awarded a YES.** | ☐ Yes<br>☐ No |

For Yes to PICO:
- ☐ Population.
- ☐ Intervention.
- ☐ Comparator group.
- ☐ Outcome.
- ☐ Time frame for follow-up.

| | | |
|---|---|---|
| 2 | **Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? The protocol must be accessible to check that the parameters below are covered.** | ☐ Yes<br>☐ Partial Yes<br>☐ No |

For Partial Yes: **Protocol must be reported as prepared and accessible.**

The authors state that they had a written protocol or guide that included ALL the following:
- ☐ Review question(s).
- ☐ A search strategy.
- ☐ Inclusion/exclusion criteria.
- ☐ A Risk of Bias (RoB) assessment.

For 'full' Yes: **Protocol must be registered and accessible.**

As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ A meta-analysis/synthesis plan, if appropriate.

*AND*
- ☐ A plan for investigating causes of heterogeneity.

*AND*
- ☐ Justification for any deviations from the protocol.

| | | |
|---|---|---|
| 3 | **Did the review authors explain their selection of the study designs for inclusion in the review?**<br>**Must have justified their rationale for selecting the study design to be awarded a YES.**<br>**If they provide the study design a-priori but not an explanation, they are to be awarded a NO.** | ☐ Yes<br>☐ No |

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs.

*OR*
- ☐ *Explanation for* including only NRSI.

*OR*
- ☐ *Explanation for* including both RCTs and NRS.I

| | | |
|---|---|---|
| 4 | **Did the review authors use a comprehensive literature search strategy?** | ☐ Yes<br>☐ Partial Yes<br>☐ No |

For Partial Yes (all the following):
- ☐ Searched at least two databases (relevant to research question) **(fewer than two is a fatal flaw, exclude).**
- ☐ Provided keyword and/or search strategy.
- ☐ Justified publication restrictions (e.g. language and/or duration of search).

For 'full' Yes, should have **(two or more of the following)**:
- ☐ Searched the reference lists/bibliographies of included studies (moved from below and considered necessary step).
- ☐ Searched trial/study registries.
- ☐ Where relevant, searched for grey literature.
- ☐ Conducted search within 24 months of completion of the review.
- ☐ Included/consulted experts in the field.

| | | |
|---|---|---|
| 5 | **Did the review authors perform study selection in duplicate?** | ☐ Yes<br>☐ No |

For Yes, either ONE of the following:
- ☐ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include.

*OR*
- ☐ Two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer.

| | | |
|---|---|---|
| 6 | **Did the review authors perform data extraction in duplicate?** | ☐ Yes<br>☐ No |

For Yes, either ONE of the following:

- At least two reviewers independently agreed on selection of eligible studies and achieved consensus on what data to extract.
  *OR*
- Two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer.

| | | |
|---|---|---|
| 7 | **Did the review authors provide a list of excluded studies and justify the exclusions?** | Yes<br>Partial Yes<br>No |

For Partial Yes:
- Provided a list of all potentially relevant studies that were read in full text form but excluded from the review.

For 'full' Yes, must also have:
- Justified the exclusion from the review of each potentially relevant study.

| | | |
|---|---|---|
| 8 | **Did the review authors describe the included studies in adequate detail?** | Yes<br>Partial Yes<br>No |

For Partial Yes (ALL the following):
- **Adequately** described populations.
- **Adequately** described interventions.
- Described comparators.
- Described outcomes.
- Described research designs.

For 'full' Yes, should also have ALL the following:
- Described study's setting.
- Time frame for follow-up.

**Removed points on detailed description as overlap with criteria above.**

| | | |
|---|---|---|
| 9 | **Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?**<br>**No quality assessment or RoB completed on primary studies (fatal flaw, exclude)**<br>**Did the authors use the correct instrument for the included study design(s)?**<br>**Did the authors assess the relevant points, see below?** | Yes<br>Partial Yes<br>No<br>Includes only |

**Randomised controlled or clinical trials**

For Partial Yes, must have assessed RoB from:
- Unconcealed allocation **(randomization and blinding combined when allocating the intervention).**
  *AND*
- Lack of blinding assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality or admission to hospital).

For 'full' Yes, must have assessed RoB from:

- Allocation sequence that was not truly random (individual randomisation versus group randomization).

*AND*

- Selection of the reported result from among multiple measurements or analyses of a specified outcome, known as selective reporting **(using only the outcomes or measurements that provide the researchers with their desired answer and ignoring other outcomes that may contradict the desired findings).**

**Non-randomised epidemiological studies**

For Partial Yes, must have assessed RoB:

- From confounding.

*AND*

- From selection bias.

For Yes, must also have assessed RoB:

- Methods used to ascertain exposures and outcomes.

*AND*

- Selection of the reported result from among multiple measurements or analyses of a specified outcome, known as selective reporting **(using only the outcomes or measurements that provide the researchers with their desired answer and ignoring other outcomes that may contradict the desired findings).**

| | | |
|---|---|---|
| 10 | **Did the review authors report on the sources of funding for the studies included in the review?** | Yes<br>No |

For Yes:

- Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information, but it was not reported by study authors also qualifies.

| | | |
|---|---|---|
| 11 | **If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?** | Yes<br>No<br>No MA |

**Randomised controlled or clinical trials**

For Yes:

- The authors justified combining the data in a meta-analysis.

AND

- They used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.

AND

- Investigated the causes of any heterogeneity conducted.

**If heterogeneity present: completed feasibility analysis to decide what studies to include (PICO for clinical heterogeneity) and what type of meta-analysis to use (pairwise [2 arm trials and two competing interventions] versus network [three or more arm trials and more than two competing interventions]), used a random effects model if statistical heterogeneity is greater than an pre-agreed level (25%, 50% or 75%), estimate statistical heterogeneity (Q or $I^2$ test), determine influence of highly weighted studies (any one study influencing the outcome), high risk or**

**unclear risk of bias studies (removed from analysis), or studies with different populations, comparators and intervention formats through sensitivity or subgroup analysis**

**Non-randomised epidemiological studies**

- ☐ The authors justified combining the data in a meta-analysis.

AND

- ☐ They used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present.

AND

- ☐ They statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available.

AND

- ☐ They reported separate summary estimates for RCTs and NRSI separately when both were included in the review.

**If heterogeneity present: completed feasibility analysis to decide what studies to include (PICO for clinical heterogeneity) and what type of meta-analysis to use (pairwise [2 arm trials and two competing interventions] versus network [three or more arm trials and more than two competing interventions]), studied controls for confounding, used confounding adjusted risk or odds ratios, used a random effects model if statistical heterogeneity is greater than an pre-agreed level (25%, 50% or 75%), estimate statistical heterogeneity (Q or $I^2$ test), determine influence of highly weighted studies (any one study influencing the outcome), high risk or unclear risk of bias studies (removed from analysis), or studies with different populations, comparators and intervention formats through sensitivity or subgroup analysis.**

| | | |
|---|---|---|
| 12 | **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** | ☐ Yes<br>☐ No<br>☐ No MA |

For Yes:

- ☐ Included only low risk of bias RCTs **(sensitivity analysis)**

**Note: It is not good practice to combine RCT and NRSI, therefore separate results should be provided, and their similarities or differences discussed.**

| | | |
|---|---|---|
| 13 | **Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?** | ☐ Yes<br>☐ No |

For Yes:

- ☐ Included only low risk of bias RCTs in the review.
- ☐ Included only low risk of bias RCTs (in meta-analysis or a sensitivity analysis and discuss differences).

*OR*

- ☐ If RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results **and quality of evidence or limitations in conclusions or summary.**

**Generally, NRSI have more positive results that RCTs because of self-selection bias and lack of randomization and readers should be reminded of this.**

**Confounding should be controlled for in the meta-analysis by using adjusted odds ratios. Loss to follow-up should be controlled for in the inclusion criteria. Loss to follow-up of over 20% introduces a serious bias to longitudinal studies.**

**Risk of bias should also be discussed for narrative analysis.**

**Risk of bias should concentrate of the areas that were at high risk or unclear risk of bias its effect on the direction of the results.**

| | | |
|---|---|---|
| 14 | **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** | ☐ Yes<br>☐ No |

For Yes:

☐ There was no significant heterogeneity in the results.

*OR*

☐ If heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results **(feasibility assessment, random effects model, sensitivity and subgroup analysis)** and discussed the impact of this on the results of the review **and the quality of evidence.**

**If narrative analysis completed, the effects of clinical heterogeneity on the results and quality of evidence should be discussed.**

| | | |
|---|---|---|
| 15 | **If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** | ☐ Yes<br>☐ No<br>☐ No MA |

For Yes:

☐ Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias.

**Publication bias occurs when results of published studies are systematically different from unpublished or grey literature studies. Publication bias is trying to estimate the influence of unpublished studies on the results of the systematic review. Publication bias can be controlled for through a good comprehensive search strategy that includes unpublished studies, yet to be published studies, or studies published in grey literature and a wide selection of databases.**

**Publication bias can be measured using a funnel plot and its p-value. A funnel plot is a scatter plot of estimates of the treatment effects of each study against the measure of its precision (1/Standard Error). In the absence of publication bias, plot will look like symmetric inverted funnel. A minimum of ten studies are required to run the funnel plot analysis.**

**The effect of publication bias should be considered in the GRADE quality of evidence.**

| | | |
|---|---|---|
| 16 | **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** | ☐ Yes<br>☐ No |

For Yes:

☐ The authors reported no competing interests.

*OR*

☐ The authors described their funding sources and how they managed potential conflicts of interest.

**In this case, the industry producing dental products are may main source of conflict of interest.**

## (b) Critical domains

*Table 96 Critical domains in AMSTAR 2*

| Item Number | Shea *et al.*, 2017 AMSTAR 2 critical domains | Results of HRB GRADE assessment on critical items |
|---|---|---|
| Item 1 | - | - |
| Item 2 | Protocol registered before commencement of the review | 30% received a rating of 'Yes', 33% received a rating of 'Partial yes', and 37% received a rating of 'No'. |
| Item 3 | - | - |
| Item 4 | Adequacy of the literature search | 97% received a rating of 'Yes' and 5% received a rating of 'Partial yes'. |
| Item 5 | - | - |
| Item 6 | - | - |
| Item 7 | Justification for excluding individual studies | 55% received a rating of 'Yes' and 44% received a rating of 'No' (N/A for 1%). |
| Item 8 | - | - |
| Item 9 | Risk of bias assessment of the individual studies included in the review | 88% received a rating of 'Yes', 9% received a rating of 'Partial yes', and 3% received a rating of 'No'. |
| Item 10 | - | - |
| Item 11 | Appropriateness of meta-analytical methods | 1% received a rating of 'Yes' and 71% received a rating of 'No' (N/A for 28%). |
| Item 12 | - | - |
| Item 13 | Consideration of risk of bias when interpreting the results of the review | 80% received a rating of 'Yes' and 20% received a rating of 'No'. |
| Item 14 | - | - |
| Item 15 | Assessment of presence and likely impact of publication bias | 15% received a rating of 'Yes' and 27% received a rating of 'No' (N/A for 58%). |
| Item 16 | - | - |

## (c) Rating overall confidence in the results of the review

*Table 97 Rating the overall confidence in the results of the review*

| Score | Criteria |
|---|---|
| **High** | No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest |
| **Moderate** | More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review |
| **Low** | One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest |
| **Critically low** | More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies |
| ***Downgrade** | *Multiple non-critical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence. |

# Appendix F Quality assessment results for included reviews

*Table 98 Quality assessment results for included reviews*

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary dentition | | | | | | | | | | | | | | | | | | |
| Attendance for dental assessment (n = 3) | | | | | | | | | | | | | | | | | | |
| Scheduled dental appointments (n = 2) | | | | | | | | | | | | | | | | | | |
| Fee *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |
| Joury *et al.* (2017) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | Not applicable | No | Critically low | 4 no, 3 yes |
| Scheduled primary care appointments (n = 1) | | | | | | | | | | | | | | | | | | |
| Chou *et al.* (2021) | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No | No | Critically low | 2 no, 5 yes |
| Dental hygiene (n = 3) | | | | | | | | | | | | | | | | | | |
| Supervised toothbrushing (n = 3) | | | | | | | | | | | | | | | | | | |
| Hujoel *et al.* (2018) | Yes | No | No | Yes | No | Yes | No | No | Yes | Yes | No | No | No | Yes | Not applicable | No | Critically low | 5 no, 2 yes |
| Akera *et al.* (2022) | Yes | Yes | No | Yes | No | Yes | Yes | No | Partial yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Dos Santos *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 3 no, 3 yes |
| Flossing (n = 0) | | | | | | | | | | | | | | | | | | |
| Interdental cleaning devices (n = 0) | | | | | | | | | | | | | | | | | | |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | | | | | | | | |
| Systemic fluoride (n = 5) | | | | | | | | | | | | | | | | | | |
| Milk (n = 2) | | | | | | | | | | | | | | | | | | |
| Yeung *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cagetti *et al.* (2012) | No | No | No | Yes | Yes | No | Yes | Partial yes | No | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Salt (n = 1) | | | | | | | | | | | | | | | | | | |
| Cagetti *et al.* (2012) | No | No | No | Yes | Yes | No | Yes | Partial yes | No | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Sugar (n = 1) | | | | | | | | | | | | | | | | | | |
| Cagetti *et al.* (2012) | No | No | No | Yes | Yes | No | Yes | Partial yes | No | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Supplements (n = 3) | | | | | | | | | | | | | | | | | | |
| Tubert-Jeannin *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Partial yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 2 partial, 3 yes |
| Zhou *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | No | No | No | Yes | No | No | No | Yes | No | No | Yes | Critically low | 5 no, 1 partial, 1 yes |
| Chou *et al.* (2021) | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No | No | Critically low | 2 no, 5 yes |
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | | | | | | |
| Vitamin D (n = 0) | | | | | | | | | | | | | | | | | | |
| Calcium (n = 0) | | | | | | | | | | | | | | | | | | |
| Sialagogues (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Zinc (n = 0) | | | | | | | | | | | | | | | | | | |
| Topical fluoride (n = 9) | | | | | | | | | | | | | | | | | | |
| Toothpaste (n = 2) | | | | | | | | | | | | | | | | | | |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Walsh *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Santos *et al.* (2013) | Yes | No | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 6 no, 1 yes |
| Mouthrinses (n = 0) | | | | | | | | | | | | | | | | | | |
| Foams (n = 0) | | | | | | | | | | | | | | | | | | |
| Gels (n = 1) | | | | | | | | | | | | | | | | | | |
| Marinho *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Solution (n = 2) | | | | | | | | | | | | | | | | | | |
| Oliveira *et al.* (2019) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Chou *et al.* (2021) | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No | No | Critically low | 2 no, 5 yes |
| Slow-release fluoride devices (n = 1) | | | | | | | | | | | | | | | | | | |
| Chong *et al.* (2018) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial, 4 yes |
| Varnishes (n = 3) | | | | | | | | | | | | | | | | | | |
| Marinho *et al.* (2013) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Carvalho *et al.* (2010) | Yes | No | No | Partial yes | Yes | No | Yes | No | Partial yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | No | Critically low | 3 no, 3 yes |
| Smith *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Mixed (n = 0) | | | | | | | | | | | | | | | | | | |
| Topical other chemicals (n = 11) | | | | | | | | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | | | | | | | | |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antimicrobial agents (minus CHX) (n = 2) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Wang *et al.* (2017) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Arginine and its derivatives (n = 0) | | | | | | | | | | | | | | | | | | |
| CHX (n = 5) | | | | | | | | | | | | | | | | | | |
| Walsh *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| James *et al.* (2010) | Yes | No | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | No | Critically low | 4 no, 2 yes |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Wang *et al.* (2017) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Smith *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Calcium phosphate agents (n = 3) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Wang *et al.* (2017) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Singal *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Ozone (n = 0) | | | | | | | | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | | | | | | | | |
| Probiotics (n = 3) | | | | | | | | | | | | | | | | | | |
| Hao *et al.* (2021) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 4 no, 3 yes |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jørgensen *et al.* (2016) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Twetman *et al.* (2021) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | Yes | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Propolis (n = 0) | | | | | | | | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | | | | | | | | |
| Riley *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Chou *et al.* (2021) | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No | No | Critically low | 2 no, 5 yes |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Wang *et al.* (2017) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Sorbitol (n = 0) | | | | | | | | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Sealants (n = 3) | | | | | | | | | | | | | | | | | | |
| Resin (n = 2) | | | | | | | | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |
| Lam *et al.* (2020) | Yes | No | No | Yes | Yes | Yes | No | No | No | No | No | No | Yes | Yes | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Glass-ionomer (n = 2) | | | | | | | | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |
| Lam *et al.* (2020) | Yes | No | No | Yes | Yes | Yes | No | No | No | No | No | No | Yes | Yes | Not applicable | Yes | Critically low | 5 no, 2 yes |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ormocer (n = 0) | | | | | | | | | | | | | | | | | | |
| Hybrid (n = 0) | | | | | | | | | | | | | | | | | | |
| Combined (n = 1) | | | | | | | | | | | | | | | | | | |
| Akera *et al.* (2022) | Yes | Yes | No | Yes | No | Yes | Yes | No | Partial yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Other (n = 0) | | | | | | | | | | | | | | | | | | |
| Laser (n = 1) | | | | | | | | | | | | | | | | | | |
| Pagano *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | No | Yes | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 3 no, 1 partial, 2 yes |
| Subgroup: Mother of unborn/toddlers (treatment given to mothers, outcomes tested on children) | | | | | | | | | | | | | | | | | | |
| Systemic fluoride (n = 2) | | | | | | | | | | | | | | | | | | |
| Supplements (n = 2) | | | | | | | | | | | | | | | | | | |
| Takahashi *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |
| Xiao *et al.* (2019) | Yes | No | No | Yes | Yes | No | Yes | No | Yes | No | No | No | No | Yes | No | No | Critically low | 5 no, 2 yes |
| Topical other chemicals (n = 2) | | | | | | | | | | | | | | | | | | |
| Xylitol (n = 2) | | | | | | | | | | | | | | | | | | |
| Riggs *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Xiao *et al.* (2019) | Yes | No | No | Yes | Yes | No | Yes | No | Yes | No | No | No | No | Yes | No | No | Critically low | 5 no, 2 yes |
| Topical other chemicals (n = 3) | | | | | | | | | | | | | | | | | | |
| CHX (n = 3) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Smith *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 2 yes |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Riggs *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Subgroup: Combined interventions delivered to mothers of unborn/toddlers | | | | | | | | | | | | | | | | | | |
| Topical other chemicals + topical other chemicals (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Topical other chemicals + other (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| CHX + other (n = 1) | | | | | | | | | | | | | | | | | | |
| Riggs *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Complex combined interventions (n = 1) | | | | | | | | | | | | | | | | | | |
| Xiao *et al.* (2019) | Yes | No | No | Yes | Yes | No | Yes | No | Yes | No | No | No | No | Yes | No | No | Critically low | 5 no, 2 yes |
| Subgroup: Combined interventions in primary dentition | | | | | | | | | | | | | | | | | | |
| Topical fluoride + topical fluoride (n = 1) | | | | | | | | | | | | | | | | | | |
| Carvalho *et al.* (2010) | Yes | No | No | Partial yes | Yes | No | Yes | No | Partial yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | No | Critically low | 3 no, 3 yes |
| Topical fluoride + topical other chemicals (n = 4) | | | | | | | | | | | | | | | | | | |
| Wang *et al.* (2017) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Walsh *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Singal *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Gupta *et al.* (2020a) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | No | Yes | No | Yes | Critically low | 5 no, 2 yes |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Topical fluoride + other (n = 7) | | | | | | | | | | | | | | | | | | |
| Smith *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Lam *et al.* (2020) | Yes | No | No | Yes | Yes | Yes | No | No | No | No | No | No | Yes | Yes | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Dos Santos *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 3 no, 3 yes |
| Walsh *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Dos Santos *et al.* (2013) | Yes | No | No | Yes | Yes | Yes | No | No | Yes | No | No | No | No | No | No | No | Critically low | 7 no |
| Marinho *et al.* (2016) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Partial yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Critically low | 1 no, 2 partial, 4 yes |
| de Sousa *et al.* (2019) | Yes | Yes | No | Yes | No | Yes | No | No | Yes | No | No | No | No | Yes | Yes | Yes | Critically low | 5 no, 2 yes |
| Systemic fluoride + topical other chemicals (n = 1) | | | | | | | | | | | | | | | | | | |
| Jørgensen *et al.* (2016) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Sealants + other (n = 1) | | | | | | | | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |
| Complex combined interventions (n = 4) | | | | | | | | | | | | | | | | | | |
| Yu *et al.* (2021) | Yes | Yes | No | Yes | No | Yes | No | No | Yes | No | No | No | No | No | Not applicable | Yes | Critically low | 6 no, 1 yes |
| de Sousa *et al.* (2019) | Yes | Yes | No | Yes | No | Yes | No | No | Yes | No | No | No | No | Yes | Yes | Yes | Critically low | 5 no, 2 yes |
| Chou *et al.* (2021) | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No | No | Critically low | 2 no, 5 yes |
| Dos Santos *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 3 no, 3 yes |
| Permanent dentition | | | | | | | | | | | | | | | | | | |
| Attendance for dental assessment (n = 2) | | | | | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scheduled dental appointments (n = 2) | | | | | | | | | | | | | | | | | | |
| Fee *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |
| Joury *et al.* (2017) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | Not applicable | No | Critically low | 4 no, 3 yes |
| Scheduled primary care appointments (n = 0) | | | | | | | | | | | | | | | | | | |
| Dental hygiene (n = 3) | | | | | | | | | | | | | | | | | | |
| Supervised toothbrushing (n = 2) | | | | | | | | | | | | | | | | | | |
| Hujoel *et al.* (2018) | Yes | No | No | Yes | No | Yes | No | No | Yes | Yes | No | No | No | Yes | Not applicable | No | Critically low | 5 no, 2 yes |
| Dos Santos *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 3 no, 3 yes |
| Flossing (n = 0) | | | | | | | | | | | | | | | | | | |
| Interdental cleaning devices (n = 1) | | | | | | | | | | | | | | | | | | |
| Worthington *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | | | | | | | | |
| Systemic fluoride (n = 4) | | | | | | | | | | | | | | | | | | |
| Milk (n = 2) | | | | | | | | | | | | | | | | | | |
| Yeung *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Moderate | 1 partial, 5 yes |
| Cagetti *et al.* (2012) | No | No | No | Yes | Yes | No | Yes | Partial yes | No | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Salt (n = 1) | | | | | | | | | | | | | | | | | | |
| Cagetti *et al.* (2012) | No | No | No | Yes | Yes | No | Yes | Partial yes | No | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Sugar (n = 1) | | | | | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cagetti *et al.* (2012) | No | No | No | Yes | Yes | No | Yes | Partial yes | No | No | Not applicable | Not applicable | No | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Supplements (n = 2) | | | | | | | | | | | | | | | | | | |
| Tubert-Jeannin *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Partial yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 2 partial, 3 yes |
| Zhou *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | No | No | No | Yes | No | No | No | Yes | No | No | Yes | Critically low | 5 no, 1 partial, 1 yes |
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | | | | | | |
| Vitamin D (n = 0) | | | | | | | | | | | | | | | | | | |
| Calcium (n = 0) | | | | | | | | | | | | | | | | | | |
| Sialagogues (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Zinc (n = 0) | | | | | | | | | | | | | | | | | | |
| Topical fluoride (n = 9) | | | | | | | | | | | | | | | | | | |
| Toothpaste (n = 2) | | | | | | | | | | | | | | | | | | |
| Walsh *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Mouthrinses (n = 2) | | | | | | | | | | | | | | | | | | |
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Wierichs *et al.* (2015) | Yes | No | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Critically low | 3 no, 4 yes |
| Foams (n = 0) | | | | | | | | | | | | | | | | | | |
| Gels (n = 3) | | | | | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marinho *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Chan *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Partial yes | No | Yes | Yes | Yes | No | No | Yes | Critically low | 3 no, 4 yes |
| Solution (n = 4) | | | | | | | | | | | | | | | | | | |
| Grandjean *et al.* (2021) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | No | Yes | Yes | No | Critically low | 5 no, 2 yes |
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Subbiah *et al.* (2018) | Yes | Partial yes | No | Yes | Yes | No | No | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Chan *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Partial yes | No | Yes | Yes | Yes | No | No | Yes | Critically low | 3 no, 4 yes |
| Slow-release fluoride devices (n = 1) | | | | | | | | | | | | | | | | | | |
| Chong *et al.* (2018) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial, 4 yes |
| Varnishes (n = 4) | | | | | | | | | | | | | | | | | | |
| Marinho *et al.* (2013) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Wierichs *et al.* (2015) | Yes | No | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Critically low | 3 no, 4 yes |
| Chan *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Partial yes | No | Yes | Yes | Yes | No | No | Yes | Critically low | 3 no, 4 yes |
| Mixed (n = 0) | | | | | | | | | | | | | | | | | | |
| Topical other chemicals (n = 8) | | | | | | | | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Toothpaste (n = 0) | | | | | | | | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Arginine and its derivatives (n = 0) | | | | | | | | | | | | | | | | | | |
| CHX (n = 4) | | | | | | | | | | | | | | | | | | |
| Walsh *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Wierichs *et al.* (2015) | Yes | No | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Critically low | 3 no, 4 yes |
| James *et al.* (2010) | Yes | No | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | No | Critically low | 4 no, 2 yes |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Calcium phosphate agents (n = 2) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Singal *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Ozone (n = 0) | | | | | | | | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | | | | | | | | |
| Probiotics (n = 0) | | | | | | | | | | | | | | | | | | |
| Propolis (n = 0) | | | | | | | | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | | | | | | | | |
| Riley *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Riggs *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Antonio *et al.* (2011) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | No | Critically low | 3 no, 3 yes |
| Sorbitol (n = 0) | | | | | | | | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 2) | | | | | | | | | | | | | | | | | | |
| Antonio *et al.* (2011) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | No | Critically low | 3 no, 3 yes |
| Sealants (n = 10) | | | | | | | | | | | | | | | | | | |
| Resin (n = 8) | | | | | | | | | | | | | | | | | | |
| Alsabek *et al.* (2021) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Alirezaei *et al.* (2018) | Yes | No | No | Yes | Yes | Yes | No | No | Partial yes | No | No | No | No | No | Yes | Yes | Critically low | 7 no |
| Alharthy *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | Not applicable | No | Yes | No | No | No | No | Yes | No | Yes | Critically low | 4 no, 2 yes |
| Rashed *et al.* (2022) | Yes | Yes | No | Yes | Yes | No | No | No | Yes | No | No | No | No | Yes | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Kashbour *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Ahovuo-Saloranta *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| CADTH (2016) | Yes | No | No | Partial yes | No | No | No | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | No | Critically low | 5 no, 1 yes |
| Li *et al.* (2020) | No | No | No | Yes | Yes | Yes | Yes | Partial yes | Yes | No | No | No | No | No | No | Yes | Critically low | 5 no, 1 partial, 1 yes |
| Glass-ionomer (n = 4) | | | | | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kashbour *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Ahovuo-Saloranta *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Wright *et al.* (2016) | Yes | No | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 5 no, 2 yes |
| CADTH (2016) | Yes | No | No | Partial yes | No | No | No | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | No | Critically low | 5 no, 1 yes |
| Ormocer (n = 1) | | | | | | | | | | | | | | | | | | |
| Ahovuo-Saloranta *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Hybrid (n = 1) | | | | | | | | | | | | | | | | | | |
| Wright *et al.* (2016) | Yes | No | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 5 no, 2 yes |
| Combined (n = 4) | | | | | | | | | | | | | | | | | | |
| Wright *et al.* (2016) | Yes | No | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 5 no, 2 yes |
| CADTH (2016) | Yes | No | No | Partial yes | No | No | No | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | No | Critically low | 5 no, 1 yes |
| Akera *et al.* (2022) | Yes | Yes | No | Yes | No | Yes | Yes | No | Partial yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Li *et al.* (2020) | No | No | No | Yes | Yes | Yes | Yes | Partial yes | Yes | No | No | No | No | No | No | Yes | Critically low | 5 no, 1 partial, 1 yes |
| Other (n = 0) | | | | | | | | | | | | | | | | | | |
| Laser (n = 1) | | | | | | | | | | | | | | | | | | |
| Pagano *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | No | Yes | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 3 no, 1 partial, 2 yes |
| Subgroup: Combined interventions in permanent dentition | | | | | | | | | | | | | | | | | | |
| Topical fluoride + topical fluoride (n = 4) | | | | | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Yu *et al.* (2021) | Yes | Yes | No | Yes | No | Yes | No | No | Yes | No | No | No | No | No | Not applicable | Yes | Critically low | 6 no, 1 yes |
| Wierichs *et al.* (2015) | Yes | No | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Critically low | 3 no, 4 yes |
| Chan *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Partial yes | No | Yes | Yes | Yes | No | No | Yes | Critically low | 3 no, 4 yes |
| Topical fluoride + topical other chemicals (n = 4) | | | | | | | | | | | | | | | | | | |
| Gupta *et al.* (2020a) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | No | Yes | No | Yes | Critically low | 5 no, 2 yes |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Singal *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Riley *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Topical fluoride + other (n = 8) | | | | | | | | | | | | | | | | | | |
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Dos Santos *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 3 no, 3 yes |
| Walsh *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Konradsson *et al.* (2020) | Yes | No | No | Yes | Yes | No | No | Partial yes | Yes | Yes | No | No | Yes | No | No | Yes | Critically low | 4 no, 1 partial, 2 yes |
| Marinho *et al.* (2016) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Partial yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Critically low | 1 no, 2 partial, 4 yes |
| Pagano *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | No | Yes | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 3 no, 1 partial, 2 yes |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Riggs *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Akera *et al.* (2022) | Yes | Yes | No | Yes | No | Yes | Yes | No | Partial yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Topical fluoride + oral health instruction/education (n = 5) | | | | | | | | | | | | | | | | | | |
| Hendre *et al.* (2017) | Yes | No | No | Yes | No | No | No | No | Partial yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Oliveira *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 4 no, 3 yes |
| Subbiah *et al.* (2018) | Yes | Partial yes | No | Yes | Yes | No | No | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 4 no, 1 partial, 1 yes |
| Zhang *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 4 no, 3 yes |
| Chan *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Partial yes | No | Yes | Yes | Yes | No | No | Yes | Critically low | 3 no, 4 yes |
| Topical other chemicals + other (n = 5) | | | | | | | | | | | | | | | | | | |
| Hendre *et al.* (2017) | Yes | No | No | Yes | No | No | No | No | Partial yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 4 no, 2 yes |
| Slot *et al.* (2011) | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 5 yes |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Tubert-Jeannin *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Partial yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 2 partial, 3 yes |
| Riggs *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Sealants + other (n = 4) | | | | | | | | | | | | | | | | | | |
| Kashbour *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ahovuo-Saloranta *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Pagano *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | No | Yes | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 3 no, 1 partial, 2 yes |
| Zhang *et al.* (2019) | Yes | No | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Complex combined interventions (n = 3) | | | | | | | | | | | | | | | | | | |
| Antonio *et al.* (2011) | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | No | Critically low | 3 no, 3 yes |
| Kashbour *et al.* (2020) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Not applicable | Yes | Low | 1 no, 1 partial yes, 5 yes |
| Dos Santos *et al.* (2018) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | Yes | Not applicable | Yes | Critically low | 3 no, 3 yes |
| Mixed dentition | | | | | | | | | | | | | | | | | | |
| Attendance for dental assessment (n = 0) | | | | | | | | | | | | | | | | | | |
| Scheduled dental appointments (n = 0) | | | | | | | | | | | | | | | | | | |
| Scheduled primary care appointments (n = 0) | | | | | | | | | | | | | | | | | | |
| Dental hygiene (n = 0) | | | | | | | | | | | | | | | | | | |
| Supervised toothbrushing (n = 0) | | | | | | | | | | | | | | | | | | |
| Flossing (n = 0) | | | | | | | | | | | | | | | | | | |
| Interdental cleaning devices (n = 0) | | | | | | | | | | | | | | | | | | |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | | | | | | | | |
| Systemic fluoride (n = 0) | | | | | | | | | | | | | | | | | | |
| Milk (n = 0) | | | | | | | | | | | | | | | | | | |
| Salt (n = 0) | | | | | | | | | | | | | | | | | | |
| Sugar (n = 0) | | | | | | | | | | | | | | | | | | |
| Supplements (n = 0) | | | | | | | | | | | | | | | | | | |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | | | | | | |
| Vitamin D (n = 1) | | | | | | | | | | | | | | | | | | |
| Hujoel (2013) | Yes | No | No | Yes | No | No | Yes | Yes | Partial yes | Yes | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 5 yes |
| Calcium (n = 0) | | | | | | | | | | | | | | | | | | |
| Sialagogues (n = 0) | | | | | | | | | | | | | | | | | | |
| Zinc (n = 0) | | | | | | | | | | | | | | | | | | |
| Topical fluoride (n = 1) | | | | | | | | | | | | | | | | | | |
| Toothpaste (n = 1) | | | | | | | | | | | | | | | | | | |
| Figuero *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Mouthrinses (n = 1) | | | | | | | | | | | | | | | | | | |
| Figuero *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Foams (n = 0) | | | | | | | | | | | | | | | | | | |
| Gels (n = 0) | | | | | | | | | | | | | | | | | | |
| Solution (n = 0) | | | | | | | | | | | | | | | | | | |
| Slow-release fluoride devices (n = 0) | | | | | | | | | | | | | | | | | | |
| Varnishes (n = 0) | | | | | | | | | | | | | | | | | | |
| Mixed (n = 0) | | | | | | | | | | | | | | | | | | |
| Topical other chemicals (n = 6) | | | | | | | | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 0) | | | | | | | | | | | | | | | | | | |
| Arginine and its derivatives (n = 0) | | | | | | | | | | | | | | | | | | |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CHX (n = 2) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Figuero *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Calcium phosphate agents (n = 0) | | | | | | | | | | | | | | | | | | |
| Ozone (n = 0) | | | | | | | | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | | | | | | | | |
| Probiotics (n = 1) | | | | | | | | | | | | | | | | | | |
| Poorni *et al.* (2019) | Yes | No | No | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Not applicable | Yes | No | Not applicable | Yes | Critically low | 5 no, 1 yes |
| Propolis (n = 0) | | | | | | | | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | | | | | | | | |
| Marghalani *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | Yes | No | No | Critically low | 3 no, 1 partial, 3 yes |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Newton *et al.* (2020) | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 3 no, 4 yes |
| Riley *et al.* (2015) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | No | Not applicable | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Sorbitol (n = 0) | | | | | | | | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 0) | | | | | | | | | | | | | | | | | | |
| Sealants (n = 1) | | | | | | | | | | | | | | | | | | |
| Resin (n = 0) | | | | | | | | | | | | | | | | | | |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Glass-ionomer (n = 0) | | | | | | | | | | | | | | | | | | |
| Ormocer (n = 0) | | | | | | | | | | | | | | | | | | |
| Hybrid (n = 0) | | | | | | | | | | | | | | | | | | |
| Combined (n = 0) | | | | | | | | | | | | | | | | | | |
| Other (n = 1) | | | | | | | | | | | | | | | | | | |
| Singal *et al.* (2022) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | No | Not applicable | Yes | Critically low | 5 no, 2 yes |
| Laser (n = 0) | | | | | | | | | | | | | | | | | | |
| Subgroup: Mother of unborn/toddlers (treatment given to mothers, outcomes tested on mixed dentition of offspring) | | | | | | | | | | | | | | | | | | |
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | | | | | | |
| Calcium (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Subgroup: Combined interventions in mixed dentition | | | | | | | | | | | | | | | | | | |
| Topical fluoride + topical other chemicals (n = 2) | | | | | | | | | | | | | | | | | | |
| Gupta *et al.* (2020b) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 4 no, 3 yes |
| Sharda *et al.* (2021) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Critically low | 4 no, 3 yes |
| Topical other chemicals + topical other chemicals (n = 1) | | | | | | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Yes | Partial yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | Yes | No | Yes | Critically low | 2 no, 1 partial, 4 yes |
| Topical other chemicals + other (n = 1) | | | | | | | | | | | | | | | | | | |
| Zhou *et al.* (2019) | Yes | Partial yes | No | Yes | Yes | No | No | No | Yes | No | No | No | Yes | No | No | Yes | Critically low | 5 no, 1 partial, 1 yes |
| Complex combined interventions (n = 2) | | | | | | | | | | | | | | | | | | |

| Author (year) | PICO | *Protocol prior to review and report deviations | Justify primary study design for inclusion | Comprehensive literature search | Duplicate screening | Duplicate data extraction | *List of excluded studies | *Detailed characteristics of primary studies | Method for assessment of bias | *Source of funding for primary studies | Methods for meta-analysis | *Meta-analysis and risk of bias in analysis | *Risk of bias in discussion of results | *Discussed heterogeneity | Publication bias (search, measure [10 sources], and GRADE) | Conflicts of interest and funding | Overall quality rating of review | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yu *et al.* (2021) | Yes | Yes | No | Yes | No | Yes | No | No | Yes | No | No | No | No | No | Not applicable | Yes | Critically low | 6 no, 1 yes |
| Figuero *et al.* (2017) | Yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | Critically low | 2 no, 1 partial, 4 yes |

# Appendix G Joanna Briggs Institute data extraction form for systematic reviews and research syntheses

We extracted information from each full text systematic review into the JBI tabular format.304 The extracted data comprised citation details, objectives of the review, participants, setting, interventions, comparators, search information, study date range, number of primary studies, study design, risk of bias tool used, risk of bias assessment including publication bias, analysis methods, outcomes assessed, and results by outcome(s).

## (a) Example extraction table

*Table 99 Example extraction table*

| Parameter | Author *et al.* (year) extraction |
|---|---|
| **First Author and year of publication** | First author *et al.* (year), e.g. Jones et al. 2020<br>OR<br>Sole author (year), e.g. Jones (2020) |
| **Objectives (exact review question(s) and page number)** | PICOT |
| **Participants (characteristics and numbers)**<br><br>The defining characteristics of the participants in studies included in the research syntheses/review should be detailed, for example this may include diagnostic criteria, age, or ethnicity.<br><br>The total number of participants that inform the outcomes relevant to the umbrella review question from all studies included studies should be presented. | Generation, type, and surfaces of teeth as exact as possible<br>Number of participants and teeth<br>Age<br>Gender |
| **Setting/context**<br><br>Details of the setting of interest such as acute care, primary health care, or the community or a geographical location should be included. For some umbrella reviews, particularly those that draw upon qualitative research syntheses, the context that underpins the review question will be important to clearly reveal to the reader and may include but is not limited to consideration of cultural factors such as geographic location and specific racial or gender-based interests. | Countries (alphabetic order) and setting (university, public or private clinic) |

| | |
|---|---|
| **Description of Interventions/ phenomena of interest**<br><br>Clear, succinct details of the interventions or phenomena of interest should be presented as described by systematic review author(s), including the type of intervention, the frequency, and/or intensity of the intervention. A statement of the phenomena of interest is also required where applicable. | Authors exact definition of the intervention(s)<br>Comparator |
| **Databases and sources searched**<br><br>The number of sources searched should be reported. Although this will have been considered during critical appraisal of the research synthesis, reporting to the reader of the review will allow rapid and easy comparison between differences across included reviews and also consideration of potential for publication bias in the event that no formal analysis has been conducted. Where possible the names of databases and sources should be listed (i.e. if <5-10). The search range of each database should also be included. | Based on previous search by:<br>Number and names of databases and other sources including grey literature<br>Search start and finish dates<br>Search limits<br>Other follow-up searches such as reference chasing<br>Protocol prepared Yes/No, Published Yes/No and If yes Number<br>Screening was completed in duplicate and agreed.<br>Extraction was completed in duplicate and agreed<br>Funding source<br>Conflicts of interest |
| **Date range (years) of included studies**<br><br>The date range spanning from the earliest study that informs the included research synthesis to the latest should be reported. This is important information that allows for consideration of the currency of the evidence base not necessarily reflected in the year of publication of the research synthesis. If this is not readily identifiable in the table of study characteristics provided by the included synthesis, it should be discerned by scanning the date range of publications through the results section of the included systematic review. | Exact years for included studies<br>Date range of publications or date range of studies data collection using baseline and final follow-up dates |
| **Number of primary studies included in the systematic review**<br><br>Summary descriptive details of the included studies in the research synthesis should be reported. This | Number of studies and (if required) number of studies by study design<br>Details of study design<br>Study years<br>Study funding |

| | |
|---|---|
| includes the number of studies in the included research synthesis, the types of study designs included in the research synthesis, for example randomized controlled trials, prospective cohort study, phenomenology, ethnography etc. | |
| **Types of studies included** | Planned study design to be included (copy from primary studies)<br>List of included studies<br>List of excluded studies and reason for exclusion available in appendix |
| **Country of origin of included studies** | Country names in alphabetic order (copy from context) |
| **Appraisal instrument(s)**<br><br>The instrument or tool used to assess risk of bias, rigour or study quality should be reported along with some summary estimate of the quality of primary studies in the included research synthesis. For example, for umbrella reviews that use the Jadad Scale, a mean score for quality may be reported whereas for checklist appraisals, reporting of cut-off score or any ranking of quality should be reported. An example of the latter would be exclusion of studies that score <3/10, and inclusion of four moderate quality studies (4-6/10) and two high quality studies (7-10/10). | The full name of the tool used |
| **Appraisal rating** | Number of studies by high or uncertain risk of bias (low quality), and low risk of bias (high quality)<br>Number of studies out of total number of studies that were at low risk of bias for randomisation and at low risk of bias for outcome ascertainment<br>Authors exact comments on risk of bias and how it affected analysis and quality of evidence<br>Comment of how author dealt with publication bias |
| **Method of analysis**<br><br>The type of research synthesis as stated by the authors of the included review should be detailed. The method of analysis or synthesis used by the included research synthesis should be reported. For example, this may include narrative synthesis, vote counting, random effects meta-analysis, fixed effect meta-analysis, network meta-analysis, thematic | Description as per author<br>Justification for narrative or meta-analysis |

| | |
|---|---|
| synthesis, meta- aggregative synthesis, or meta-ethnography. | |
| **Outcome(s) assessed**<br><br>Included here should be the outcomes of interest to the umbrella review question reported on by the research synthesis, i.e. the names or labels of the outcomes (see below for presentation of results). | List of outcomes assessed and intended time frames<br>Actual timeframes<br>Primary studies by outcome |
| **Outcome(s) excluded from umbrella review**<br><br>Listed here should be outcomes that are of interest to the umbrella review question and otherwise would be included in the research synthesis, but cannot contribute to the findings for methodological reasons, which should be outlined. | |
| **Results/findings**<br><br>The relevant findings or results presented by the included research syntheses must be extracted. For quantitative reviews, this will ideally be an effect estimate with 95% Cis or measure from a presented meta-analysis. Measures of heterogeneity should also be extracted where applicable. In the absence of this a statement indicating the key result relevant to an outcome may be inserted in the required field. For qualitative syntheses, the key synthesized finding should be extracted. | Findings by outcome<br>Use metaanalysis results if available (relative risk, odds ratio, or standardised mean difference; 95% confidence intervals, $I^2$, number of trials or studies, number of participants or teeth, random or fixed effects, GRADE)<br>Use relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available, GRADE) |
| **Significance/direction** | See above if results listed by outcome |
| **Heterogeneity** | See above if $I^2$ listed above<br>Authors comment on heterogeneity in findings and discussion |
| **Summary for GRADE assessment for HRB report** | Summary for GRADE assessment for HRB report |
| **References to previously published versions** | Example:<br>Hiiri A, Ahovuo-Saloranta A, Nordblad A, Mäkelä M. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No: CD003067. [DOI: 10.1002/14651858.CD003067.pub2]. |

# Appendix H Data extractions for included reviews

*Table 100 Data extractions for included reviews*

| Parameter | Kashbour et al. (2020) extraction |
|---|---|
| **First Author and year of publication** | Kashbour *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To evaluate the relative effectiveness of dental sealants (fissure sealant) compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents.<br><br>To evaluate whether effectiveness is influenced by sealant material type and length of follow-up.<br><br>To report data concerning adverse events associated with sealants and fluoride varnishes (p9). |
| **Participants (characteristics and numbers)** | Permanent dentition (first permanent molars); sealants, resin, glass-ionomer; combined intervention.<br><br>Baseline caries was reported in nine out of 11 included trials.<br><br>The review included child and adolescent participants from the general population, who were younger than 20 years of age at the start of the trials. The included trials randomised 3,374 children aged 5-10 years to sealant or varnish groups and evaluated 2,553 children. All trials included both boys and girls.<br><br>The total number of participants in the ten (out of 11) included trials that inform this umbrella review was approximately 2,010 (9 trials) and 641 teeth (1 trial). |
| **Setting/context** | The trials were conducted In Brazil (2 trials), China (3 trials), Germany (1 trial), Iran (1 trial), Latvia (1 trial), Norway (1 trial), Spain (1 trial), and the UK (1 trial).<br><br>In 10 trials, children were recruited from public dental clinics or schools. In the trial based in Germany, children were enrolled from a private dental practice. |
| **Description of Interventions/ phenomena of interest** | The intervention group was either the sealant group or the sealant plus fluoride varnish group. The control group was the fluoride varnish group. The review authors compared two types of interventions:<br>1. The pit and fissure sealants of all materials (except first-generation resin-based sealants) versus fluoride varnish, and |

2. The pit and fissure sealants plus fluoride varnish versus fluoride varnish.

The review authors included trials in which applications were placed on occlusal surfaces of permanent posterior teeth for the purpose of preventing caries, regardless of who did the application. Materials could be applied on sound surfaces or on enamel lesions (if scored using the ICDAS II scale, codes 0, 1, 2 and 3 were accepted). The sealant application method used in the trial could consist of direct application to the tooth surface or application after mechanical preparation of the enamel surface.

The trials were grouped and analysed based on sealant material type: resin-based sealant or glass-ionomer-based sealant (glass-ionomer and resin-modified glass-ionomer sealant).

Six studies included other interventions in combination with the sealants and varnish and/or involved background exposure to fluoride. In Florio 2001, tap water was fluoridated and all children received professional prophylaxis during dental examination visits. In Raadal 1984, participants followed a fluoride rinsing programme at schools during follow-up, and use of fluoride tablets was recommended. Splieth 2001 reported that 5% of children used fluoride tablets during the trial; however, it was not clear which participants were involved. Six studies reported motivation and instruction of participants towards good oral hygiene and use of fluoridated toothpaste (Florio 2001; Liu 2012; Raadal 1984; Salem 2014; Splieth 2001; Tagliaferro 2011).

**Databases and sources searched**

The review authors searched the following sources:

- Cochrane Oral Health's Trials Register (searched 19 March 2020)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2020
- Issue 2) in the Cochrane Library (searched 19 March 2020)
- MEDLINE Ovid (1946 to 19 March 2020)
- Embase Ovid (1980 to 19 March 2020)
- The US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 19 March 2020), and
- The World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 19 March 2020).

Reference lists of all potentially eligible trials and relevant systematic reviews for further trials were searched. There were no restrictions in relation to language, publication year, or publication status.

The protocol was prepared but the review authors did not provide a link to the protocol. Differences between the protocol and published review are noted.

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| | At least two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion with a third review author.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>Three authors declared no conflicts of interest. One author was a Co-ordinating Editor with Cochrane Oral Health until early 2020. |
| **Date range (years) of included studies** | The 11 included trials were published between 1984 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included 11 randomised controlled trials, both parallel-group and split-mouth study designs, with at least of 12 months follow-up, in which fissure sealants, or fissure sealants plus pit and fissure sealants versus fluoride varnishes for preventing dental decay in the occlusal surfaces of permanent teeth of children and adolescents were compared with fluoride varnishes alone.<br><br>The unit of randomisation could be the individual, the group (e.g. school, school class), or the tooth or tooth pair and the trials were published between the years 1984 and 2017.<br><br>Six trials were funded by governmental or academic sources or by independent research foundations. The other five trials provided no information on funding source. |
| **Types of studies included** | The review included 11 randomised control trials: Bravo (2005), Chestnutt (2017), Florio (2001), Ji (2007), Kalnina (2016), Liu (2012), Raadal (1984), Salem (2014), Splieth (2001), Tagliaferro (2011), and Tang (2014).<br><br>The results of ten randomised control trials informed the outcomes of interest to this umbrella review: Bravo (2005), Chestnutt (2017), Florio (2001), Ji, (2007), Kalnina (2016), Liu (2012), Raadal (1984), Splieth (2001), Tagliaferro (2011), and Tang (2014).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Brazil (2), China (3), Germany (1), Iran (1), Latvia (1), Norway (1), Spain (1), and the UK (1). |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of included trials using the Cochrane tool (Higgins 2011a). Disagreements were resolved by |

discussion to reach consensus. The review authors contacted the authors of included trials to request additional information when required.

The following seven domains were assessed for each trial:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting, and
7. Other sources of bias (e.g. baseline comparability).

For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias.

The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as (Higgins 2011):

- Low risk of bias (plausible bias unlikely to seriously alter the results) defined above were graded as low risk of bias
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were graded as high risk of bias, or
- Unclear risk of bias (plausible bias that raises some doubt about the results) if all the domains were graded as low or unclear risk of bias.

**Appraisal rating**

The review authors considered the blinding of outcome assessment to be at high risk of bias in all trials as the presence or absence of the sealant would reveal the intervention, reporting that “The overall risk of bias was high for all studies [trials] due to being unable to blind the interventions when undertaking outcome assessment” (p20).

Nine out of 11 trials had two or more high risk of bias scores. Of the ten trials relevant to this umbrella review, eight had two or more high risk of bias scores.

Eight trials were at low risk of bias for randomisation. Of the ten trials relevant to this umbrella review, one trial was at high risk of bias for randomisation, seven were at low risk of bias for randomisation, and two were at unclear risk of bias for randomisation.

No trials were at low risk of bias for outcome ascertainment. Only two trials blinded participants and service providers, both of which are among the ten trials relevant to this umbrella review.

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| | The overall high risk of bias lowered the certainty of evidence. The review authors assessed the certainty of the body of evidence with reference to overall risk of bias of included trials at each outcome, directness of evidence, consistency of results, precision of estimates, and risk of publication bias.<br><br>To diminish the risk of publication bias, the review authors contacted authors of relevant trial abstracts to ask whether a full-text report of the trial (unpublished or published) was available. |
| **Method of analysis** | The review authors grouped and analysed trials based on sealant material type (resin-based sealant and glass-ionomer-based sealant: glass-ionomer and resin-modified glass-ionomer) and follow-up period (short term (up to 12 months); medium term (from 12 months to three years); long term (more than four years).<br><br>The review authors conducted meta-analyses in Review Manager 2014, using the generic inverse variance method. When feasible, the review authors pooled in the same meta-analysis odds ratios from parallel-group trials and from split-mouth trials by using guidance by Stedman 2011.<br><br>As data were insufficient, it was not possible to create subgroups for further analyses. Sensitivity analysis was also not feasible as the overall score for each trial was high risk of bias.<br><br>Summary of findings tables for main outcomes were provided. |
| **Outcome(s) assessed** | Primary outcome 1: occurrence of a new dentinal carious lesion on treated occlusal surfaces of molars or premolars observed within 12 months from the initial treatment<br><br>Primary outcome 2: changes from baseline in Decayed, Missing and Filled (DMFS/T) figures at surface, tooth, and whole mouth levels<br><br>Secondary outcome 1: time taken to apply pit and fissure sealant or fluoride varnish over a 2-year study period<br><br>Secondary outcome 2: number of visits to the dentist for repair of sealant or fluoride varnish application<br><br>Secondary outcome 3: safety of using sealants and fluoride varnishes assessed by presence or absence of adverse events<br><br>*Note*. Primary outcomes 1 and 2 are identified as primary outcomes in the review. Secondary outcome 1 is identified as a primary outcome in the review, but for the HRB's purposes is considered a secondary outcome. |

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| | Secondary outcomes 2 and 3 are identified as secondary outcomes in the review. |
| **Results/findings** | **Primary outcome 1a: Occurrence of a new dentinal carious lesions – sealant versus fluoride varnish**<br><u>Comparison 1: Resin fissure sealant versus fluoride varnish:</u><br>It is unclear whether resin fissure sealants are better than fluoride varnish in preventing dentinal carious lesions on treated occlusal surfaces of molars or premolars within 2–3 years after initial treatment (odds ratio 0.67, 95% CI 0.37 to 1.19; $I^2$= 84%; 1,683 participants; 4 trials; very low certainty of evidence). It should be stressed that these trials assessed odds of caries at different levels: person/child (2 trials), tooth (1 trial), and surfaces (1 trial), which could have affected precision of different estimates. One trial found a significant difference in favour of visible-light-polymerised resin sealant compared with fluoride varnish, with a relative risk of 0.42 (95% CI 0.21 to 0.84; 1 trial; very low certainty of evidence) at 4 years and 0.48 (95% CI 0.29 to 0.79; 1 trial; random effects, very low certainty of evidence) at 9 years follow-up (five years after the four years of active intervention). Dropout rates were high after the 9-year follow-up (Bravo, 2005).<br><br>*Note*. One out of the four pooled trials delivered combined interventions, wherein all participants were encouraged to use fluoride tablets (fluoride concentration not specified), received annual information and motivation about dental care, and participated in fluoride rinsing with 0.5% sodium fluoride solution at school. In addition, participants in one out of the four pooled trials used fluoride toothpaste. However, this can be considered existing/background fluoride exposure, rather than part of the interventions of interest.<br><br><u>Comparison 2: Glass-ionomer fissure sealant versus fluoride varnish:</u><br>Three trials reported on this outcome (n = 995 participants). The review authors concluded that there was no evidence of a difference between the interventions after 1, 2, and 3 years. They were unable to perform meta-analyses and assessed the certainty of the evidence to be very low. The findings were not presented narratively.<br><br>*Note*. The authors reported, however, that one trial included oral health education for both groups and found a benefit for sealant among children at high risk of caries.<br><br>**Primary outcome 1b: Occurrence of a new dentinal carious lesions – sealant plus fluoride varnish versus fluoride varnish alone**<br><u>Comparison 1: Resin fissure sealant plus fluoride varnish versus fluoride varnish:</u><br>One trial made this comparison on occlusal tooth surfaces of permanent first molars and reported that the combined therapies was better than fluoride |

varnish alone (odds ratio 0.30, 95% CI 0.17 to 0.55; 92 participants; 1 trial; very low certainty of evidence).

Comparison 2: Glass-ionomer fissure sealant plus fluoride varnish versus fluoride varnish:
No trial included in the review made this comparison.

**Primary outcome 1c: Occurrence of a new dentinal carious lesions – resin-modified glass-ionomer cement plus oral health education versus fluoride varnish plus oral health education**
One study provided results for comparison of resin-modified glass-ionomer cement plus oral health education for 1 hour every three months versus fluoride varnish application biannually plus oral health education every three months (Tagliaferro 2011). The comparison was performed separately for high-caries-risk children and for low-caries-risk children. Groups to be compared were HRS (high-risk children with sealant application plus oral health education) versus HRV (high-risk children with fluoride varnish application plus oral health education); and LRS (low-risk children with sealant application plus oral health education) versus LRV (low-risk children with fluoride varnish application plus oral health education).

After 24 months, the HRS group (n = 47) showed significantly smaller caries increments when compared with the HRV group (n = 48) (mean DMF increments on occlusal surfaces of first permanent molars was 0.06 (SD 0.25) in the HRS group and 0.29 (SD 0.68) in the HRV group (MD 0.23, 95% CI 0.02 to 0.44; P = 0.03). For low-risk groups, there were no statistically significant differences among treatments with mean DMF increment of 0.02 (SD 0.15) for LRS and 0.09 (SD 0.29) for LRV groups (MD 0.07, 95% CI –0.03 to 0.17; P = 0.16). The study authors concluded "that in a 2-year period, oral health education was sufficient to control occlusal caries in low-risk children while for high-risk children, sealant application in addition to oral health education was considered the best strategy."

*Note*. The review authors reported that participants in this trial had exposure to fluoride toothpaste (93% of participants) and fluoridated water. However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest.

**Primary outcome 2a: changes from baseline in Decayed, Missing and Filled (DMFS/T) figures at surface, tooth and whole mouth levels – sealant versus fluoride varnish**
Comparison 1: Resin fissure sealant versus fluoride varnish:
One trial of 542 participants found a slight benefit of resin-based sealant on DMFT (MD -0.08, 95% CI -0.14 to -0.02) and DMFS (MD -0.09, 95% CI -0.15 to -0.03) compared to 0.1% fluoride varnish applied every 6 months (4 applications in total) at 2 years follow-up. The slight benefit that was observed in DMFT seems not to be clinically important on a scale from 0 to

28/32; however, if only existing permanent teeth of a child are considered when assessing this index, the difference could be relevant. Both groups also received “regular” oral health education.

Comparison 2: Glass-ionomer fissure sealant versus fluoride varnish:
No trial included in the review made this comparison.

**Primary outcome 2b: changes from baseline in Decayed, Missing and Filled (DMFS/T) at surface, tooth and whole mouth levels – sealant plus fluoride varnish versus fluoride varnish alone**
Comparison 1: Resin fissure sealant plus fluoride varnish versus fluoride varnish:
In one trial of 92 children who were required to have ≥ 1 pair of equivalent first permanent molar without carious defects, fluoride varnish was applied to all teeth including the sealed tooth. Children were examined semi-annually for 2 years; sealants were resealed if necessary and fluoride varnish was applied to all teeth at examinations. In addition, children received oral hygiene instruction and brushed their teeth under supervision.

The authors examined changes in DMFS index and found that the mean DMFS score of the whole mouth in the study population increased from 0.2 to 0.6 after 1 year and to 1.1 at 2 years follow-up. The authors reported that most caries still occurred on occlusal surfaces of first permanent molars (50.9%).

When examining occurrence of new caries on sound occlusal surfaces (primary outcome 1), they found a significant difference in favour of the sealant plus fluoride varnish compared with fluoride varnish alone (OR 0.30, 95% CI 0.17 to 0.55). There was a caries increment of 5.5% (9 children) in sealed teeth compared to 17.5% (30 children) in teeth that received fluoride varnish only.

Comparison 2: Glass-ionomer fissure sealant plus fluoride varnish versus fluoride varnish:
No trial included in the review made this comparison.

**Secondary outcome 1: Time taken to apply pit and fissure sealant or fluoride varnish over 2-year-study-period**
Comparison 1: Sealant versus fluoride varnish:
No trials comparing sealant to fluoride varnish measured this outcome.

Comparison 2: Sealant plus fluoride varnish versus fluoride varnish alone:
One trial measured this outcome (n = 362) when comparing these interventions. The total time needed for sealing and resealing of two teeth was on average 29 minutes over the 2-year-period, of which most of the time was spent on initial sealants (about 17 minutes per tooth). The mean treatment time for each fluoride varnish application was under 3 minutes

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| | (total time during intervention: 9 minutes; standard deviation (SD) not reported).<br><br>**Secondary outcome 2: Number of visits to the dentist for repair of sealant or fluoride varnish application**<br><u>Comparison 1: Sealant versus fluoride varnish:</u><br>One trial reported the number of visits for repair or reapplication of sealants or fluoride varnish applications. The mean number of treatment visits per child during the active phase of the programme was 2.2 (SD ±1.1) (maximum 6) for children in the resin sealant group and 7.3 (SD ±1.0) (maximum 8) for children in the varnish group indicating a mean difference of 5.02 (95% CI 4.55 to 5.94; fewer visits in the sealant group). This difference is greater because the varnish was systematically reapplied while the sealant was reapplied only when partial or total loss occurred.<br><br><u>Comparison 2: Sealant plus fluoride varnish versus fluoride varnish alone:</u><br>No trials comparing sealants plus fluoride varnish to fluoride varnish alone measured this outcome.<br><br>**Secondary outcome 3: Safety of using sealants and fluoride varnishes assessed by presence or absence of adverse events**<br><u>Comparison 1: Sealant versus fluoride varnish:</u><br>Five trials considered adverse events associated with sealants and fluoride varnishes. Participants detected and reported no adverse events.<br><br><u>Comparison 2: Sealant plus fluoride varnish versus fluoride varnish alone:</u><br>No trials comparing sealants plus fluoride varnish to fluoride varnish alone measured this outcome. |
| **Significance/direction** | The review authors found no evidence suggesting the superiority of resin-based (or glass-ionomer based) fissure sealants over fluoride varnish or vice versa, although the certainty of evidence was very low. It should be noted that other Cochrane Reviews have shown that both interventions are effective for preventing occlusal caries in the first permanent molars.<br><br>The review authors did find some very low-certainty evidence for placing resin-based sealant and applying fluoride varnish rather than applying fluoride varnish only. Available data are insufficient to reach conclusions about whether it is better to apply sealants or fluoride varnishes on occlusal surfaces of permanent molars, and so either intervention, or both, can be used.<br><br>Available data are also insufficient to reach conclusions about changes from baseline in decayed, missing and filled (DMF) figures at surface, tooth and whole-mouth levels, observed within 12 months from the initial treatment. |

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| **Heterogeneity** | The review authors comment on heterogeneity in the findings and discussion, indicating that interventions may be more effective when caries prevalence in the population is higher and/or when targeted at populations classified as high risk for caries. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the quality of evidence for caries outcomes as very low, downgraded due to the high risk of detection bias, high heterogeneity, and effect imprecision (primary outcome 1a), and the date that the trial was conducted, lack of information pertaining to baseline caries among control group, and lack of blinding of outcome measurement in the only trial (primary outcome 1b).<br><br>The HRB authors graded the certainty of evidence in this review as low. The disparity is likely due to differences between assessment tools (the review authors assessed the certainty of the body of evidence with reference to overall risk of bias of included studies at each outcome, directness of evidence, consistency of results, precision of estimates and risk of publication bias). |
| **References to previously published versions** | Ahovuo-Saloranta A, Forss H, Hiiri A, Nordblad A, Mäkelä M. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No: CD003067. [DOI: 10.1002/14651858.CD003067.pub4].<br><br>Hiiri A, Ahovuo-Saloranta A, Nordblad A, Mäkelä M. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No: CD003067. [DOI: 10.1002/14651858.CD003067.pub3].<br><br>Hiiri A, Ahovuo-Saloranta A, Nordblad A, Mäkelä M. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No: CD003067. [DOI: 10.1002/14651858.CD003067.pub2]. |
| Parameter | Fee *et al.* (2020) extraction |
| **First Author and year of publication** | Fee *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To determine the optimal recall interval of dental check-up for oral health in a primary care setting (p15). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); attendance for dental assessment, scheduled dental appointments. |

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| | Baseline caries was reported in one out of the two included trials.<br><br>The two included randomised control trials involved a total of 1,736 participants (children, adolescents, and adults) receiving dental check-ups in primary care settings, regardless of their level of risk for oral disease.<br><br>Participants in the UK trial were dentate adults (aged 18 years and older) who had visited their dentist at least once within the previous two years, and who received dental care in part or fully as a National Health Service patient (including dental examination). The number of participants evaluated varied substantially by outcome. The mean age was 45 years and % female ranged from 53–59% across recall periods. Baseline caries was not reported.<br><br>The results of the Norwegian trial informed the outcome of interest to this umbrella review. Participants in that trial were from one of three age groups (3-, 16- and 18-year-olds). All had previously received regular dental care, including preventive services and health promotion. Children classified as 'risk' patients were not included. The study evaluated 185 participants. Mean age and sex were not reported. Baseline caries was provided for each age group who were recalled at the three different intervals. |
| **Setting/context** | The trials were conducted in Norway (1 trial) and the UK (1 trial).<br><br>Participants in the Norwegian trial were children and adolescents who received regular dental care in 1 public dental service clinic in Norway. Participants in the UK trial were adults recruited at one of 51 dental practices in the UK. |
| **Description of Interventions/ phenomena of interest** | A 'recall visit' can be defined as "the planned, unprecipitated return of a patient who, when last seen was in good oral health" (Royal College 1997). A 'recall examination' (or 'routine dental check-up' or 'oral health review') is the examination performed at this planned return appointment. The 'recall interval' is the time period, usually specified in months or years, between recall examinations.<br><br>A 'routine dental check-up' can be considered as involving many of the following components: clinical examination (including documenting a patient's medical history), the provision of advice, and charting (including assessment and recording of any malocclusion and monitoring of periodontal status).<br><br>In the Norwegian trial, follow-up periods were 12 months, 24 months, and two years. In the UK trial, follow-up periods were six months, 24 months, and four years. Time periods from risk-based check-ups (time between check-ups was set by dentists and depended on an individual's risk of dental disease) were also included. |

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| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (searched 17 January 2020)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2019) in the Cochrane Library (searched 17 January 2020)<br>• MEDLINE Ovid (1946 to 17 January 2020)<br>• Embase Ovid (1980 to 17 January 2020)<br>• The US National Institutes of Health Ongoing Trials Register (searched 17 January 2020), and<br>• The World Health Organization International Clinical Trials Registry Platform (searched 17 January 2020).<br><br>Reference lists of all potentially eligible trials and relevant systematic reviews for further trials were searched. There were no language, publication year, or publication status restrictions.<br><br>Where possible, the review authors contacted the author(s) of eligible published studies and any researchers involved in the ongoing debate on recall intervals to obtain information on additional published or unpublished studies that were possibly eligible for inclusion.<br><br>The protocol was published in 2003, and the review was originally published in 2005. Differences between the protocol and published review were noted.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved by discussion among all review team members.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Oral Health.<br><br>Two review authors declared no conflicts of interest. Four review authors were involved with one of the included trials (UK trial) but were not involved with the data extraction from that trial study or assessment of its risk of bias. Two of those four authors were Co-ordinating Editors with Cochrane Oral Health. |
| **Date range (years) of included studies** | The Norwegian trial was published in 1992. The UK trial was published in 2020. |

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| **Number of primary studies included in the systematic review** | The review authors included two randomised control trials, both parallel-group randomised control trials.<br><br>The Norwegian trial incorporated two arms; participants were randomised to either 12-month or 24-month recall.<br><br>The UK trial incorporated three trial arms within two strata; participants classified by the recruiting dentist as clinically suitable for 24-month interval were randomised to either 6-month, 24-month, or risk-based interval, and those classified as clinically unsuitable were randomised to either a 6-month or risk-based interval. The decision that a patient was (in)eligible for a 24-month recall was based on routine clinical examination and risk assessment.<br><br>Unit of randomisation was the individual.<br><br>A funding source was not reported in the Norwegian trial. The UK trial was funded by the NIHR Health Technology Assessment (HTA) programme (project number 06/35/99). |
| **Types of studies included** | The review authors included two randomised controlled trials: Wang (1992; Norwegian trial) and INTERVAL (2020; UK trial).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Norway (1 trial) and the UK (1 trial). |
| **Appraisal instrument(s)** | The review authors independently assesses the risk of bias of included trials using the Cochrane tool (Higgins 2011a). The authors did not indicate how disagreements in assessing risk of bias were resolved.<br><br>The following six domains were assessed for each trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of outcome assessment (detection bias)<br>4. Incomplete outcome data (attrition bias)<br>5. Selective reporting (reporting bias), and<br>6. Other bias (any other potential source of bias that may feasibly alter the magnitude of the effect estimate)<br><br>For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias. |

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| **Appraisal rating** | The required information to assess two domains in the risk of bias assessment in the Norwegian trial was not available. The Norwegian trial was at high risk of detection bias and therefore at high risk of bias overall. The UK study was at low risk of bias across all domains and therefore at low risk of bias overall.<br><br>The Norwegian trial had an uncertain risk of bias for randomisation, whereas the UK trial was at low risk of bias for randomisation. The required information to assess risk of bias for outcome detection was not available in the Norwegian trial. The UK trial was at low risk of bias for outcome detection.<br><br>The review authors assessed the certainty of the body of evidence with reference to overall risk of bias of included trials at each outcome, directness of evidence, consistency of results, precision of estimates, and risk of publication bias. To deal with bias, the review authors downgraded the certainty of the evidence by two levels for the caries outcomes reported in the Norwegian trial. They noted concerns over a) selection bias arising from unclear methods of sequence generation and allocation concealment, and b) detection bias due to an absence of blinding of the personnel assessing clinical outcomes. As the UK trial was at low risk of bias in all key domains, the review authors did not downgrade the certainty of evidence in that trial.<br><br>The likelihood of publication bias could not be assessed due to the low number of included trials. To diminish the risk of publication bias, the review authors conducted a comprehensive search for relevant trials which included a sensitive search, without language restrictions, of electronic databases and clinical trials registers. |
| **Method of analysis** | For continuous outcomes (e.g. caries – decayed, missing, filled surfaces), the review authors used the mean values and standard deviations reported in the study to express the estimate of effect of the intervention as mean difference (MD) with 95% confidence interval (CI). For dichotomous outcomes (e.g. presence/absence of mucosal lesions), they expressed the estimate of effect of the intervention as a risk ratio (RR) with 95% CI.<br><br>It was not possible to perform meta-analyses, which would only have been possible if trials of similar comparisons reported the same outcomes. As the review only included two trials, it was not possible to create subgroups for further analyses or conduct sensitivity analyses.<br><br>The following recall intervals were compared:<br>1. 24-month recall versus 12-month recall (Norwegian trial)<br>2. Risk-based recall versus 6-month recall (UK trial)<br>3. 24-month recall versus 6-month recall (UK trial), and |

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| | 4. Risk-based recall versus 24-month recall (UK trial).<br><br>Unit of analysis issues did not arise in the review.<br><br>Summary of findings tables for main outcomes were provided. |
| **Outcome(s) assessed** | Primary outcome 1: incremental number of decayed, missing, filled and sound tooth surfaces (dmfs/DMFS) among participants who had a dmfs/DMFS score (primary/permanent dentition) of 0 at baseline<br><br>Primary outcome 2: number of tooth surfaces with any caries (ICDAS 1 to 6)<br><br>Secondary outcome 1: oral-health-related quality of life<br><br>*Note*. Primary outcomes 1 and 2 are identified as primary outcomes in the review. Secondary outcome 1 is identified as a primary outcome in the review, but for the HRB's purposes is considered a secondary outcome. |
| **Results/findings** | **Primary outcome 1: Incremental number of decayed, missing, filled and sound tooth surfaces (dmfs/DMFS)**<br><u>Comparison 1: 24-month recall versus 12-month recall at 2 years follow-up:</u><br>For 3- to 5-year-olds with primary teeth, the mean difference in dmfs increment was 0.90 (95% CI −0.16 to 1.96; 1 trial; 58 participants; very low certainty of evidence).<br><br>For 16- to 20-year-olds with permanent teeth, the mean difference in DMFS increment was 0.86 (95% CI −0.03 to 1.75; 1 trial, 127 participants)<br><br>It is unclear if there is an important difference between the groups.<br><br><u>Comparison 2: Risk-based recall versus 6-month recall at 4 years follow-up:</u><br>The trial comparing these recall intervals did not report this outcome.<br><br><u>Comparison 3: 24-month recall versus 6-month recall at 4 years follow-up:</u><br>The trial comparing these recall intervals did not report this outcome.<br><br><u>Comparison 4: Risk-based recall versus 24-month recall at 4 years follow-up:</u><br>The trial comparing these recall intervals did not report this outcome.<br><br>**Primary outcome 2: Number of tooth surfaces with any caries**<br><u>Comparison 1: 24-month recall versus 12-month recall at 2 years follow-up:</u><br>The trial comparing these recall intervals did not report this outcome.<br><br><u>Comparison 2: Risk-based recall versus 6-month recall at 4 years follow-up:</u> |

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| | There was little to no difference between the groups in the number of tooth surfaces with any caries: MD 0.15, 95% CI −0.77 to 1.08; 1478 participants, high-certainty evidence.<br><br>Comparison 3: 24-month recall versus 6-month recall at 4 years follow-up: There was little to no difference between the groups in the number of tooth surfaces with any caries: MD −0.60, 95% CI −2.54 to 1.34; 1 trial, 271 participants; moderate certainty of evidence.<br><br>Comparison 4: Risk-based recall versus 24-month recall at 4 years follow-up: There was little to no difference between the groups in the number of tooth surfaces with any caries: MD 1.40 (95% CI −0.69 to 3.49; 1 trial, 279 participants; moderate certainty of evidence.<br><br>**Secondary outcome 1: Oral-health-related quality of life**<br>Comparison 1: 24-month recall versus 12-month recall at 2 years follow-up: The trial comparing these recall intervals did not report this outcome.<br><br>Comparison 2: Risk-based recall versus 6-month recall at 4 years follow-up: There was little to no difference between the groups in oral-health-related quality of life measured using OHIP-14 (scale from: 0 to 56 points, with lower scores indicating better quality of life): mean score 5.6; mean difference 0.35 points lower, from 1.02 lower to 0.32 higher; 1 trial; 1,551 participants; high certainty of evidence.<br><br>Comparison 3: 24-month recall versus 6-month recall at 4 years follow-up: There was little to no difference between the groups: mean score 5.04; mean difference 0.24 points lower, from 1.55 lower to 1.07 higher; 1 trial; 305 participants; high certainty of evidence.<br><br>Comparison 4: Risk-based recall versus 24-month recall at 4 years follow-up: There was little to no difference between the groups: mean score 4.47; mean difference 0.37 points lower, from 1.69 lower to 0.95 higher; 1 trial; 298 participants; high certainty of evidence.<br><br>*Note*. A standard NHS dental check-up (INTERVAL UK trial) involves clinical examination, advice, charting including monitoring of periodontal status and report. |
| **Significance/direction** | Overall, the review authors conclude that there is little to no difference in the number of permanent tooth surfaces with any caries for adults when comparing 6-month recall interval with a risk-based recall interval, or when comparing a 24-month recall interval with either 6-month or risk-based intervals.<br><br>They also concluded that the available evidence on recall intervals between dental check-ups for children and adolescents is uncertain, and that there is |

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| | a paucity of evidence pertaining to the effects of different recall intervals on the oral health of children and adolescents. |
| **Heterogeneity** | Meta-analyses were not conducted due to heterogeneity between the study populations and measures used. |
| **Summary for GRADE assessment for HRB report** | The certainty of evidence in the Norwegian trial was assessed by the review authors as very low. The certainty of evidence was downgraded by one level for imprecision and by two levels for risk of bias, leading to an over very low certainty of evidence grading.<br><br>The certainty of evidence in the UK trial was assessed by the review authors as moderate or high. The certainty of evidence was by one level for imprecision in comparisons 2 and 4, and by two levels for imprecision in comparison 3, leading to moderate- and high-certainty of evidence gradings across the review outcomes.<br><br>The HRB authors graded the certainty of evidence in this review as moderate. |
| **References to previously published versions** | Beirne P, Forgie A, Clarkson JE, Worthington HV. Recall intervals for oral health in primary care patients. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No: CD004346. [DOI: 10.1002/14651858.CD004346.pub2]<br><br>Beirne P, Clarkson JE, Worthington HV. Recall intervals for oral health in primary care patients. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No: CD004346. [DOI: 10.1002/14651858.CD004346.pub3]<br><br>Riley P, Worthington HV, Clarkson JE, Beirne PV. Recall intervals for oral health in primary care patients. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No: CD004346. [DOI: 10.1002/14651858.CD004346.pub4] |
| Parameter | Ramamurthy *et al.* (2022) extraction |
| **First Author and year of publication** | Ramamurthy *et al.* (2022) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effects of sealants compared to no sealant or a different sealant in preventing pit and fissure caries on the occlusal surfaces of primary molars in children and to report the adverse effects and the retention of different types of sealants (p16). |
| **Participants (characteristics and numbers)** | Primary dentition (primary molars); sealants, resin, glass-ionomer; combined intervention. |

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| | Baseline caries was only reported in four out of nine included trials; however, an inclusion criterion in all trials was participants had at least one pair of fully erupted caries-free first or second primary molars.<br><br>The review included 1,120 children who ranged in age from 18 months to eight years and evaluated 1,977 primary tooth surfaces. Two trials did not report on sex. Of the seven trials that did report on sex, the % female ranged from 42.3% to 60%.<br><br>All samples were representative of the general population, except in two studies which included children from high-caries areas (1 trial) and children with high risk for caries (1 trial). |
| **Setting/context** | The trials were conducted in Brazil (1 trial), China (1 trial), Denmark (1 trial), France (1 trial), India (2 trials), Spain (1 trial), Turkey (1 trial), and the UK (1 trial).<br><br>In seven trials, interventions were delivered at school clinics, paediatric clinics in dental schools, and community clinics. The two remaining trials did not report the settings of the intervention. |
| **Description of Interventions/ phenomena of interest** | The review authors included trials that compared sealants with no sealant or, one type of fissure sealant with another sealant, for the prevention of caries in primary molars. There were no restrictions on the type of sealant (resin-based, glass-ionomer-based, or hybrid sealants). Trials that used co-interventions such as oral health preventive measures, oral health education, or tooth brushing demonstrations were included if they used the same adjunct with the intervention and comparator (i.e. that the use of sealant was the only systematic difference in interventions between the trial arms).<br>Three studies reported the use of co-interventions along with the sealants. Chadwick 2005 provided motivation and oral health instruction to study participants; Joshi 2019 instructed participants in both groups to use a low fluoride toothpaste, along with a demonstration on proper tooth brushing technique; Chabadel 2021 gave oral hygiene and dietary recommendations to participants in both groups.<br><br>The review authors compared three types of interventions:<br>1. Sealant versus no sealant (comparator)<br>2. Resin-based sealants versus other sealant types (comparator), and<br>3. Newer types of sealant materials versus more conventional materials (comparator).<br><br>The sealant application method was direct application on the tooth surface only. The review authors excluded trials that compared any other caries-preventive treatments (such as fluoride varnish, acidulated phosphate |

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| | fluoride gel, laser, etc.) with sealants, as well as trials involving complex interventions for the prevention of dental caries in primary teeth (e.g. preventive resin restorations), trials involving the use of sealants in cavitated lesions, and trials that compared sealants with restorations. There were no restrictions placed on the duration of follow-up, the personnel applying sealants, or the unit of randomisation (tooth or teeth, the quadrant, the individual or a cluster, e.g. school, class).<br><br>Follow-up periods ranged from 6 months to 36 months, and included follow-up periods of 12 months, 18 months, 24 months, 30 months. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (11 February 2021)<br>• Cochrane Central Register of Controlled Trials (CENTRAL, 2021, Issue 1) in the Cochrane Library (11 February 2021)<br>• MEDLINE Ovid (1946 to 11 February 2021)<br>• Embase Ovid (16 September 2017 to 11 February 2021)<br>• The US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 11 February 2021), and<br>• The World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 11 February 2021).<br><br>Reference lists of all potentially eligible trials and relevant systematic reviews for further trials were searched. There were no restrictions on the language, date of publication.<br><br>The protocol for the review was first published in 2018; no registration number provided. One change from the planned analyses in the protocol to those performed in the published review is noted.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening). Disagreements were resolved by discussion with a third review author.<br><br>Two review authors independently extracted data from all included studies in duplicate. Information on resolving disagreements at this stage was not provided.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>None of the authors declared a conflict of interest; one author declared that they were a clinical advisor with Cochrane Oral Health and another and |

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| | another declared that they were a Statistical Editor with Cochrane Oral Health. |
| **Date range (years) of included studies** | The nine included trials were published between 1998 and 2021. |
| **Number of primary studies included in the systematic review** | The review authors included nine randomised controlled trials. One trial used a parallel-group design (Chadwick 2005), and eight used split-mouth designs. Among the split-mouth trials, one trials randomised quadrants (Baca 2007), and seven randomised teeth within a tooth pair (Chabadel 2021; Corona 2005; Fei 2011; Ganesh 2006; Hotuman 1998; Joshi 2019; Unal 2015).<br><br>One trial was funded by the NHS Research and Development Programme in Primary Dental Care, five trials did not report funding source, and the remaining three did not have any funding. |
| **Types of studies included** | The review authors included nine randomised control trials, all of which reported outcomes relevant to this umbrella review: Baca (2007), Chabadel (2021), Chadwick (2005), Corona (2005), Fei (2011), Ganesh (2006), Hotuman (1998), Joshi (2019), and Unal (2015).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Brazil (1 trial), China (1 trial), Denmark (1 trial), France (1 trial), India (2 trials), Spain (1 trial), Turkey (1 trial), and the UK (1 trial). |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of included studies using the Cochrane domain-based, RoB 1 tool as described in Chapter 8 of the Cochrane Handbook for Systemic Reviews of Interventions (Higgins 2011). Disagreements were resolved through discussion or consulting a third review author to reach a consensus if required. The review authors contacted study authors for clarification or missing information.<br><br>The following eight domains were assessed in each trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of operator (performance bias)<br>5. Blinding of outcome assessment (detection bias)<br>6. Incomplete outcome data (attrition bias)<br>7. Selective reporting (reporting bias), and |

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| | 8. Other bias<br><br>For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias.<br><br>The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as (Higgins 2011):<br>• Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at a low risk of bias<br>• High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains was at high risk of bias, or<br>• Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains was at unclear risk of bias, but none was at high risk of bias. |
| **Appraisal rating** | None of the included studies had an overall score of low risk of bias. The review authors assessed risk of bias as unclear for most studies for selection bias (the domains of random sequence generation and allocation concealment); high for most studies for performance and detection bias (the domains of blinding of participants, blinding of operator and blinding of outcomes assessor); and low for most studies for attrition bias (incomplete outcome data), reporting bias (selective reporting domain), and other bias. All studies were judged at overall high risk of bias, primarily due to issues around blinding, with the exception of Unal 2015, which they judged at unclear risk of bias overall.<br><br>The review authors assessed the certainty of the body of evidence for each comparison and outcome by considering study design limitations (i.e. the overall risk of bias of the included studies, in particular, which (if any) domains were assessed at high risk of bias), the directness of the evidence, the consistency of the results, the precision of the estimates and publication bias. Overall, the certainty of evidence was assessed as low.<br><br>To minimise risk of publication bias, the authors contacted authors of potentially eligible abstracts to seek the availability of full-text study reports, published or unpublished. They also contacted all the authors of included studies to obtain any additional information for assessment of study bias. Articles in native languages were translated to English to assess its eligibility for inclusion. |
| **Method of analysis** | The review authors grouped and analysed studies according to whether they compared a sealant with placebo or no sealant, or with a different sealant type. They planned to carry out any meta-analyses using the generic inverse variance method and random-effects model using Review Manager 5 (Review Manager 2020). For each comparison, they planned to pool the |

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| | results of studies with similar characteristics in terms of participants, interventions and outcome measures. However, the studies were too heterogenous to conduct a meta-analysis, sensitivity analysis, or sub-group analyses.<br><br>In parallel-group studies and cluster-randomised studies, the review authors chose an individual participant to be the unit of analysis. In split-mouth studies, they considered each participant to be the cluster usually comprising a single tooth pair in which one tooth was considered the intervention and one the comparator, and the tooth to be the unit of analysis.<br><br>The review authors carried out analyses at prespecified follow-up times based on available data. Outcomes for caries were analysed closest to six months for incipient lesions; outcomes for sealant retention were analysed closest to six, 12, and 24 months.<br><br>Summary of findings tables for main outcomes were provided. |
| **Outcome(s) assessed** | Primary outcome 1: incidence of new dental caries on the treated occlusal surface(s) of sound surfaces of primary molar(s) (dichotomous outcome, presence or absence of a new carious lesion) at 6 months to 36 months follow-up<br><br>Primary outcome 2: mean caries increment, measured as the change in decayed, missing and filled teeth/surfaces (dmft/s)<br><br>Secondary outcome 1: retention of sealant (dichotomous outcome, fully or partially retained/non-retained) at 6 months to 36 months follow-up<br><br>Secondary outcome 2: adverse events (any type) and safety of sealant<br><br>*Note*. Both primary and secondary outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Incidence of new dental caries**<br><u>Comparison 1: fluoride-releasing resin-based sealant versus no sealant</u>:<br>The risk of developing ≥ 1 new carious lesion (or increased caries incidence) at 12 months was 36 per 1,000 (no sealant) compared to 44 per 1,000 (95% CI 14 to 130; odds ratio 1.21, 95% CI 0.37 to 3.94; 88 children (3–7-years) with caries-free primary molars; 274 teeth; 1 trial; low certainty of evidence). The risk of developing ≥ 1 new carious lesion (or increased caries incidence) at 24 months was 205 per 1,000 (no sealant) compared to 164 per 1,000 (95% CI 95 to 268; odds ratio 0.76, 95% CI 0.41 to 1.42; 85 children; 255 teeth; 1 trial; low certainty of evidence). |

This trial involved a combined intervention in which participants in both groups received oral hygiene and dietary recommendations.

Comparison 2: glass-ionomer-based sealant versus no sealant: Due to differences in study design (e.g. age of participants, duration of follow-up), data from these two studies could not be pooled, but were presented individually by the review authors.

One trial reported similar caries incidence in children allocated to receive glass-ionomer-based sealants to those in
the no-sealant group. The risk of developing ≥ 1 new carious lesion (or increased caries incidence) at 12-30 months was 235 per 1,000 (no sealant) compared to 229 per 1,000 (95% CI 162 to 314; OR 0.97, 95% CI 0.63 to 1.49; 449 children (1–5-years) with caries-free primary molars; 1 trial; low certainty of evidence). This trial involved a combined intervention in which participants were provided with motivation and oral health instruction.

The risk of developing ≥ 1 new carious lesion (or increased caries incidence) at 6- and 12-month follow-up were lower for the sealant group than the no-sealant group at both time points in another trial; 6-month odds ratio 0.031 (95% CI 0.002 to 0.601; 107 children; 175 tooth pairs; 1 trial; low certainty of evidence); 12-month odds ratio 0.033 (95% CI 0.007 to 0.149; 107 children; 175 tooth pairs; 1 trial; low certainty of evidence). This trial involved a combined intervention in which participants in both groups were instructed to use a low fluoride toothpaste and provided with a demonstration on proper tooth brushing technique.

Comparison 3: glass-ionomer-based sealant versus resin-based sealant:
The review authors were unable to determine the outcome at 6–24 months; due to inadequate availability of information the review authors were unable to pool data from 2 trials involving 200 children in total (3–5 years) with caries-free second primary molars. The certainty of evidence in both trials was judged to be very low.

Comparison 4: fluoride releasing resin-based sealant versus resin-based sealant:
The review authors were unable to determine the outcome at 6–24 months; due to inadequate availability of information the review authors were unable to pool data from 2 trials involving 69 children (4–8 years) with caries-free second primary molars. The certainty of evidence in both trials was judged to be low.

Comparison 5: flowable resin composite versus resin-based sealants:
No trials comparing these interventions reported this outcome.

Comparison 6: auto-polymerised resin-based sealant versus light polymerised resin-based sealant:

The risk of developing ≥ 1 new carious lesion (or increased caries incidence) was not different at 24-36 months was 98 per 1000 (light polymerised) compared with 59 per 1000 (95% CI 16 to 192; OR 0.58, 95% CI 0.15 to 2.19; 52 children (2–4-years) with caries free primary molars; 52 tooth pairs; 1 trial; very low certainty of evidence. This trial did not include a combined intervention.

**Primary outcome 2: Mean caries increment, measured as the change in decayed, missing and filled teeth/surfaces**

Of the seven trials that reported caries incidence as dichotomous data, three of these also reported caries increment at follow-up as mean decayed, missing and filled teeth or surfaces, or as mean number of new cavitated occlusal lesions.

Comparison 1: fluoride-releasing resin-based sealant versus no sealant:

In one single trial, 85 children were examined at 24 months follow-up the authors reported that the mean number of new, cavitated occlusal lesions was 0.23 (SD 0.06) in the sealed molars and 0.29 (SD 0.06) in the control molars (Wilcoxon matched pairs signed rank test P = 0.42). Mean d3ft at baseline, 12 and 24 months was reported overall but not by group.

Comparison 2: glass-ionomer-based sealant versus no sealant:

Statistical analysis could not be conducted for this outcome. One trial reported caries at various time points from baseline up to 12 months follow-up; however, caries increment was not specifically calculated or reported. At 12 months follow-up, the authors reported that dmft was lower in the sealants group than the no-sealant group (8.43 (SD 5.84) with sealant versus 10.05 (SD 6.16) with no sealant), but there was insufficient information to determine the threshold for caries (ICDAS score). Another trial reported that, "there was no significant difference between test and control groups in caries increment at the occlusal surfaces of first primary molars or for any other measured variables." There were no summary data provided for this outcome. The total number of participants in these two trials is 619.

Comparison 3: glass-ionomer-based sealant versus resin-based sealant:

No trials reported mean caries increment.

Comparison 4: fluoride releasing resin-based sealant versus resin-based sealant:

No trials reported mean caries increment.

Comparison 5: flowable resin composite versus resin-based sealants:

No trials reported mean caries increment.

Comparison 6: auto-polymerised resin-based sealant versus light polymerised resin-based sealant:

No trials reported mean caries increment.

**Secondary outcome 1: Retention of sealant**

Comparisons 1 and 2:

Effect estimate was not calculable as one group did not receive sealants.

Comparison 3: glass-ionomer-based sealant versus resin-based sealant:

Complete or partial retention of glass-ionomer-based sealants was significantly lower compared with retention of resin-based sealants at 24 months (70 per 1000 compared with 320 per 1000, 95% CI 208 to 458; odds ratio 0.20, 95% CI 0.11 to 0.36; 100 children (3–5 years) with caries-free second primary molars; 100 tooth pairs; 1 trial; very low certainty of evidence).

Comparison 4: fluoride releasing resin-based sealant versus resin-based sealant:

Complete or partial retention of fluoride-releasing resin-based sealants compared with resin-based sealants at 6–24 months could not be determined from 2 trials involving 69 children in total (4–5 years) with caries-free second primary molars. The certainty of evidence in both trials was judged to be very low.

Comparison 5: flowable resin composite versus resin-based sealants:

Effect estimate was not calculable as all sealants were retained or partially retained in both groups at 12 months; 40 children who were regular dental attenders with caries-free first or second primary molars; 1 trial; low certainty of evidence.

Comparison 6: auto-polymerised resin-based sealant versus light polymerised resin-based sealant:

Complete or partial retention of auto-polymerised sealant compared with light polymerised sealant was not different at 24–36 months follow-up (904 per 1000 compared with 865 per 1000, 95% CI 756 to 931; odds ratio 0.68 95% CI 0.33 to 1.44; 52 children (2–4-years) with caries free primary molars; 52 tooth pairs; 1 trial; very low certainty of evidence).

**Secondary outcome 2: Adverse events**

Comparison 1: fluoride-releasing resin-based sealant versus no sealant:

No trials comparing these interventions reported this outcome.

Comparison 2: glass-ionomer-based sealant versus no sealant: No trials comparing these interventions reported this outcome.

Comparison 3: glass-ionomer-based sealant versus resin-based sealant:

Adverse events such as nausea were examined for some children (among 100) in 1 trial. One child reported feeling uncomfortable and experienced a

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| | strong gag reflex following application of the glass-ionomer-based sealant, and eight children reported feeling uncomfortable after the fluoride resin-based applications.<br><br>Comparison 4: fluoride releasing resin-based sealant versus resin-based sealant:<br>No trials comparing these interventions reported this outcome.<br><br>Comparison 5: flowable resin composite versus resin-based sealants:<br>No trials comparing these interventions reported this outcome.<br><br>Comparison 6: auto-polymerised resin-based sealant versus light polymerised resin-based sealant:<br>No trials comparing these interventions reported this outcome. |
| **Significance/direction** | The review authors concluded that the effectiveness of pit and fissure sealants and the relative effectiveness of different types of sealants in preventing caries on the occlusal surfaces of primary teeth has yet to be established. |
| **Heterogeneity** | Three studies compared sealants with no sealants, and six studies compared different materials or processes to seal the tooth surface. Given important differences in the study designs (e.g. sealant types, age of the children at the beginning of the trial, and the length of follow-up), the data could not be pooled. The certainty of the evidence for the comparisons and outcomes in the review was low/very low, reflecting the fragility and uncertainty of the evidence base. The volume of evidence was limited, which typically included small studies in which the number of events was low. Most studies in the review used a split-mouth design. While this is an efficient study design for this research questions, there were often shortcomings in the analyses and reporting of results that made synthesising the evidence difficult. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as low for the following interventions: fluoride-releasing resin-based sealants versus no sealants (downgraded once due to lack of blinding and once due to imprecision), glass-ionomer-based sealants versus no sealants (downgraded twice due to lack of blinding, imprecision, and inconsistency), fluoride-releasing resin-based sealant versus resin-based sealant (downgraded twice due to imprecision), and flowable resin composite versus resin-based sealants (downgraded twice due to lack of blinding and imprecision).<br><br>The certainty of evidence for the following interventions was graded as very low: glass-ionomer based sealants versus fluoride releasing resin-based sealants (downgraded three times for lack of blinding and imprecision) and auto-polymerised sealant versus light polymerised sealant (downgraded three times for lack of blinding, imprecision, and indirectness). |

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| | The HRB authors graded the certainty of evidence in this review as moderate, downgraded twice; once for lack of randomisation and once lack of blinding of outcome assessors. |
| **References to previously published versions** | Ramamurthy P, Rath A, Sidhu P, Fernandes B, Nettem S, Muttalib K, et al. Sealants for preventing dental caries in primary teeth. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No: CD012981. [DOI: 10.1002/14651858.CD012981] |
| Parameter | Marinho *et al.* (2015) extraction |
| **First Author and year of publication** | Marinho *et al.* (2015) |
| **Objectives (exact review question(s) and page number)** | To determine the effectiveness and safety of fluoride gels in preventing dental caries in the child and adolescent population (p7). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate) (first molars, approximal surfaces, etc.); topical fluoride, gels.<br><br>Baseline caries was reported in 25 out of 28 included trials. Only one of these 25 trials included only caries-free participants at baseline.<br><br>Participants were 9,140 children and adolescents between the ages of two and 15 years old at baseline. There were similar numbers of males and females (where these data were reported), except for one study, which included male participants only. |
| **Setting/context** | The trials were conducted in Brazil (4 trials), Canada (1 trial), China (1 trial), Europe (7 trials), Israel (1 trial), the USA (13 trials), and Venezuela (1 trial).<br><br>Participants were recruited from school settings, except in the three trials assessing caries in pre-school children, where information in one trial was unclear, and in the remaining two trials nurseries and paediatric clinics were the settings. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was topical fluoride in the form of gels only, operator- or self-applied, using any fluoride agent, at any concentration (ppm F), amount or duration of application, and with any technique of application, prior to or post application. The frequency of application was required to be at least once a year. The fluoride concentrations ranged from 2425 ppm F (SnF2) to 12,500 ppm F (AmF and NaF). Fourteen trials used the common 12,300 ppm F APF gel concentration. The three studies that did not report the<br>APF gel concentration are likely to have used the standard 12,300 ppm F. Two studies reported the use of other APF concentrations: 9000 ppm F and |

9150 ppm F. The application frequency ranged from once a year (reported in 7 studies) to 140 times a year (reported in Englander 1967), but it varied greatly among the studies, with 8 studies reporting the more common twice a year application frequency.

With the exception of Shern 1976 (with 5 consecutive once-a-day or once-a-week applications in 1 year), all 17 studies where fluoride gel was professionally applied reported a frequency of application of 4 times a year or less. With 1 exception (Trubman 1973), where frequency of application was 4 times a year, the 11 studies of self-applied gel reported a frequency of application of 5 times a year or more. Reported application times ranged from 2 to 10 minutes, with 16 studies reporting 3 to 5 minutes gel application time.

The control group was placebo (for any method of gel application) or no treatment (for tray or cotton-tips methods of gel application, but not for brushing or flossing methods). Thus, the review authors compared two types of interventions:

1. Fluoride gel compared with a placebo, and
2. Fluoride gel compared with no treatment.

Trials in which the intervention consisted of any other caries-preventive agent or procedure (for example, other fluoride-based measures, chlorhexidine, sealants, oral hygiene interventions, xylitol chewing gums, glass-ionomers) used in addition to fluoride gel were excluded.

The review authors assessed the risk of bias in relation to intervention contamination/co-intervention. Seven trials were assessed as at being at a low risk of bias in this domain. These trials provided information to suggest that there was no difference between groups in co-interventions that could have affected the outcomes observed, such as supervised brushing, oral hygiene instructions, or gel application procedures (DePaola 1980, Englander 1967, Englander 1978, Heifetz 1970, Ran 1991, Truin 2005, Van Rijkom 2004). In the other studies the risk of bias was unclear as no information (or not enough information) was provided.

Sixteen trials reported information about the performance of some form of prior (professional or self-performed) tooth prophylaxis before administering the gel: 2 trials were performed with no paste (Cobb 1980; Hagan 1985), and 14 trials were performed with a non-fluoride paste (if with a fluoride paste the trial would have been excluded). The review authors considered the prior tooth cleaning as a possible part of the technique of gel application and not as a separate intervention on its own. Post-hoc metaregression analyses showed no significant association between estimates of D(M)FS PFs and prior prophylaxis.

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| | Follow-up periods varied and ranged from 1 year to 4 years. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (to 5 November 2014)<br>• Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library 2014, Issue 1)<br>• MEDLINE via OVID (1946 to 5 November 2014)<br>• EMBASE via OVID (1980 to 5 November 2014)<br>• CINAHL via EBSCO (1980 to 5 November 2014)<br>• LILACS via BIREME Virtual Health Library (1980 to 5 November 2014)<br>• BBO via BIREME Virtual Health Library (1980 to 5 November 2014)<br>• ProQuest Dissertations and Theses (1861 to 5 November 2014)<br>• Web of Science Conference Proceedings (1945 to 5 November 2014)<br>• The US National Institutes of Health Trials Register (http:// clinicaltrials.gov) (to 5 November 2014), and<br>• The World Health Organization Clinical Trials Registry Platform (http://apps.who.int/trialsearch/default.aspx) (to 5 November 2014).<br><br>The review authors scanned all eligible trial reports, previous meta-analyses, and review articles for relevant references. There were no restrictions on language or date of publication in database searches.<br><br>For the original version of this review, the review authors searched reference lists of relevant chapters from preventive search dentistry textbooks on topically applied fluoride interventions, and carried out handsearching in the following journals:<br>• Community Dentistry and Oral Epidemiology (1990 to 1999)<br>• British Dental Journal (1999 to 2000)<br>• Caries Research (1999 to 2000)<br>• Community Dentistry and Oral Epidemiology (1999 to 2000)<br>• Journal of the American Dental Association (1999 to 2000)<br>• Journal of Dental Research (1999 to 2000)<br>• Journal of Public Health Dentistry (1999 to 2000), and<br>• European Journal of Oral Sciences (1999 to 2000).<br><br>For the update of the review, the authors did not undertake any handsearching. |

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| | For the original review, the review authors contacted experts in the field of preventive dentistry, author(s) of the included studies to obtain potentially eligible unpublished trials eligible, to clarify reported information, or to obtain missing data. They also contacted six fluoride gel manufacturers in October 2000 to request data from potentially eligible unpublished trials.<br><br>The review protocol was first published in 2000 (no registration number provided). The review authors describe some changes between the protocol and the published review.<br><br>At least two review authors did the title and abstract, and full text screening for eligibility in duplicate. Trials thought to be potentially relevant in other languages were translated. At least two review authors extracted data from all included studies in duplicate (disagreement resolution in screening and/or extraction was not reported).<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners. No conflicts of interest of reported. |
| **Date range (years) of included studies** | The review included 44 reports describing 28 trials, including 25 from the original 2002 review and three additional trials.<br><br>The 44 reports were published between 1967 and 2005. The 25 previously included trials were conducted between 1964 and 1996 (12 during the 1960s, 7 during the 1970s, 5 during the 1980s, and 1 in the 1990s). The three additional trials were conducted in the late 1990s and early 2000s.<br><br>The study durations ranged from 1 to 4 years: 3 trials lasted 4 years, 9 trials lasted 3 years, 11 trials lasted around 2 years, 2 trials lasted 1.5 years, and 2 trials lasted 1 year. |
| **Number of primary studies included in the systematic review** | This review authors included 28 trials (3 of which were new since the original review). All trials used parallel-group designs, one being cluster randomised. Eight had more than one fluoride gel treatment group compared to a control. Among the eight, one trial had two treatment groups and two placebo control groups. Ten trials used a no-treatment control group, and the remaining 18 used a placebo-control group, of which 4 used an inactive treatment other than gel ("placebo solution").<br><br>Seventeen of the included trials reported operator applied gel and 11 reported self-applied gel under supervision (by dental personnel in 4 trials, by trained non-dental personnel in 5 trials, and by mothers and dental personnel in 1 trial; data were not available for 1 of the studies). Gel was usually administered using a tray (18 trials), a brush (6 trials), floss (1 trial) or cotton-tip paint application (3 trials). A variety of fluoride gel types were used, including acidulated phosphate fluoride (APF) (21 trials), sodium |

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| | fluoride (NaF) (7 trials), amine fluoride (AmF) (5 trials) and stannous fluoride (SnF2) (1 trial). Fluoride concentrations ranged from 2425 ppm F (SnF2) to 12,500 ppm F (AmF and NaF). Fourteen 14 trials used the common 12,300 ppm F APF gel concentration. Three trials did not report the APF gel concentration but are likely to have used the standard 12,300 ppm F. Two trials reported the use of 9000 ppm F and 9150 ppm F.<br><br>The unit of randomisation was participants (27 trials) or school class (1 trial).<br><br>Five trials acknowledged financial support from a fluoride gel manufacturer: seven trials acknowledged only some assistance or the supply of fluoride gel from manufacturers; one trial indicated involvement with a manufacturer by the affiliation of one of the authors; seven trials acknowledged support from non-commercial sources (grants); and the remaining eight trials provided no information on source of funding or any other assistance. |
| **Types of studies included** | The review authors included 28 randomised and quasi-randomised controlled trials: Abadia (1978), Bijella (1981), Bryan (1970), Cobb (1980), Cons (1970), DePaola (1980), Englander (1967), Englander (1971), Englander (1978), Gisselsson (1999), Hagan (1985), Heifetz (1970), Horowitz (1971), Horowitz (1974), Ingraham (1970), Jiang (2005), Mainwaring (1978), Marthaler (1970), Marthaler, (1970a), Mestrinho (1983), Olivier (1992), Ran (1991), Shern (1976), Szwejda (1972), Treide (1988), Trubman (1973), Truin (2005), Van Rijkom (2004).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Brazil (3 trials), Canada (1 trial), China (1 trial), Europe (7 trials), Israel (1 trial), USA (13 trials), and Venezuela (1 trial). |
| **Appraisal instrument(s)** | At least two review authors independently assessed the risk of bias of included trials using the Cochrane Collaboration's tool for assessing risk of bias as outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1 (Higgins 2011), but according to pre-defined criteria that were adapted and refined for the Cochrane topical-fluoride reviews updates. Disagreements were resolved by discussion or by the involvement of another review author.<br><br>The following eight domains were assessed in each trial:<br>1. Random sequence generation<br>2. Allocation concealment<br>3. Blinding of participants/personnel<br>4. Blinding of outcome assessment<br>5. Incomplete outcome data |

6. Selective outcome reporting
7. Balance of baseline characteristics, and
8. Free from contamination or co-intervention

For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias.

The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as (Higgins 2011):

- Low risk of bias (plausible bias unlikely to seriously alter the results; all eight domains assessed as at low risk of bias)
- High risk of bias (plausible bias that seriously weakens confidence in the results; at least one domain assessed as at high risk of bias), or
- Unclear risk of bias (plausible bias that raises some doubt about the results; at least one domain assessed as at unclear risk of bias, but none at high risk of bias).

**Appraisal rating**

Overall, none of the included trials were categorised as being at low risk of bias. Eight trials were categorised as being at unclear risk of bias. The remaining 20 trials were categorised as being at high risk of bias. The domains most categorised as being at high risk of bias were random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias) and incomplete outcome data (attrition bias).

Eleven out of 28 trials had two or more high risk of bias scores. Six out of 28 trials were categorised as being at low risk of bias for randomisation. Sixteen out of 28 trials were categorised as being at low risk of bias for outcome ascertainment.

For the primary outcome (DMFS increment), the review authors downgraded the quality of the evidence because of methodological limitations, but overall considered the quality of evidence for this outcome for permanent dentition to be moderate (moderate confidence in the effect estimate). The evidence quality for this outcome for primary dentition was considered low (low confidence in the effect estimate) because only three trials reported the results of the effect on the primary dentition.

Only 2 trials reported on acute toxicity, and both had serious limitations in methodology. Therefore, the review authors downgraded further for imprecision and so the quality of evidence for this outcome was very low.

The overall certainty of evidence was assessed as moderate. The review authors assessed the certainty of the body of evidence with reference to

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| | overall risk of bias of included trials at each outcome, directness of evidence, consistency of results, precision of estimates, and risk of publication bias. The overall high risk of bias lowered the certainty of evidence.<br><br>Regarding publication bias, the review authors observed a degree of asymmetry in the funnel plot because of one large trial (not relevant to the outcomes extracted for this umbrella review) which reported the largest positive effect. The review authors noted that the clinical significance of this result is unclear. |
| **Method of analysis** | Primary and permanent teeth were analysed separately.<br><br>The chosen measure of treatment effect for the primary outcome measure, caries increment, was the prevented fraction. The meta-analyses for the prevented fractions were conducted as inverse variance weighted averages in Review Manager software (RevMan 2014), where the prevented fraction data were entered using the generic inverse variance option. They performed random-effects meta-analyses. They also used random-effects models to calculate a pooled estimate of effect for outcomes other than caries increment.<br><br>For most outcomes other than caries increment, the review authors summarised continuous data as average mean differences (MD) in treatment effects and their 95% confidence intervals (95% CI), or if different scales had been used to measure the same outcome in different trials, standardised mean differences (SMD) and their 95% CI. They analysed dichotomous outcome data by calculating risk ratios or, for adverse effects of fluoride treatment, risk differences.<br><br>In the trials with more than one relevant intervention group and a common control group, the review authors combined summary statistics from all relevant experimental groups in order to obtain a measure of treatment effect. Where any cluster-randomised trials did not report results adjusted for the clustering present in the data, the review authors estimated the design effect with the intraclass correlation coefficient (ICC) if reported, or a value of 0.05 (Lawrence 2008; ICC = 0.045). This was then used to modify the numbers in the intervention and control groups by calculating the effective sample size (Higgins 2011).<br><br>The review authors specified four potential sources of heterogeneity a priori:<br>1. The baseline levels of caries severity<br>2. Exposure to other fluoride sources (in water, toothpastes, etc.)<br>3. Mode (self-applied supervised or operator applies) and method (self-applied tray or toothbrush) or application, and<br>4. Frequency of application and fluoride concentration. |

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| | They examined these factors with estimated effects by using random-effects meta-regression analyses in Stata version 12.0. Post hoc, the authors investigated further potential sources of heterogeneity by meta-regression: for different types of control groups (placebo or no treatment), use or not of prior prophylaxis, length of follow-up (years) and dropout rate (%).<br><br>The review authors planned to undertake a sensitivity analysis including the trials with an overall assessment of low risk of bias, but there were no trials satisfying this criterion. They undertook a sensitivity analysis excluding trials where they imputed missing standard deviations. They also undertook a sensitivity analysis excluding trials at high risk of bias for allocation concealment and another excluding trials at high and unclear risk of bias for blinding of outcome assessment.<br><br>The unit of analysis was not explicitly stated but is presumed to be the individual (in at least the 27 parallel-group designs where the unit of randomisation was the individual).<br><br>A summary of findings table for the main outcomes was provided. |
| **Outcome(s) assessed** | Primary outcome 1: caries increment in permanent tooth surfaces (D(M)FS), reported as change from baseline (and D(M)FT, when reported)<br><br>Primary outcome 2: caries increment in primary tooth surfaces (d(e/m)fs), reported as change from baseline (and d(e/m)ft, when reported)<br><br>Primary outcome 3: development of new caries, reported as change in the proportion of children developing new caries; 1 trial; 3-year follow-up<br><br>Primary outcome 4: change in proportion of children not remaining caries-free; reported as a change in the proportion; 2 trials; 3-year follow-up in one trial and 0.5-, 1.5-, and 2.3-year follow-up in the other trial<br><br>Secondary outcome 1: tooth staining, measured as changes in proportion of children<br><br>Secondary outcome 2: signs of acute toxicity during application of gel/treatment; 2 trials; 1-year follow-up in one trial and 2-year follow-up in the other trial<br><br>Secondary outcome 3: mucosal irritation/oral soft-tissue allergic reaction<br><br>*Note*. Primary outcomes 1 and 2 are identified as primary outcomes in the review. Primary outcomes 3 and 4 are identified as secondary outcomes in the review, but for the HRB's purposes are considered primary outcomes. All secondary outcomes are identified as secondary outcomes in the review. |

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| **Results/findings** | **Primary outcome 1: Caries increment in permanent tooth surfaces (and whole teeth, when reported)**<br>The D(M)FS prevented fraction pooled estimate was 0.28 (95% CI 0.19 to 0.36; P < 0.0001; $I^2$ = 82%; 8,479 participants; 25 trials; moderate quality of evidence), suggesting a large caries-preventive benefit from the use of fluoride gel (nearest to 3 years follow-up). A sensitivity analysis, restricting the pooling of trials to those that were fully reported and suitable for analysis (21 trials), revealed similar findings to the full meta-analysis. Sensitivity analyses excluding 7 trials a high risk of bias for allocation concealment also showed similar results to the full meta-analysis. A sensitivity analysis excluding 12 trials at high risk of bias for blinding of outcome assessments showed smaller prevented fraction values than the results of the full meta-analysis (PF = 0.22, 95% CI 0.16 to 0.29, $I^2$ = 75% instead of 82%).<br><br>*Note*. 10 of the 25 pooled trials reported the performance of some form of prior (professional or self-performed) tooth prophylaxis before administering the gel. However, the review authors considered prior tooth cleaning as a possible part of the technique of gel application and not as a separate intervention on its own, and post-hoc meta regression analyses showed no significant association between effect estimates and prior prophylaxis. In addition, 13 out of the 25 pooled trials reported exposure to additional forms of fluoride (water, salt, tablets, and/or toothpaste). However, this was considered background fluoride exposure, rather than part of the intervention of interest. It should also be noted that one out of the 25 included trials tested of a combined intervention involving oral health instruction and supervised brushing with fluoridated toothpaste.<br><br>Ten trials reported data that allowed the calculation of the D(M)FT prevented fraction. The pooled estimate was 0.32 (95% CI 0.19 to 0.46; P < 0.0001; $I^2$ = 91%; 3,198 participants; 10 trials; low quality of evidence), suggesting that fluoride gel leads to a reduction in decayed, missing and filled tooth surfaces in permanent dentition.<br><br>*Note*. Nine of the 10 pooled trials reported the performance of some form of prior (professional or self-performed) tooth prophylaxis before administering the gel. However, the review authors considered prior tooth cleaning as a possible part of the technique of gel application and not as a separate intervention on its own, and post-hoc meta regression analyses showed no significant association between effect estimates and prior prophylaxis. In addition, 2 out of the 10 pooled trials reported exposure to fluoridated water. However, this was considered background fluoride exposure, rather than part of the intervention of interest.<br><br>**Primary outcome 2: Caries increment in primary tooth surfaces (and whole teeth, when reported)** |

The d(e/m)fs prevented fraction pooled estimate was 0.20 (95% CI 0.01 to 0.38; P = 0.04; 1,254 participants; 3 trials; $I^2$ = 0%), suggesting a benefit of fluoride gel in the primary dentition (nearest to 3 years follow-up). The review authors note that results should be viewed with a degree of caution given that standards deviations were imputed in two of the three trials. No data on d(m)ft were available.

Two of these trials involved self-application and one involved professional application. The concentration of fluoride was 5000 ppm (applied approximately 76 times per year) and 12,500 ppm (applied approximately 130 times per year) in the self-application trials, and 4500 ppm (applied twice per year) in the professional-application trial.

*Note*. 1/3 of these trials involved some form of prior (professional or self-performed) tooth prophylaxis before administering the gel. The review authors considered the prior tooth cleaning as a possible part of the technique of gel application and not as a separate intervention on its own. In addition, 1/3 of these trials reported exposure to additional forms of fluoride (water, tablets and/or toothpaste). However, this was considered background fluoride exposure, rather than part of the intervention of interest.

**Primary outcome 3: Development of new caries**

The proportion of children developing one or more new caries (tooth surface in the permanent dentition; new DFS) was lower in the fluoride gel treatment groups (NaF group = 4500 ppm F, SnF2 group = 2425 ppm F) than in the placebo group at 3-year follow-up, risk ratio (assumed for NaF group) 0.82, (95% CI 0.68 to 0.99; 280 participants; 1 trial; certainty of evidence not reported).

**Primary outcome 4: Change in proportion of children not remaining caries free**

The proportion of children not remaining caries-free on tooth surfaces in permanent dentition was lower in the fluoride gel treatment group (NaF group = 4500 ppm F, SnF2 group = 2425 ppm F) compared to the placebo group at 3-year follow-up, risk ratio (assumed for NaF group) 0.72 (95% CI 0.46 to 1.14; 280 participants; 1 trial; certainty of evidence not reported).

The proportion of children not remaining caries-free on tooth surfaces in primary dentition was lower in the fluoride gel treatment group (APF group = 5000 ppm F applied approximately 76 times per year) compared to the placebo group at 1.5-year follow-up (risk ratio 0.53, 95% CI 0.26 to 1.07; 145 participants; 1 trial; certainty of evidence not reported).

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| | *Note*. Participants in this trial had exposure to fluoridated water. However, this was considered background fluoride exposure, rather than part of the intervention of interest.<br><br>**Secondary outcome 1: Tooth staining**<br>No trials included in the review reported this outcome.<br><br>**Secondary outcome 2: Signs of acute toxicity during application**<br>Two trials (490 participants) reported useable data on adverse events, but one of these had no events in either arm. The pooled estimate of the risk difference between the gel and placebo arms was 0.01 (95% CI -0.01 to 0.02, $Chi^2$ 0.8 on 1 degree of freedom, P = 0.36, $I^2$ = 0), that marginally favoured the placebo/no-treatment arms, although the difference was not statistically significant, and the certainty of evidence was very low.<br><br>**Secondary outcome 3: Mucosal irritation/oral soft-tissue allergic reaction**<br>No trials included in the review reported this outcome. |
| **Significance/direction** | The risk of participants having developed new caries on tooth surfaces in permanent dentition at the 3-year recall was lower than that for those in the control group. There was low quality evidence suggesting that fluoride gel leads to a 20% (95% CI 1% to 38%) reduction in decayed, missing and filled tooth surfaces; there was no heterogeneity in this estimate. Overall, the review authors were less certain of the large reduction observed in the primary dentition relatively to permanent dentition.<br><br>The change in the proportion of participants not remaining caries free on tooth surfaces in permanent dentition at the 3-year and 1.5-year recalls (2 trials, respectively) was lower than the change in the proportion of participants not remaining caries free in the control group. There was no significant increase in the risk of acute toxicity during application of fluoride gel compared to application of a placebo. |
| **Heterogeneity** | Substantial heterogeneity was observed for primary outcome 1. Univariate meta-regression suggested no significant association between estimates of D(M)FS PFs and the prespecified trial characteristics. Further univariate meta-regression analyses on other characteristics not specified a priori showed no significant association between estimates of D(M)FS PFs and length of follow-up, prior prophylaxis, or dropout rate. However, subgroup and meta-regression analyses showed that the effect of fluoride gel varied according to type of control group used, with D(M)FS PF on average being 17% (95% CI 3% to 31%; P = 0.018) higher in non-placebo-controlled trials; whether the study employed a placebo, or a no-treatment control group was the only factor that was significantly related to heterogeneity of effect. This finding should be interpreted with caution given as this was a post hoc analysis. |

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| | The review authors did not comment on heterogeneity in the remaining outcomes of interest to the umbrella review. |
| **Summary for GRADE assessment for HRB report** | The certainty of evidence was graded by outcome, but only two outcomes relevant to this umbrella review were graded. The findings related to the DMFS outcome were graded as moderate, downgraded once for unclear sequence generation/allocation concealment. The findings related to the dmfs outcomes were graded as low, downgraded twice due to a small proportion of studies reporting bias and imprecision of results.<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride gels for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No: CD002280. [DOI: 10.1002/14651858.CD002280] |
| Parameter | Takahashi *et al.* (2017) extraction |
| **First Author and year of publication** | Takahashi *et al.* (2017) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effects of women taking fluoride supplements (tablets, drops, lozenges or chewing gum) compared with no fluoride supplementation during pregnancy to prevent caries in the primary teeth of children (p6). |
| **Participants (characteristics and numbers)** | Primary dentition; systemic fluoride, supplements (taken by mother during pregnancy).<br><br>No caries (the review included pregnant women, regardless of their dental caries to examine subsequent caries in their offspring).<br><br>Participants were 1,400 pregnant women in the first trimester (6 months prenatal) residing in communities served by fluoride-deficient drinking water. There were 1,175 babies born to participants and of these, 938 children were followed up at 3 years of age (intervention 464 versus control 484) and 798 children were followed up at 5 years of age (intervention 398 versus control 400). Information pertaining to the sex of the children was not reported.<br><br>The review authors included pregnant women, regardless of their dental caries, exposure to fluorides, level of dental treatment, nationality, or level of education, who may or may not have had access to fluoridated water (naturally or artificially). |
| **Setting/context** | The trial was conducted in the USA. |

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| | Participants were recruited from communities with unfluoridated drinking water in Southern Maine. |
| **Description of Interventions/ phenomena of interest** | The review focused on trials of fluoride supplementation (tablets, drops, lozenges, or chewing gum) of any dosage, frequency, duration, and timing of delivery, which may or may not have included the use of topical fluorides such as fluoride dentifrice, fluoride rinse and topical fluoride application, compared with no fluoride supplementation.<br><br>Control groups of interest were placebo or no treatment. Follow-up periods were 3.5 and 3.5 years (when children were 3 and 5 years old, respectively). In the only included trial, the intervention group received one 2.2 mg dose of sodium fluoride (NaF) (1 mg active fluoride ion) in the form of one tablet to be taken daily from the fourth month of pregnancy. The control group received placebo tablets (no fluoride during pregnancy). Both the intervention and control groups received fluoride drops from birth to 2 years of age and one 0.5 mg tablet daily for children aged 2 to 3 years. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (searched 25 January 2017)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 11) in the Cochrane Library (searched 25 January 2017)<br>• MEDLINE Ovid (1946 to 25 January 2017)<br>• Embase Ovid (1980 to 25 January 2017)<br>• LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; 1982 to 25 January 2017)<br>• CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 25 January 2017)<br>• The US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 25 January 2017), and<br>• The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 25 January 2017).<br><br>The review authors searched reference lists of included studies and relevant systematic reviews. There were no language, publication year or publication status restrictions in database searches.<br><br>The review authors did not report when the protocol was published or the registration number but noted two differences between the protocol and the review. From an online search, the protocol appears to have been published in 2015. |

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| | Two review authors independently screened the titles and abstracts and completed handsearching. Two authors also independently completed full-text screening. Disagreements in title and abstract screening and full-text screening were resolved by discussion or consulting a third author.<br><br>Two review authors independently extracted data. Disagreements were resolved by discussion and consultation with a third review author.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners. None of the authors declared a conflict of interest. |
| **Date range (years) of included studies** | The review included 1 trial that was published in 1997. |
| **Number of primary studies included in the systematic review** | The review authors included 1 RCT study with two groups. The intervention group received tablet fluoride supplements (1 dose of 2.2 mg sodium fluoride (NaF); 1 mg active fluoride ion) in the form of one tablet taken daily from 4th month of pregnancy. The control group received placebo tablets. Both the intervention and control groups received fluoride drops from birth to 2 years of age and 1 0.5 mg tablet daily for children aged 2 to 3 years.<br><br>The unit of randomisation was the individual. |
| **Types of studies included** | The review authors included one randomised controlled trial: Leverett (1997).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trial was completed in the USA (1 trial). |
| **Appraisal instrument(s)** | Two review authors assessed the risk of bias assessment independently using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Disagreements were resolved by discussion or by involving a third assessor.<br><br>The following seven domains were assessed in each trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants/personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias) |

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| | 6. Selective outcome reporting (reporting bias), and<br>7. Other bias (recruitment bias, bias influenced by funding source, etc.).<br><br>For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias.<br><br>The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as (Higgins 2011):<br>• Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias<br>• High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias), or<br>• Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains had an unclear risk of bias, but none at high risk of bias. |
| **Appraisal rating** | The only trial included in the review was assessed as being at high risk of bias overall, mainly due to attrition bias.<br><br>The trial was assessed as being at unclear risk of bias for both randomisation and outcome ascertainment. The review authors noted that they attempted to minimize the potential biases in the review a priori, following the guidance provided in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).<br><br>The quality of the body of evidence for each outcome was assessed under five domains (study limitations, consistency of effect, imprecision, indirectness and publication bias) and judged to be of high, moderate, low or very low quality.<br><br>The review authors described potential limitations in the blinding of outcome assessment which, when coupled with high attrition, were likely to lower confidence in the estimate of effect and imprecision (CI included appreciable benefits and harms).<br><br>Publication bias could not be assessed because only one trial was included. |
| **Method of analysis** | For dichotomous outcomes, the review authors calculated risk ratios for differences between the intervention and comparison groups, along with 95% confidence intervals. For continuous outcomes, they calculated the mean difference and 95% CIs where means and standard deviations were presented or were calculable. They did not calculate the standardised mean difference. |

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| | The review authors could not conduct meta-analysis, subgroup analyses, or analyses of heterogeneity because the review included only one trial.<br><br>A summary of findings table for the main outcomes was provided. |
| **Outcome(s) assessed** | Primary outcome 1: the number of children with caries in the primary teeth<br><br>Primary outcomes 2: decayed, missing and filled primary teeth (dmft) and components<br><br>Primary outcome 3: decayed, missing and filled primary tooth surfaces (dmfs) and components<br><br>Secondary outcome 1: fluorosis<br><br>Secondary outcome 2: adverse effects (apart from fluorosis, e.g. miscarriage, premature delivery, or dental and any other possible negative effects)<br><br>*Note*. Primary outcomes 1-3 are identified as primary outcomes in the review. Secondary outcome 1 is identified as a primary outcome in the review, but for the HRB's purposes is considered a secondary outcome. Secondary outcome 1 is identified as a secondary outcome in the review. |
| **Results/findings** | **Primary outcome 1: Number of children with caries**<br>There was no difference in effect for children with caries in the primary teeth at 3 years in the fluoride supplementation (1 dose of 2.2mg NaF tablet once daily from the 4th months of pregnancy) group compared to the control group, 43 per 1,000 compared to 30 per 1,000 (placebo) (95% CI 22 to 84, risk ratio 1.46, 95% CI 0.75 to 2.85; 938 children; 1 trial; very low certainty of evidence.<br><br>There was also no difference in effect at 5 years (risk ratio 0.84, 95% CI 0.53 to 1.33; 798 children; 1 trial; certainty of evidence not reported).<br><br>**Primary outcome 2: Decayed, missing, and filled primary teeth (dmft) and components**<br>This outcome was not assessed in the only included trial.<br><br>**Primary outcome 3: Decayed, missing, and filled primary tooth surfaces (dmfs) and components**<br>There was no difference in effect on decayed surfaces at 3 years (mean difference 0.05, 95% CI -0.02 to 0.12; 938 children; 1 trial; certainty of evidence not reported).<br><br>There was no difference in effect on filled surfaces at 3 years (mean difference 0.07, 95% CI -0.07 to 0.21; 938 children; 1 trial; certainty of evidence not reported). |

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| | There was no difference in effect on decayed or filled surfaces at 3 years (mean difference 0.12, 95% CI -0.05 to 0.29; 938 children; 1 trial; very low certainty of evidence).<br><br>There was no difference in effect on decayed surfaces at 5 years (mean difference -0.06, 95% CI -0.17 to 0.05; 798 children; 1 trial; certainty of evidence not reported).<br><br>There was no difference in effect on filled surfaces at 5 years (mean difference 0.03, 95% CI -0.28 to 0.34; 798 children; 1 trial; certainty of evidence not reported).<br><br>There was no difference in effect on decayed or filled surfaces at 5 years (mean difference -0.05, 95% CI -0.42 to 0.32; 798 children; 1 trial; certainty of evidence not reported).<br><br>**Secondary outcome 1: Fluorosis**<br>There was no difference in effect for fluorosis (maxillary teeth) at 5 years (63 per 1,000 compared to 35 per 1,000 (placebo), 95% CI 33 to 119, risk ratio 1.79, 95% CI 0.95 to 3.40; 798 children; 1 trial; very low certainty of evidence).<br><br>There was no difference in effect for fluorosis (mandibular teeth) at 5 years (risk ratio 0.89, 95% CI 0.35 to 2.29; 798 children; 1 trial; certainty of evidence not reported).<br><br>**Secondary outcome 2: Other adverse events**<br>Adverse events other than fluorosis were not assessed in the only included trial.<br><br>*Note*. Both the intervention and control groups received fluoride drops from birth to 2 years of age and one 0.5 mg tablet daily for children aged 2 to 3 years. |
| **Significance/direction** | There is no evidence that fluoride supplements taken by women during pregnancy are effective in preventing dental caries in their offspring. |
| **Heterogeneity** | Heterogeneity could not be assessed because the review included only one trial. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as very low for both primary outcomes 1 and 2. The evidence for primary outcome 1 (the number of children with caries) was downgraded three times for imprecision and risk of bias. The evidence for primary outcome 2 (dmfs) was downgraded three times for high risk of bias and imprecision. |

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| | The HRB authors graded the certainty of evidence in this review as very low (downgraded from moderate due to the review being a single trial review). |
| **References to previously published versions** | N/A |
| Parameter | Marinho *et al.* (2013) extraction |
| **First Author and year of publication** | Marinho *et al.* (2013) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effectiveness and safety of fluoride varnishes in preventing dental caries in the child/adolescent population (p6). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate) (tooth surfaces); topical fluoride, varnishes.<br><br>Baseline caries in permanent dentition was reported in 11 out of 22 included trials (D(M)FS ranged from 0 to 29.2), and baseline caries in primary dentition was reported in eight out of 22 trials (dmfs ranged from 0 (ds) to 12.4).<br><br>The included trials randomised 12,455 children and adolescents, and 9,595 were evaluated in analyses. Age at baseline ranged from 1 to 15 years old, with similar numbers from both sexes (where these data were reported). Fourteen trials included participants who were over six years of age at baseline, and eight trials included children aged between one and five years. |
| **Setting/context** | The trials were conducted in Brazil (3 trials), Canada (2 trials), China (3 trials), Germany (2 trials), India (2 trials), Spain (1 trial), Sweden (6 trials), the UK (2 trials), and the USA (1 trial).<br><br>Eleven trials were conducted in schools or nurseries, and eight were conducted in clinics. The setting was unclear in the remaining three trials. |
| **Description of Interventions/ phenomena of interest** | The review authors included trials where the intervention of interest was topical fluoride in the form of varnishes only, using any fluoride agent, at any concentration (ppm F), amount or duration of application, and with any technique of application, prior or post- application.<br><br>The fluoride concentration in 18 trials was 22,600 ppm F; the other trials ranged from 7000 ppm F (Difluorsilane) to 56,300 ppm F (6% NaF + 6% calcium fluoride (CaF)). Two trials had arms with fluoride varnish applied with less than 5% fluoride. |

Frequency of application was required to be at least once a year. The application frequency of twice a year was tested in 17 trials and that of four times a year in only three trials. One trial applied the varnish three times in one week with no other applications. The amount of varnish applied was usually of around 0.5 ml per child (reported in five trials).

The control group was placebo or no treatment resulting in the following comparison: Fluoride varnish compared with a placebo or no treatment.

Studies reporting no dental caries data, reporting only on plaque/gingivitis, calculus, dentine hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentine, salivary secretion levels, etc.) were excluded. Trials where the intervention consisted of any other caries preventive agent or procedure (e.g. other fluoride-based measures, chlorhexidine, sealants, oral hygiene interventions, xylitol chewing gums) used in addition to fluoride varnish were excluded.

Regarding 'background exposure to other fluoride sources', only three trials were conducted in water fluoridated communities (Holm 1984; Sköld 2005; Weintraub 2006) and only one (Borutta 1991) clearly reported no exposure to fluoride toothpastes; 13 trials reported some other exposure to fluoride (rinses, tablets), with one study mentioning fluoridated milk (Hardman 2007). Seven studies reported that both groups received oral hygiene advice or instruction (Arruda 2012; Chu 2002; Gugwad 2011; Lawrence 2008; Liu 2012; Tagliaferro 2011; Weintraub 2006).

The performance of some form of tooth prophylaxis prior to administering the varnish was reported in seven trials, with four trials with no paste and three with a non-fluoride paste.
Thirteen trials (59%) were assessed at low risk of bias in relation to intervention contamination/co-intervention (Arruda 2012, Chu 2002, Gugwad 2011, Hardman 2007, Holm 1984, Koch 1975, Lawrence 2008, Liu 2012, Milsom 2011, Modeer 1984, Tagliaferro 2011, Tewari 1990, Weintraub 2006). In Sköld 2005, 95% of the study participants, including those in the no treatment control group, had at least one fluoride varnish treatment, so this trial was assessed at high risk of bias due to co-intervention. In the remaining seven included trials there were some differences between the groups regarding co-interventions or contamination but the risk of bias from these was assessed as unclear.

**Databases and sources searched**

The review authors searched the following sources:

- Cochrane Oral Health's Trials Register (to 13 May 2013)
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 4)
- MEDLINE via OVID (1946 to 13 May 2013)

- EMBASE via OVID (1980 to 13 May 2013)
- CINAHL via EBSCO (1980 to 13 May 2013)
- LILACs via BIREME Virtual Health Library (1980 to 13 May 2013)
- BBO via BIREME Virtual Health Library (1980 to 13 May 2013)
- ProQuest Dissertations and Theses (1861 to 13 May 2013), and
- Web of Science Conference Proceedings (1945 to 13 May 2013).

All eligible trial reports, previous meta-analyses, and review articles were scanned for relevant references. For the original review, reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions had also been consulted. No restrictions were placed on language or date of duplication in the search of the electronic databases.

A search of the National Institutes of Health registry and results service (ClinicalTrials.gov) for ongoing trials was undertaken on 13 May 2013. All eligible trial reports, previous meta-analyses and review articles were scanned for relevant references.

For the original review, handsearching was carried out on journals identified as having the highest yield of eligible randomised control trials / controlled clinical trials:

- Community Dentistry and Oral Epidemiology (1990 to 1999)
- British Dental Journal (1999 to 2000)
- Caries Research (1999 to 2000)
- Community Dentistry and Oral Epidemiology (1999 to 2000)
- Journal of the American Dental Association (1999 to 2000)
- Journal of Dental Research (1999 to 2000)
- Journal of Public Health Dentistry (1999 to 2000), and
- European Journal of Oral Sciences (1999 to 2000).

For the update of this review, only handsearching done as part of the Cochrane Worldwide Handsearching Programme was carried out.

For the original review, the review authors contacted experts in the field of preventive dentistry to identify any unpublished trials or trials which may not be indexed by the major databases. A letter was sent to the study author(s) to obtain information on possible unpublished trials eligible for inclusion, clarify reported information, or to obtain missing data. They also contacted three fluoride varnish manufacturers in October 2000 and December 2012 to request data from potentially eligible unpublished trials.

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| | The review protocol was first published in 2000 (no registration number provided). The review authors describe some changes between the protocol and the published review.<br><br>The screening for eligibility was done in duplicate by at least two review authors for all potential studies identified from all searches performed. Trials thought to be potentially relevant in other languages were translated. At least two review authors extracted data from all included studies in duplicate (disagreement resolution in screening and/or extraction was not reported).<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>No conflicts of interest were reported. Tanya Walsh and Helen Worthington were authors of the report of the Milsom 2011 trial, which was included in the review, but they were not involved in the risk of bias assessment for this study. |
| **Date range (years) of included studies** | The included trials were published between 1975 and 2012. |
| **Number of primary studies included in the systematic review** | The review authors included 22 randomised and quasi-randomised controlled trials (13 of which are new trials since the original review). All the included trials used parallel group designs (the split-mouth trials were excluded), five being cluster randomised trials. Six trials had more than one fluoride varnish treatment group compared to a placebo or no treatment. Regarding type of control group used, 14 trials used a no treatment control group, and the remaining eight used a placebo control group, however; five of these used an inactive treatment other than varnish ('placebo' solution/distilled water).<br><br>The study duration ranged from one to five years among the included trials (12 of these lasted two years). Studies were of moderate size with seven trials allocating less than 100 children to relevant study groups. The total number of children participating in the 22 included trials (given by the sample analysed at the end of the trial period) was 9,595, ranging from 95 in the smallest trial to 2,604 in the largest trial (which was a cluster trial).<br><br>The unit of randomisation was either the individual child or cluster.<br><br>Only one study acknowledged partial financial support from a fluoride varnish manufacturer and acknowledged support from a sugar company. |
| **Types of studies included** | The review authors included 22 randomised and quasi-randomised controlled trials: Arruda (2012), Borutta (1991), Borutta (2006), Bravo |

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| | (1997), Chu (2002), Clark (1985), Frostell (1991), Gugwad (2011), Hardman (2007), Holm (1979), Holm (1984), Koch (1975), Lawrence (2008), Liu (2012), Milsom (2011), Modeer (1984), Salazar (2008), Sköld (2005), Tagliaferro (2011), Tewari (1990), Weintraub (2006), Yang (2008).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Brazil (3), Canada (2), China (3), Germany (2), India (2), Spain (1), Sweden (6), UK (2), and the USA (1). |
| **Appraisal instrument(s)** | At least two review authors undertook the assessment of the risk of bias in all of the included trials independently using using the Cochrane Collaboration's tool for assessing risk of bias as outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1 (Higgins 2011), but according to pre-defined criteria which were adapted and refined for the Cochrane topical fluoride reviews updates. Disagreements were resolved by discussion or the involvement of another review author.<br><br>The following eight domains were assessed in each trial:<br>1. Sequence generation<br>2. Allocation concealment<br>3. Blinding of participants<br>4. Blinding of outcome assessment<br>5. Incomplete outcome data<br>6. Selective outcome reporting<br>7. Baseline balance, and<br>8. Free from contamination or co-intervention.<br><br>For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias.<br><br>The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as (Higgins 2011):<br>• Low risk of bias (plausible bias unlikely to seriously alter the results: all eight domains assessed as at low risk of bias)<br>• Moderate risk of bias (plausible bias that raises some doubt about the results: at least one domain assessed as at unclear risk of bias, but none at high risk of bias), or<br>• High risk of bias (plausible bias that seriously weakens confidence in the results: at least one domain assessed as at high risk of bias). |

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| **Appraisal rating** | Overall, none of the trials included in this review were assessed at low risk of bias for all domains. Fifteen trials (68%) were at high risk of bias in at least one domain and the remaining seven trials were at moderate risk of bias due to the lack of clear information for at least one domain.<br><br>Eight of the 22 trials were at low risk of bias for randomisation, six were categorised as at a high risk of bias for randomisation and eight were at an unclear risk of bias for randomisation.<br><br>Twenty trials were low risk of bias for outcome ascertainment; in two trials blind outcome assessment was not reported so these trials were therefore assessed at moderate risk of detection bias.<br><br>Overall, the review authors assessed the quality of the evidence as moderate, as it included mainly high risk of bias studies (68%), with the remaining assessed as unclear risk of bias. They also noted that the influence of bias on the results of the review could not be determined. Overall, the quality of the reporting in many of the included trials was poor.<br><br>An investigation of the degree of asymmetry of the funnel plots (as an indicator of publication bias and other biases related to sample size) was planned. However, funnel plots were only generated and analysed for outcomes other than the outcome relevant to this umbrella review. |
| **Method of analysis** | Primary and permanent teeth were analysed separately.<br><br>Prevented fraction was the measure of treatment effect presented for caries increment. For outcomes other than caries increment, dichotomous data were analysed by calculating risk ratios.<br><br>The meta-analyses were conducted as inverse variance weighted averages. Prevented fraction variances were estimated using the formula presented in Dubey 1965. Random-effects meta-analyses were performed throughout. The prevented fraction data were entered using the GIV option. Meta-analysis using a random-effects model was conducted to calculate a pooled estimate of effect. Dichotomous outcome data were analysed by calculating risk ratios and randomised data were analysed by calculated risk ratios.<br><br>In the trials with more than one relevant intervention group and a common control group, summary statistics from all relevant intervention groups in each trial were combined in order to obtain a measure of treatment effect.<br><br>The review authors specified three potential sources of heterogeneity a priori, hypothesising that:<br>1. The effect of fluoride varnishes differs according to the baseline levels of caries severity |

2. The effect of fluoride varnishes differs according to exposure to other fluoride sources (in water, in toothpastes, etc.), and
3. The effect of fluoride varnishes differs according to characteristics of use (fluoride concentration or application features, such as frequency of use and prophylaxis).

If sufficient number of trials were included, the review authors planned to examine the association of these factors with estimated effects by performing random-effects meta-regression analyses in Stata version 12.0. Further potential sources of heterogeneity were investigated post hoc by meta-regression.

The review authors intended to undertake a sensitivity analysis including the trials with an overall assessment of low risk of bias, however there were no trials satisfying this criterion. They did undertake a sensitivity analysis excluding trials where they imputed missing data such as standard deviations and the design effect in cluster randomised trials.

Regarding unit of analysis, not all the cluster randomised trials reported results adjusted for the clustering present in the data. In such cases, the review authors estimated the design effect with the intra-class correlation coefficient (ICC) if reported or a value of 0.05.

A summary of findings table for the main outcomes was provided.

**Outcome(s) assessed**

Primary outcome 1: caries increment, as measured by change from baseline in the number of decayed (missing) and filled permanent tooth surfaces (D(M)FS) and whole teeth (D(M)FT)

Primary outcome 2: caries increment, as measured by change from baseline in the number of decayed (extracted/missing) and filled primary tooth surfaces (d(m)fs) and whole teeth (d(m)ft)

Primary outcome 3: the proportion of children developing one or more new caries over the follow-up periods – five trials in permanent dentition five trials in primary dentition

Secondary outcome 1: adverse events (e.g. tooth loss, dental pain, oral allergic reactions, mucosal irritation, and other adverse symptoms such as nausea, gagging, vomiting).

Secondary outcome 2: use of health service resources (e.g. visits to dental care units, length of dental treatment time).

*Note*. Primary outcomes 1 and 2 are identified as primary outcomes in the review. Primary outcome 3 appears to be identified as a secondary outcome

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| | in the review, but for the HRB's purposes is considered a primary outcome. Secondary outcomes 1 and 2 are identified as secondary outcomes in the review. |
| **Results/findings** | **Primary outcome 1: Caries increment in permanent tooth surfaces and whole teeth**<br>The D(M)FS prevented fraction pooled estimate was 0.43 (95% CI 0.30 to 0.57; P < 0.0001; $I^2$ = 75%; 6,478 participants; 13 trials; nearest to 3 years follow-up; moderate quality of evidence), suggesting a substantial caries-preventive benefit from the use of fluoride varnish. Univariate meta-regression suggested no significant association between effect estimates the pre-specified factors, nor factors tested post hoc (time since treated teeth had erupted (<= 2 years), whether a placebo or no treatment control was used, and whether individual randomisation or cluster randomised design was used). Sensitivity analysis of the influence of data imputation indicated greater effect estimates when restricting the pooling of trials to the eight trials in which data were fully imported and suitable for analysis (not imputed) (PF = 0.55; 95% CI 0.42 to 0.68; $I^2$ = 62% instead of 75%).<br><br>*Note*. Five out of 13 pooled trials reported some form of non-fluoride tooth prophylaxis prior to administering the varnish, and all 13 trials reported some existing exposure to fluoride (water, mouthrinses, toothpaste, milk or unspecified). However, this was considered background exposure, rather than part of the intervention of interest. Five out of 13 pooled trials delivered combined interventions involving supervised mouthrinsing (2 trials) or oral health education/instruction (3 trials), and one trial delivered a complex intervention involving supervised toothbrushing + oral health instruction + dietary advice.<br><br>The pooled estimate of D(M)FT prevented fraction was 0.44 (95% CI 0.11 to 0.76; P = 0.009; $I^2$ = 86%; 3,902 participants; 5 trials; nearest to three years follow-up), suggesting a considerable benefit of fluoride varnish.<br><br>*Note*. Two out of five pooled trials reported some form of non-fluoride tooth prophylaxis prior to administering the varnish, and all five trials reported some existing exposure to fluoride (water, mouthrinses, toothpaste or unspecified). However, this was considered background exposure, rather than part of the intervention of interest. One out of five pooled trials delivered combined interventions involving oral health instruction, and one trial delivered a complex intervention involving supervised toothbrushing + oral health instruction + dietary advice.<br><br>**Primary outcome 2: Caries increment in primary tooth surfaces and whole teeth**<br>The pooled estimate of d(e/m)fs prevented fraction was 0.37 (95% CI 0.24 to 0.51; P < 0.0001; $I^2$ = 59%; 3,804 participants; 10 trials; moderate quality of |

evidence) at nearest to 3 years follow-up, suggesting a substantial benefit of fluoride varnish in the primary dentition. Univariate meta-regression suggested no significant association between effect estimates the pre-specified factors, nor factors tested post hoc. However, the effects of background exposure to fluoride toothpaste and background exposure to any reported fluoride source were inestimable due to collinearity in the data set. Sensitivity analysis of the influence of data imputation indicated slightly different effect estimates when restricting the pooling of trials to the eight trials in which data were fully imported and suitable for analysis (not imputed) (PF = 0.45; 95% CI 0.29 to 0.62; $I^2$ = 52% instead of 59%).

*Note*. Four out of 10 pooled trials involved combined interventions involving oral health education/counselling/instruction. In eight out of 10 trials, participants had exposure to other forms of fluoride (water, toothpaste, milk, tablets, mouthrinse, or unspecified source). However, this was considered background exposure, rather than part of the intervention of interest. In two out of 10 trials, participants received some form of prophylaxis prior to the intervention.

The pooled estimate of d(e/m)ft prevented fraction was 0.65 (95% CI 0.48 to 0.82; P < 0.0001; $I^2$ = 0%; 322 participants; 2 trials; nearest to three years follow-up), suggesting a considerable benefit of fluoride varnish in the primary dentition.

*Note*. One out of the two pooled trials delivered a combined intervention involving oral health instruction. In one out of the two trials, participants had exposure to other forms of fluoride (unspecified source). However, this was considered background exposure, rather than part of the intervention of interest. In one out of two trials, participants received some form of prophylaxis prior to the intervention.

**Primary outcome 3: Proportion developing one or more new caries**
There was no evidence of effectiveness of fluoride varnish in permanent dentition (risk ratio 0.75, 95% CI 0.53 to 1.05, P = 0.10; 3,253 participants; 5 trials), or primary dentition (risk ratio 0.81, 95% CI 0.62 to 1.06, P = 0.13; 1,228 participants; 5 trials).

*Note*. One out of five pooled trials in permanent dentition delivered a combined intervention involving oral health education, and in all five trials, participants had exposure to other forms of fluoride (water, toothpaste, milk and/or mouthrinse). However, this was considered background exposure, rather than part of the intervention of interest. In addition, one out of the five pooled trials reported some form of non-fluoride tooth prophylaxis prior to administering the varnish.

*Note*. Two out of five pooled trials in primary dentition delivered combined interventions involving oral health counselling and in three out of five trials,

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| | participants had exposure to other forms of fluoride (water, toothpaste, milk and/or tablets). However, this was considered background exposure, rather than part of the intervention of interest.<br><br>There was substantial heterogeneity in both pooled analyses ($Chi^2$ = 37.18 on 4 degrees of freedom, P < 0.0001, $I^2$ = 89% and $Chi^2$ = 21.68 on 4 degrees of freedom, P = 0.0002, $I^2$ = 82%). However there was a statistically significant difference between the study design subgroups for both analyses, with the individual child randomisation subgroup showing a benefit over the cluster randomisation subgroup.<br><br>**Secondary outcome 1: Adverse events**<br>No trials included in the review reported on this outcome.<br><br>**Secondary outcome 2: Use of health service resources**<br>No trials included in the review reported on this outcome. |
| **Significance/direction** | The use of fluoride varnish is associated on average with a 43% reduction in decayed, missing and filled tooth surfaces in the permanent dentition, and with a 37% reduction in decayed, missing and filled tooth surfaces in the primary dentition. The sensitivity analysis showed results with larger effect estimate than the full meta-analysis, with a similar level of heterogeneity. The review concluded that the application of fluoride varnishes two to four times a year, either in the permanent or primary dentition, is associated with a substantial reduction in caries increment.<br><br>There was no evidence for the effectiveness of fluoride varnish in reducing the proportion of participants with one or more new caries in primary or permanent dentition.<br><br>Overall, the quality of the evidence was assessed as moderate, as it included mainly high risk of bias studies, with considerable heterogeneity. |
| **Heterogeneity** | The review authors reported substantial heterogeneity in the body of evidence which addresses the research questions of their review. They were unable to find a conclusive explanation for this but noted that there was substantial variability between the trials in the review regarding the factors which may influence the effect estimate in each study. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence for both DMFS and dmfs increment as moderate, downgraded once for considerable heterogeneity.<br><br>The HRB authors graded the certainty of evidence in this review as very low, downgraded due to inadequate randomisation, study design, and considerable heterogeneity. The discrepancy is likely because the review |

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| | authors upgraded the evidence to moderate as the body of evidence showed a consistent, large clinically important effect. |
| **References to previously published versions** | Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride varnishes for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No: CD002279. [DOI: 10.1002/14651858.CD002279]. |
| Parameter | Riggs *et al.* (2019) extraction |
| **First Author and year of publication** | Riggs *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To assess the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age) (p13). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); topical other chemicals, xylitol, CHX (taken by pregnant women, new mothers, or other primary caregivers); combined intervention.<br><br>Baseline caries in new mothers or other primary caregivers was not reported in included trials.<br><br>The review included 17 randomised controlled trials involving a total of 23,732 caregivers and their foetuses or infants. Caregivers were mostly pregnant women or new mothers; however, one trial involved mothers and fathers of infants younger than 1 year at baseline, and in another trial, some of the primary caregivers were grandmothers due to the absence of mothers and fathers. A breakdown of sex among primary caregivers was not provided. It was not possible to provide an accurate number for the total number of foetuses/infants randomised in the included trials.<br><br>In nine of the 17 included trials, data reported on socioeconomic status suggested to the review authors that participants were socioeconomically disadvantaged. In one trial, participants were of mixed socioeconomic status, and in the remaining seven trials the review authors were unable to determine socioeconomic status of the participants.<br><br>Thirteen out of 17 trials reported maternal age in years; the mean maternal age at recruitment or at baseline was 26.9 years, ranging from 17 to 44 years old (one reported maternal age range as a proportion and three did not report maternal age). Regarding infants, seven trials commenced with infants in utero and three trials reported infants as newborns (not further defined). One trial included infants between one and five days old, and another included 10-week-old infants. The remaining five trials commenced when infants were between 3 and 13 months old. |

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| | Half of the trials did not report the ethnic or racial background of participants. Of those that did:<br>• Three trials reported the proportion of black/white participants. In the first trial, 60.8% (50.7%) of the intervention (control) group were white and 39.2% (49.3%) were black, mixed, or other. In the second trial, 48% (32%) of the intervention (control) group were white and 52% (68%) were black. In the third trial, 84% (97%) of the intervention (control) group were black, 11% (3%) were white, and 5% were other.<br>• Two trials reported the Indigenous background of participants; all participants were First Nations people in one trial, and all participants were American Indians or Alaskan Natives in the other.<br>• Two trials reported specific ethnicity/language of participants. In the first trial, 100% of participants were Portuguese-speaking Brazilians. In the second trial, 49 mothers were Spanish speaking (10 also spoke English), and 45 mothers were English-speaking but also spoke their native languages, including Chinese (N = 1), Bengali (N = 5), Russian (N = 2), and Turkish (N = 1).<br>• One trial reported the proportion of white participants. In both the intervention and control group, 50% of participants were white.<br><br>The total number of participants in the six (out of 17) included trials that inform this umbrella review was 907 caregivers and their foetuses or infants. |
| **Setting/context** | The trials were conducted in Australia (1 trial), Brazil (3 trials), Belarus (1 trial), Canada (2 trials), Finland (2 trials), Sweden (1 trial), Uganda (2 trials), the UK (1 trial), and the USA (3 trials). Country location was not reported in one trial.<br><br>Thirteen trials were conducted in hospitals, health units, or clinics. The remaining four trials were conducted in local districts/communities. |
| **Description of Interventions/ phenomena of interest** | The review evaluated a variety of different intervention types; however, only the clinical treatment interventions are relevant to this umbrella review. Colonisation of the oral cavity by cariogenic bacteria can occur even before teeth erupt in infants of mothers/other primary caregivers who themselves have poor oral health, and periodontal disease, and high counts of cariogenic bacteria. Suppression of cariogenic oral flora in pregnant women and/or new mothers may inhibit colonisation in offspring and prevent/delay caries development.<br><br>The clinical interventions evaluated in the included studies were antimicrobial treatments and Xylitol. Antimicrobial treatments included (i) CHX (chlorhexidine, a commonly prescribed antiseptic agents) and (ii) iodine-NaF solution and prophylaxis (teeth cleaning). The review authors compared: |

1. Prophylaxis (teeth cleaning) and CHX or iodine-NaF solution applied to caregiver's dentition compared with a placebo varnish or placebo treatment, and
2. Consumption of xylitol gum compared with consumption of CHX/xylitol gum or CHX varnish applied to caregiver's dentition.

The review authors included interventions as standalone or combined. Interventions that involved clinical treatment (including application of fluoride) to the infants themselves were excluded.

Follow-up periods ranged from six months to six years.

**Databases and sources searched**

The review authors searched the following sources:

- Cochrane Oral Health's Trials Register (searched 14 January 2019)
- Cochrane Pregnancy and Childbirth Group Trials Register (to 22 January 2019)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 12) in the Cochrane Library (searched 14 January 2019)
- MEDLINE Ovid (1946 to 14 January 2019)
- Embase Ovid (1980 to 14 January 2019)
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 14 January 2019)
- The US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov (clinicaltrials.gov; searched 14 January 2019).
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 14 January 2019).

The review authors searched all references cited in the included papers for additional relevant studies. They also sought unpublished trials by contacting experts in the field. Only studies reported in English were included. There were no language, publication year, or publication status restrictions.

The protocol was first published in 2016; no registration number provided. Differences between the protocol and published review were noted.

Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion with a third review author.

The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.

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| | All authors declared no conflicts of interest. |
| **Date range (years) of included studies** | The 17 included trials were published between 1993 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included 17 randomised controlled trials (RCTs). Five of these trials were cluster-randomised – three randomising community units and two randomising health service units. In addition, three of the included trials were multi-arm trials.<br><br>The unit of randomisation was either the individual or the cluster.<br><br>Fifteen trials were funded by non-commercial organisations (e.g. government funding bodies, health services, or other not-for-profit foundations). In the remaining two trials, commercial organisations provided some or all funding. |
| **Types of studies included** | The review authors included 17 randomised controlled trials: Birungi (2015), Chaffee (2013), Dasanayake (1993), Dasanayake (2002), Feldens (2007), Hallas (2015), Harrison (2012), Kramer (2001), Lapinleimu (1995), Muhoozi (2017), Plutzer (2008), Robertson (2013), Soderling (2000), Thorild (2003), Veronneau (2010), Watt (2009), Zanata (2003).<br><br>The results of six randomised control trials informed the outcomes of interest to this umbrella review: Dasanyake (1993), Dasanayake (2002), Robertson (2013), Soderling (2000), Thorild (2003), Zanata (2003).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Brazil (3 trials), Belarus (1 trial), Canada (2 trials), Finland (2 trials), Sweden (1 trial), Uganda (2 trials) the UK (1 in trial), and the USA (3 trials). |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of each included study using the Cochrane domain-based, two-part tool as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Disagreements were resolved through discussion, consulting a third review author to achieve consensus when required, and<br>consulting study authors to check missing information, where feasible.<br><br>The following seven domains were assessed in each trial:<br>1. Sequence generation<br>2. Allocation concealment<br>3. Blinding of participants and personnel |

4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias(e.g. baseline imbalance).

For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias.

**Appraisal rating**

The authors did not provide an overall assessment of risk of bias for each trial. However, graphical information provided in the paper indicates that, overall, none of the included trials can be categorised as being at low risk of bias, two trials can be categorised as being at unclear risk of bias, and 15 trials can be categorised as being at high risk of bias. Of the six trials relevant to this umbrella review, two were at high risk of bias and four were at unclear risk of bias.

Eight out of 17 trials had two or more high risk of bias scores. Of the six trials relevant to this umbrella review, two had two or more high risk of bias scores. Overall, most of the included trials were at a high or unclear risk of attrition bias. Of the six trials relevant to this umbrella review, five were at unclear risk of attrition bias and 1 was at low risk of attrition bias.

Eight of the 17 included trials were categorised as being at low risk of bias for randomisation. All six trials relevant to this umbrella review were at unclear risk of bias for randomisation.

Nine of the 17 included trials were categorised as being at low risk of bias for outcome ascertainment. Of the six trials relevant to this umbrella review, two were at high risk of bias for outcome ascertainment, two were at low risk of bias for outcome ascertainment, and two were at unclear risk of bias for outcome ascertainment.

The quality of the body of evidence for each outcome
was assessed under five domains (study limitations, consistency of effect, imprecision, indirectness and publication bias) and judged to be of high, moderate, low or very low quality.

The review authors reported a general lack of methodological details provided, across the included trials, leading to many ‘unclear’ judgements. In addition, blinding of participants and personnel was not possible in most of the trials given the nature of the intervention assessed, which could lead to high performance bias. However, according to the review authors, the likelihood that this introduced bias for objective outcomes such as caries was not high. In addition, the review authors graded the certainty of evidence for both clinical intervention comparisons as very low. As a result,

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| | evidence was predominantly downgraded due to design limitations (risk of bias) and imprecision (uncertain effect estimates, and at times small sample sizes and low event rates).<br><br>Fifteen out of 17 trials were included in one of several meta-analyses conducted by the review authors. Of these, seven were judged to be at a high risk of bias in only one risk of bias domain. These seven trials could therefore be included in sensitivity analyses, which mostly supported findings of the main analyses.<br><br>The review authors had planned to generate funnel plots and assess publication bias according to the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). However, no meta-analysis conducted by the review authors included more than 10 studies. |
| **Method of analysis** | For dichotomous outcomes, the review authors calculated risk ratios for the proportional difference between the intervention and comparison groups, along with 95% CIs. For continuous outcomes, the authors extracted and used the mean values and standard deviations reported in the studies in order to express the estimate of effect as a mean difference with 95% confidence interval.<br><br>The unit of analysis for the primary outcome in the review was the child. For secondary outcomes, the unit of analysis was the child or mother.<br><br>For cluster-randomised trials, the review authors adjusted the samples sizes and event rates of included trials using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. For included multi-arm trials, the review authors used methods described in the Cochrane Handbook for Systematic Reviews of Interventions to overcome possible unit-of analysis errors (Higgins 2011).<br><br>Meta-analyses were performed in Review Manager 5, combining outcome data only from studies evaluating similar included interventions (as standalone or combined interventions) against placebo or standard care. Mean differences were combined (using standardised mean differences where studies used different scales) for continuous outcomes, and relatively risks were combined for dichotomous outcomes, using a fixed-effect model (as there were only two or three studies in each analysis).<br><br>The review authors planned to examine heterogeneity as a function of: |

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| | 1. Difference in intervention features and characteristics of participants through subgroup analysis (including intervention start (prenatal versus postnatal)<br>2. Intervention duration, ≤ 6 months versus > 6 months<br>3. Child age at caries assessment; ≤ 3 years versus > 3 years<br>4. Socioeconomic status, low versus mixed or any.<br><br>However, the influence of potential effect moderators could not be examined given the small number of trials included in the meta-analyses. Where relevant, the review authors undertook sensitivity analyses to assess the robustness of the results by excluding studies categorised as being at high risk of bias in two or more domains.<br><br>A summary of findings table for the main outcomes was provided. |
| **Outcome(s) assessed** | Primary outcome 1: caries presence [incidence] in primary teeth in children up to six years of age (yes/no; including non-cavitated (white spot lesion) and/or cavitated lesions)<br><br>Primary outcome 2: d(m/e)ft index (decayed (missing/extracted) and filled deciduous teeth)<br><br>Primary outcome 3: D(M)FT index, permanent teeth (mother)<br><br>Primary outcome 4: d(m/e)fs index (decayed (missing/extracted) and filled surfaces, deciduous teeth)<br><br>Primary outcome 5: D(M)FS index, permanent teeth (mother)<br><br>Secondary outcome 1: microbiological presence (e.g. streptococcus mutans count) (infant/child)<br><br>Secondary outcome 2: microbiological presence (e.g. streptococcus mutans count) (mother)<br><br>Secondary outcome 3: plaque (infant/child)<br><br>Secondary outcome 4: plaque (mother)<br><br>Secondary outcome 5: adverse events (for the infant/child and the mother)<br><br>*Note*. Primary outcomes 1, 2 and 4 are identified as primary outcomes in the review. Primary outcomes 3 and 5 are identified as secondary outcomes in the review, but for the HRB's purposes are considered primary outcomes. All secondary outcomes 1 are identified as secondary outcomes in the review. |

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| **Results/findings** | **Primary outcome 1: Caries presence in primary teeth in children up to six years of age**<br><u>Comparison 1: Antimicrobial treatment (CHX or iodine-NaF and prophylaxis) in caregiver dentition versus placebo:</u><br>Caries presence in primary teeth following application of antimicrobial treatment (prophylaxis and CHX or iodine-NaF solution) in dentition of women compared to a placebo treatment was not different in the primary teeth of children 0-6 years (436 per 1000 compared with 423 per 10000, 95% CI 349 to 519, relative risk 0.97, 95% CI 0.80 to 1.19; 497 children; 3 trials; very low certainty of evidence). Moderate statistical heterogeneity was observed ($Chi^2 = 4.14$, P = 0.13, $I^2 = 52\%$).<br><br>*Note*. This finding will not be included in the HRB evidence synthesis because the nature of the intervention is unclear given the fact that the data were pooled.<br><br><u>Comparison 2: Xylitol gum versus CHX + xylitol gum or CHX varnish:</u><br>In one trial, involving maternal consumption of xylitol chewing gum (three months after the birth of the baby, continuing until the child was three years of age, average daily dose of xylitol 6-7g, average consumption frequency four times per day) versus CHX varnish applied to the dentition of mothers at 6, 12 and 18 months after the birth of the child, the differences in risk (at the age of 2 years) between the chlorhexidine and the xylitol groups (RR = 1.39; 95% CI, 0.69-2.79; 159 women and their offspring) were not statistically significant. The dmft index was used in this study to assess caries in the dentition of children, with only lesions extending to the dentin, and fillings, included in the diagnosis of caries presence.<br><br>In another trial, the risk of caries presence in primary teeth following consumption of xylitol chewing gum (650 mg xylitol) compared with consumption of CHX + xylitol gum (containing 532.5 mg xylitol, 5.0 mg chlorhexidine, and 141.9 mg sodium fluoride, chewed 1 piece for 5 minutes 3 times per day commencing 6 months postpartum until 18 months postpartum) was not different in the primary teeth of offspring 0-6 years (250 per 1000 compared with 155 per 1000, 95% CI 68 to 348, relative risk 0.62, 95% CI 0.27 to 1.39; 96 children; 1 trial; very low certainty of evidence), at follow-up when the children were aged 4 years. In this trial, defs score and defs categories (1-3; 3-4; ≥ 5) were used to assess caries in the dentition of children.<br><br>**Primary outcome 2: d(m/e)ft index**<br><u>Comparison 1: Antimicrobial treatment (CHX or iodine-NaF and prophylaxis) in caregiver dentition versus placebo:</u><br>No trials included in the review reported on d(m/e)ft increment as an outcome for this comparison.<br><br><u>Comparison 2: Xylitol gum versus CHX or CHX + xylitol gum:</u> |

Mean dmft index score in primary teeth following maternal consumption of xylitol chewing gum (two of three times per day continuing until the child was three years of age) compared to CHX varnish (applied to the dentition of mothers at 6, 12 and 18 months after the birth of the child) was lower in children at 5 years (mean difference -2.39, 95% CI -4.10 to -0.68; 113 children; 1 trial; low certainty of evidence).

**Primary outcome 3: D(M)FT index, permanent teeth (mother)**

Comparison 1: Antimicrobial treatment (CHX) in caregiver dentition versus placebo:

One trial assessing the effect of 10% CHX varnish applied to the dentition of mothers (four treatments, one per week over four weeks, started when babies were about six months, i.e. around the time of first tooth emergence) compared to placebo varnish, reported DMFT increment (change in DMFT score) and showed no evidence of a difference between the groups (MD -0.30, 95% CI -1.86 to 1.26; 66 participants; 1 trial).

*Note*. In this trial, participants received prophylaxis prior to application of the varnish, presumably as a preparation measure for the varnish.

Comparison 2: Xylitol gum versus CHX or CHX + xylitol gum:

No trials included in the review reported on DMFT increment as an outcome for this comparison.

**Primary outcome 4: d(m/e)fs index**

Comparison 1: Antimicrobial treatment (CHX or iodine-NaF and prophylaxis) in caregiver dentition versus placebo:

No trials included in the review reported on d(m/e)fs increment for this comparison.

Comparison 2: Xylitol gum versus CHX or CHX + xylitol gum:

One trial reported on defs index and showed no evidence of a difference between the xylitol gum group (maternal consumption of 1 piece of gum for 5 minutes, 3 times per day beginning at 6 months postpartum up until 18 months postpartum) and CHX/xylitol gum group (mean difference -0.28, 95% -0.83 to 0.27; 96 participants; 1 trial; very low certainty of evidence) in the primary dentition of offspring. The same trial also analysed defs score categories and similarly observed no evidence of a difference.

**Primary outcome 5: D(M)FS index**

Comparison 1: Antimicrobial treatment (CHX or iodine-NaF and prophylaxis) in caregiver dentition versus placebo:

Two trials reported this outcome and observed no evidence of a difference between the antimicrobial treatment group and placebo or no antimicrobial treatment groups (MD -0.21, 95% CI -2.22 to 1.79; 130 participants; 2 trials). Both trials assessed the effectiveness of iodine-NaF solution plus prophylaxis

(6 applications in one trial and three applications in another trial) compared to a placebo.

*Note*. One of these trials involved the delivery of a complex interventions in which participants received oral health education at baseline at a follow-up (at 6 months and at 12 months).

Comparison 2: Xylitol gum versus CHX or CHX + xylitol gum:
No trials included in the review reported on DMFS increment for this comparison.

**Secondary outcome 1: Microbiological presence (infant/child)**
Comparison 1: Antimicrobial treatment (CHX or iodine-NaF and prophylaxis) in caregiver dentition versus placebo:
Two trials reported on this outcome; however, the review authors could not pool the data. One trial reported that although the crude overall incidence of mutans streptococci acquisition in children of the treated mothers was 36% greater than that of the control children, the difference was not statistically significant. A second trial found no significant differences in the percentage of children with detectable levels of Streptococcus mutans in plaque during the study period or in the mean times to oral colonization.

Comparison 2: Xylitol gum versus CHX or CHX + xylitol gum:
Analyses of two trials indicated a lower risk of mutans streptococci colonisation in the children of mothers who were in the xylitol intervention compared with CHX or CHX combined with xylitol intervention group (risk ratio 0.60; 95% CI 0.45 to 0.8; 203 participants; 2 trials; certainty of evidence not reported). No statistical heterogeneity was observed ($Chi^2 = 0.01$, df = 1 (P = 0.93), $I^2 = 0\%$).

However, one of those trials reported mutans streptococci colonisation score categories. When the review authors analysed the four categories, they observed no evidence of a difference in risk between the xylitol intervention and xylitol combined with CHX intervention group in any category.

**Secondary outcome 2: Microbiological presence (mother)**
Comparison 1: Antimicrobial treatment (CHX or iodine-NaF and prophylaxis) in caregiver dentition versus placebo:
Two trials reported on this outcome; however, the review authors could not pool the data. The first trial reported a significant reduction of MS by 70% (P = 0.04), a 45% decline in lactobacilli (P = 0.04), a 46% decline in total streptococci (P = 0.002) and a 42% decline in total cultivable bacteria (P = 0.004) in the treatment group. S. sattguis increased significantly (32%; P = 0.01) in the control group. None of the post-treatment values in the treatment group was significantly different from the corresponding values in the control group.

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| | In the second trial, the treatment group exhibited a significant reduction in the S. mutans levels in stimulated saliva compared to the control group. The reduction remained significant for about 12 months, and the treatment effect was statistically significant over time (p = 0.0002).<br><br><u>Comparison 2: Xylitol v gum versus CHX or CHX + xylitol gum:</u><br>One trial reported mutans streptococci colonisation level in mothers, assessed at the three-year child caries assessment time point. The review authors observed a lower level of colonisation in the xylitol intervention compared with the<br>CHX intervention group (mean difference 0.50, 95% CI 0.15 to 0.85; 126 participants; 1 trial; certainty of evidence not reported).<br><br>**Secondary outcome 3: Plaque (infant/child)**<br>No trials included in the review reported this outcome.<br><br>**Secondary outcome 4: Plaque (mother)**<br>No trials included in the review reported this outcome.<br><br>**Secondary outcome 5: Adverse events (for the infant/child and mother)**<br><u>Comparison 1: Antimicrobial treatment (CHX or iodine-NaF and prophylaxis) in caregiver dentition versus placebo:</u><br>Two trials reported information relating to adverse events for mother or child. In both trials, adverse events were reported related to the topical application of treatment solutions. However, there were no statistically significant differences in the number of reported adverse events between participants in the treatment and control groups in either study.<br><br><u>Comparison 2: Xylitol gum versus CHX or CHX + xylitol gum:</u><br>No trials included in the review reported this outcome. |
| **Significance/direction** | The review authors observed no evidence of a difference between groups in caries presence in primary teeth (very low of certainty evidence). There was a lower mean dmft in children of mothers who received xylitol compared with the CHX antimicrobial intervention group (low certainty of evidence), but no evidence of a difference between these two groups in caries presence in primary teeth (very low certainty of evidence).<br><br>The effectiveness of the clinical interventions examined in this review for preventing early childhood caries is uncertain. Additional adequately powered, well-designed randomised control trials are required to assess the effectiveness of these interventions with mothers and other primary caregivers during pregnancy and/or the first year of a child's life for preventing early childhood caries. |

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| | *Note*. The finding in primary outcome 1 will not be included in the HRB evidence synthesis because the nature of the intervention is unclear given the fact that the data were pooled. |
| **Heterogeneity** | This review included diverse interventions and the review authors anticipated heterogeneity of intervention content, outcomes, and outcome measures.<br><br>The review authors were unable to investigate sources of heterogeneity due to the small number of studies included in analyses. They highlighted that the included trials used a variety of definitions of outcomes including the definition/diagnosis of caries, and different assessment time points, which further complicates interpretation of the data, and may limit the applicability of the results. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as very low. In the xylitol chewing gum versus CHX varnish antimicrobial treatment in caregiver dentition comparisons, the review authors graded the certainty of evidence as low to very low.<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Ahovuo-Saloranta *et al.* (2017) extraction |
| **First Author and year of publication** | Ahovuo-Saloranta *et al.* (2017) |
| **Objectives (exact review question(s) and page number)** | To compare the effects of different types of fissure sealants in preventing caries in occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. Specifically:<br>• To evaluate the effectiveness of resin/composite-based fissure sealants compared with no sealant at different follow-up times<br>• To evaluate the effectiveness of glass-ionomer-based fissure sealants compared with no sealant at different follow-up times<br>• To evaluate the effectiveness of new types of fissure sealants (such as ormocer-based sealants) compared with no sealant at different follow-up times, and<br>• To evaluate the relative effectiveness of different sealant material types.<br><br>The review authors reported the safety of sealants and possible harmful |

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| | effects and the retention of sealants (although retention of sealants was not studied as an objective of the review). |
| **Participants (characteristics and numbers)** | Permanent dentition (first or second molars); sealants, resin, glass-ionomer, ormocer; combined intervention.<br><br>Baseline caries was reported in six out of 38 included trials, and all reported mean (sd) index scores above zero. In three other trials conducted in the 1970s, caries-free children were not included.<br><br>The review included child and adolescent participants from the general population, aged up to 20 years at the start of the study. The included trials involved a total of 7,924 children, aged from 5 to 16 years. There were similar numbers of males and females (where these data were reported). |
| **Setting/context** | The trials were conducted in Australia (1 trial), Brazil (5 trials), Canada (1 trial), China (6 trials), Colombia (1 trial), Egypt (1 trial), Finland (2 trials), France (1 trial), India (2 trials), New Zealand (1 trial), Norway (1 trial), Spain (1 trial), Sweden (1 trial), the Syrian Arab Republic (1 trial), Thailand (1 trial), Turkey (3 trials), the UK (4 trials), and the USA (5 trials).<br><br>The children in the included trials were representative of the general child population. In most trials, children were recruited from selected schools or dental clinics. |
| **Description of Interventions/ phenomena of interest** | This review was concerned with a) comparing sealant material with no sealant (all sealant materials accepted except the first-generation resin-based sealants), and b) comparing one type of fissure sealant with another sealant, for preventing dental caries. In this update, the review authors considered two main types of sealant materials: resin-based and glass-ionomer-based sealants with subtypes. Trials that compared compomers (hybrids) to resins/composites were excluded.<br><br>The review authors compared four types of interventions:<br>1. Resin-based sealant versus no sealant (comparator)<br>2. Glass-ionomer-based sealant versus no sealant (comparator)<br>3. New types of fissure sealants (e.g. ormocer-based sealants) versus no sealants (no included trial reported on this intervention), and<br>4. Glass-ionomer-based sealant versus resin sealant (comparator).<br><br>Trials in which sealants were placed on occlusal surfaces of permanent premolar or molar teeth, not sealed previously, and for the purpose of preventing caries were included. Applications of sealants could be either on sound surfaces or on enamel lesions (if scored using the ICDAS II scale, codes 0, 1, 2 and 3 were accepted). The sealant application method used in the study could either be (a) direct application on the tooth surface or (b) |

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| | application after mechanically preparing the tooth surface. Trials where fissure sealants were used concurrently with fillings were excluded.<br><br>Trials were excluded that tested any other caries-preventive treatments (such as fluoride varnishes) used concurrently with sealants. However, the review authors did include trials where fissure sealants were used concurrently both in test and control groups with fluoride toothpaste or with fluoridated water, or the children received oral health instruction or education. Specifically, tap water was fluoridated in areas where six studies took place. Half the children in Hunter 1988 used fluoridated water. Water was not fluoridated in seventeen trials, and the remaining trials did not report if water was fluoridated. Motivation and instruction, such as achieving good oral hygiene and use of fluoridated toothpaste, were reported in eight trials (Amin 2008, Chen 2013, Dhar 2012, Ganesh 2006, Liu 2014a, Muller-Bolla 2013, Tagliaferro 2011, Tang 2014). Information on diet (e.g. snacking habits) was provided only by Liu 2012 and Liu 2014a.<br><br>Follow-up periods ranged from 12 months to 72 months. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (searched 3 August 2016)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 7) in the Cochrane Library (searched 3 August 2016)<br>• MEDLINE Ovid (1946 to 3 August 2016)<br>• Embase Ovid (1980 to 3 August 2016)<br>• The US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 6 August 2016), and<br>• The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 3 August 2016).<br><br>In previous versions of this review, the following electronic databases were also searched: SCISEARCH, CAplus, INSPEC, JICST- EPLUS, NTIS, PASCAL, DARE, NHS EED, HTA, OpenSIGLE and OpenGrey. However, these searches were discontinued due to poor yield results.<br><br>Reference lists of all potentially eligible trials and relevant systematic reviews for further trials were searched. In the original 2008 review, seven companies known to manufacture sealant materials were contacted and data and references from all published and unpublished trials on sealants were requested. No restrictions were placed on language, date of publication, or publication status.<br><br>The protocol for the review was first published in 1999; no registration number was provided. Differences between the protocol and published review were noted. |

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| | Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. The review authors contacted trial authors to request additional information if the information in the report was insufficient to inform final assessment of inclusion or exclusion. Disagreements during screening were resolved by discussion with a third reviewer. Disagreement resolution in the data extraction phase was not described.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>None of the authors declared a conflict of interest; however, they noted that one author was an Editor with Cochrane Oral Health, and another was one of two Co-ordinating Editors of Cochrane Oral Health. |
| **Date range (years) of included studies** | The 38 included trials were published between 1976 and 2014. |
| **Number of primary studies included in the systematic review** | The review authors included 38 randomised controlled trials (seven of which were new for this update), all with a follow-up period of at least 12 months. Eleven used parallel-group designs and 27 used split-mouth designs.<br><br>Trials were grouped and analysed based on sealant material type (resin or composite-based sealant, glass-ionomer-based sealant and ormocer-based sealant) using different follow-up periods. Fifteen trials evaluated the effects of resin-based sealant versus no sealant (3,620 participants in 14 trials plus 575 tooth pairs in one trial), three evaluated glass-ionomer sealants versus no sealants (905 participants), and 24 evaluated one type of sealant versus another (4,146 participants). Of these 24 trials, 23 compared glass-ionomer-based sealant versus resin-based sealant, and one compared ormocer-based sealant versus low-viscosity glass-ionomer. Two trials were included in all three comparisons.<br><br>The unit of randomisation was the individual, the group (e.g. school, school class), or the tooth or tooth pair.<br><br>Twelve trials were supported by government or academic sources or independent research foundations. Three trials were supported by government or academic sources or independent research foundations, but one or more sealant material was donated by a sealant manufacturer. Six trials were at least partly supported by a sealant manufacturer. Two authors of one trial were affiliated with a sealant manufacturer. One trial reported receiving no institutional, private, or corporate financial support (the authors were from universities). Fifteen trials did not report on funding sources. |

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| **Types of studies included** | The review included 38 randomised controlled trials, all of which reported outcomes relevant to this umbrella review: Amin (2008), Antonson (2012), Arrow (1995), Barja-Fidalgo (2009), Baseggio (2010), Bojanini (1976), Bravo (2005), Brooks (1979), Charbeneau (1979), Chen (2012), Chen (2013), De Luca-Fraga (2001), Dhar (2012), Erdoğan (1987), Forss (1998), Ganesh (2006), Guler (2013), Hunter (1988), Karlzén-Reuterving (1995), Kervanto-Seppälä (2008), Liu (2012), Liu (2014a), Liu (2014b), Mills (1993), Muller-Bolla (2013), Pardi (2005), Poulsen (2001), Raadal (1996), Reisbick (1982), Richardson (1978), Rock (1978), Rock (1996), Sheykholeslam (1978), Sipahier (1995), Songpaisan (1995), Tagliaferro (2011), Tang (2014), Williams (1996).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Brazil (5 trials), Canada (1 trial), China (6 trials), Colombia (1 trial), Egypt (1 trial), Finland (2 trials), France (1 trial), India (2 trials), New Zealand (1 trial), Norway (1 trial), Spain (1 trial), Sweden (1 trial), the Syrian Arab Republic (1 trial), Thailand (1 trial), Turkey (3 trials), the UK (4 trials), and the USA (5 trials). |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of included studies using the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Higgins 2011a). Disagreements were resolved by consensus. The review authors contacted the authors of included studies to request additional information, where required.<br><br>The following six domains were assessed for each trial:<br>1. Random sequence generation<br>2. Allocation concealment<br>3. Blinding of outcome assessment<br>4. Incomplete outcome data<br>5. Selective outcome reporting, and<br>6. Other sources of bias (baseline comparability of the groups and co-interventions).<br><br>For each trial, the review authors judged each domain as having 'low', 'high' or 'unclear' risk of bias, with the latter indicating lack of information or uncertainty over the potential for bias.<br><br>The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as (Higgins 2011):<br>• Low risk of bias (plausible bias unlikely to seriously alter results) if all domains defined above were graded as low risk of bias |

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| | • Unclear risk of bias (plausible bias that raises some doubt about results) if one or more of the domains were graded as unclear risk of bias, and<br>• High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were graded as high risk of bias. |
| **Appraisal rating** | Overall, the risk of bias was assessed as high for all included trials. This was because all trials had high detection bias (outcome assessment blinded was not possible). Eleven out of 38 trials had two or more high risk of bias scores.<br><br>Twenty-eight trials were categorised as being at low risk of bias for randomisation and no trials were categorised as being at low risk of bias for outcome ascertainment.<br><br>The certainty of the body of evidence was assessed with reference to the overall risk of bias of included trials at each outcome, directness of evidence, inconsistency of results, precision of estimates, and risk of publication bias.<br><br>To diminish the risk of publication bias, the review authors contacted the authors of relevant abstracts to request if full-text reports (unpublished or published) were available. In addition, if more than 10 trials were included in any meta-analysis, the review authors planned to assess for publication bias according to the recommendations on testing for funnel plot asymmetry described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Sterne 2011). However, no meta-analysis performed included more than 10 studies. |
| **Method of analysis** | For dichotomous outcomes and data, odds ratios were calculated for differences between sealant and no sealant (or different sealant materials), along with appropriate standard errors and 95% confidence intervals. For split-mouth studies, odds ratios were calculated using the Becker-Balagtas method (BB odds ratio) outlined in Curtin 2002. This method was chosen because the review authors intended to pool data from split-mouth and parallel-group trials in the same meta-analyses, and this method facilitated data synthesis. For continuous outcomes and data, means and standard deviations were used to obtain mean differences and 95% confidence intervals.<br><br>Meta-analyses were conducted in RevMan 2014, using the generic inverse variance method and fixed-effect or random-effects models. The fixed-effect model was used in meta-analyses of up to three trials, and the random-effects model in meta-analyses of four or more trials. Meta-analyses were not conducted where review authors found significant heterogeneity or divergent results between trials. Instead, those results were presented narratively. |

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| | Subgroup analyses were performed. Subgroups were created based on the glass-ionomer material subtype (low-viscosity, high-viscosity, and resin-modified glass-ionomers). In analyses comparing resin sealant with no sealant, sensitivity analyses were undertaken to assess the robustness of results (for caries outcomes) by excluding split-mouth trials with data presented only in marginals.<br><br>In the parallel-group trials (11 trials), the individual was the unit of analysis. In split-mouth trials (27 trials), the tooth pair of an individual was the unit of analysis.<br><br>A summary of findings table for the main outcomes was provided. |
| **Outcome(s) assessed** | Primary outcome 1: incidence of carious lesions on treated occlusal surfaces of molars or premolars, measured dichotomously<br><br>Primary outcome 2: dentine caries in permanent molars, measured continuously as changes in decayed, missing and filled (DMF) rates at occlusal surfaces<br><br>Secondary outcome 1: adverse events<br><br>Secondary outcome 2: sealant retention<br><br>*Note*. Both primary and secondary outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Incidence of carious lesions on treated occlusal surfaces of molars or premolars**<br><u>Comparison 1: Resin/composite-based fissure sealant versus no sealant:</u><br>Second-, third- and fourth-generation resin-based sealants prevented caries in first permanent molars in children aged 5 to 10 years at 24 months follow-up (odds ratio 0.12, 95% CI 0.08 to 0.19; 1,322 participants; 7 trials; moderate certainty of evidence).<br><br>Assuming 16% of the control tooth surfaces were decayed throughout 24 months follow-up, applying a resin-based sealant reduced the proportion of carious surfaces to 5.2% (95% CI 3.13% to 7.37%, 160 per 1000 compared with 52 per 1000, 95% CI 31 to 74, odds ratio 0.12, 95% CI 0.08 to 0.19).<br><br>Assuming 40% of the control tooth surfaces were decayed throughout 24 months follow-up, applying a resin-based sealant reduced the proportion of carious surfaces to 6.25% (95% CI 3.84% to 9.63%, 400 per 1000 compared with 63 per 1000, 95% CI 38 to 96, odds ratio 0.12, 95% CI 0.08 to 0.19).<br><br>Assuming 70% of the control tooth surfaces were decayed throughout 24 months follow-up, applying a resin-based sealant reduced the proportion of |

carious surfaces to 19% (95% CI 12.3% to 27.2%, 700 per 1000 compared with 189 per 1000, 95% CI 123 to 272, odds ratio 0.12, 95% CI 0.08 to 0.19).

There was considerable heterogeneity in these estimates ($Chi^2$ = 21.83, df = 6 (P = 0.001); $I^2$=72.51%).

This caries-preventive effect was also evident at 12 months follow-up and maintained 36-, 48-, and 54-months follow-up; however, the numbers of trials and children evaluated were reduced as follow-up periods. For example, 48 to 54 months: odds ratio 0.21 (95% CI 0.16 to 0.28; 482 children; 4 trials), risk ratio 0.24 (95% CI 0.12 to 0.45; 203 children; 1 trial). One trial demonstrated a continued caries-preventive effect resin-based sealants compared to no sealants at 60 months, and another trial at 72 months, 84 months, and 9 years.

*Note*. In four out of seven pooled trials, participants had background exposure to fluoride (water and toothpaste). However, this was considered background exposure, rather than part of the intervention of interest.

Comparison 2: Glass-ionomer-based fissure sealant versus no sealant:
No trials making this comparison and reporting this outcome were included in the review.

Comparison 3: New types of fissure sealants compared with no sealant:
No trials comparing new types of fissure sealants with no sealants were included in the review.

Comparison 4a: One sealant material versus another sealant material – glass-ionomer-based sealant versus resin-based sealant
Results from the trials are categorised by the following follow-up periods: 12 months, 24 months, 36-48 months, 60 months, and 84 months. Meta-analyses were conducted where possible.

12 months
Four trials compared low-viscosity glass-ionomers to resin sealants and two trials compared resin-modified glass-ionomers to resin sealants at 12 months follow-up. None reported differences between the resin-based and glass-ionomer-based sealants at 12 months (pooled Becker-Balagtas (BB) odds ratio 1.47, 95% CI 0.64 to 3.37; approximately 562 children; 6 trials; P = 0.37, $I^2$=0%; certainty of evidence not reported).

*Note*. One of these trials involved the delivery of a combined intervention wherein participants received OHI at baseline, which was reinforced at every visit. In addition, it was reported in two of the pooled trials that participants had exposure to fluoride (water or toothpaste). However this was considered background exposure rather than part of the intervention of interest.

24 months

A subgroup analysis comparing the incidence of caries between low and high viscosity glass-ionomers to resin-based sealants at 24 months follow-up did not find a difference between either form of glass-ionomers and resins (odds ratio 1.67, 95% CI 0.87 to 3.20; approximately 743 children; 10 trials (number of children evaluated only reported in 9 trials); P = 0.12; $I^2$=41.57%) and odds ratio 1.36, 95% CI 0.56 to 3.32; 2 trials; P = 0.50; $I^2$=0%, respectively).

*Note*. Three out of the 10 trials in the first pooled analysis involved combined interventions in which participants received OHI at leach clinic visit (1 trial), oral prophylaxis (1 trial), and a complex intervention (OHE, dietary counselling, fluoride toothpaste (600 ppm), and fluoride foam (6000 ppm) at each clinic visit (at 6 and 12 months). In addition, two of the 10 trials reported participant exposure to other forms of fluoride (water or toothpaste). However this was considered background exposure rather than part of the intervention of interest. In addition, one of the two trials in the second pooled analysis involved a combined intervention whereby participants in both groups received oral health education at baseline. In addition, both trials reported participant exposure to fluoridated water. However this was considered background exposure rather than part of the intervention of interest.

However, the subgroup analysis comparing resin-modified glass-ionomers with resin-based sealants at 24 months follow-up favoured resins over glass-ionomers (odds ratio 2.92, 95% CI 1.77 to 4.81; approximately 353 children; 2 trials; P < 0.0001; $I^2$=0%; certainty of evidence not reported). However, 1 of the 2 trials reported low retention rates for glass-ionomers (80% of sealants lost after 24 months) but high retention for resins (0% lost).

*Note*. One out of the two pooled trials involved a combined intervention in which participants in both groups received oral health instruction at baseline and used fluoridated toothpaste for the duration of the trial intervention.

36-48 months

It was not possible to conduct a pooled analysis at the 36-48 months follow-up period due to significant heterogeneity and divergent results among the trials. As such, results were presented narratively.

When comparing glass-ionomer based sealant to resin-based sealant, five trials found that resin-based sealants were significantly superior to glass-ionomer-based sealants (participants in one trial had background exposure to fluoridated water). Three compared low-viscosity glass-ionomers with resins (Kervanto-Seppälä 2008; Poulsen 2001; Rock 1996) and two compared resin-modified glass-ionomer with resins (Baseggio 2010; Raadal 1996). Poulsen 2001 found a benefit for second-generation resin sealant (BB OR

4.03, 95% CI 2.23 to 7.29) compared to low-viscosity glass-ionomers, Kervanto-Seppälä 2008 found benefit for third-generation sealant (BB OR 3.98, 95% CI 1.80 to 8.80), and Rock 1996 found benefit for fourth-generation sealant (BB OR 7.13, 95% CI 2.45 to 20.76). Baseggio 2010 found a significant benefit in favour of fluoride-releasing resin-based sealant (BB OR 2.56, 95% CI 1.84 to 3.56) compared to resin-modified glass-ionomer, and Raadal 1996 found in favour of second-generation resin sealant (BB OR 11.38, 95% CI 1.47 to 88.42).

Two other trials did not find differences between low-viscosity glass-ionomers with resins at 36 to 48 months (Karlzén-Reuterving 1995; Williams 1996) (participants in one trial had background exposure to fluoridated water)

Two trials found glass-ionomer-based sealants to be superior (Arrow 1995; Chen 2012). The split-mouth study by Arrow 1995 found a difference in favour of low-viscosity glass-ionomer sealant compared to second-generation resin sealant at 44 months (BB OR 0.18, 95% CI 0.08 to 0.41; n = 412 children). In Chen 2012, the cumulative survival rate of dentin caries lesion-free pits and fissures in atraumatic restorative treatment (ART) high-viscosity glass-ionomer with light-curing groups (98%) was statistically significantly higher than in the resin-composite group (96.4%, P = 0.04; n = 201 participants (from 2 out of 4 groups)) after 48 months.

<u>60 months</u>
One small parallel-group study found no difference in the incidence of caries between high-viscosity glass-ionomer and resin sealants over 60 months follow-up (risk ratio 0.38, cluster corrected 95% CI 0.09 to 1.60; 36 participants; 1 trial; certainty of evidence not reported).

<u>84 months</u>
One split-mouth study compared low-viscosity glass-ionomer sealants and resin sealants at 84 months follow-up and did not find a statistically significant difference between materials (risk ratio 1.44, 95% CI 0.88 to 2.35; 97 children; 1 trial; certainty of evidence not reported).

<u>Comparison 4b: One sealant material versus another sealant material – Ormocer-based sealant versus glass-ionomer-based sealant:</u>
One trial compared ormocer sealant with low-viscosity glass ionomer sealant and found glass-ionomer sealant performed better at 24 months; the presence of caries was 16% for glass-ionomer and 32% for ormocer (P < 0.05). However, the review authors note that data in the trial were unclear, and the dropout rate of the children was high (26%) (n = 50; effective n = 37).

**Primary outcome 2: Dentine caries in permanent molars**
<u>Comparison 1: Resin/composite-based fissure sealant versus no sealant:</u>

One trial with a 24-month follow-up period compared light-cured, fluoride-releasing resin-based sealant + oral health education with oral health education only and found significantly more caries in the control group children, with a mean difference of increments of DMFS of permanent first molars (DMFS -0.24, 95% CI -0.36 to -0.12; P < 0.0001; 450 children; 1 trial; certainty of evidence not reported).

A second trial comparing second generation (auto-polymerised) resin sealant with no sealants in children aged from 12 to 13 years found significantly more caries in the no sealant group, with a difference in increment of Decayed and Filled Surfaces of -0.65 (95% CI -0.83 to -0.47, p < 0.00001; 1 trial; certainty of evidence not reported) at 24 months follow-up (n = 276 participants).

*Note*. Participants in this trial were exposed to fluoridated water and toothpaste. However, this was considered background exposure rather than part of the intervention of interest.

Comparison 2: Glass-ionomer-based fissure sealant versus no sealant:
The incidence of caries following application of glass-ionomer-based sealants compared with no sealant was evaluated in 1 trial, which indicated no significant difference in caries incidence between the glass-ionomer based sealant group and no sealant group at 24 months follow-up (DFS MD -0.18, 95% CI -0.39 to 0.03; P = 0.0; n = 404 participants).

*Note*. Participants in one of the pooled trials had exposure to fluoridated water. However, this was considered background fluoride exposure, rather than part of the intervention of interest.

One trial (Tagliaferro 2011) with a 24-month follow-up period compared resin-modified glass ionomer cement plus oral health education every three months versus oral health education alone every three months alone, and versus the application of fluoride varnish (applied biannually) + oral health education. High risk children with sealant and oral health education programme showed statistically higher DMF increments on occlusal surfaces of first permanent molars compared with high-risk children who received education only or who received fluoride varnish + oral health education. No statistical difference was observed between low-risk groups.

Comparison 3: New types of fissure sealants compared with no sealant:
No trials comparing new types of fissure sealants with no sealants were included in the review.

Comparison 4a: One sealant material versus another sealant material – glass-ionomer-based sealant versus resin-based sealant
No trials included in the review comparing new types of fissure sealants with no sealants reported this outcome.

Comparison 4b: One sealant material versus another sealant material – Ormocer-based sealant versus glass-ionomer-based sealant:
No trials included in the review comparing new types of fissure sealants with no sealants reported this outcome.

**Secondary outcome 1: Adverse events**
Four trial assessment adverse events of the sealants. No adverse events were detected or reported.

**Secondary outcome 2: Sealant retention**
The review authors could not conduct statistical analysis to examine this outcome. Instead, results are presented narratively.

Comparison 1: Sealant versus no sealant
Four of the eight trials that reported on retention at 12 months follow-up reported 90% complete retention of resin-based sealants (lowest was 53%). Seven of the 10 trials that reported on retention at 24 months follow-up reported over 80% complete retention for resin sealants. At 36 months follow-up, complete retention ranged from 41% to 87% across 14 trials. In three of the five trials that reported on retention after 48 to 54 months, complete retention of resin-based sealants was 70%. One trial reported 39% complete retention of resins at 108 months follow-up. One trial compared resin-modified glass-ionomer with a control without sealant and found that 16% of resin-modified glass-ionomer sealants were lost after 24 months. One trial reported 85% complete retention for resin-based sealants and under 1% for glass-ionomer sealants at 24 months follow-up. One trial reported 7% loss of sealants among children in the resin group and 35% in the glass-ionomer group.

Comparison 2: Low-viscosity glass-ionomer versus resin sealant:
Eight trials comparing resin-based sealants with low-viscosity glass-ionomers reported better retention for resin-based sealants than glass-ionomers. At 36 to 48 months follow-up, the mean complete retention rate for resin-based sealants was 76%, and 8% for glass-ionomers (based on 5 trials that reported data at these follow-up points). One trial reported a significantly higher retention rate for resin-based sealants than glass-ionomers at 84 months follow-up (10.3% of glass-ionomers and 45.4% of resin sealants were fully present).

In four trials, retention was fairly high in both groups after 24 months. Three trials reported some better retention figures for resins than low-viscosity glass-ionomers (0% to 7% of sealants were lost in resin groups and 11% to 35% lost in glass-ionomer groups). The other trial reported better retention figures for glass-ionomers than resins (6% of sealants in the glass-ionomer group and 25% in the resin group were lost).

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| | Three trials reported low retention of both sealant materials. In the first trial, complete retention for both materials was less than 5% at 24 months follow up. In the second, 80% of resin sealants (without preparation of the surface before sealant application) and 100% of glass-ionomer sealants (without preparation of the surface before sealant application) were lost after 24 months. In the third, nearly two-thirds of participants had lost both sealant materials by 44 months follow-up.<br><br><u>Comparison 3: High-viscosity glass-ionomer versus resin sealant:</u><br>The three trials provided data for this comparison, with divergent retention rates. In the first trial, 20% of sealants were lost from the glass-ionomer and 14% from resin groups after 24 months. In the second trial, better retention rates for resins, 55% and 79% of sealants were completely or partially retained in the glass-ionomer and resin groups after 24 months, respectively. In the third trial, better retention rates for glass-ionomers (58%); complete or partial retention rates for resins were 42% after 60 months.<br><br><u>Comparison 4: Resin-modified glass-ionomer versus resin sealant:</u><br>Two trials made this comparison at 36 months; both reported clearly better complete retention rates for resins (mean 94% for resins and 5% for resin-modified glass-ionomers). |
| **Significance/direction** | Overall, there were too few data to enable robust conclusions to be drawn about the effectiveness of sealants in relation to the different caries incidence levels among the populations studied. Resin-based sealants applied on occlusal surfaces of permanent molars are effective for preventing caries in children and adolescents. The review found moderate-quality evidence that resin-based sealants reduced caries by between 11% and 51% compared to no sealant, when measured at 24 months (7 trials). Similar benefit was seen at timepoints up to 48 months; however, the quantity and quality of evidence was reduced beyond this.<br><br>There was insufficient evidence to determine the effectiveness of glass-ionomer sealants. The quality of the available evidence for glass-ionomer sealants compared to no sealants (based on 3 months) was assessed as very low due to inconsistent effects on caries outcomes (e.g., due to diversity among interventions, comparisons, and follow-up periods).<br><br>There was insufficient and low-quality evidence to determine the relative effectiveness of different types of sealants; the effectiveness of one sealant material over another could not be determined due to the inconsistency in effect between studies evaluating relative effectiveness (differences in products, comparisons, outcomes, and outcome reporting times were observed and could have contributed to the variable results).<br><br>Information on adverse effects was limited but none occurred where this outcome was reported on. Further research with long follow-up is needed. |

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| **Heterogeneity** | There was considerable heterogeneity in the estimate comparing the relative effect of resin-based sealant compared to no sealant at several time points ($I^2$ = 73%, P = 0.001). While there was incomplete information to investigate the underlying reasons, the review authors did not downgrade evidence because of it; results from individual trials showed clear significant benefit for the sealant. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence on resin-based sealant at moderate, downgraded by one level due to indirectness of evidence. They graded the certainty of evidence on glass-ionomer based sealant as very low, downgraded by three levels due to inconsistent effects on caries outcomes, diversity in the interventions, and methodological limitations of the studies.<br><br>The HRB authors graded the overall certainty of evidence in this review as moderate. |
| **References to previously published versions** | Ahovuo-Saloranta A, Forss H, Walsh T, Nordblad A, Mäkelä M, Worthington HV. Pit and fissure sealants for preventing dental decay in permanent teeth. Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No: CD001830. [DOI: 10.1002/14651858.CD001830.pub5].<br><br>Ahovuo-Saloranta A, Forss H, Walsh T, Hiiri A, Nordblad A, Mäkelä M, Worthington HV. Sealants for preventing dental decay in the permanent teeth. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No: CD001830. [DOI: 10.1002/14651858.CD001830.pub4].<br><br>Ahovuo-Saloranta A, Hiiri A, Nordblad A, Mäkelä M, Worthington HV. Pit and fissure sealants for preventing dental decay in the permanent teeth of children and adolescents. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No: CD001830. [DOI: 10.1002/14651858.CD001830.pub3].<br><br>Ahovuo-Saloranta A, Hiiri A, Nordblad A, Worthington HV, Mäkelä M. Pit and fissure sealants for preventing dental decay in the permanent teeth of children and adolescents. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No: CD001830. [DOI: 10.1002/14651858.CD001830.pub2]. |
| Parameter | Walsh *et al.* (2019) extraction |
| **First Author and year of publication** | Walsh *et al*. (2019) |
| **Objectives (exact review question(s) and page number)** | To determine and compare the effects of toothpastes of different fluoride concentrations (parts per million (ppm)) in preventing dental caries in children, adolescents, and adults (p15). |

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| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); topical fluoride, toothpaste; combined intervention.<br><br>Baseline caries was reported in 90 out of 96 included trials. Of these 90 trials, two included caries-free participants at baseline.<br><br>Children, adolescents, and adults were included, irrespective of the initial level of dental caries, background exposure to fluoride, receipt of dental treatment, nationality, setting where the intervention was received or age at recruitment to the trial. Studies where participants were selected based on special (general or oral) health conditions were excluded. Overall:<br>• Three trials including 2,675 randomised participants (2,162 evaluated) assessed the effects of fluoride toothpaste on the mature permanent dentition in adults, whose age ranged from 18 to 93 years at baseline.<br>• Eight trials including 13,856 randomised participants (9,055 evaluated) assessed the effects of fluoride toothpaste on the primary dentition, with participants aged from 1 to 4 years of age at baseline. Supervised toothbrushing was used in 4 trials.<br>• Eighty-six trials including 51,304 randomised participants (42,074 evaluated) assessed the effects of fluoride toothpaste on the immature permanent dentition in children and adolescents aged from 5 to 18 years of age at baseline (one study also reported on the effects on the primary dentition). Supervised toothbrushing was used in 24 trials.<br><br>There were similar numbers of males and females (reported in 66 out of 96 included trials), except for three trials which included males only, and two trials which included females only.<br><br>The total number of participants randomised in the 27 (out of 96) included trials that inform this umbrella review was approximately 41,807 (28,871 evaluated). |
| **Setting/context** | The trials were conducted in Australia (2 trials), Brazil (3 trials), Canada (2 trials), China (1 trial), Denmark (1 trial), France (5 trials), Germany (2 trials), Guatemala (2 trials), Iceland (1 trial), India (1 trial), Italy (2 trials), Japan (1 trial), Lithuania (1 trial), Puerto Rico (1 trial), Sweden (6 trials), Switzerland (6 trials), the UK (22 trials), and the USA (37 trials).<br><br>The setting for most trials was in primary and secondary schools, but other settings included orphanages, nurseries, universities, dental clinics, and hospitals. Some trials did not report setting. |
| **Description of Interventions/ phenomena of interest** | Trials were included that compared toothbrushing with a fluoride toothpaste with toothbrushing with a) another fluoride toothpaste of a different concentration or b) with a non-fluoride toothpaste or c) no toothpaste. The |

review authors created seven groups based on fluoride concentrations of toothpastes in regular use:

1. 0 (parts per million (ppm)) fluoride (F) (non-fluoride or placebo toothpaste)
2. 250 ppm F
3. 440 to 550 ppm F
4. 1000 to 1250 ppm F
5. 1450 to 1500 ppm F
6. 1700 to 2200 ppm F, and
7. 2400 to 2800 ppm F.

There were no restrictions placed on the fluoride agents which could be used singly or in combination. Toothpastes could be formulated with any compatible abrasive system (including dicalcium phosphate, sodium metaphosphate, calcium carbonate, silica, zirconium silicate, or calcium pyrophosphate).

There was no restriction on fluoride concentration (ppm), amount or duration of application, frequency of use, toothbrushing technique (including supervised toothbrushing), or post-toothbrushing procedure.

The review authors excluded trials where the intervention group, or both the intervention and control groups, received any additional active agent or caries preventive measure as part of the trial.

Trials where the intervention group alone received any additional potentially active agent in the toothpaste (such as xylitol, triclosan, N-lauroyl sarcosinate, and casein phosphopeptide-amorphous calcium phosphate (CPP–ACP)) were excluded. Trials where both the intervention and control group received any additional potentially active agent in the toothpaste were included. Trials where both the intervention and control groups included participants receiving additional measures as part of their routine oral care (e.g. supervised brushing, fissure sealants) were included, as were trials that were undertaken in areas with fluoridation of the community water supply.

The review authors assessed the risk of bias in relation to intervention contamination/co-intervention. One study (Biesbrock 2001) was judged to be at high risk of bias in this domain when a concurrent fluoride rinse programme was introduced to study participants. Sixty-seven trials (70%) were judged free from the possibility of any inadvertent application of the intervention being evaluated to people in the control group (contamination) or any additional treatment being given to one of the groups differentially (co-intervention) or both, and hence were judged to be at low risk of bias. In

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| | 28 trials (29%) there was insufficient information to enable a judgement to be made. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (searched 15 August 2018)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7) in the Cochrane Library (searched 15 August 2018)<br>• MEDLINE Ovid (1946 to 15 August 2018)<br>• Embase Ovid (1980 to 15 August 2018)<br>• US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 15 August 2018), and<br>• World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 15 August 2018).<br><br>There were no language or publication date restrictions. Previously published systematic reviews of fluoride toothpastes were also screened to identify any reports that met the inclusion criteria.<br><br>The protocol was published in 2009 (no registration number provided), and the review was originally published in 2010. Differences between the protocol and published review were noted.<br><br>Two review authors independently and in duplicate screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements in relation to screening were resolved by discussion; however, disagreement resolution at the extraction phase was not reported.<br><br>The review was supported by funding from the Department of Health Cochrane Review Incentive Scheme 2008, the National Institute for Health Research (NIHR), Cochrane Oral Health Group Global Alliance partners, and the Cochrane Review Support Programme.<br><br>No conflicts of interest were reported by any of the five review authors. Two authors were Co-ordinating Editors of Cochrane Oral Health, and three authors were Cochrane Oral Health Editors. One of the Co-ordinating Editors was involved in the design and analysis of three included trials but did not undertake the risk of bias assessment or the data extraction for these trials. |
| **Date range (years) of included studies** | The 96 included trials were published between 1995 and 2014. |
| **Number of primary studies included in the systematic review** | This review authors included 96 randomised controlled trials (13 of which were new since the original review), with a follow-up period of at least 1 year. These trials were placebo-controlled trials and compared one active intervention to at least one other active intervention, in the form of two-, |

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| | three, four- and five-arm trials. One trial was cluster-randomised, though reported as an individually randomised trial. Split-mouth trials were excluded due the high possibility of contamination of one part of the mouth from another.<br><br>The unit of randomisation was either the individual or the cluster. In trials with more than one relevant intervention group and a common comparator group, the review authors combined summary statistics from all relevant intervention groups to obtain a measure of treatment effect. When cluster-randomised trials did not report results adjusted for clustering present in the data, the review authors performed an approximately correct analysis by estimating the design effect for such trials (Higgins 2011) by using an intra-class correlation coefficient (ICC) value of 0.05 (a value commonly used in caries prevention trials) to reduce the numbers in intervention and control groups to their 'effective sample size.'<br><br>At least 53 trials were funded in some part by commercial manufacturers. Twenty-seven trials did not report funding source. Fifteen trials were supported by government or academic sources or independent research foundations, and in one trial the funding source was unclear.<br><br>Follow-up periods ranged from 12 months to 7 years in the included trials. |
| **Types of studies included** | The review authors included 96 randomised controlled trials: Abrams (1980), Andlaw (1975), Ashley (1977), Beiswanger (1989), Biesbrock (2001), Biesbrock (2003a), Biesbrock (2003b), Blinkhorn (1983), Brudevold (1966), Buhe (1984), Cahen (1982), Cardoso (2014), Chesters (2002), CL-213 (1983), CL-216 (1982), CL-220 (1986), Conti (1988), Davies (2002), Di Maggio (1980), Fan (2008), Fanning (1968), Fogels (1979), Fogels (1988), Forsman (1974), Forsman (1974a), Gish (1966), Glass (1978), Glass (1983), Hanachowicz (1984), Held (1968), Held (1968a), Held (1968b), Hodge (1980), Howat (1978), Jackson (1967), James (1967), James (1977), Jensen (1988), Kinkel (1972), Kleber (1996), Koch (1990), Lima (2008), Lind (1974), Lu (1980), Lu (1987), Mainwaring (1978), Mainwaring (1983), Marks (1994), Marthaler (1965), Marthaler (1965a), Marthaler (1970), Marthaler (1970a), Marthaler (1974), Mergele (1968), Mitropolous (1984), Muhler (1955), Muhler (1957), Muhler (1962), Muhler (1970), Naylor (1967), Naylor (1979), O'Mullane (1997), Peterson (1967), Peterson (1979), Petersson (1991), Piccione (1979), Powell (1981), Rao (2009), Reed (1973), Reed (1975), Ringelberg (1979), Ripa (1988), Rule (1984), Segal (1967), Slack (1964), Slack (1967), Slack (1967a), Slack (1971), Stephen (1988), Stephen (1994), Stookey (2004), Sønju Clasen (1995), Takeuchi (1968), Thomas (1966), Torell (1965), Torell (1965a), Torell (1965b), Vilhena (2010), Weisenstein (1972), Winter (1989), Zacherl (1970), Zacherl (1970a), Zacherl (1972), Zacherl (1972a), Zacherl (1973), Zacherl (1981). |

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| | The results of 27 randomised controlled trials informed the outcomes of interest to this umbrella review: Cardoso (2014), Conti (1988), Davies (2002), Fan (2008), Fanning (1968), Fogels (1979), Fogels (1988), Forsman (1974), Forsman (1974a), Glass (1983), Hanachowicz (1984), Jackson (1976), James (1967), Kleber (1996), Koch (1990), Marthaler (1974), Muhler (1962), Naylor (1967), Roa (2009), Rule (1984), Slack (1964), Slack (1967), Slack (1967a), Sønju Clasen (1995), Stephen (1994), Torell (1965). Winter (1989).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Australia (2 trials), Brazil (3 trials), Canada (2 trials), China (1 trial), Denmark (1 trial), France (5 trials), Germany (2 trials), Guatemala (2 trials), Iceland (1 trial), India (1 trial), Italy (2 trials), Japan (1 trial), Lithuania (1 trial), Puerto Rico (1 trial), Sweden (6 trials), Switzerland (6 trials), the UK (22 trials), and the USA (37 trials). |
| **Appraisal instrument(s)** | The review authors assessed all studies included in the review for risk of bias independently and in duplicate as part of the data extraction process, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). The following domains were assessed in each trial:<br>1. Sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias) and outcome assessment (detection bias)<br>4. Incomplete outcome data (attrition bias)<br>5. Selective reporting (reporting bias), and<br>6. Other bias (baseline imbalance, contamination or co- intervention).<br><br>A judgement of 'high' indicated a high risk of bias, 'low' indicated low risk of bias, and 'unclear' indicated either a lack of information or uncertainty over the potential for bias.<br><br>The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as:<br>• Low risk of bias (plausible bias unlikely to seriously alter the results: all domains assessed as at low risk of bias)<br>• Moderate risk of bias (plausible bias that raises some doubt about the results: at least one domain assessed as at unclear risk of bias, but none at high risk of bias), or<br>• High risk of bias (plausible bias that seriously weakens confidence in the results: at least one domain assessed as at high risk of bias). |

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| **Appraisal rating** | Only one trial was assessed at low risk of bias for all domains, and therefore at low risk of bias overall. Fourteen trials were assessed at high risk of bias for at least one domain, and therefore at high risk of bias overall. The most frequent high risk of bias judgement was in the incomplete outcome data domain, followed by other potential sources of bias form baseline imbalance, selective reporting, and potential contamination or co-intervention. The remaining 81 trials were assessed at being at unclear overall risk of bias. Of the 27 trials relevant to this umbrella review, two were categorised as being at high risk of bias overall, and the remaining 25 were categorised as being at unclear risk of bias overall.<br><br>Thirty-three out of 96 trials were categorised as being at low risk of bias for randomisation. Of the 27 trials relevant to this umbrella review, nine trials were at low risk of bias for randomisation, and 18 trials were at unclear risk of bias for randomisation. Blinding of participants and personnel and outcome assessment were reported together under a single domain. Ten out of 96 trials were categorised as being at low risk of bias for this domain. Of the 27 trials relevant to this umbrella review, 23 trials were at low risk of bias for this domain, three trials were at unclear risk of bias for this domain, and one trial was a high risk of bias for this domain.<br><br>The review authors assessed the certainty of the body of evidence for each direct comparison and outcome by considering the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, and the precision of the estimates.<br><br>In general, the review authors considered the trials to be largely free from bias in terms of the key domains identified, except for randomisation, allocation concealment, and incomplete outcome data as discussed above, where most trials received a judgement of 'unclear.' For the comparisons evaluating effects on the adult dentition and the primary dentition, the evidence for the caries increment outcome was downgraded for study limitations (as indicated above) and for imprecision, with either a negligible benefit from the higher fluoride concentration or a null effect.<br><br>Regarding publication bias, the review authors had intended to assess publication bias according to the recommendations on testing for funnel plot asymmetry (Higgins, 2011). However, they were not able to because, although they had a sufficient number of trials in their meta-analyses for the main comparisons, they were analysed as pairwise comparisons of fluoride concentrations that each contained fewer than 10 studies. |
| **Method of analysis** | The review authors analysed studies evaluating the caries preventive effects on the primary and permanent dentition separately throughout. Results related to the outcomes relevant to this umbrella review were described narratively. |

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| | For continuous outcomes, the review authors pooled data with the mean difference (MD), or standardised mean difference (SMD) if different measures were used to assess the same outcome. In the absence of an agreed consensus of minimally important clinical effect for caries increment, the review authors chose an SMD value of 0.30 to indicate clinical importance, representing a small to moderate effect size. For dichotomous outcomes, the review authors pooled data with the risk ratios (RR).<br><br>The analyses were conducted and reported separately for the effects on the primary dentition of young children, the immature permanent dentition of children and adolescents, and the mature permanent dentition of adults. The review authors proposed seven different categories of fluoride concentration, ranging from non-fluoride toothpaste, 0 ppm F through to 2800 ppm F, and resulting in 21 possible comparisons of fluoride concentration. Where sufficient data were available, the review authors planned to undertake a network meta-analysis to compare the caries increments of the different fluoride concentrations. However, due to the small number of trials measuring outcomes relevant to this umbrella review, only results from pairwise random-effects meta-analyses were applicable.<br><br>If important heterogeneity or inconsistency, or both, was observed, the review authors planned to explore possible sources through subgroup analysis or meta-regression. Two potential sources of heterogeneity were specified a priori:<br>1. Supervised toothbrushing, and<br>2. Community water fluoridation.<br><br>The review authors had planned to undertake sensitivity analyses removing studies where both the intervention group and control group received any additional potentially active agents, and also removing studies with the shortest observed follow-up period. However, due to insufficient data available this was not possible.<br><br>In parallel-group studies and cluster-randomised studies, individual participants were the unit of analysis. If clustered data were provided, the review authors adjusted the SEs of estimates to take clustering into account (Higgins 2011b). |
| **Outcome(s) assessed** | Primary outcome 1: Proportion of participants developing new caries<br><br>Secondary outcome 1: Adverse effects such as irritation, dental staining/discoloration, etc.<br><br>*Note*. Both primary and secondary outcomes are identified in the review as presented here. |

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| **Outcome(s) excluded from umbrella review** | Primary outcome: Change from baseline in the decayed, (missing), and filled surface or teeth index (D(M)FS/T), in all permanent teeth erupted at the start and erupting over the course of the study<br><br>Primary outcome: Change from baseline in the decayed, (missing/extraction indicated), and filled surface or teeth index (d(e/m)fs/t) in all primary teeth.<br><br>Upon inspection of these outcomes in the review, the authors extracted and analysed data for dental cavitated/cavitated caries lesions at the $D_3$ level only, and so it was not possible to distinguish caries initiation from caries progression. These outcomes could therefore not be included. |
| **Results/findings** | **Primary outcome 1: Proportion of participants developing new caries**<br>1. Effects of fluoride toothpaste on dental caries in young children (primary dentition).<br><br><u>Comparison 1: 1450 ppm F compared with 250 ppm F:</u><br>One trial compared the caries-preventive effects of supervised toothbrushing with toothpaste containing fluoride concentrations of 1450 ppm or 250ppm (combined intervention). The proportion of children developing new caries on primary dentition was not significantly lower in the higher fluoride group at 22 months follow-up (risk ratio (RR) 0.92, 95% CI 0.54 to 1.57; 69 participants; 1 trial; low certainty of evidence).<br><br><u>Comparison 2: 1055 to 1100 ppm F compared with 500 to 550 ppm F:</u><br>One trial measured the effects of supervised toothbrushing on the proportion of young children developing new caries with toothpaste containing fluoride concentrations of 1055 ppm compared with 550 ppm (combined intervention). The proportion of children developing new caries on primary dentition was significantly lower in the higher fluoride group at 36 months follow-up (RR 0.86, 95% CI 0.74 to 0.99; 905 participants; 1 trial low certainty of evidence).<br><br><u>Comparison 3: 1450 ppm F compared with 440 ppm F:</u><br>One trial compared the effects of brushing with toothpaste containing fluoride concentrations of 440 ppm F with 1450ppm F (singular intervention). The proportion of children developing new caries on primary dentition was lower in the higher fluoride group at 60 months follow-up (RR 0.87, 95% 0.81 to 0.94; 2,362 participants; 1 trial; moderate certainty of evidence). In the same trial, the mean dmft increment was lower in the higher fluoride group (MD -0.34, 95% CI -0.59 to -0.09; 2,362 participants; 1 trial; moderate certainty of evidence). The review authors note that the possibility of contamination / co-intervention was a possibility in this above trial. |

2. Effects of fluoride toothpaste on dental caries in the permanent dentition of older children and adolescents (immature permanent dentition).

Comparison 1: 250 ppm F compared with 0 ppm F:
Analyses showed the proportion of children developing new caries was similar in the lower and higher fluoride concentration groups (singular intervention) at 2 years follow-up (RR 1.07, 95% CI 0.91 to 1.27; 684 participants; 2 trials; low certainty of evidence, $I^2$ = 0%).

*Note*. Participants used fluoride mouthrinse and were exposed to fluoridated water. However, this was considered background fluoride exposure, rather than part of the intervention of interest.

Comparison 2: 1000 to 1250 ppm F compared with 0 ppm F:
The analysis showed the risk of developing caries was lower in the higher fluoride group (singular intervention) at 12-60 months follow-up (RR 0.90, 95% CI 0.77 to 1.06; 1,898 participants; 7 trials; low certainty of evidence, $I^2$ = 80%). *Note*. One of the included trials included a combined intervention (fluoride toothpaste and supervised toothbrushing).

*Note*. Participants in at least six out of the seven pooled trials had additional exposure to fluoride (in water, mouthrinse or salt; additional fluoride exposure was not reported on in the seventh trial). Once again, however, this was considered background fluoride exposure, rather than part of the intervention of interest.

Comparison 3: 1450 to 1500 ppm F compared with 0 ppm F:
Statistical analysis could not be conducted. The risk of developing new caries was significantly lower in the higher fluoride group (singular intervention) at 36 months follow-up (RR 0.95, 95% CI 0.91 to 0.98; 945 participants; 1 trial; low certainty of evidence).

*Note*. Participants in this trial were exposed to fluoridated water, which again was considered background fluoride exposure, rather than part of the intervention of interest.

Comparison 4: 1450 to 1500 ppm F compared to 1000 to 1250 ppm F:
The analysis showed the proportion of children developing new caries was similar in the lower and higher fluoride concentration groups at 36 months follow-up (RR 1.02, 95% CI 0.93 to 1.11; 4,328 participants; 2 trials; low certainty of evidence, $I^2$ = 82%).

*Note*. Both trials included a combined intervention (fluoride toothpaste and daily supervised toothbrushing). The review authors also reported that participants in both trials had exposure to fluoridated water. However, this

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| | was considered background fluoride exposure rather than part of the intervention of interest.<br><br>3. Effects of fluoride toothpaste on dental caries in adults (mature permanent dentition).<br><br>No trials reported on the proportion of adults developing new caries for this group.<br><br>**Secondary outcome 1: Adverse effects**<br>1. Effects of fluoride toothpaste on dental caries in young children (primary dentition).<br><br>Only one trial, comparing 1055 to 1100 ppm F to 500 to 550 ppm F, reported on this outcome. The trial authors stated, "There were no reports on adverse effects, but some children complained about the taste of the dentifrice." (p.6).<br><br>2. Effects of fluoride toothpaste on dental caries in the permanent dentition of older children and adolescents (immature permanent dentition).<br><br>Statistical analyses could not be conducted. Sixteen trials assessed possible side effects arising from toothpaste use, principally in terms of oral (soft tissue) pathologies and tooth staining. Six studies reported either nor untoward events of no untoward event which could be attributed to the use of the toothpaste on the soft tissue. Six studies reported a greater incidence of staining in the stannous fluoride group. One trial reported no differential in staining between the groups (2.5% fluoride group versus 1% placebo group) and no staining was found in another. No side effects of toothpaste were observed or reported in four trials.<br><br>3. Effects of fluoride toothpaste on dental caries in adults (mature permanent dentition)<br><br>No trials reported on the adverse effects of toothpaste for this group. |
| **Significance/direction** | There appears to be some evidence of a dose-response relationship in the caries-preventive effects of fluoride in toothpastes, with the magnitude of the caries-preventive effect estimate increasing as the distance between the lower and higher fluoride concentration increases. However, overall, the evidence for the caries-preventive effects of different fluoride toothpaste concentrations on the primary dentition of young children is particularly scarce.<br><br>Further research that directly compares the effects of fluoride toothpastes at lower fluoride concentrations with higher concentrations would greatly enhance the current evidence base, adding data and securing more precise estimates of effect. |

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| **Heterogeneity** | The review authors assessed the presence of clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants (e.g. age, community water fluoridation), and the interventions (e.g. additional potential active agents added to the toothpastes, supervised toothbrushing). Meta-analysis was restricted to studies of similar comparisons that reported the same outcomes. In standard meta-analyses, the review authors estimated different heterogeneity variances for each pairwise comparison.<br><br>The review authors do not comment on the potential impact of heterogeneity on the findings in relation to the development of new caries outcome. |
| **Summary for GRADE assessment for HRB report** | The evidence on the effect of fluoride toothpaste on dental caries in young children (primary dentition) was graded as either low or moderate, with downgrades applied due to study limitations (high risk of attrition bias and/or imprecision).<br><br>The evidence on the effect of fluoride toothpaste on dental caries in the permanent dentition of older children and adolescents (immature permanent dentition) was graded as low, with downgrades applied primarily due to within-study bias, heterogeneity, and imprecision.<br><br>The HRB authors graded the overall certainty of evidence in this review as low. |
| **References to previously published versions** | Walsh T, Worthington HV, Glenny AM, Appelbe P, Marinho VCC, Shi X. Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No: CD007868. [DOI: 10.1002/14651858.CD007868.pub2]. |

| Parameter | Walsh *et al.* (2015) extraction |
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| **First Author and year of publication** | Walsh *et al.* (2015) |
| **Objectives (exact review question(s) and page number)** | To assess the effects of chlorhexidine-containing oral products (toothpastes, mouthrinses, varnishes, gels, gums and sprays) on the prevention of dental caries in children and adolescents (p8). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); topical other chemicals, CHX; combined intervention.<br><br>Baseline caries was adequately reported in six out of the eight included trials. Of these six trials, two included caries-free participants at baseline. |

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| | The included trials randomised a total of 2,876 children and adolescents, of whom 2,276 (79%) were evaluated. Ages ranged from 0 to 15 years at baseline. In trials where sex was reported, percentage of females ranged from 48% to 52%, aside from 1 female-only trial. Two trials did not report on sex. Access to dental care varied among participants. |
| **Setting/context** | The trials were conducted in Australia (2 trials), Brazil (1 trial), China (1 trial), Scotland (1 trial), Spain (1 trial), Suriname (1 trial), and Sweden (1 trial).<br><br>Three trials were carried out in school settings, two trials were carried out in residential homes, and one trial each was carried out in an orphanage, a district polyclinic and a youth dental care centre. |
| **Description of Interventions/ phenomena of interest** | The intervention(s) of interest was chlorhexidine-containing oral products such as gels, toothpastes, varnishes, mouthrinses, chewing gums and sprays compared to placebo or to no intervention (which could've included routine dental care).<br><br>Studies that directly compared different chlorhexidine interventions, compared different concentrations of individual interventions, or compared different frequencies of application were also eligible for inclusion. The review authors excluded studies reporting only on combined interventions of chlorhexidine and fluoride, and/or comparisons between chlorhexidine and fluoride interventions.<br><br>The active interventions in the included trials consisted of chlorhexidine varnish of different concentrations (1%, 10%, 40%), each with a different application regimen, and one formulation of chlorhexidine gel at a concentration of 0.12%. Alas, only two types of interventions were compared by the review authors:<br>1. Chlorhexidine varnish (1% in 2 trials, 10% in 2 trials, 40% in 2 trials) compared with either no treatment or placebo, and<br>2. Chlorhexidine gel (0.12% in 2 trials) plus fluoride toothpaste (0.304%) compared with no treatment.<br><br>In the 1% CHX interventions, CHX was professionally applied in both trials, every 3 months over 2 years in 1 trial and every 4 months over 2 years in the second trial.<br><br>In the 10% CHX interventions, CHX was professionally applied in both trials, 1-2 times at baseline and the 3 months recall period in 1 trial, and every week for 1 month and then at 3 and 6 months recalls for 3 years in the second trial.<br><br>In the 40% CHX interventions, CHX was professionally applied in both trials, every 6 months in both trials. |

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| | In the CHX gel intervention, both trials reported that CHX gel was applied by caregivers after the evening toothbrushing with 0.304% fluoride toothpaste.<br><br>Oral instructions following professional application of the active interventions and placebo varied between studies. In one trial, both groups "received comprehensive caries advice...and demonstrations in oral hygiene techniques". In another trial, all groups were instructed "twice daily tooth-brushing using 0.304 percent fluoride toothpastes" and provided with free toothpastes and toothbrushes for the duration of the study. Oral health education provided to all mothers at each clinical examination. In a third trial, all groups were instructed "twice daily toothbrushing using 0.304 percent fluoride toothpastes" as soon as the first tooth erupted. General oral health education including feeding and dietary advice was also given. Free toothbrushes, CHX pastes, and tubes of low-dose fluoride dentifrice were mailed to the mothers after completion of the first telephone contact at 6 months and again at 12 and 18 months.<br><br>Follow-up periods ranged from six months to 36 months. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health Group Trials Register (searched 25 February 2015)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 12)<br>• MEDLINE via OVID (1946 to 25 February 2015)<br>• EMBASE via OVID (1980 to 25 February 2015)<br>• CINAHL via EBSCO (1937 to 25 February 2015)<br>• US National Institutes of Health Trials Register (ClinicalTrials.gov) (until 25 February 2015), and<br>• World Health Organization International Clinical Trials Registry Platform (ICTRP) http://apps.who.int/ trialsearch/ (until 25 February 2015).<br><br>The review authors examined the reference lists of relevant articles and attempted to contact the investigators of included trials by e-mail to ask for details of additional published and unpublished trials and any missing trial details.<br><br>The following journals recommended by the Cochrane Oral Health Group were also hand-searched:<br>• Caries Research (2003 to January 2014)<br>• Community Dentistry and Oral Epidemiology (January 2014)<br>• Journal of Dental Research (2003 to January 2014), and<br>• Journal of Dentistry for Children (2002 to January 2014). |

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| | The review authors attempted to contact the manufacturers of several of the relevant chlorhexidine-based products for information about any unpublished studies; however, this proved unsuccessful.<br><br>There were no language restrictions on the included studies as the review authors had arranged to translate any studies that were not in the English language.<br><br>It was not stated when the protocol was published, nor was a registration number provided. However, differences between the protocol and published review were noted.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion and/or consulting a third review author.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>No conflicts of interest were reported. |
| **Date range (years) of included studies** | The eight included trials were published between 1997 and 2013. |
| **Number of primary studies included in the systematic review** | The review authors included eight randomised controlled trials (RCTs). Six trials had a parallel design and randomisation at the individual level, and two trials had a parallel design and randomisation at the cluster level (school class).<br><br>The unit of randomisation was either the individual or the cluster.<br><br>Funding sources for the trials included:<br>• Consejeria de educacion y Ciencia and Fondo de Investigaciones del MSC, Spain (1 trial)<br>• A grant from Explore, Nijmegen, the Netherlands (1 trial)<br>• Ministry of Science and Technology, National Committee for Oral Health, People's Republic of China (1 trial)<br>• Oralife Group, Canada (1 trial)<br>• Dental Board of Queensland. Curaden Swiss donated Curasept. Colgate Oral Care, Australia donated toothbrushes and pastes (1 trial)<br>• Dental Board of Queensland and the following Queensland Health Departments: Office of Health and Medical Research Fellowship, Health |

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| | Practitioners Research Grant, and Metro South Health Service District, Oral Health Programme (Logan-Beaudesert Division) (1 trial).<br><br>Two trials did not report funding source. |
| **Types of studies included** | This review included eight randomised controlled trials (RCTs): Baca (200X), Bretz (1997), De Soet (2002), Du (2006), Forgie (2000), Nordling (1999), Plonka (2013), Pukallus (2013).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Australia (2 trials), Brazil (1 trial), China (1 trial), Scotland (1 trial), Spain (1 trial), Suriname (1 trial), and Sweden (1 trial). |
| **Appraisal instrument(s)** | Two review authors carried out the risk of bias assessment independently and in duplicate by following the domain-based evaluation described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Disagreements were resolved through consensus. Each included study was assessed as at low risk of bias, unclear risk of bias or high risk of bias for the following domains:<br>1. Random sequence generation<br>2. Allocation concealment<br>3. Blinding of participants and personnel<br>4. Blinding of outcome assessment<br>5. Incomplete outcome data<br>6. Selective reporting, and<br>7. Other sources of bias.<br><br>The review authors categorised risk of bias in any included studies according to the following:<br>• Low risk of bias (plausible bias unlikely to seriously alter the results).<br>• Unclear risk of bias (plausible bias that raises some doubt about the results) if we assessed one or more domains as unclear.<br>• High risk of bias (plausible bias that seriously weakens confidence in the results) if we assessed one or more domains as high risk of bias. |
| **Appraisal rating** | No trials were assessed at low risk of bias overall. Six trials were assessed at high risk of bias for at least one domain, and therefore at high risk of bias overall. The remaining two trials were assessed at being at unclear risk of bias overall. |

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| | Four out of the eight trials were categorised as being at low risk of bias for randomisation and four trials were categorised as being at an unclear risk of bias for randomisation.<br><br>Five out of the eight trials were categorised as being at low risk of bias for outcome ascertainment; one was categorised as being at high risk and two were categorised as being at an unclear risk of bias for outcome ascertainment.<br><br>The review authors assessed the quality of the body of evidence regarding the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates and the risk of publication bias.<br><br>The review authors graded the quality of evidence as very low due in part to concerns about possible bias in the included trials. For the trials at high risk of bias, the most common issue was with blinding of participants and personnel (performance bias). Incomplete outcome data (attrition bias) and selective reporting (reporting bias) were the next most common reasons for judging trials to be at high risk of bias. Furthermore, of the two trials at unclear risk of bias, unclear reporting of allocation concealment (selection bias) was common to both trials. In addition to this risk of bias, the review authors downgraded the quality of the evidence due to imprecision (low numbers of events), inconsistency, and indirectness of the included trials to the review question.<br><br>The review authors had planned to generate funnel plots and assess publication bias according to the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). However, no meta-analysis conducted by the review authors included more than 10 studies. The review authors did report that the possibility of publication bias cannot be ruled out as two of the included studies, which were unpublished, were not cited in any previous systematic reviews and there exists the possibility of other unpublished studies. |
| **Method of analysis** | For the primary outcome of caries increment in permanent teeth and primary teeth, the effect measure was the difference in means (standardised difference in means where the same outcome was measured using different scales). The same effect measure was used for levels of mutans streptococci expressed on a continuous scale.<br><br>For dichotomous data, or for continuous data that was reported as dichotomised data, the effect measure used was the risk ratio (RR). All effect measures were accompanied by 95% confidence intervals (CI). For continuous data, the effect measure was the difference in means (standardised difference in means where the same outcome was measured using different scales). |

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| | Where sufficiently homogeneous data to inform a clinically important question, the review authors performed a quantitative meta-analysis using RevMan (RevMan 2014). A fixed-effect model was used to pool effect estimates where only a small number of studies were identified per comparison and heterogeneity was low. A pooled estimate of effect together with the corresponding 95% CI was calculated.<br><br>Unit of analyses errors were reported in the two cluster-randomised trials. These were managed by reporting point estimates alone (no CIs or P values) where re-analysis was not possible. Where re-analysis was possible, the review authors used intraclass correlation coefficient values to calculate the appropriate design effect and adjust the standard error of the effect estimate accordingly.<br><br>Subgroup and sensitivity analyses were planned; however, due to an insufficient number of included trials, these were not carried out. |
| **Outcome(s) assessed** | Primary outcome 1: caries increment at the dentine level measured by change from baseline (or final measurement where caries increment was not reported) in the decayed, (missing) and filled surface/teeth (D(M)FS/T) index in all permanent teeth or molar teeth (Baca 200X, De Soet 2002, Forgie 2000, Nordling 1999)<br><br>Primary outcome 2: caries increment at the dentine level measured by change from baseline (or final measurement where caries increment was not reported) in the decayed, (missing) and filled surface/teeth (d(m)fs/t) index in all primary teeth<br><br>Primary outcome 3: incidence of caries (number of children developing caries over the course of the study)<br><br>Primary outcome 4: % sound surfaces<br><br>Secondary outcome 1: mutans streptococci bacteria in permanent and primary dentition<br><br>Secondary outcome 2: pain<br><br>Secondary outcome 3: adverse events<br><br>*Note*. Primary outcomes 1-3 are identified as primary outcomes in the review. Primary outcome 4 is not explicitly identified as an outcome in the methods section but is identified as an outcome in the results section. Secondary outcome 1 is identified as a primary outcome in the review, but for the HRB's purposes is considered a secondary outcome. Secondary outcomes 2 and 3 are identified as secondary outcomes in the review. |

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| **Results/findings** | **Primary outcome 1: Caries increment (D(M)FS/T)**<br><u>Comparison 1: chlorhexidine varnish compared with no treatment or placebo:</u><br>The DMFS increment in the intervention groups (10% and 40% CHX) at 30- and 36-months follow-up was 0.53 higher (1.53 higher to -0.47 lower) ($I^2$=0%; 690 participants; 2 trials; very low certainty of evidence), which the review authors considered an imprecise result of no appreciable difference between the chlorhexidine and placebo groups. To note, four trials in total made this comparison; however, only data from two could be pooled. Varnish was applied every week for 1 month and then at 3- and 6-month recall intervals for 3 years in one trial, and every 6 months in the other trial.<br><br><u>Comparison 2: chlorhexidine gel (0.12% CHX) compared with no treatment:</u><br>No trials reported on this outcome for this comparison.<br><br>**Primary outcome 2: Caries increment (d(m)fs/t)**<br><u>Comparison 1: chlorhexidine varnish compared with no treatment or placebo:</u><br>When the review authors re-analysed the two cluster-randomised trials using a range of intraclass correlation coefficients to take into account the clustering, they found no statistically significant difference in mean d(m)fs/t-molar increment between the groups at 24 months follow-up (1% CHX varnish applied every 3 months over 2 years in 1 trial, and 40% CHX varnish applied every 6 months over approx. 3 years in the other trial). In relation to additional oral health provision, no preventive treatment was given before or during the study period in one trial, and this information was not reported in the other trial.<br><br><u>Comparison 2: chlorhexidine gel (0.12%) plus fluoride toothpaste (0.304%) compared with no treatment:</u><br>Two studies that reported the incidence of caries (dmft) found the pooled best estimate of effect to be 1.00 (RR 1.00,95% CI 0.36 to 2.77; $I^2$=0%; 487 participants; 2 trials) at 24 months. On the basis of these analyses, the review authors were unable to exclude the possibility that chlorhexidine gel has no caries preventive effect. CHX gel was applied by caregivers every 6 months after evening toothbrushing.<br><br>**Primary outcome 3: Incidence of caries**<br><u>Comparison 1: chlorhexidine varnish compared with no treatment or placebo:</u><br>No trials reported on this outcome for this comparison.<br><br><u>Comparison 2: chlorhexidine gel plus fluoride toothpaste (0.304%) compared with no treatment:</u><br>The presence of new caries in the primary teeth of children following application of a chlorhexidine concentration 0.12% gel applied by caregivers |

every 6 months after evening toothbrushing with 0.304% fluoride toothpaste was not different at 24 months from children who received no treatment (RR 1.00, 95% CI 0.36 to 2.77; 487 participants; 2 trials; $I^2$ = 0%; very low quality of evidence).

**Primary outcome 4: % sound surfaces**

Comparison 1: chlorhexidine varnish compared with no treatment or placebo in permanent dentition:

No significant difference in dental decay parameters were found between test (Chlorzoin 10% chlorhexidine applied after 3 months; n = 43) and control group (n = 40) at six months of follow up (unknown dentition type).

Comparison 2: chlorhexidine gel compared with no treatment:

No trials reported on this outcome for this comparison.

**Secondary outcome 1: Mutans streptococci bacteria in permanent and primary dentition**

Comparison 1: chlorhexidine varnish compared with no treatment or placebo in permanent dentition:

Data could not be pooled presumably due to differences in chlorhexidine concentrations and follow-up periods. In two trials involving a totally of 579 participants, a statistically significant difference in mutans streptococci levels was observed at 6 months in favour of chlorhexidine, but this finding was not replicated at longer follow-up of 12, 24 and 36 months. One trial also measured mutans streptococci but did not fully report numerical estimates of mutans streptococci levels at the end of the study period and intermediate measurements. The trial authors simply reported "no significant differences between the two treatment groups". The quality of evidence was very low.

Comparison 2: chlorhexidine gel compared with no treatment in primary dentition:

Levels of mutans streptococci in children following application of a chlorhexidine 0.12% concentration gel was higher at 24 months compared to children who received no treatment; however this difference was not statistically significant (RR 1.26, 95% CI 0.95 to 1.66; 490 participants; 2 trials; $I^2$ = 54.41%; very low quality of evidence).

**Secondary outcome 2: Pain**

No trials reported on this outcome.

**Secondary outcome 3: Adverse events**

Comparison 1: chlorhexidine varnish compared with no treatment or placebo:

In one trial, no adverse events such as ulceration or other mucosal lesions or tooth staining were observed. In another trial, the investigators reported that “side-effects due to the CHX treatment were not noted".

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| | <u>Comparison 2: chlorhexidine gel compared with no treatment:</u><br>In two trials, no adverse events such as ulceration or other mucosal lesions or tooth staining were observed. |
| **Significance/direction** | There is little evidence from the eight studies included in this review to either support or refute the assertion that chlorhexidine is more effective than placebo or no treatment in the prevention of caries or the reduction of mutans streptococci levels in children and adolescents. |
| **Heterogeneity** | The inconsistency of results (heterogeneity) lowered the quality of the evidence. In addition, due to the wide variation in chlorhexidine concentration used in the studies and variation in outcome measures and length of follow-up, the review authors were unable to pool many of the studies. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence for primary outcomes 1-3 are very low, downgrading primarily because of risk of bias and inconsistency (as well as indirectness for primary outcome 3 specifically)<br><br>The HRB authors graded the overall certainty of the evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Worthington *et al.* (2019) extraction |
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| **First Author and year of publication** | Worthington et al. (2019) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effectiveness of interdental cleaning devices used at home, in addition to toothbrushing, compared with toothbrushing alone, for preventing and controlling periodontal diseases, caries, and plaque.<br><br>A secondary objective was to compare different interdental cleaning devices with each other (p23).<br><br>*Note*. Only approximately half of the included trials involved supervised use of interdental cleaning devices. The HRB were unable to determine which trials of these were relevant to the purposes of the umbrella review. Therefore, the findings were excluded from data synthesis. |

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| **Participants (characteristics and numbers)** | Permanent dentition; Dental hygiene, interdental cleaning devices.<br><br>Baseline caries was not reported in any of the included trials.<br><br>The included 35 trials randomised 3,929 participants, and approximately 3,734 were evaluated in analyses. In trials that reported on age, ages at baseline ranged from 18 to 78 years; 21 studies reported the mean age, which ranged from 20 to 53 years. Most trials included both males and females (two did not report on sex, but inclusion criteria implied both male and female participants were included). Twelve trials did not report the ratio of males to females. In the other 23 trials, the proportion of males to females, in percentage, ranged from 7/53 to 60/40 (11% to 60% males). Twenty trials reported including more females than males, and three trials reported including more males than females.<br><br>Twenty-four trials did not report the smoking status of participants. The other eight trials did report smoking status, and the percentage of participants who smoked ranged from 0% to 95%. |
| **Setting/context** | The trials were conducted in Canada (2 trials), Germany (1 trial), Guatemala (1 trial), Italy (1 trial), the Netherlands (3 trials), the UK (2 trials), and the USA (23 trials). Two trials did not report location.<br><br>Eighteen trials were conducted in an academic setting, and one was conducted in a private practice dental centre. The remaining 16 trials did not report the type of setting. |
| **Description of Interventions/ phenomena of interest** | The review authors included all trials that compared a combination of toothbrushing and any home-use mechanical interdental cleaning device with toothbrushing alone, or with another mechanical interdental cleaning device.<br><br>Trials were excluded where the intervention or control groups received any additional active agents (i.e. caries-preventive agents) as part of the study (e.g. chlorhexidine mouthwash, additional fluoride-based procedures, oral hygiene procedures, xylitol chewing gum), in addition to interdental cleaning procedures or toothbrushing. However, trials that used floss impregnated with active agents such as chlorhexidine or fluoride were included. Trials that involved participants in both groups receiving additional measures as part of their routine oral care, such as oral hygiene advice, supervised brushing, fissure sealants, etc. were also included. Most studies provided some type of training. Eighteen studies used supervised instruction (51%), but there were insufficient studies in any one meta-analysis to make subgroup analyses meaningful.<br><br>The included trials evaluated the use of floss (automated or manual), interdental brush, tooth cleaning stick - wooden or rubber (manual or |

electric), and oral irrigation to remove plaque from the teeth. Thus, the review authors compared ten interventions:

1. Flossing plus toothbrushing compared with toothbrushing alone
2. Interdental brushing with toothbrushing compared to toothbrushing alone
3. Wooden interdental cleaning stick plus toothbrushing compared to toothbrushing alone
4. Rubber/elastomeric interdental cleaning stick plus toothbrushing compared to toothbrushing alone
5. Oral irrigation plus toothbrushing compared to toothbrushing alone
6. Interdental brushing compared to flossing
7. Wooden cleaning stick compared to flossing
8. Rubber/elastomeric cleaning stick compared to flossing
9. Oral irrigation compared to flossing, and
10. Rubber/elastomeric interdental cleaning stick compared to interdental brushing.

Participants in 33 trials used a manual toothbrush, participants in one trial used a sonic toothbrush, and participants in one trial used a powered toothbrush.

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| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (searched 16 January 2019)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 12) in the Cochrane Library (searched 16 January 2019)<br>• MEDLINE Ovid (1946 to 16 January 2019)<br>• Embase Ovid (1980 to 16 January 2019)<br>• CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 16 January 2019)<br>• US National Institutes of Health Trials Register (http://clinicaltrials.gov) (to 16 January 2019)<br>• The WHO Clinical Trials Registry Platform (http://apps.who.int/trialsearch/default.aspx) (to 16 January 2019)<br><br>The reference lists of included studies and relevant systematic reviews for further studies were searched. No restrictions were placed on language, publication year, or publication status. |

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| | It was not stated when the protocol was published, nor was a registration number provided. However, differences between the protocol and published review were noted.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and at least two review authors performed data extraction. At least one review author who performed data extraction was a methodologist and at least one was a topic area specialist. Disagreements were resolved through consensus and discussion with other review authors.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>No conflicts of interest were reported. Two authors were Co-ordinating Editor of Cochrane Oral Health, one author was a Managing Editor with Cochrane Oral Health, and one author was an Editor with Cochrane Oral Health. Two review authors were also authors on two of the included trials; however, these trials were assessed by other review authors. |
| **Date range (years) of included studies** | The 35 included trials were published between 1972 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included 35 randomised controlled trials. Thirty trials used a parallel-group design, and three trials used a split-mouth design. One trial was a cross-over study; however, the second period was used to measure preference, with no clinical data measured. Therefore, the review authors used the data from the first period only, treating it as a parallel-group study. The review authors also used first-period data only for another trial as, although it was described as a cross-over study, the same control group was used throughout the study.<br><br>The unit of randomisation was not specified.<br><br>Most trials were funded through manufacturers or grant awards. Eight trials did not report on funding.<br><br>Follow-up periods ranged from 28 days to nine months. |
| **Types of studies included** | The review included 35 randomised controlled trials: Barnes (2005), Bauroth (2003), Biesbrock (2007), Christou (1998), Cronin (1997), Cronin (2005), Finkelstein (1990), Frascella (2000), Gordon (1996), Goyal (2012), Graziana (2017), Hague (2007), Imai (2011), Isaacs (1999), Ishak (2007), Jackson (2006), Jared (2005), Kazmierczak (1994), Lewis (2004), Lobene (1982), Meklas (1972), Mwatha (2017), NCT00855933, NCT01250769, Rosema (2008), Rosema (2011), Schiff (2006), Sharma (2002), Smith (1988), Vogel |

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| | (1975), Walsh (1985), Walsh (1989), Yankell (2002), Yost (2006), Zimmer (2006).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Canada (2 trials), Germany (1 trial), Guatemala (1 trial), Italy (1 trial), the Netherlands (3 trials), the UK (2 trials), and the USA (23 trials). |
| **Appraisal instrument(s)** | At least two review authors, a methodologist and a topic area specialist, independently carried out the assessment of risk of bias. It was not stated how disagreements were resolved. The risk of bias was assessed in each study using Cochrane's 'Risk of bias' tool as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).<br><br>The following seven domains were assessed for each trial:<br>1. Random sequence generation<br>2. Allocation sequence concealment<br>3. Blinding of participants and personnel<br>4. Blinding of outcome assessment<br>5. Incomplete outcome data<br>6. Selective outcoming reporting, and<br>7. Other biases.<br><br>A judgement of low, high or unclear risk of bias for each domain within each included study was assigned. For split-mouth and cross-over designs, the risk of bias assessment included additional considerations such as suitability of the design, and risk of carry-over or spill-over effects.<br><br>The review authors did not include the domain of performance bias in the assessment of the overall risk of bias in a study. All studies were at high risk of this because it was not possible to blind study participants to the interventions in an ethical experimental situation. Removing performance bias from consideration, the review authors categorised a study as high risk of bias if they had judged at least one domain as having high risk of bias, unclear if at least one domain was unclear, and none were high, and low if all domains were assessed as being at low risk of bias. |
| **Appraisal rating** | All trials were at high risk in the domain of performance bias, meaning all trials were categorised at high risk of bias overall. The review authors, therefore, did not include the domain of performance bias in their assessment of the overall risk of bias. When this domain was excluded from |

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| | the overall risk of bias assessment, only one of the 35 included trials was assessed as being at high risk of bias in more than one of the key domains. In addition, the review authors judged two trials to be at low risk of bias, 27 trials to be at unclear risk of bias, and six trials to be at high risk of bias when the domain of performance bias was excluded from the overall assessment of bias present each study.<br><br>Eleven of the 35 included trials were at low risk of bias for randomisation; the remaining 24 trials were at unclear risk of bias for randomisation.<br><br>Twenty-two of the 35 included trials were at low risk of bias for outcome ascertainment; the remaining 13 trials were assessed as having unclear risk of bias for outcome ascertainment.<br><br>The review authors assessed the certainty of the body of evidence with reference to overall risk of bias of included trials at each outcome, directness of evidence, consistency of results, precision of estimates, and risk of publication bias. The risk of bias in the included trials downgraded the quality of evidence. For all comparisons and outcomes, the body of evidence was assessed at low- or very low- certainty. The largest body of evidence was for flossing and toothbrushing compared with toothbrushing only. The body of evidence for this comparison was graded as very low certainty due to the risk of bias in the trials, substantial unexplained heterogeneity, and the lack of precision in the effect estimates.<br><br>The review authors had planned to assess for publication bias by creating a funnel plot of effect estimates against their standard errors; however, as all meta-analyses included fewer than 10 trials, this was not possible. It was acknowledged, however, that of the included studies were funded by pharmaceutical companies who made the intervention being evaluated. The review authors were unsure whether this may have introduced publication bias into the effect estimates but noted that there are similar numbers of head-to-head studies and studies comparing the intervention with toothbrushing alone. |
| **Method of analysis** | The review authors used the mean difference (or difference in means) or standardised mean difference when combining different clinical indices (e.g. plaque indices). The corresponding 95% confidence intervals for each result was also calculated.<br><br>The units of analysis were individual participants or groups of measuring sites within individual participants. Split-mouth, cross-over, and cluster trials were analysed as described in Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). For multi-arm studies, the review authors either combined groups (if straightforward) or presented the arms separately. The number of trial arms in the included studies varied from two to six, and the number of arms used in the review |

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| | analyses varied from two to four. In one trial, the review authors combined waxed, unwaxed, and minted floss arms (Lobene 1982).<br><br>Meta-analyses were undertaken only including trials reporting the same outcomes. Where there were several different indices measuring the same outcome, the review authors used the standardised mean difference, along with the appropriate 95% CI to aggregate the data. Risk ratios were combined for binary data. A random-effects model was used as considerable heterogeneity was expected a priori.<br><br>Subgroup analyses were planned; however, none were carried out due to an insufficient number of included trials.<br><br>Sensitivity analyses were conducted excluding studies:<br>• At high risk of bias (excluding participant blinding from this overall study-level assessment of risk of bias)<br>• With estimated standard deviations, and<br>• Using split-mouth and cross-over designs.<br><br>Summary of findings tables were provided for the main outcomes. |
| **Outcome(s) assessed** | Primary outcome 1: interproximal caries, assessed by change in decayed, missing and filled tooth surfaces (D(M)FS) index<br><br>Secondary outcome 1: plaque<br><br>Secondary outcome 2: adverse effects<br><br>*Note*. Primary outcome 1 is identified as a primary outcome in the review. Both secondary outcomes are identified as primary outcomes in the review, but for the HRB's purposes are considered secondary outcomes. |
| **Results/findings** | **Primary outcome 1: Interproximal caries**<br>No trials comparison reported this outcome for any of the ten comparisons.<br><br>**Secondary outcome 1: Plaque**<br><u>Comparison 1: Toothbrushing plus flossing versus toothbrushing alone:</u><br>The pooled estimate at 1 month follow-up showed a possible small benefit for flossing plus toothbrushing (standardised mean difference -0.42, 95% CI -0.85 to 0.02; 7 trials, 542 participants; P = 0.06; $I^2$ = 83%, P < 0.0001; very low certainty of evidence). A possible benefit for flossing was found at the three-month time point (standardised mean difference -0.20, 95% CI -0.36 to -0.04; 5 trials, 594 participants; $I^2$ = 0%, P = 0.74). At six months, there was no evidence of a benefit for flossing plus toothbrushing (standardised mean difference -0.13, 95% CI -0.30 to 0.05; P = 0.53; 3 trials, 487 participants; no heterogeneity). |

Comparison 2: Toothbrushing plus interdental brushing versus toothbrushing alone:
The plaque score in the interdental crushing group was lower compared to the toothbrushing group at 1 month follow-up (standardised mean difference -1.07, 95% CI -1.58 to -0.69; 2 trials, 93 participants; $I^2$ = 0%, P = 0.48; low certainty of evidence).

Comparison 3: Toothbrushing plus use of wooden cleaning sticks versus toothbrushing alone:
There was no evidence that wooden cleaning sticks reduced more plaque than toothbrushing alone at three months follow-up (mean difference in mean proportion of sites with plaque0.03, 95% CI -0.13 to 0.07; 1 trial, 24 participants, very low certainty of evidence).

Comparison 4: Toothbrushing plus use of rubber/elastomeric cleaning sticks versus toothbrushing alone:
The plaque score in the toothbrushing plus use of rubber/elastomeric cleaning sticks group was lower than in the toothbrushing alone group at 1 month follow-up (mean difference in full mouth plaque score -0.22, 95% CI -0.41 to -0.03; 1 trial, 30 participants; very low certainty of evidence).

Comparison 5: Toothbrushing plus oral irrigation versus toothbrushing alone:
There was no evidence that the use of oral irrigation reduced more plaque than toothbrushing alone at 1 month follow-up (standardised mean difference -0.16, 95% CI -0.41 to 0.10; 3 trials, 235 participants; no heterogeneity; low certainty of evidence). There was also no evidence of a change in plaque at three months (standardised mean difference 0.06, -0.25 to 0.37; 2 trials, 163 participants; no heterogeneity) or six months (mean difference 0.22, -0.59 to 0.15; 1 trial, 109 participants).

Comparison 6: Interdental brush versus floss:
Conflicting results were found. Plaque in the interdental brushing group was lower at 1 month follow-up in the parallel-group trials when interdental brushes were used (standardised mean difference -0.47, 95% CI -0.84 to -0.11; 5 trials, 290 participants; $I^2$ = 57%, P = 0.05; very low certainty of evidence). This finding, however, was not supported by the outcome of the meta-analysis performed on data from three split-mouth trials at 1 month follow-up (standardised mean difference -0.07, 95% CI -0.32 to 0.18; $I^2$ = 90%, P < 0.001), nor from the data analysed at three months follow-up (mean difference -0.12, 95% -0.33 to 0.10; 2 trials, 106 participants; $I^2$= 80%, P = 0.02).

Comparison 7: Wooden cleaning stick versus floss:
There was no evidence that wooden cleaning sticks reduced plaque at three months follow-up (mean difference in mean proportion of sites with plaque

0.02, 95% CI -0.06 to 0.10; 1 trial, 24 participants; very low certainty of evidence).

Comparison 8: Rubber/elastomeric interdental cleaning stick versus floss:
There was no evidence that one intervention performed better than the other with regards to plaque control at 4 to 6 weeks' follow-up (standardised mean difference -0.08, 95% CI -0.46 to 0.29; 6 trials, 273 participants; $I^2$ = 57%, P = 0.04; very low certainty of evidence).

Comparison 9: Oral irrigation versus floss:
There was no evidence of a difference in plaque at 1 month follow-up for either oral irrigation or flossing (standardised mean difference 0.31, 95% CI -0.08 to 0.70; 2 trials, 133 participants; $I^2$ = 22%, P = 0.26; very low certainty of evidence).

Comparison 10: Interdental cleaning stick versus interdental brush:
There was no evidence that one intervention performed better than the other with regards to plaque control at 4 to 6 weeks' follow-up (standardised mean difference 0.08, 95% CI -0.33 to 0.49; 2 trials, 92 participants; no heterogeneity; very low certainty of evidence).

The results from the sensitivity analyses did not undermine the findings in the main analyses.

**Secondary outcome 2: Adverse effects**
Comparison 1: Toothbrushing plus flossing versus toothbrushing alone:
Adverse effects were assessed and reported in seven trials. Three reported no adverse events on the oral hard or soft tissues. Four reported sporadic adverse events with mild severity, with no evidence of a difference between the flossing plus toothbrushing group and toothbrushing only group.

Comparison 2: Toothbrushing plus interdental brushing versus toothbrushing alone:
No trials assessing this comparison reported on adverse effects.

Comparison 3: Toothbrushing plus use of wooden cleaning sticks versus toothbrushing alone:
No trials assessing this comparison reported on adverse effects.

Comparison 4: Toothbrushing plus use of rubber/elastomeric cleaning sticks versus toothbrushing alone:
No trials assessing this comparison reported on adverse effects.

Comparison 5: Toothbrushing plus oral irrigation versus toothbrushing alone:
Three trials reported that there were no adverse events. One trial reported one incidence of aphthous ulcer in irrigator group, and one trial reported oral lacerations but found no difference between the interventions.

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| | Comparison 6: Interdental brush versus floss:<br>Five trials reported there were no adverse events. Two trials reported on problems with the use of interdental brushes or floss, which sometimes caused soreness.<br><br>Comparison 7: Wooden cleaning stick versus floss:<br>No trials assessing this comparison reported on adverse effects.<br><br>Comparison 8: Rubber/elastomeric interdental cleaning stick versus floss:<br>Four trials reported either no adverse events or minor adverse events that did not significantly differ between interventions.<br><br>Comparison 9: Oral irrigation versus floss:<br>No trials assessing this comparison reported on adverse effects.<br><br>Comparison 10: Interdental cleaning stick versus interdental brush:<br>No trials assessing this comparison reported on adverse effects. |
| **Significance/direction** | Using floss or interdental brushes in addition to toothbrushing may reduce plaque more than toothbrushing alone. Interdental brushes may be more effective than floss. Available evidence for tooth cleaning sticks and oral irrigators is limited and inconsistent.<br><br>Overall, the evidence was low to very low-certainty, and the effect sizes observed may not be clinically important.<br><br>*Note*. Only approximately half of the included trials involved supervised use of interdental cleaning devices. The HRB were unable to determine which trials of these were relevant to the purposes of the umbrella review. Therefore, the findings were excluded from data synthesis. |
| **Heterogeneity** | Prior to performing meta-analyses, the review authors assessed studies for clinical homogeneity with respect to the type of intervention, control group, and outcomes. Results of clinically heterogenous studies were not combined. For studies judged as clinically homogenous, statistical heterogeneity was calculated. The review authors could not explore heterogeneity through formal subgroup analyses due to there being fewer than 10 studies in each of the meta-analyses. The largest body of evidence comparing flossing and toothbrushing with toothbrushing alone was downgraded in quality due to considerable unexplained heterogeneity. |
| **Summary for GRADE assessment for HRB report** | The review authors did grade the certainty of evidence. However, only approximately half of the included trials involved supervised use of interdental cleaning devices and HRB were unable to determine which trials of these were relevant to the purposes of the umbrella review. Therefore, the findings were excluded from data synthesis by the HRB authors. |

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| **References to previously published versions** | Johnson TM, Worthington HV, Clarkson JE, Poklepovic Pericic T, Sambunjak D, Imai P. Mechanical interdental cleaning for preventing and controlling periodontal diseases and dental caries. Cochrane Database of Systematic Reviews 2015, Issue 12. [DOI: 10.1002/14651858.CD012018] |

| Parameter | Tubert-Jeannin *et al.* (2019) |
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| **First Author and year of publication** | Tubert-Jeannin *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effects of fluoride supplements in the form of tablets (chewable or not), drops, lozenges and chewing gums for preventing dental caries in children.<br><br>To examine whether the effects of fluoride supplements vary according to the age of administration, background exposure to topical fluoride and type of supplements used.<br><br>To evaluate whether there is a differential effect between fluoride supplements and topical fluorides.<br><br>To evaluate whether there is a differential effect between fluoride supplements and other caries preventive measures (p6). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); systemic fluoride, supplements; combined intervention.<br><br>Baseline caries was reported in all included trials. None of these trials included only caries-free participants at baseline.<br><br>The total number of children participating in the trials was 7,196 (number of children at start), with 5,319 evaluated. The age of participants ranged from 2 to 12 years at baseline.<br><br>In two trials, participants were children with high caries risk, and in one trial participants were children with cleft lip and/or palate. All trials were conducted in communities with no water fluoride except one. No trials reported on the number of females and males included, however, three trials reported that the sex ratios at baseline were balanced. |
| **Setting/context** | The trials were conducted in Denmark (1 trial), Sweden (4 trials), Taiwan (1 trial), the UK (1 trial), and the USA (4 trials).<br><br>In seven trials, participants were recruited from school settings and in four trials participants were patients of selected dental clinics. |

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| **Description of Interventions/ phenomena of interest** | The active intervention/test group received fluoride supplements in the form of tablets, drops, lozenges (or chewing gums):<br>• With or without the use of vitamins<br>• Using any fluoride agent, at any concentration, amount, frequency of use, duration of application, and with any technique of application (sucked or not, chewed or not), and<br>• With or without the use of topical fluorides (fluoride rinse, topical fluoride application, fluoride varnish or fluoride toothpaste) or non-fluoride-based measures (chlorhexidine, xylitol, sealants, oral hygiene interventions, etc).<br><br>The control group received no fluoride supplements:<br>• No treatments<br>• Use of a placebo supplements (with or without the use of vitamins)<br>• Use of topical fluorides (fluoride rinse, topical fluoride application, fluoride varnish or fluoride toothpaste), or<br>• Use of other preventive measures (chlorhexidine, xylitol, sealants, oral hygiene interventions, etc).<br><br>Trials were excluded when the active intervention consisted of any other systemically delivered fluoride (water, milk, salt) provided in addition to fluoride supplements. Trials were also excluded when a topical fluoride-based measure or a non-fluoride-based preventive measure applied in a control group was different from the one administered in the intervention group in addition to fluoride supplements. Slow-release devices and fluoridated toothpicks as interventions were also excluded.<br><br>All trials were judged free from the possibility of the administration of the intervention to children in the control group (contamination) or of the application of an additional treatment to one of the groups (co-intervention).<br><br>Fluoride supplements were administered using tablets in seven trials, lozenges in three trials, drops in one trial, and tablets diluted in a solution in one trial. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health Group's Trials Register (to 12 October 2011<br>• Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 3, 2011)<br>• MEDLINE via Ovid (1950 to 12 October 2011)<br>• EMBASE via Ovid (1974 to 12 October 2011) |

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| | • LILACS via BIREME Virtual Health Library (1982 to 12 October 2011)<br>• PanAmerican via BIREME Virtual Health Library (1982 to 12 October 2011)<br>• WHOLIS via BIREME Virtual Health Library (1982 to 12 October 2011)<br>• MedCarib via BIREME Virtual Health Library (1982 to 12 October 2011)<br>• Brazilian Bibliography of Dentistry (BBO) via BIREME Virtual Health Library (1982 to 12 October 2011), and<br>• Current Controlled Trials (www.controlled-trials.com/) (to 12 October 2011).<br><br>Bibliographic references of identified trials and review articles were checked for additional studies. The review authors contacted organisations and experts known to be involved in the field when necessary to find unpublished studies. They also sent letters to authors of selected studies asking them for clarifications and other known unpublished or ongoing research.<br><br>Ten journals in which trials in this field were likely to be reported were handsearched as part of The Cochrane Collaboration's handsearching programme: *Journal of Dental Research, Acta Odontologica Scandinavica, Journal of the American Dental Association, Swedish Dental Journal, British Dental Journal, ASDC Journal of Dentistry for Children, Archives of Oral Biology, Caries Research, Community Dentistry and Oral Epidemiology, Community Dental Health, Journal of Public Health Dentistry.*<br><br>There were no restrictions regarding language, date of publication or publication status. The review authors translated non-English papers for languages such as French, German, Spanish, and Russian. Cochrane Collaboration translators carried out translations for any other languages.<br><br>The protocol was first published in 2009; no registration number provided. Differences between the protocol and published review were noted.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through consensus or discussion with a third review author.<br><br>The review was supported by funding from the British Orthodontic Society (BOS).<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 11 included trials were published between 1968 and 2008. |

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| **Number of primary studies included in the systematic review** | The review authors included 11 randomised controlled trials with a follow-up period of at least two years. This included placebo-controlled trials but also trials comparing the treatment group to other active interventions or to no treatment. In three trials, placebo supplements were administered to control groups. In two trials, the control groups received no treatment. In three trials, the effect of fluoride supplements was compared to the use of fluoride rinse. In two trials, the effect of fluoride supplements was compared to fluoride varnish, and in one trial the effect of fluoride supplements was compared to fluoridated toothpaste. In one trial, the effect of xylitol and xylitol/fluoride containing lozenges were compared. One trial evaluated the effect of two comparisons.<br><br>The review included trials with two to five arms. Three trials had more than one treatment group in addition to a control group, and two trials used more than one control group.<br><br>The unit of randomisation was at the level of the child or group (cluster).<br><br>Funding sources of the included trials were not reported. |
| **Types of studies included** | The review included 11 randomised controlled trials: Aasenden (1972), DePaola (1968), Driscoll (1974), Heifetz (1987), Holm (1975), Källestål (2000), Lin (2000), O'Rourke (1988), Petersson (1985), Poulsen (1981), Stecksen-Blicks (2008).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Denmark (1 trial), Sweden (4 trials), Taiwan (1 trial), the UK (1 trial), and the USA (4 trials). |
| **Appraisal instrument(s)** | Two review authors independently carried out risk of bias assessments following the domain-based evaluation described in Chapter 8 of the Cochrane Handbook (Higgins 2011). The evaluations were compared, and any inconsistencies were discussed and resolved. Study author(s) were contacted to seek clarification in case of uncertainty over data.<br><br>The following six domains were assessed for each trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants, personnel and outcome assessors (performance bias and detection bias)<br>4. Incomplete outcome data (attrition bias)<br>5. Selective reporting (reporting bias), and |

6. Other bias.

Each trial was assessed as either low, high, or unclear risk of bias in each of the six domains. After considering the additional information provided by the authors of the trials, the review authors made an overall assessment of each trial and categorised them into one of three categories.

- Low risk of bias: low risk of bias for all key domains
- Unclear risk of bias: unclear risk of bias for one or more key domains, or
- High risk of bias: high risk of bias for one or more key domains.

**Appraisal rating**

Overall, no trials were assessed as having low risk of bias. Ten trials were assessed as having unclear risk of bias, and one trial was assessed as having high risk of bias. Of the two trials relevant to this umbrella review, both were assessed as having an unclear risk of bias overall.

All trials were categorised as being at an unclear risk of bias for randomisation.

Blinding of participants and personnel and outcome assessment were reported together under a single domain. Seven out of 11 trials were categorised as being at low risk of bias in this domain, 1 was categorised as being a high risk of bias and 3 were categorised as being at an unclear risk of bias in this domain.

The review authors noted that the risk of bias in the included trials was difficult to evaluate, with the various bias domains frequently assessed as being at unclear risk of bias. This impacted the quality appraisals of the included trials, which were generally low. Many trials lacked important data or methodological information, presumably because 9 out of 11 trials were conducted in the 60s, 70s and 80s.

The review authors produced forest plots and used formal tests for homogeneity based on the $I^2$ statistics.

**Method of analysis**

For the main outcome variable, the review authors estimated the treatment effect in each study by the prevented fraction (PF) and calculated the 95% confidence interval using Stata following the formula of Dubey (Dubey 1965).

PF values were separately for caries increment data at the surface and tooth level and for deciduous and permanent teeth.

When data could be pooled, random-effects meta-analyses were conducted using Review Manager (RevMan 2011) and STATA software.

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| | For outcome data that could not be pooled due to insufficient and non-homogenous data, results were presented narratively.<br><br>Subgroup analyses were planned but not conducted due to insufficient data. There was no mention of sensitivity analysis being conducted in the review. |
| **Outcome(s) assessed** | Primary outcome 1: changes in caries increment in primary teeth, as measured by the difference between the number of decayed, missing and filled teeth (dmft) or surfaces (dmfs) at baseline and at the time of final evaluation for the same children<br><br>Primary outcome 2: changes in caries increment in permanent teeth, as measured by the difference between the number of decayed, missing and filled teeth (DMFT) or surfaces (DMFS) at baseline and at the time of final evaluation for the same adults<br><br>Primary outcome 3: differences in final caries experience in primary teeth as measured by the final number of decayed, missing and filled teeth (dmft) or surfaces (dmfs) in the treatment and control groups (if the groups were comparable at baseline)<br><br>Primary outcome 4: differences in final caries experience in permanent teeth as measured by the final number of decayed, missing and filled teeth (DMFT) or surfaces (DMFS) in the treatment and control groups (if the groups were comparable at baseline)<br><br>Primary outcome 5: new manifest carious tooth surfaces<br><br>Secondary outcome 1: plaque<br><br>Secondary outcome 2: adverse events - fluorosis<br><br>*Note*. The nature of the outcomes (primary/ secondary) in relation to the caries indexes was not made explicit in the review. As the aim of the review was to examine the effectiveness of fluoride supplements for caries prevention, we considered all outcomes pertaining to these indexes as primary outcomes (1-4). Primary outcome 5 is not explicitly identified as an outcome in the methods section but is identified as an outcome in the results section. Secondary outcome 1 is not explicitly identified as an outcome in the methods section but is identified as an outcome in the results section. Secondary outcome 2 is identified as a secondary outcome in the review. |
| **Results/findings** | **Primary outcome 1: Changes in caries increment in primary teeth (dmft/dmfs)**<br>The findings for this outcome were not presented. |

**Primary outcome 2: Changes in caries increment in permanent teeth (DMTF/DMFS)**

The findings for this outcome were not presented.

**Primary outcome 3: Differences in final caries experience in primary teeth (dmft/dmfs)**

Comparison 1: Effect of fluoride supplements versus no supplement, 24 - 36 months:

No significant effect was found for one trial which compared administration of fluoride tablets (1 mg NaF, 1 per day) at school was compared with no treatment (dmft PF 0.13; 95% CI -0.09 to 0.35; 581 participants) at 24-36 months follow-up. The certainty of evidence was not reported.

A strong beneficial effect of fluoride tablets (0.5 mg NaF, 1 per day) or fluoride drops (0.25 mg NaF, 2 drops per day) compared to no fluoride supplementation was observed in another study which included 115 children with cleft lip and/or palate for dmft PF (0.65; 95% CI 0.47 to 0.84; P < 0.00001; 98 participants; very low certainty of evidence) and for dmfs PF (0.73; 95% CI 0.46 to 0.99; P < 0.00001; 115 participants; very low certainty of evidence) at 24 months follow-up. Participants had background exposure to fluoride water in this trial.

Comparison 2: Effect of fluoride supplements versus topical fluoride (rinse, varnish, toothpaste), 24 - 36 months:

The d(m)fs PF pooled estimate was not statistically significant at 24-36 months follow-up (PF = 0.13; 95% CI -0.07 to 0.33; P > 0.05; $I^2$ = 0%; 1,051 participants; 2 trials; moderate certainty of evidence). One of the pooled trials administered 0.25mg NaF sucking tablets twice per day, and the other administered 1mg NaF chewing tablets once per day. The review authors reported that participants had background exposure to fluoride water in both trials trial and fluoride toothpaste in one trial.

**Primary outcome 4: Differences in final caries experience in permanent teeth (DMTF/DMFS)**

Comparison 1: Effect of fluoride supplements versus no supplement, 24 - 36 months:

The D(M)FS PF pooled estimate was 0.24 (95% CI 0.16 to 0.33; P < 0.00001; $I^2$ = 0%; 1,240 participants; 3 trials; moderate certainty of evidence) suggesting a benefit from the use of fluoride supplements. In two of these trials, participants had background exposure to fluoride (water and unspecified source)

The D(M)FT PF pooled estimate was 0.29 (95% CI 0.19 to 0.39; P < 0.00001; $I^2$ = 0%; 1,208 participants; 3 trials; moderate certainty of evidence) suggesting a substantial benefit from the use of fluoride supplements. In one of these trials, participants had background exposure to fluoride (unspecified source).

In the second trial, participants had no access or exposure to fluoride. In the third trial, exposure to fluoride was not reported.

Comparison 2: Effect of fluoride supplements versus no supplement, 55 and 72 months:
In one trial that evaluated the effect of APF tablets (1 mg F) administered once or twice a day, the DMFS PFs varied from 0.25 (95% CI 0.12 to 0.38; P < 0.0001; 529 participants) after 55 months of follow-up to 0.28 (95% CI 0.16 to 0.41; P < 0.0001; 437 participants) after 72 months, indicating a benefit from the use of fluoride supplements. The certainty of evidence was not reported.

Comparison 3: Effect of fluoride supplements versus topical fluoride (rinse, varnish, fluoridated toothpaste), 24-36 months:
The D(MF)S PF pooled estimate was 0.10 (95% CI -0.25 to 0.05; participants; $I^2$ = 0%; 2,047 participants; 4 trials; moderate certainty of evidence) suggesting no benefit from the use of fluoride supplements (tablets or lozenges) when compared with the use of topical fluoride, resulting in a 10% reduction in DMFS. In three of the pooled trial, participants had background exposure to other sources of fluoride (water in 2 trials, and water and toothpaste in 1 trial).

Comparison 4: Effect of fluoride supplements versus topical fluoride (rinse, varnish, fluoridated toothpaste), 48, 60, and 96 months:
There was no effect from the use of fluoride supplements when compared with the use of topical fluoride was observed after 48 months (472 participants; 1 trial) or 60 months ($I^2$ = 66.8%; 971 participants; 2 trials).

A beneficial effect of fluoride supplements was noticed with a DMFS PF of 0.21 (95% CI 0.04 to 0.38; P = 0.02; 428 participants; 1 trial) for the longer follow-up (96 months), but it is noted that a very high level of dropouts (> 60%) was observed in this trial for this length of follow-up. The certainty of evidence was not reported.

Comparison 5: Effects of fluoride supplements when compared with other preventive measures on DMFS approximal PFs, 24 months:
No significant effect was observed in this analysis which concerned only one trial. The DMFS approximal PF was 0.00 (95% CI -0.59 to 0.59; 115 participants; low certainty of evidence) when fluoride (NaF, 0.5 mg) given in addition to 422mg xylitol in lozenges was compared with xylitol alone. Participants consumed two lozenges, three times per day.

*Note*. In this trial, all the participants were encouraged to brush their teeth with fluoride toothpastes two times a day during the entire study period. In addition, participants had exposure to fluoridated water. However, this was considered background fluoride exposure, rather than part of the intervention of interest.

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| | **Primary outcome 5: New manifest carious tooth surfaces**<br>The review authors note that two trials reported other dental caries data as the frequency distribution of new manifest carious surfaces and the distribution of the children according to the number of erupted surfaces, group, baseline DMFS and caries increment. However, the findings were not reported in the review.<br><br>**Secondary outcome 1: Plaque**<br>There was no difference between the groups (fluoride supplements versus fluoride rinses) for the mean plaque scores after 2 years (1 trial; 357 participants; unclear risk of bias).<br><br>**Secondary outcome 2: Adverse events - fluorosis**<br>In one trial, data were given concerning the distribution of children according to Dean's fluorosis classification after 55 months of study. Fluorosis was recorded on teeth that erupted lately during the study period. For all study groups, 18.9% of the children showed signs of dental fluorosis (questionable to severe). The percentages varied slightly from 15% in the placebo control group, 20% in the group with one acidulated phosphate tablet (APF) tablet per day and 22% in the group with two APF tablets per day (1 trial; 640 participants, unclear risk of bias). |
| **Significance/direction** | There was evidence that the use of fluoride supplements in preventing dental caries in permanent teeth. There was only weak evidence that the use of fluoride supplements in preventing dental caries in deciduous teeth.<br><br>When fluoride supplements were compared with the use of topical fluorides in six trials (varnish, rinses, toothpastes) or with the use of other preventive measures in one trial (Xylitol lozenges), there was no clear evidence of a differential effect on permanent dentition nor on primary teeth. |
| **Heterogeneity** | Due to the non-homogenous data that related to outcomes relevant to this umbrella review, meta-analyses could not be conducted. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as moderate for the outcome changes in caries increment on permanent tooth surfaces (DMFS) and whole teeth (DMFT). Downgrading occurred for unclear random sequence generation and allocation concealment.<br><br>The review authors graded the certainty of evidence as very low for changes in caries increment on primary tooth surfaces (dmfs) and whole teeth (dmft). Downgrading for dmfs occurred for unclear random sequence generation and allocation concealment as well as including a study with a very small sample size and large effect. Downgrading for dmft occurred for unclear random sequence generation and allocation concealment, high heterogeneity, and a wide confidence interval. |

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| | The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Yeung *et al.* (2015) extraction |
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| **First Author and year of publication** | Yeung *et al.* (2015) |
| **Objectives (exact review question(s) and page number)** | To assess the effects of milk fluoridation for preventing dental caries at a community level. |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); systemic fluoride, milk.<br><br>No caries at baseline.<br><br>A total of 180 children aged three years old were randomised, and 166 evaluated. Information pertaining to the sex of the children was not reported. |
| **Setting/context** | The only included trial was conducted in Russia.<br><br>Participants were recruited from nursery schools. |
| **Description of Interventions/ phenomena of interest** | Children in the intervention group consumed fluoridated milk (2.5 mg per litre). Children in the control group consumed non-fluoridated milk. All children regularly consumed 180-200 ml milk per day using a 200 g cup and were followed-up after a period of three years.<br><br>The milk was provided directly to the children or their family.<br><br>The review authors excluded trials with an intervention or follow-up period of less than two years (trials lasting an equivalent of two school years were included). |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health Group's Trials Register (to November 2014)<br>• Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2014, Issue 10)<br>• MEDLINE via OVID (1946 to November 2014)<br>• EMBASE via OVID (1980 to November 2014) |

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| | • The U.S. National Institutes of Health Trials Register (https://clinicaltrials.gov) (to November 2014), and<br>• The WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch) (to November 2014).<br><br>They also contacted the Burrow Foundation to identify any unpublished or ongoing studies. The *Journal of Public Health Dentistry* was handsearched for the original review; however, for this update the only handsearching performed was done as part of the Cochrane Worldwide Handsearching Programme.<br><br>The reference lists of all included studies and relevant reviews were checked manually to identify any additional studies. No restrictions were placed on language or date of publication.<br><br>The protocol was published in 2002, and the original review was published in 2005. No differences between the protocol and published review were noted.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved by discussion and/or consultation with a third review author.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The review included one trial, which was published in 2004 as an abstract only. However, the investigators provided the review authors with unpublished trial data. |
| **Number of primary studies included in the systematic review** | The review authors included one randomised controlled trial, with a parallel-group design.<br><br>The unit of randomisation was the individual.<br><br>The trial was funded by The Borrow Foundation, UK. |
| **Types of studies included** | The review authors included one randomised controlled trial: Maslak (2004).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |

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| **Country of origin of included studies** | The trial was conducted in Russia. |
| **Appraisal instrument(s)** | Two authors independently assessed the risk of bias of the included trial as part of the data extraction process. The Cochrane Collaboration 'Risk of bias' assessment tool<br>(Higgins 2011) available in Review Manager (RevMan) was used.<br><br>The following seven domains were assessed:<br>1. Sequence generation<br>2. Allocation concealment<br>3. Blinding of participants and personnel<br>4. Blinding of outcomes assessment<br>5. Incomplete outcome data<br>6. Selective outcome reporting, and<br>7. Other bias.<br><br>The review authors judged the risk of bias for each domain as 'high', 'low' or 'unclear' based on the criteria listed in Section 8.5 of the Cochrane Handbook for Systematic Reviews of Interventions. |
| **Appraisal rating** | The authors did not state their overall assessment of risk of bias for the included trial. However, graphical information provided in the paper indicates that, overall, the trial was assessed as having a high risk of bias due to an assessment of high risk in the domain of performance bias.<br><br>The trial was categorised as being at unclear risk of bias for randomisation and low risk of bias for outcome ascertainment.<br><br>The quality of the body of evidence was assessed for each outcome with reference to the overall risk of bias, indirectness of evidence, inconsistency, imprecision of effect estimates or potential publication bias. Overall, the quality of evidence was low. This was primarily due to the lack of relevant trials, the high risk of bias in the one identified trial, and concerns over the applicability of the results to different settings and populations.<br><br>Publication bias could not be assessed because only one trial was included. |
| **Method of analysis** | Prevented fraction was the measure of treatment effect<br>presented for caries increment, calculated as the mean increment in the control group minus the mean increment in the intervention group, divided by the mean increment in the control group. |

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| | For continuous outcomes, the review authors reported mean differences and standard deviations, except for outcomes which had used difference scales, in which case the standardised mean difference would have been pooled.<br><br>The review authors could not conduct meta-analysis, subgroup analyses, or sensitivity analyses because the review included only one trial.<br><br>The unit of analyses was the individual. |
| **Outcome(s) assessed** | Primary outcome 1: changes in caries experience or caries increment, as measured by changes in decayed, missing and filled figures on permanent teeth or surfaces (DMFT or DMFS)<br><br>Primary outcome 2: changes in caries experience or caries increment, as measured by changes in decayed, missing and filled figures on primary teeth or surfaces (dmft or dmfs)<br><br>Secondary outcome 1: adverse effects - fluorosis<br><br>Secondary outcome 2: dental pain due to decay<br><br>Secondary outcome 3: antibiotics due to dental infections<br><br>Secondary outcome 4: requirement for general anaesthesia due to dental procedures for caries<br><br>*Note*. Primary outcomes 1 and 2 are identified as primary outcomes in the review. Secondary outcome 1 is identified as a primary outcome in the review, but for the HRB's purposes is considered a secondary outcome. Secondary outcomes 2, 3 and 4 are identified as secondary outcomes in the review. |
| **Results/findings** | **Primary outcome 1: Changes in caries experience/increment (DMFT or DMFS)**<br>The mean caries in permanent teeth (DMFT) of children was lower in the fluoridated milk group compared to the non-fluoridated milk group at three years follow-up (mean difference -0.13, 95% CI -0.24 to -0.02, 1 trial; 166 participants; low certainty of evidence).<br><br>**Primary outcome 2: Changes in caries experience/increment (dmft or dmfs)**<br>The mean caries in primary teeth (dmft) of children was lower in the fluoridated milk group compared to the non-fluoridated milk group at three years follow-up (mean difference -1.14, 95% CI -1.86 to -0.42, 1 trial; 166 participants; low certainty of evidence).<br><br>**Secondary outcome 1: Adverse effects - fluorosis** |

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| | The trial did not report on this outcome.<br><br>**Secondary outcome 2: Dental pain due to decay**<br>The trial did not report on this outcome.<br><br>**Secondary outcome 3: Antibiotics due to dental infections**<br>The trial did not report on this outcome.<br><br>**Secondary outcome 4: Requirement for general anaesthesia due to dental procedures for caries**<br>The trial did not report on this outcome. |
| **Significance/direction** | Only one small trial examining the effects of fluoridated milk in preventing dental caries was included in the review, and it had serious methodological limitations. The findings suggest that fluoridated milk may be beneficial to schoolchildren in preventing ("reducing the level of") caries, with a substantial effect size for primary teeth. However, there was no information about the potential harms. Moreover, the study was conducted in a setting where the baseline level of caries was high and the level of fluoride in drinking water was low. Therefore, the potential to replicate the benefits observed in this trial in other settings should be considered on a case-by-case basis. The data need to be supplemented by further trials to provide a high level of evidence for practice. |
| **Heterogeneity** | Heterogeneity could not be assessed because the review included only one trial. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence for the relevant outcomes as low. Downgrading occurred due to a high risk of bias (as the participants were not blinded and the sequence generation method was unclear) and due to indirectness (where the applicability of evidence to different settings and populations was unclear and there was not much baseline information about the population in the study).<br><br>The HRB authors graded the certainty of evidence as very low (downgraded from moderate due to the review being a single trial review). |
| **References to previously published versions** | Yeung A, Hitchings JL, Macfarlane TV, Threlfall AG, Tickle M, Glenny AM. Fluoridated milk for preventing dental caries. Cochrane Database of Systematic Reviews 2005, Issue 3. [DOI: 10.1002/14651858.CD003876.pub2]<br><br>Yeung CA, Tickle M. Fluoridated milk for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2002, Issue 3. [DOI: 10.1002/14651858.CD003876] |

Yeung A, Hitchings JL, Macfarlane TV, Threlfall AG, Tickle M, Glenny AM. Fluoridated milk for preventing dental caries. Cochrane Database of Systematic Reviews 2005, Issue 3. [DOI: 10.1002/14651858.CD003876.pub2]

| Parameter | Marinho et *al.* (2016) Extraction |
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| **First Author and year of publication** | Marinho et *al.* (2016) |
| **Objectives (exact review question(s) and page number)** | To determine the effectiveness and safety of fluoride mouthrinses in preventing dental caries in the child/ adolescent population (p8). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); combined intervention.<br><br>Baseline caries was reported in 35 out of 37 included trials, and all reported DMFS scores above zero.<br><br>The review included 37 trials involving 15,813 children and adolescents, from 95 participants in the smallest trial to 1238 participants in the largest trial. The age of children at the start of trials ranged from five to 14 years, with similar numbers of males and females (where these data were reported). |
| **Setting/context** | The trials were conducted in Brazil (3 trials), Canada (2 trials), Chile (1 trial), Denmark (2 trials), Finland (1 trial), the Netherlands (1 trial), New Zealand (2 trials), Puerto Rico (1 trial), South Africa (1 trial), Sweden (6 trials), the UK (4 trials), and the USA (13 trials).<br><br>Participants were recruited from school settings in all included trials. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was topical fluoride in the form of a mouthrinse that was swished and expectorated, not swallowed. Any fluoride mouthrinse, irrespective of formulation, concentration (ppm F), volume, frequency of application, or application technique, was included. The control group was placebo or no treatment. Thus, the review authors made the following comparison: fluoride mouthrinse versus placebo or no treatment.<br><br>Studies where the intervention consisted of use of any additional caries-preventive agents or procedures (e.g. other fluoride-based measures, chlorhexidine, sealants, oral hygiene interventions, xylitol chewing gums) were excluded.<br><br>All trials tested supervised use of fluoride mouthrinse as part of school-based mouthrinsing programmes, with two studies also including home use. The trials used a variety of different formulations: In 33 trials, rinsing with sodium fluoride was tested; in four trials, acidulated phosphate fluoride was |

tested; in two trials, stannous fluoride was tested; and in one trial each sodium monofluorophosphate, amine fluoride and ammonium fluoride were tested.

The fluoride concentration used in tested mouthrinses ranged from 100 ppm F (0.02% NaF) to 3000 ppm F (0.66% NaF), and frequency of application ranged from three to 330 times a year; however, these were unusually low and high concentrations and frequencies. Eighteen trials used concentrations of 230 ppm F (180 and 250 ppm F in a few studies), and 20 trials used concentrations of 900 ppm F (1000 ppm F in a few studies). In 17 trials, rinsing was performed either once a week or once every two weeks, and investigators would usually employ a concentration of 900 ppm F. Conversely, in 13 trials, rinsing was performed once or twice a day, and investigators would employ a concentration of approximately 230 ppm F. In one trial information on rinsing frequency was not available. The most usual amounts of mouthrinse used per application was 5 or 10 mL, and usual rinsing time was one or two minutes. Four trials reported performance of some form of prior tooth prophylaxis.

The review authors assessed the risk of bias in relation to intervention contamination/co-intervention. Ten trials were assessed as being at a low risk of bias owing to freedom from contamination. These trials provided information suggesting no differences between groups in co-interventions that could have affected the observed outcomes, such as toothbrushing practices, oral hygiene instructions, dental check-ups / preventive treatments or rinsing procedures. In the other studies, the risk of bias in this domain was unclear, as the researchers provided no or not enough information.

Follow-up periods ranged from 19.2 months (1.6 years) to three years.

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| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (searched 22 April 2016)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3) in the Cochrane Library (searched 22 April 2016)<br>• MEDLINE Ovid (1946 to 22 April 2016)<br>• Embase Ovid (1980 to 22 April 2016)<br>• CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 22 April 2016)<br>• LILACS BIREME (Latin American Caribbean Health Sciences Literature; 1980 to 22 April 2016)<br>• BBO BIREME (Brazilian Bibliography of Odontology; 1980 to 22 April 2016) |

- Proquest Dissertations and Theses (1861 to 22 April 2016)
- Web of Science Conference Proceedings (1990 to 22 April 2016)
- The US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov/; searched 22 April 2016), and
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 22 April 2016).

The review authors scanned all eligible trial reports, previous meta-analyses, and review articles for relevant references. There were no restrictions on language or date of publication in database searches.

For the original version of this review, the review authors searched reference lists of relevant chapters from preventive search dentistry textbooks on topically applied fluoride interventions, and carried out handsearching in the following journals:

- Community Dentistry and Oral Epidemiology (1990 to 2000)
- British Dental Journal (1999 to 2000)
- Caries Research (1999 to 2000)
- Journal of the American Dental Association (1999 to 2000)
- Journal of Dental Research (1999 to 2000)
- Journal of Public Health Dentistry (1999 to 2000), and
- European Journal of Oral Sciences (1999 to 2000).

For the update of the review, the authors did not undertake any handsearching.

For the original review, the review authors contacted experts in the field of preventive dentistry, author(s) of the included studies to obtain potentially eligible unpublished trials eligible, to clarify reported information, or to obtain missing data. They also contacted six fluoride rinse manufacturers in October 2000 to request data from potentially eligible unpublished trials.

At least two review authors performed screening for eligibility independently. Trials thought to be potentially relevant in other languages were translated. At least two review authors extracted data from all included studies in duplicate (disagreement resolution in screening and/or extraction was not reported).

The protocol was first published in 2000, and the original review was published in 2003. Differences between the protocol and published review were noted.

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| | The review was supported by funding from the National Institute for Health Research (NIHR), the Cochrane Oral Health Global Alliance partners, and CAPES (Ministry of Education in Brazil).<br><br>None of the review authors declared a known conflict of interest. Two authors were editors with Cochrane Oral Health, and one author was a Co-ordinating editor with Cochrane Oral Health. |
| **Date range (years) of included studies** | The 37 included trials were published between 1965 and 2005. |
| **Number of primary studies included in the systematic review** | The review authors included 37 randomised and quasi-randomised controlled trials. All the included trials used parallel group designs, and one was cluster randomised. Sixteen trials had more than one fluoride mouthrinse treatment group compared with a control; among these, one trial had two treatment groups and two placebo control groups. Six trials used a factorial design to investigate the effects of multiple topical fluoride intervention. With regard to type of control group used, five trials used a no treatment control group, and the remaining 32 trials used a placebo control group, of which two used tap water as 'placebo solution'.<br><br>Eleven trials acknowledged assistance (e.g. product provision) and/or financial support from fluoride mouthrinse manufacturers; 13 trials acknowledged support from non-commercial sources, and 16 trials provided no information on sources of funding. |
| **Types of studies included** | The review authors included 37 randomised and quasi-randomised controlled trials: Ashley (1977), Bastos (1989), Blinkhorn (1983), Brandt (1972), Craig (1981), De Liefde (1989), DePaola (1977), DePaola (1980), Driscoll (1982), Duany (1981), Finn (1975), Gallagher (1974), Heidmann (1992), Heifetz (1973), Heifetz (1982), Horowitz (1971), Horowitz (1971a), Koch (1967), Koch (1967a), Koch (1967b), Laswell (1975), McConchie (1977), Moberg Sköld (2005), Molina (1987), Moreira (1972), Moreira (1981), Packer (1975), Petersson (1998), Poulsen (1984), Radike (1973), Ringelberg (1979), Ringelberg (1982), Rugg-Gunn (1973), Ruiken (1987), Spets-Happonen (1991), Torell (1965), van Wyk (1986).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Brazil (3 trials), Canada (2 trials), Chile (1 trial), Denmark (2 trials), Finland (1 trial), the Netherlands (1 trial), New Zealand (2 trials), Puerto Rico (1 trial), South Africa (1 trial), Sweden (6 trials), the UK (4 trials), and the USA (13 trials). |
| **Appraisal instrument(s)** | At least two review authors independently undertook assessment of risk of bias in all included trials using the tool of The Cochrane Collaboration for |

assessing risk of bias, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Disagreements were resolved by discussion or consultation with another review author.

The following eight domains were assessed in each included trial:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants/personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Balance of baseline characteristics, and
8. Freedom from contamination or co-intervention.

For each trial, the review authors judged each domain as having a 'low risk of bias' or 'high risk of bias' as appropriate. Where trial methods were unclear, the review authors judged a domain as at 'unclear risk of bias'.

The review authors also assessed the overall risk of bias in included trials over all domains, categorising each trial as:

- Low risk of bias (plausible bias unlikely to seriously alter the results: all eight domains assessed as at low risk of bias)
- Moderate risk of bias (plausible bias that raises some doubt about the results: at least one domain assessed as at unclear risk of bias, but none at high risk of bias), or
- High risk of bias (plausible bias that seriously weakens confidence in the results: at least one domain assessed as at high risk of bias).

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| **Appraisal rating** | Overall, none of the trials included in this review were categorised as being at low risk of bias. Nine trials were categorised as being at unclear risk of bias, and the remaining 28 trials were categorised as being at high risk of bias. Of the seven trials relevant to this umbrella review, three trials were categorised as being at unclear risk of bias, and four trials were categorised as being at high risk of bias.<br><br>Eight trials were at categorised as being at low risk of bias for randomisation, 7 trials were categorised as being at high risk for randomisation, and 22 trials were categorised as being at an unclear risk of bias for randomisation.<br><br>Twenty-nine trials were categorised as being at low risk of bias for outcome ascertainment and 8 were categorised as being at an unclear risk of bias for outcome ascertainment. |

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| | The quality of evidence was assessed with reference to study limitations (risk of bias), directness of evidence, consistency of results, precision of estimates, and risk of publication bias. Overall, the quality of evidence in the review was moderate. The reason for downgrading was primarily due to study limitations (risk of bias).<br><br>When possible, an investigation of the degree of asymmetry of the funnel plots (as an indicator of publication bias and other biases related to sample size) was conducted. There was no relationship between prevented fraction and study precision. |
| **Method of analysis** | The chosen measure of treatment effect for the primary outcome, caries increment, was the prevented fraction (PF). For outcomes other than caries increment, the review authors summarised continuous data as average mean differences (MDs) in treatment effects along with their 95% confidence intervals (95% CIs), or, if different scales were used to measure the same outcome in different trials, standardised mean differences (SMDs) and their 95% CIs. They analysed dichotomous outcome data by calculating risk ratios (RRs) or, for adverse effects of fluoride treatment, risk differences (RDs).<br><br>Regarding unit of analysis, in trials with more than one relevant intervention a common control group, summary statistics were combined from all relevant experimental groups to obtain a measure of treatment effect. When cluster-randomised trials did not report results adjusted for clustering present in the data, the review authors performed an approximately correct analysis by estimating the design effect for such trials (Higgins 2011) by using the intraclass correlation coefficient (if reported) or intraclass correlation values obtained from a similar study.<br><br>The review authors conducted meta-analyses for the PFs as inverse variance weighted averages in Review Manager 5.3 (RevMan 2014), where the prevented fraction and standard error data [PF (SE)] were entered by using the generic inverse variance (GIV) method. The review authors estimated variances using the formula presented in Dubey 1965. They also used random-effects models to calculate a pooled estimate of effect for outcomes other than caries increment data.<br><br>The review authors specified three potential sources of heterogeneity a priori, hypothesising that the effect of fluoride mouthrinses on caries differs according to:<br>1. Baseline levels of caries severity<br>2. Exposure to other fluoride sources (in water, in toothpastes, etc), and<br>3. Frequency of application and fluoride concentration. |

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| | They examined the association of these factors with estimated effects (D(M)FS PFs) by performing random-effects metaregression analyses in Stata version 12.0 using the 'Metareg' command (Sharp 1998).<br><br>For the main meta-analysis of D(M)FS prevented fraction, the review authors planned to undertake a sensitivity analysis including trials with an overall assessment of low risk of bias but found no trials satisfying this criterion. Using a random-effects model, they did perform sensitivity analyses excluding trials:<br>• There they imputed missing standard deviations<br>• At high risk of bias for allocation concealment, and<br>• At unclear risk of bias for blinding of outcome assessment. |
| **Outcome(s) assessed** | Primary outcome 1: caries increment in permanent tooth surfaces (D(M)FS) and whole teeth (D(M)FT) (when reported), reported as changes from baseline<br><br>Primary outcome 2: caries increment in primary tooth surfaces (d(e)fs) and whole teeth (d(e)ft) (when reported)<br><br>Primary outcome 3: proportion of children developing new caries<br><br>Primary outcome 4: children not remaining caries free<br><br>Primary outcome 5: caries incidence/attack rate in permanent teeth/surfaces<br><br>Secondary outcome 1: adverse event - tooth staining<br><br>Secondary outcome 2: adverse event - signs of acute toxicity<br><br>Secondary outcome 3: adverse event - mucosal irritation/oral allergic reaction<br><br>*Note*. Primary outcomes 1 and 2 are identified as primary outcomes in the review. Primary outcomes 3 and 4 are identified as secondary outcomes in the review, but for the HRB's purposes are considered primary outcomes. Primary outcome 5 is not explicitly identified as an outcome in the methods section but is identified as an outcome in the results section. All secondary outcomes are identified as secondary outcomes in the review. |
| **Results/findings** | **Primary outcome 1: Caries increment in permanent tooth surfaces (D(M)FS) and whole teeth (D(M)FT)**<br>Thirty-five out of 37 included trials reported on D(M)FS increment. The pooled estimate of D(M)FS PF was 0.27 (95% confidence interval (CI), 0.23 to 0.30; $P < 0.0001$; $I^2 = 42\%$; 15,305 participants; 35 trials; moderate certainty |

of evidence), suggesting a large caries-preventive benefit from the use of fluoride mouthrinse versus placebo or no treatment at nearest to 3 years follow-up.

*Note*. In 15 out of the 35 pooled trials, participants were reported to have exposure to fluoride (water, toothpaste, varnish, tablets, or unspecified systemic fluoride). However, this was considered background fluoride exposure rather than part of the intervention of interest.

*Note*. One out of the 35 pooled trials involved the delivery of a complex intervention, in which participants in both groups received oral health instruction and professional prophylaxis in addition to the supervised used of fluoride mouthrinse.

Thirteen out of 37 included trials reported on D(M)FT increment. The pooled estimate of D(M)FT PF was 0.23 (95% CI 0.18 to 0.29; P < 0.0001; $I^2$ = 54%; 5,105 participants; 13 trials; moderate certainty of evidence), suggesting moderate to large benefit of fluoride mouthrinse versus placebo or no treatment within relatively narrow confidence intervals at nearest to 3 years follow-up.

*Note*. In one out of the 13 pooled trials, participants were reported to have exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. None of the pooled trials involved the delivery of a complex intervention.

**Primary outcome 2: Caries increment in primary tooth surfaces (d(e)fs) and whole teeth (d(e)ft)**
No trials included in the review reported on this outcome for primary teeth.

**Primary outcome 3: Proportion of children developing new caries**
There was no evidence that fluoride mouthrinse reduced the risk of developing 1 ≥ or more new caries compared to placebo or no treatment at 2-3 years follow-up (risk ratio 0.77, 95% CI 0.46 to 1.29; 3 trials; 2,030 participants; $I^2$ = 96%, very low certainty of evidence). All three trials examined the risk of developing new caries on permanent teeth.

*Note*. In one out of the three pooled trials, participants were reported to have exposure to fluoride toothpaste. However, this was considered background fluoride exposure rather than part of the intervention of interest. None of the pooled trials involved the delivery of a complex intervention.

**Primary outcome 4: Children not remaining caries free**
No included trials reported on this outcome.

**Primary outcome 5: Caries incidence/attack rate in permanent teeth/surfaces**
The review authors noted that these outcomes were simply other measures/indices for dental caries increment in permanent teeth/surfaces and required no further consideration.

**Secondary outcome 1: Adverse event - Tooth staining**
One trial reported a significant difference in stain score in children who used amino fluoride mouthrinse (n = 84; mean score = 3.57) compared to a control group (n = 44; mean score = 1.05). The same trial reported a non-significant difference in children who used a sodium fluoride mouthrinse (n = 87; mean score = 0.97) compared to a control group (n = 52; mean score = 0.31). The certainty of evidence was very low.

Two trials that tested stannous fluoride mouthrinsing against placebo rinsing incompletely reported on tooth staining. In one trial, researchers stated that "some staining was observed in a very small number of children in the trial, where approximately six children had tenacious staining that required a rubber cup prophylaxis carried out", but they did not indicate to which groups these children belonged. In the other trial, researchers stated that "most of the participants who exhibited poor oral hygiene had some amount of yellow pigmentation, somewhat more noticeable in the children in the test group". The certainty of evidence was very low.

**Secondary outcome 2 Adverse event - Signs of acute toxicity**
No included trials reported on this outcome.

**Secondary outcome 3: Adverse event - Mucosal irritation/oral allergic reaction**
One trial reported incompletely on oral soft tissue irritation/signs of sensitivity (allergic reaction) to the rinse. The researchers described no cases of mucosal hypersensitivity after periodical examinations of every subject (1 trial; 434 participants; very low certainty of evidence).

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| **Significance/direction** | An average caries reduction in terms of decayed, missing and filled tooth surfaces (DMFS) in permanent teeth of about 27% can be expected from use of fluoride mouthrinse (on a daily or weekly/fortnightly basis and at two main strengths: 230ppm F and 900 ppm F). The meta-analysis of the 35 studies assessing the effect of fluoride mouthrinse on the permanent dentition suggests that this reduction falls within narrow confidence intervals (23% to 30%).<br><br>There was insufficient information available to draw any reliable conclusions on the effect of mouthrinse at reducing the development of new caries and on the possible adverse effects of the procedure, such as tooth staining or oral soft tissue irritation/allergic reactions. |

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| **Heterogeneity** | The review authors specified three potential sources of heterogeneity a priori:<br>1. Baseline levels of caries<br>2. Exposure to other fluoride sources, and<br>3. Frequency of application and fluoride concentration.<br><br>The review authors examined the association of these factors with estimated effects. Univariate metaregression suggested no significant association between estimates of D(M)FS prevented fractions and prespecified factors. Further univariate metaregression analyses on other characteristics not specified a priori showed no significant associations. Therefore, the heterogeneity observed in the analyses measuring proportion of children developing new caries was not explained. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as moderate for primary outcome 1 as moderate (downgraded for unclear or high risk of bias s in sequence generation and allocation concealment). The certainty of evidence for primary outcome 3 was not reported.<br><br>The HRB authors graded the certainty of evidence in this review as very low, downgraded for study design (included of quasi-randomised RCTs, high proportion of trials with inadequate randomisation, high heterogeneity in findings, and overall review quality. |
| **References to previously published versions** | Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride mouthrinses for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No: CD002284.[DOI:0.1002/14651858.CD002284] |

| Parameter | Riley *et al.* (2015) extraction |
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| **First Author and year of publication** | Riley *et al.* (2015) |
| **Objectives (exact review question(s) and page number)** | To assess the effects of different xylitol-containing products on preventing dental caries in children and adults (p7). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); topical other chemicals, xylitol; combined intervention.<br><br>Baseline caries was reported in seven out of 10 included trials. Only one of these seven trials included caries-free participants at baseline. |

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| | The included 10 trials randomised 7,969 participants, and 5,903 were evaluated in analyses. One trial investigated the effects of xylitol in adults, while the remaining nine trials included children only. Of the nine trials, five included children ranging from 8 to 13 years of age, and four included children ranging from 1 month to 3 years of age. In the trial including adults, approximately two thirds of the participants were females, while all other trials had roughly equal proportions of females and males. |
| **Setting/context** | The trials were conducted in Costa Rica (2 trials), Estonia (1 trial), Finland (2 trials), the Republic of the Marshall Islands (1 trial), Sweden (2 trials), the USA (2 trials).<br><br>Four trials were conducted in a dental clinical setting, two trials were conducted in a school setting, and two trials were conducted in both a school (where the intervention was given) and dental clinic (where the clinical examinations took place) setting. The remaining two trials were conducted in a community setting and a healthcare centre setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was xylitol-containing products, and the intervention had to be provided for at least one year for the trial to be included. The control group was placebo or no treatment (which included routine care). Placebos considered appropriate were non-cariogenic placebos without claims of active anti-caries properties. The review authors also included trials comparing one xylitol-containing product with another.<br><br>Of the included trials, four involved the use of xylitol products (defined as lozenges, sucking tablets and candies) which were to be sucked, three involved xylitol-containing fluoride toothpaste, one involved xylitol tablets, one involved a xylitol syrup, and one involved xylitol wipes. Alas, in total, the review authors compared eight interventions:<br>1. Xylitol lozenges versus control lozenges in adults<br>2. Xylitol candy versus control (sorbitol) candy in children<br>3. Xylitol lozenges versus no treatment in children<br>4. Xylitol syrup versus control (low-dose xylitol) syrup in children<br>5. Xylitol sucking tablets versus no treatment in children<br>6. Xylitol-containing fluoride toothpaste versus control toothpaste in children<br>7. Xylitol tablet versus control (sorbitol tablet) in children, and<br>8. Xylitol wipes versus control wipes in children<br><br>The dosage of xylitol ranged from 200mg to 600mg per day to 8g per day. In the three toothpaste trials, the total daily dosage was unclear. Of the four trials including younger children, two used very low daily doses of 200mg to 600mg and 1g, whilst two used higher daily doses of 4.2g and 8g. In the two |

trials with older children, the daily dose was 7.5g and 4.7g. In the adult trial, the dose was 5g per day.

Follow-up periods ranged from one to three years.

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| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health Group's Trials Register (to 14 August 2014)<br>• Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2014, Issue 7)<br>• MEDLINE via OVID (1946 to 14 August 2014)<br>• EMBASE via OVID (1980 to 14 August 2014)<br>• CINAHL via EBSCOhost (1980 to 14 August 2014)<br>• Web of Science Conference Proceedings (1990 to 14 August 2014)<br>• ProQuest Dissertations and Theses (1861 to 14 August 2014)<br>• The US National Institutes of Health Trials Register (http://clinicaltrials.gov) (to 14 August 2014), and<br>• The WHO Clinical Trials Registry Platform (http://apps.who.int/trialsearch/default.aspx) (to 14 August 2014).<br><br>No restrictions were placed on language or date of publication. Any non-English papers identified were translated and assessed for eligibility.<br><br>To identify possible unpublished or ongoing studies, the review authors contacted experts and organisations known in the field. They also examined the reference lists of included clinical trials to help identify additional studies. Results of handsearching done as part of the Cochrane Worldwide Handsearching Programme and uploaded to CENTRAL were also included.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion and consensus, and where necessary, consultation with a third review author.<br><br>It was not stated when the protocol was published, nor was a registration number provided. However, differences between the protocol and published review were noted.<br><br>The review was supported by funding from the National Institute for Health Research (NIHR) and the Cochrane Oral Health Group Global Alliance partners.<br><br>None of the review authors declared a conflict of interest. |

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| **Date range (years) of included studies** | The 10 included trials were published between 1991 and 2014. |
| **Number of primary studies included in the systematic review** | The review authors included 10 randomised controlled trials. Of these, eight were of parallel design, and the remaining two used a cluster-randomised design.<br><br>Two trials stated that they had received non-industry funding. Three trials stated that they received non-industry funding, but that industry supplied the interventions. Four trials were clearly industry funded, in other words industry provided economical support. The remaining trial only stated that industry provided the interventions. |
| **Types of studies included** | The review authors included 10 randomised controlled trials: Bader (2013), Honkala (2014), Lenkkeri (2012), Milgrom (2009), Oscarson (2006), Petersson (1991), Sintes (1995), Sintes (2002), Taipale (2013), Zhan (2012).<br><br>A list of excluded trials and the reasons for exclusion are available in a tabular appendix. |
| **Country of origin of included studies** | The trials were conducted in Costa Rica (2 trials), Estonia (1 trial), Finland (2 trials), the Republic of the Marshall Islands (1 trial), Sweden (2 trials), the USA (2 trials). |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of the included studies using the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Disagreements were resolved through discussion or consensus with a third review author.<br><br>The following seven domains were assessed in each trial:<br>1. Sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessors (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective outcome reporting (reporting bias)<br>7. Other bias<br><br>The review authors also categorised the overall risk of bias of individual trials. Individual trials were categorised as being at: low, high or unclear risk of bias according to the following:<br>• Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias |

- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains had an unclear risk of bias, or
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias.

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| **Appraisal rating** | Overall, only one of the trials included in this review were categorised as being at low risk of bias. Two trials were categorised as being at unclear risk of bias, and the remaining seven trials were categorised as being at high risk of bias.<br><br>Six trials were at categorised as being at low risk of bias for randomisation and four were categorised as being at unclear risk of bias for randomisation.<br><br>All included trials were categorised as being at low risk of bias for outcome ascertainment.<br><br>The quality of evidence was assessed with reference to the overall risk of bias of the included studies, the directness of evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias. Overall, the quality of evidence in the review was low to very low due to the small number of available studies, uncertain studies, and study limitations (risk of bias).<br><br>The review authors had planned to generate funnel plots and assess publication bias according to the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). However, no meta-analysis conducted by the review authors included more than 10 studies. |
| **Method of analysis** | The measure of treatment effect was the Prevented Fraction (PF). For dichotomous outcomes (for example, with/without caries increment), the estimate of effect of an intervention was expressed as a risk ratio (RR) together with 95% confidence interval (CI).<br><br>The meta-analysis was conducted using inverse variance weighted averages. This was only possible for xylitol toothpastes. Variances were estimated using the formula presented in Dubey 1965. A fixed-effect model was used as there were less than four studies in the meta-analysis. Random-effects models were used if there were four or more studies in a meta-analysis. Risk ratios were combined for dichotomous data using random-effects models if there were at least four trials in a meta-analysis and fixed-effect models if there were less than four trials.<br><br>Subgroup analyses were planned, investigating the effect of:<br>1. Preparation type (toothpastes, mouthrinses, chewing gum, etc.)<br>2. Age |

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| | 3. Doses and concentration of preparations, and<br>4. Deciduous and permanent teeth.<br><br>A sensitivity analysis was planned, excluding studies with an unclear or high risk of bias overall, but not carried out due an insufficient number of included trials.<br><br>Regarding unit of analysis, the review authors used mean dental caries increments which were calculated for each patient. They included cluster randomised trials and used the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to take the clustering into account if the published report did not do so. This involved using an intra-class correlation coefficient (ICC) of 0.05 to estimate the design effect. |
| **Outcome(s) assessed** | Primary outcome 1: caries increment as a continuous outcome, measured by change from baseline in decayed-filled teeth/surfaces (DFT/DFS) or decayed-missing-filled teeth/surfaces (DMFT/DMFS) for permanent teeth, or dmfs/d(e)fs and dmM/d(e)M for deciduous teeth<br><br>Primary outcome 2: caries increment as a dichotomous outcome<br><br>Secondary outcome 1: adverse events<br><br>*Note*. Both primary and secondary outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Caries increment as a continuous outcome**<br><u>Comparison 1: Xylitol lozenges versus control lozenges in adults, permanent dentition:</u><br>The results from one trial that compared xylitol (5g per day) lozenges with control lozenges over 33 months showed no difference in caries increment for DFS (MD -0.64; 95%<br>CI -1.58 to 0.30; P = 0.18; 669 participants; 1 trial; low risk of bias), translating to a non-significant PF of 8%. Participants in this trial had exposure to fluoride toothpaste, water and had experience of professionally applied fluoride. However, this was considered background fluoride exposure, rather than part of the intervention of interest.<br><br><u>Comparison 2: Xylitol candy versus control (sorbitol) candy in children, assumed mixed dentition:</u><br>One trial compared xylitol (7.5 g per day) candy with control (sorbitol) candy over 36 months in 252 children. However, the review authors were unable to use the data in analyses.<br><br><u>Comparison 3: Xylitol lozenges versus no treatment in children, permanent dentition:</u> |

The results from one trial that compared xylitol (4.7g per day) lozenges with no treatment over 24 months with a 48-month follow-up showed no difference in caries increment for DMFS (MD 0.28; 95% CI -0.99 to 1.55; P = 0.67; 200 participants; 1 trial; high risk of bias), translating to a non-significant PF of 10% in favour of the no treatment group. Participants in this trial had exposure to fluoride water. However, this was considered background fluoride exposure, rather than part of the intervention of interest.

Comparison 4: Xylitol syrup versus control (low-dose xylitol) syrup in children, primary dentition:
One trial compared xylitol (8 g per day) syrup with low-dose xylitol (2.67g per day) syrup over 12 months. The higher dose of xylitol syrup resulted in a statistically significant reduction in the mean number of decayed primary teeth (MD -1.10; 95% CI -2.03 to -0.18; P = 0.02; 94 participants; 1 trial; unclear risk of bias), translating to a 58% reduction in caries.

Comparison 5: Xylitol sucking tablets versus no treatment in children, primary dentition:
One trial compared xylitol (0.48-1 g per day) sucking tablets with no treatment over 18 months, with a 24-month follow-up. There was no difference in caries increment for dmfs (MD -0.42; 95% CI -1.12 to 0.28; P = 0.24; 118 participants; 1 trial; high risk of bias), although when this was converted into PF it was marginally statistically significant and equated to a 53% reduction in caries in favour of the xylitol group.

Comparison 6: Xylitol toothpaste versus control toothpaste in children, permanent dentition:
Three studies made this comparison over 30 to 36 months. One of the studies, analysing 248 children, did not report data in a usable format, but found no difference in the number of DFS between any group.

The review authors were able to pool the data from the other two studies in a meta-analysis, which revealed that fluoride toothpaste containing 10% xylitol (two daily brushing) resulted in a 13% reduction in caries increment for DFS (PF -0.13; 95% CI -0.18 to -0.08; P < 0.00001; $I^2$ = 0%; 4,216 participants; 2 trials; low certainty of evidence). In one trial, participants used 0.243% NaF toothpaste (1100ppm fluoride) and in the other, participants under 0.836% sodium monofluorophosphate toothpaste (1100 ppm fluoride).

*Note*. The review authors reported that in both trials, participants had exposure to fluoride (water and/or salt). However, this was considered existing background exposure rather than part of the intervention of interest.

Comparison 7: Xylitol tablet versus control (sorbitol) tablet in children, permanent or primary dentition:
No trials comparing these interventions reported this outcome.

Comparison 8: Xylitol wipes versus control wipes in children, permanent or primary dentition:
No trials comparing these interventions reported this outcome.

**Primary outcome 2: Caries increment as a dichotomous outcome**
Comparison 1: Xylitol lozenges versus control lozenges in adults:
No trials comparing these interventions reported this outcome.

Comparison 2: Xylitol candy versus control (sorbitol) candy in children, assumed mixed dentition:
One trial compared xylitol (7.5g per day) candy with control (sorbitol) candy over 36 months in 252 children. However, the review authors were unable to use the data in analyses.

Comparison 3: Xylitol lozenges versus no treatment in children:
No trials comparing these interventions reported this outcome.

Comparison 4: Xylitol syrup versus control (low-dose xylitol) syrup in children:
No trials comparing these interventions reported this outcome.

Comparison 5: Xylitol sucking tablets versus no treatment in children, primary dentition:
Results from the same trial in comparison 5 of primary outcome 1 indicated no difference in the number of infants with a caries increment when comparing the effect of xylitol sucking tablets (0.48-1g per day) with no treatment over 18 months, with a 24-month follow-up (RR 0.72, 95% CI 0.35 to 1.45, P = 0.35; 1 trial; 118 participants; high risk of bias).

Comparison 6: Xylitol toothpaste versus control toothpaste in children, permanent or primary:
No trials comparing these interventions reported this outcome.

Comparison 7: Xylitol tablet versus control (sorbitol) tablet in children, primary dentition:
There was no difference in the number of infants with a dmfs increment when comparing the effect of a xylitol tablet (200-600mg per day administered via a slow-release pacifier or crushed up on a spoon) with a control tablet over 24 months, at 48 months follow-up (RR 3.08, 95% CI 0.69 to 13.65, P = 0.14; 1 trial; 62 participants, high risk of bias).

Comparison 8: Xylitol wipes versus control wipes in children, primary dentition:

There was no difference in the number of infants with a caries increment when comparing the effect of xylitol wipes (two wipes to clean the teeth and gums three times per day, 4.2g xylitol per day) with a control wipe at 1 year follow-up (RR 0.14, 95% 0.02 to 1.07, P = 0.06; 1 trial; 44 participants; unclear risk of bias).

**Secondary outcome 1: Adverse events**

Comparison 1: Xylitol lozenges versus control lozenges in adults:
One trial reported the patterns of adverse effects in (sores in the mouth, cramps, bloating, constipation, flatulence, and loose stool or diarrhoea) were similar for both groups.

Comparison 2: Xylitol candy versus control (sorbitol) candy in children:
One trial reported that there were no adverse effects for either group.

Comparison 3: Xylitol lozenges versus no treatment in children:
There were no usable data presented for this outcome.

Comparison 4: Xylitol syrup versus control (low-dose xylitol) syrup in children:
One trial reported adverse effects that were not reported in a usable format, but the reported rates of loose stools and diarrhoea were very similar in both groups. There were no serious adverse effects experienced during the trial.

Comparison 5: Xylitol sucking tablets versus no treatment in children:
No trials comparing these interventions reported this outcome.

Comparison 6: Xylitol toothpaste versus control toothpaste in children:
Two trials reported that there were no adverse effects in either group.

Comparison 7: Xylitol tablet versus control (sorbitol) tablet in children:
No trials comparing these interventions reported this outcome.

Comparison 8: Xylitol wipes versus control wipes in children: One trial reported that where no adverse effects for either group.

**Significance/direction**

There is low quality evidence that fluoride toothpastes containing xylitol may reduce caries in children when compared to fluoride-only toothpastes. There is also a very small body of low-quality evidence, consisting of one small study, that a high dose of xylitol syrup reduces caries in infants when compared to a low dose.

Overall, the evidence found was of low to very low quality and is insufficient to determine whether any other xylitol-containing products can prevent caries in infants, older children, or adults.

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| **Heterogeneity** | Meta-analyses could not be conducted for most outcomes due to the limited number of trials in the comparisons. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence for the caries increment prevented fraction outcome as low, downgraded twice due to high risk of bias and that fact that both trials reporting this outcome were conducted by the same authors on the same population.<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Alsabek *et al.* (2021) extraction |
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| **First Author and year of publication** | Alsabek *et al.* (2021) |
| **Objectives (exact review question(s) and page number)** | To determine the effectiveness of hydrophilic resin-based sealant (RBS) in preventing pits and fissures caries in permanent teeth.<br><br>To determine the retention rate of a hydrophilic RBS as compared to alternative treatments (p2). |
| **Participants (characteristics and numbers)** | Permanent teeth; sealants, resin.<br><br>The majority of permanent teeth included were sound, except in one trial, which contained molars with initial caries lesion scored 1 or 2 according to the ICDAS II.<br><br>The number of teeth evaluated in the 13 included trials was 2,561. The age of participants ranged from 5 to 15 years. Information pertaining to the sex of the participants was not reported. |
| **Setting/context** | The countries of origin of the included trials were not stated.<br><br>Eight trials were conducted at university clinics, and one trial was conducted in a private clinic. The remaining three trials either took place in outreach centres or within a school setting. |
| **Description of Interventions/ phenomena of interest** | The review included any trial in which a hydrophilic resin-based sealant was used on occlusal pits and fissures. The control group included participants who did not receive any treatment, or received standard care of topical fluoride application, conventional resin-based sealant, or other treatment |

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| | options like glass-ionomer. The intervention was the use of a hydrophilic resin-based sealant. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Scopus<br>• Ovid MEDLINE<br>• Ovid EMBASE<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Web of Science, and<br>• Pubmed.<br><br>The search was done without applying any search filters. To capture unpublished studies and ongoing clinical trials, the review authors searched the clinical trial registration database (www.clinicaltrial.gov) to identify any articles that might not have been identified from the electronic search strategy. Only studies with full text available in English were included. All studies were retrieved from inception to March 2021.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements at the screening stage were resolved through consultation with a third review author (disagreement resolution at the extraction stage was not reported).<br><br>A protocol was registered with PROSPERO (ID: CRD42021240049).<br><br>The review authors declared no funding sources and no conflicts of interest. |
| **Date range (years) of included studies** | The 13 included trials were published between 2012 and 2019. |
| **Number of primary studies included in the systematic review** | The review authors included 13 randomised controlled trials, all of which used a split-mouth design. The evaluation time for the follow-up assessments ranged from one month to 24 months.<br><br>The main comparison to the hydrophilic resin-based sealant was resin sealant. However, three trials compared it to glass-ionomer sealant, one trial compared it in a condition of enamel contamination after etching, and one trial compared it to giomer-based sealant. Some trials included more than one comparison group. Out of the six trials included in the quantitative data synthesis, four of them had the conventional resin-based comparison and two of them had the glass-ionomer sealant comparison.<br><br>Funding sources of the included trials were not reported. |

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| **Types of studies included** | The review authors included 13 randomised controlled trials: Alsabek (2019), Askarizadeh (2017), Bhat (2013), Bhatia (2012), Eskandarian (2015), G. Khatri (2015), Haricharan (2019), Khatri (2019), M. Mohanraj (2019), Prabakar (2018), Ratnaditya (2015), Schlueter (2012), BG Topal (2019).<br><br>The excluded studies were not listed, but reasons for exclusion were reported. |
| **Country of origin of included studies** | The countries of origin of the included trials were not stated. |
| **Appraisal instrument(s)** | Cochrane's risk of bias tool (version 1) was used to assess the quality of the included trials. This tool consists of the following domains:<br>• Sequence generation (selection bias)<br>• Allocation sequence concealment (selection bias)<br>• Blinding of participants and personnel (performance bias)<br>• Blinding of outcome assessors (detection bias)<br>• Incomplete outcome data (attrition bias)<br>• Selective outcome reporting (reporting bias), and<br>• Other biases.<br><br>A judgment of 'Low' indicated a low risk of bias, 'High' indicated a high risk of bias, and 'Unclear' indicated unclear or unknown risk of bias. |
| **Appraisal rating** | Overall, four of the included trials were categorised as having a low risk of bias. Six trials were categorised as having a high risk of bias as they had either at least one domain marked as a high bias or marked unclear bias in two domains that could have biased the outcome. Three trials were categorised as having an unclear risk of bias.<br><br>Seven trials were categorised as having a low risk of bias for randomisation, four trials were categorised as having an unclear risk of bias for randomisation, and two trials were categorised as having a high risk of bias for randomisation.<br><br>Ten trials were categorised as having a low risk of bias for outcome ascertainment, and three trials were categorised as having an unclear risk of bias for outcome ascertainment.<br><br>The GRADE approach for assessing the quality of the body of evidence was not used.<br><br>The review authors had planned to generate funnel plots and assess publication bias according to the recommendations described in the |

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| | Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). However, no meta-analysis conducted by the review authors included more than 10 studies. |
| **Method of analysis** | A meta-analysis was performed using Review Manager Software for only good and fair quality studies. A good quality trial was defined as a trial in which all risk of bias domains were marked as low. Trials that either did not meet a criterion in one domain or were categorized unclear in two domains and were judged to have unlikely biased outcomes, were considered fair quality. Poor-quality trials were excluded from analyses.<br><br>Dichotomous data were represented as event and total for the intervention and control groups for primary and secondary outcomes. Data were summarized by calculating the risk ratio and the 95% confidence interval and analysed using a fixed-effect model for homogenous outcomes. A random-effects model was used for heterogeneous outcomes. The I-squared ($I^2$) test and the P-value of heterogeneity were used to assess statistical heterogeneity. In contrast, sensitivity tests (excluding trials that may have caused detected heterogeneity) were conducted when outcome heterogeneity was present. |
| **Outcome(s) assessed** | Primary outcome 1: caries incidence<br><br>Secondary outcome 1: retention rate<br><br>*Note*. Primary outcome 1 is identified as a secondary outcome in the review, but for the HRB's purposes is considered a primary outcome. Secondary outcome 1 is identified as a primary outcome in the review, but for the HRB's purposes is considered a secondary outcome. |
| **Results/findings** | **Primary outcome 1: Caries incidence**<br>Of the nine trials that reported caries incidence as an outcome, five contributed data to the quantitative analyses.<br><br>There was no difference in caries incidence between teeth that received hydrophilic sealants and control teeth at six months follow-up (RR 0.97; 95% CI 0.91 to 1.03; P = 0.31; 4 trials, 392 teeth, $I^2$ = 37%). Similarly, there was no difference in caries incidence between the two groups following sensitivity tests (RR 0.99; 95% CI 0.98 to 1.01; P = 0.43).<br><br>There was also no difference in caries incidence between teeth that received hydrophilic sealants and control teeth at twelve months follow-up (RR 0.97; 95% CI 0.91 to 1.03; P = 0.31; 5 trials, 588 teeth, $I^2$ = 19%). Similarly, there was no difference in caries incidence between the two groups following sensitivity tests (RR 0.96; 95% CI 0.91 to 1.01; P = 0.31).<br><br>**Secondary outcome 1: Retention rate** |

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| | Of the 12 trials that reported retention rate as an outcome, six contributed data to the quantitative analyses.<br><br>There was no difference in retention rate between the intervention and comparison group at six months follow-up (RR 1.04; 95% CI 0.97 to 1.11; P = 0.25; 5 trials; 472 teeth; $I^2$ = 10%). When sensitivity tests were conducted including high risk of bias trials, there was no difference in the conclusion (RR 1.01, 95% CI 0.96 to 1.07, P = 0.66).<br><br>There was no difference in retention rate between the intervention and comparison group at twelve months follow-up (RR 1.03; 95% CI 0.89 to 1.19; P = 0.69; 5 trials; 588 teeth; $I^2$ = 79%). When sensitivity tests were conducted excluding high risk of bias trials, there was no significant difference in the conclusion (RR 0.80, 95% CI 0.62 to 1.04, P = 0.1). Following an additional sensitivity test excluding one trial (because of uncertainty regarding the trial authors' following of the manufacturers' instructions), the analysis showed low heterogeneity ($I^2$ = 24%) with a risk ratio of 1.07 (95% CI 0.97 to 1.19, P = 0.17). |
| **Significance/direction** | The meta-analysis showed no statistically significant difference between the hydrophilic resin-based sealant and alternative treatment options (such as conventional resin or glass-ionomer) regarding retention or caries prevention for six- and twelve-month follow-up periods. Future studies are required to investigate longer-term outcomes.<br><br>The review authors recommend the usage of hydrophilic RBS in cases where absolute isolation is not accomplished (uncooperative paediatric patient, semi-erupted teeth, outreach centers, etc.,) since they have a similar retention rate and carries preventing/arresting to the convention resin-based sealants. |
| **Heterogeneity** | The trials included in the analyses were homogenous except at the twelve-month retention rate assessment. Homogeneity was, however, achieved by excluding one trial from the sensitivity analysis. The study that was excluded had shown that hydrophilic resin-based sealant was inferior to hydrophobic resin-based sealant in terms of retention rate. However, the review authors note this trial may have yielded different findings had the trial authors followed manufacturers' instructions. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Dos Santos *et al.* (2013) extraction |
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| **First Author and year of publication** | Dos Santos *et al.* (2013) |
| **Objectives (exact review question(s) and page number)** | To assess the effects of fluoride toothpastes on the prevention of caries in the primary dentition of preschool children (p2). |
| **Participants (characteristics and numbers)** | Primary dentition; combined intervention.<br><br>Baseline caries was reported in seven out of the eight included trials. Only two of these seven trials included caries-free participants at baseline.<br><br>The eight included trials randomised a total of 13,097 children, whose ages ranged from 8 months to 7 years. Information pertaining to the sex of the participants was reported in only one trial (which included a similar proportion of females and males).<br><br>*Note*. This review is categorised as a combined intervention because 7 out of the 8 included trials evaluated fluoride toothpaste interventions delivered alongside oral health education. |
| **Setting/context** | The trials were conducted in China (4 trials), England (3 trials), and Lithuania (1 trial).<br><br>Four trials were conducted in a primary school setting, three trials were conducted in a community setting, and one trial was conducted in a healthcare centre setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was fluoride toothpastes. The control was a placebo or no intervention. Fluoride toothpastes were considered irrespective of fluoride concentration, fluoride agent, abrasive system and pH.<br><br>There were no restrictions regarding the presence or absence of fluoridated water. However, trials that included other fluoride products (gel, varnish, mouthrinse) or other non-fluoride products (chlorhexidine, xylitol, dental sealants) were excluded.<br><br>In the included trials, fluoride concentrations in the toothpastes differed markedly. In seven trials, oral health education was also part of the intervention. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials (CENTRAL/CCTR) |

- MEDLINE via PubMed
- WEB OF SCIENCE
- EMBASE
- LILACS
- BBO
- A Brazilian database of thesis and dissertations (Banco de Teses CAPES)
- A Brazilian register of ethically approved projects involving human beings (SISNEP), and
- And two international registers of ongoing trials (Current Controlled Trials and ClinicalTrials.gov).

The databases were consulted from date of online availability to January 2010. Meeting abstracts of the International Association for Dental Research (2001 –2011) and the European Organisation for Caries Research (1998–2011) were searched, and the reference lists of eligible trials and reviews were checked, to identify any additional studies. There were no language restrictions. When necessary, studies were translated.

The review authors also contacted specialists in the field which included authors of studies about fluoride and dental/oral epidemiology professors/researchers.

Sixteen dentistry journals were hand searched:

- Acta Odontologica Scandinavica
- Archives of Oral Biology
- British Dental Journal
- Caries Research
- Community Dental Health
- Community Dentistry & Oral Epidemiology
- European Archives of Paediatric Dentistry
- European Journal of Oral Sciences
- International Dental Journal
- International Journal of Paediatric Dentistry
- Journal of the American Dental Association
- Journal of Clinical Pediatric Dentistry,
- Journal of Dental Research
- Journal of Dentistry for Children

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| | • Journal of Public Health Dentistry, and<br>• Pediatric Dentistry.<br><br>The Cochrane Collaboration organised a worldwide handsearching programme, which covers all the above-mentioned journals. The review authors checked the date of the last handsearching update for each journal, and handsearching was complemented until June 2010 by two independent examiners.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through consensus after consulting a third review author.<br><br>There was no mention of a protocol being prepared or published, and no registration number was provided.<br><br>Funding sources and conflicts of interest were also not provided. |
| **Date range (years) of included studies** | The eight included trials were published between 1998 and 2008. |
| **Number of primary studies included in the systematic review** | The review authors included eight randomised controlled trials, with a follow-up period of at least one year.<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included eight randomised controlled trials: Andruškeviciene (2008), Davies (2002), Fan (2008), Jackson (2005), Rong (2003), Schwarz (1998), Whitlle (2008), You (2002).<br><br>The excluded studies were not listed, but reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in China (4 trials), England (3 trials), and Lithuania (1 trial). |
| **Appraisal instrument(s)** | The review authors used the Cochrane Collaboration's tool for assessing risk of bias. The following domains were assessed in each included trial:<br>• Generation of allocation sequence<br>• Allocation concealment<br>• Blinding of participants and outcome assessors<br>• Incomplete outcome data, and<br>• Selective outcome reporting. |

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| | Each domain was classified as having low, high or uncertain risk of bias. For this review, nonblinding of participants was judged as unlikely to introduce bias so single blinded trials, as long as the outcome assessors were blinded, were considered as having low risk of bias. Also, trials were considered to be free of selective outcome reporting, and thus having low risk of bias when the outcomes included caries increment at both surface and tooth level and the proportion of children developing caries.<br><br>Other possible sources of bias, defined by the authors of this review, included:<br>• Losses to follow-up (low risk of bias when <20%)<br>• Adequate diagnosis reliability (low risk of bias when at least food, according to Altman)<br>• Baseline balance (low risk of bias when data showed baseline balance regarding age, gender, socioeconomic status and caries level), and<br>• Free of contamination (low risk of bias when strategies to avoid contamination between groups were reported). |
| **Appraisal rating** | The authors did not provide an overall assessment of risk of bias for each trial. However, graphical information provided in the paper indicates that, overall, all the included trials were categorised as being at high risk of bias. The review authors noted that crucial aspects, such as sequence generation and allocation concealment, had not been reported adequately and thus were judged as unclear in half of the trials. The trials had also failed to provide enough information on diagnosis reliability, baseline balance and contamination and, in all studies, except for one, selective outcome reporting was present.<br><br>Three trials were categorised as being at low risk of bias for randomisation, one was categorised as being at high risk of bias for randomisation, and four were categorised as being at an unclear risk of bias for randomisation.<br><br>Six trials were categorised as being at low risk of bias for outcome ascertainment, one was categorised as being at high risk of bias for outcome ascertainment, and one was categorised as being at an unclear risk of bias for outcome ascertainment.<br><br>The GRADE approach for assessing the quality of the body of evidence was not used.<br><br>The paucity of included trials prevented the use of meta-regression to assess publication bias statistically. |
| **Method of analysis** | Meta-analyses of prevented fractions (PF) were performed to assess the effect of fluoride toothpaste on the number of decayed, missing owing to |

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| | caries and filled teeth (dmft) and dental surfaces (dmfs). PFs were calculated by subtracting<br>the mean caries increment in the test group from the mean caries increment in the control group and then dividing by the mean caries increment in the control group. They correspond to the proportion of disease in the control group that could have been prevented had the intervention been implemented. Confidence intervals of PFs were calculated using Fieller's method.<br><br>Meta-analyses were also performed to obtain a pooled relative risk to assess the effect of fluoride toothpastes on the proportion of children developing caries.<br><br>Meta-analyses were carried out separately for low (<600 ppm) and standard (1000–1500 ppm) fluoride toothpastes, using the software Stata®11.1<br><br>Heterogeneity of studies was assessed by visual inspection of forest plots, chi-square homogeneity test ($v^2$) and Higgins index ($I^2$). A random-effects model was used in the presence of heterogeneity ($v^2$ with significance level <0.10 and $I^2$ > 50%).<br><br>Subgroup and sensitivity analyses were not conducted. |
| **Outcome(s) assessed** | Primary outcome 1: dental caries increment in the primary dentition, measured by the number of decayed, missing owing to caries and filled surfaces (dmfs)<br><br>Primary outcome 2: dental caries increment in the primary dentition, measured by the number of decayed, missing owing to caries and filled teeth (dmft)<br><br>Primary outcome 3: proportion of children developing dental caries<br><br>*Note*. All outcomes are identified in the review as presented here (as primary outcomes). |
| **Results/findings** | **Primary outcome 1: Dental caries increment (dmfs)**<br>A meta-analysis of two studies comparing low fluoride (<600 ppm) toothpastes with no intervention yielded a pooled PF of 40% (95% CI 5-75; $I^2$ = 73.8%; 561 participants; 2 trials; high risk of bias), indicating a caries-preventive effect of low-fluoride toothpaste at the surface level.<br><br>A meta-analysis of five studies comparing standard fluoride (1000-1500 ppm) toothpastes with placebo or no intervention yielded a pooled PF of 31% (95% CI 18-43; $I^2$ = 65.6%; 2,644 participants; 5 trials; all high risk of bias), indicating a caries-preventive effect of standard fluoride toothpaste at the surface level. |

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| | **Primary outcome 2: Dental caries increment (dmft)**<br>A meta-analysis of two studies comparing low fluoride (<600 ppm) toothpastes and no intervention yielded a pooled PF of 24% (95% CI -17 to 66; $I^2$ = 97.4%; 2,830 participants; 2 trials; both high risk of bias), indicating a limited (or no) caries-preventive effect of low fluoride toothpaste at the whole tooth level.<br><br>One trial compared standard fluoride (1000-1500 ppm) toothpaste with no intervention showed that 12-month-old children that used 1450 ppm F toothpaste for approximately 5½ years had mean caries levels at final examination of 2.15 (±2.96) whereas those receiving no intervention had mean caries levels at final examination of 2.57 (±3.16); the PF was 16% (95% CI 8 to 25; 2,555 participants; 1 trial; high risk of bias), indicating a caries-preventive effect of standard-fluoride toothpaste at the whole tooth level.<br><br>**Primary outcome 3: Proportion of children developing dental caries**<br>The proportion of children who developed dental caries was not different in the low fluoride fluoride (<600 ppm) toothpaste group compared to the control group (RR 0.87, 95% CI 0.65 to 1.17; 2 trials; 1,328 participants; $I^2$ = 91.2%).<br><br>Conversely, the proportion of children who developed dental caries was lower in the standard fluoride (1000-1500 ppm) toothpaste group compared to the control group (RR 0.86, 95% CI 0.81 to 0.93, 2 trials; 1,338 participants, $I^2$ = 0.0%), indicating they had a significantly lower risk of developing dental caries than those who received no intervention.<br><br>NNTBs were 11 (95% CI 7–20), 15 (95% CI 10–28) and 37 (95% CI 26–59) for scenarios of high (70%), medium (50%) and low (20%) caries incidence, respectively. |
| **Significance/direction** | Preschool children who brushed their teeth with standard fluoride toothpastes experienced a significant reduction in the mean number of primary decayed, missing owing to caries and filled dental surfaces and teeth. They also had a significantly lower risk of developing dental caries than those who received no intervention. The evidence of the effectiveness of low F toothpastes on the prevention of dental caries is equivocal.<br><br>However, all the included trials were categorised as having high risk of bias. More high-quality studies are needed in the future to provide more accurate evidence on the effect of fluoride toothpaste at preventing caries.<br><br>*Note*. This review is categorised as a combined intervention because 7 out of the 8 included trials evaluated fluoride toothpaste interventions delivered alongside oral health education. |

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| **Heterogeneity** | The high heterogeneity observed in the development of caries assessment, comparing low fluoride toothpaste with no intervention, was not adequately explained. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Grandjean *et al.* (2021) |
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| **First Author and year of publication** | Grandjean *et al.* (2021) |
| **Objectives (exact review question(s) and page number)** | To determine the effectiveness of silver diamine fluoride in preventing and arresting root caries lesions in elders. |
| **Participants (characteristics and numbers)** | Permanent dentition; topical fluoride, solution.<br><br>Baseline caries were not reported in any included trial.<br><br>The three included trials reported data on a total of 552 participants, of whom were all above the age of 65. Information pertaining to the sex of participants in the included trials was not reported. |
| **Setting/context** | Information pertaining to the countries of origin and setting of the included trials was not provided. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was the professional application of silver diamine fluoride. The nature of the control group was not specified. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Medline (PubMed)<br>• Embase, and<br>• Cochrane Controlled Register of Trials (CENTRAL).<br><br>Searches by hand of relevant dental journals were performed for records that were not accessible electronically or for those without an electronic abstract available. Further searches resulting from reference cross-checks |

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| | were performed to identify studies that were not discovered online. The final update for all electronic searches was performed on 14 August 2019.<br><br>The review was registered with PROSPERO (ID: CRD42020175693).<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved by means of a consensus discussion.<br><br>Funding sources and conflicts of interest were not provided. |
| **Date range (years) of included studies** | The three included trials were published in 2010, 2013 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included three randomised controlled trials. The follow-up times for the three trials differed with one reporting a 24-month follow-up, one reporting a 30-month follow-up and one reporting a 36-month follow-up.<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included three randomised controlled trials: Tan (2010), Zhang (2013), and Li (2017).<br><br>The excluded studies were not listed, but reasons for exclusion were reported. |
| **Country of origin of included studies** | Information pertaining to the countries of origin of the included trials was not reported. |
| **Appraisal instrument(s)** | The Cochrane collaboration's tool was used for the assessment of the risk of bias of the included studies (Higgins & Green 2011). The following domains were assessed in each included trial:<br>• Sequence allocation<br>• Allocation concealment<br>• Blinding<br>• Incomplete outcome data<br>• Selective outcome reporting, and<br>• Other sources of bias. |
| **Appraisal rating** | Overall, the review authors judged the risk of bias in the three included trials to be low. However, graphical information provided in the review in relation to risk of bias indicates that each trial included at least one domain that was |

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| | assessed at unclear risk of bias. The graphical information illustrates that all three trials should be categorised as at an unclear risk of bias overall.<br><br>All three trials were categorised as having low risk of bias for randomisation. Blinding of participants and personnel and blinding of outcomes were reported under a single domain 'binding'. Two trials were categorised as having low risk of bias for blinding and one trial was categorised as having unclear risk of bias for blinding.<br><br>The risk of publication bias was explored across the included trials using a funnel plot. |
| **Method of analysis** | A meta-analysis was performed on the included trials for mean new active carious root surfaces after silver diamine fluoride application compared to controls at 24 months (3 trials) and 30-36 months (2 trials) post intervention. The weighted means across the trials were calculated using a fixed-effects model.<br><br>Heterogeneity across the included studies was assessed using the I-squared statistic ($I^2$).<br><br>The meta-analysis was performed using a meta-analysis software (CMA, version 3.0; Biostat, Englewood, NJ, USA), with confidence intervals set to 95% (95% CI).<br><br>Subgroup and sensitivity analyses were not conducted. |
| **Outcome(s) assessed** | Primary outcome 1: Root caries incidence, measured by mean new active carious root surfaces<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Mean new active carious root surfaces**<br>The mean number of new active carious root surfaces was significantly lower following application of silver diamine fluoride compared to controls at 24 months follow-up (MD 0.45; 95% CI 0.27 to 0.64; $I^2$ = 0.0%; 552 participants; 3 trials).<br><br>The mean number of new active carious root surfaces was significantly lower following application of silver diamine fluoride compared to controls at 30-36 months follow-up (MD 0.57; 95% CI 0.33 to 0.81; $I^2$ = 0.0%; unknown no. of participants; 2 trials). |
| **Significance/direction** | This systematic review and meta-analysis demonstrates the significant protective impact of SDF on the initiation of root caries lesions in older adults at both 24 months and 30-36 months. |

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| **Heterogeneity** | There was no significant heterogeneity in the meta-analyses. |
| **Summary for GRADE assessment for HRB report** | The review authors did not use GRADE to determine the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Gupta *et al.* (2020a) |
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| **First Author and year of publication** | Gupta *et al.* (2020a) |
| **Objectives (exact review question(s) and page number)** | To compare the effectiveness of topical fluoride and povidone iodine with topical fluoride alone for the prevention of dental caries among 1–12-year-old children (p560). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); combined intervention.<br><br>Baseline caries were not reported in any included trial.<br><br>In total, the review authors included seven studies: six controlled trials and a retrospective cohort study. However, the retrospective cohort study (Tut, 2010) did not meet the eligibility criteria for this umbrella review under study design and so the findings for this study were not extracted.<br><br>The six included trials evaluated a total of 1,020 children, whose ages ranged from 2 to 12 years. Information pertaining to the sex of participants was not provided. All trials included children who were at high risk of dental caries, except one which included healthy children. |
| **Setting/context** | The trials were conducted in China (1 trial), Iran (1 trial), Saudi Arabia (1 trial), and the USA (3 trials).<br><br>The settings of the included trials were not provided. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was topical fluoride (TF) and povidone iodine (PI). The control group was topical fluoride alone.<br><br>Two trials used acidulated phosphate fluoride (APF) gel and PI combined therapy, one trial applied fluoride foam and PI, two trials applied 5% sodium fluoride varnish and PI, and one trial applied a mixture of 0.2% sodium fluoride varnish and PI. Thus, in all the included trials, TF + 10% PI application was made in the experimental group. |

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| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane<br>• EBSCOhost<br>• PubMed/Medline<br>• Scopus, and<br>• Web of Science.<br><br>The databases were electronically searched in March 2019. A manual search of cross-references was done to identify any additional records. Only studies published in the English language were included.<br><br>The review was registered with PROSPERO (ID: CRD42019134530).<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements at the screening stage were resolved through consultation with a third review author (disagreement resolution at the extraction stage was not reported).<br><br>No sources of support were declared for the review. The review authors also declared no conflicts of interest. |
| **Date range (years) of included studies** | The six included trials were published between 2005 and 2016. |
| **Number of primary studies included in the systematic review** | In total, the review authors included six trials (five randomised controlled trials and one non-randomised controlled trial). The follow-up periods ranged from 1 hour (1 trial only) to 1 year (5 trials).<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included six randomised and non-randomised clinical trials: El-Housseiny (2005), Zhan (2006), Xu (2009), Milgrom (2011), Hashemi (2015), and Reilly (2016).<br><br>The results of five trials informed the outcomes of interest to this umbrella review: El-Housseiny (2005), Zhan (2006), Xu (2009), Milgrom (2011), and Hashemi (2015).<br><br>The excluded study was not listed, but the reason for exclusion was reported. |
| **Country of origin of included studies** | The trials were conducted in China (1 trial), Iran (1 trial), Saudi Arabia (1 trial), and the USA (3 trials). |

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| **Appraisal instrument(s)** | The quality of the articles that evaluated using two criteria. First, the Cochrane's Collaboration's tool was used, and the following domains were assessed in each included trial:<br>• Random sequence generation (selection bias)<br>• Allocation concealment (selection bias)<br>• Blinding of participants and personnel (performance bias)<br>• Blinding of outcome assessment (detection bias)<br>• Incomplete outcome data (attrition bias)<br>• Selective reporting (reporting bias), and<br>• Other bias.<br><br>The quality of the included trials was also evaluated using the modified Downs and Black scoring criteria. The 27-item modified Down's and Black checklist consists of five subscales, namely Reporting, External Validity, Internal Validity (Bias), Confounding (Selection Bias), and Power and has a maximum score of 28. Based on the scores obtained, each trial was graded as: "excellent" (24–28), "good" (19–23), "fair" (14–18), or "poor" (<14). |
| **Appraisal rating** | Overall, none of the included trials were categorised as having a low risk of bias. Based off graphical information provided in the review, two trials were categorised as being at unclear risk of bias and two trials were categorised as being at high risk of bias. In the remaining two trials, which were not included in quantitative synthesis, the risk of bias assessment was not provided.<br><br>Of the four trials for which the risk of bias assessment was reported, one was at low risk of bias for randomisation, one was at unclear risk of bias for randomisation, and two were at high risk of bias for randomisation. In addition, three were at low risk of bias for outcome ascertainment, and one was at high risk of bias for outcome ascertainment.<br><br>The Downs and Black quality assessment scores of the six included trials ranged from 15 to 21. Two trials were graded "fair" and four were graded "good". The two trials for which the risk of bias assessment was not reported received scores of 20 (good) and 17 (fair) on the Downs and Black quality assessment.<br><br>Overall, the review authors described the findings of the review to be "very low-quality evidence".<br><br>Publication bias was not assessed. |
| **Method of analysis** | Data from five out of the six included trials were subjected to meta-analysis using Review Manager (version 5.3). Primary outcome data from four trials |

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| | that reported caries incidence as events occurred and one trial that reported decay as mean ± SD were pooled together using generic inverse variance function.<br><br>Subgroup analysis was done for deciduous dentition and permanent dentition separately. For the post-treatment *S. mutans* count reported as a continuous variable, the inverse variance test was used to compare the experimental and control groups.<br><br>Heterogeneity among the studies was evaluated using the $I^2$ statistic. The random effects model was used to carry out the pooled analysis. The $p < 0.05$ was set as the statistical significance limit.<br><br>Sensitivity analyses were not conducted. |
| **Outcome(s) assessed** | Primary outcome 1: new carious lesions (primary teeth)<br><br>Primary outcome 2: new carious lesions (permanent teeth)<br><br>Secondary outcome 1: S. *mutans* count / plaque biofilm accumulation<br><br>Secondary outcome 2: *Lactobacillus* count<br><br>*Note*. The primary outcomes are identified in the review as presented here. It is not clear whether secondary outcomes 1 and 2 are considered primary or secondary outcomes in the review, but for the HRB's purposes they are considered secondary outcomes. |
| **Results/findings** | **Primary outcome 1: New carious lesions (primary teeth)**<br>The risk of caries incidence was not different in the topical fluoride + povidone iodine combined therapy group compared to topical fluoride use alone (SMD -0.19, 95% CI -0.65 to 0.26, p = 0.41, 3 trials; 137 participants; $I^2$ = 17%). The follow-up period analysed was not specified. However, based on information provided in the review, it appears to be 1 year.<br>The interventions applied in the 3 trials were: 1.23% APF gel + 10% PI solution every week for one month (then the gel and PI were applied alternately every 3 months for one year); 1.23% APF gel + 2mL PI application +oral prophylaxis + complete restorative therapy (one treatment); 1% PI + 5% NaF varnish 3 times a year.<br><br>The control groups were: 1.23% APF gel application at baseline then once a week application for one month (followed by one application every 3 months for one year; 1.23% APF gel application + 2mL phosphate buffer solution application + oral prophylaxis + complete restorative therapy; 5% NaF varnish three times per year.<br><br>**Primary outcome 2: New carious lesions (permanent teeth)** |

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| | For the purposes of this umbrella review, the results from the meta-analysis comparing new carious lesions in permanent teeth between groups could not be used as data from the retrospective cohort study was included in the pooled analysis alongside Xu (2009).<br><br>**Secondary outcome 1: S. *mutans* count / plaque biofilm accumulation**<br>Of the three trials that reported this outcome, only data from two could be pooled in a meta-analysis. S. mutans counts were not different in the TF + PI combined therapy group compared to the TF use alone (SMD -0.10, 95% -0.57 to +0.37, P = 0.69; 2 trials; 83 participants, $I^2$ = 0%). The follow-up period analysed was not specified, however, based on information provided in the review, it appears to be 1 year.<br><br>One trial found that a single application of 5% NaF varnish and 10% PI among high-risk children showed a subtle change in the plaque ecology in just one week, although no drastic dysbacteriosis within dental plaque was noted.<br><br>**Secondary outcome 2: *Lactobacillus* counts**<br>The three trials reporting this outcome found no statistically significantly difference in bacterial counts between the TF + PI compared to TF use alone. |
| **Significance/direction** | The findings of this review indicate very low-quality evidence that combined application of 'TF + PI' in primary teeth has no better caries preventive effectiveness compared to TF use alone. Moreover, the limited number of studies with low internal and external validities limits the generalizability of results obtained. Therefore, future clinical trials with longer follow-up period, larger sample size, and robust methodologies are recommended in order to generate conclusive evidence. |
| **Heterogeneity** | Although $I^2$ statistic for the primary and secondary outcome assessment showed low/no heterogeneity, there exists some variation among the included studies with respect to variation in study design, methodology, different follow-up period, and the frequency of application of the agents. The results of this review should therefore be interpreted cautiously. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Hao *et al.* (2021) |

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| **First Author and year of publication** | Hao *et al.* (2021) |
| **Objectives (exact review question(s) and page number)** | To explore and verify the effectiveness and safety of *Bifidobacterium* in preventing caries, explore its potential value in clinical application, and guide further clinical research (p614). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (primary for primary outcome, separate and mixed for secondary outcomes); topical other chemicals, probiotics.<br><br>One trial included participants who had initial dental caries.<br><br>The total number of participants in the ten included trials was 579, with sample sizes ranging from 30 to 104. The age of participants ranged from 0 to 25 years. Seven trials enrolled healthy participants at baseline, two trials included orthodontic patients and one trial recruited participants who had initial dental caries. Information pertaining to the sex of participants was not reported.<br><br>The total number of participants in the 8 trials relevant to this umbrella review was 479.<br><br>*Note*. Orthodontic patients were not a population of interest to this umbrella review so the findings from these two trials were excluded where possible (Pinto 2014 and Cildir 2009). |
| **Setting/context** | Information pertaining to the countries of origin and setting of the included trials was not provided. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was *Bifidobacterium.* The test group consumed products containing *Bifidobacterium* such as milk, curds, ice cream or tablets. The control group received the same products without *Bifidobacterium.*<br><br>In the included trials, the intervention duration varied from 10 days to 14.9 months, among which two weeks was the most common intervention time. The vehicles used for probiotics comprised yogurt, ice cream, curd, and slow-release pacifier or tablets. Dosage of *Bifidobacterium* taken per day varied from $6 \times 10^7$ to $1.1 \times 10^{12}$ colony forming units. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Cochrane Library<br>• Embase<br>• Web of Science, and |

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| | • Scopus.<br><br>The reference lists of the studies were also checked to identify potentially relevant papers. The search time limit was from the establishment of the databases to 1 March 2020.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements at the screening stage were resolved through consultation with a third review author (disagreement resolution at the extraction stage was not reported).<br><br>The review protocol was registered with PROSPERO (ID: RD42020180237).<br><br>The review was supported in funding by the National Natural Science Foundation of China.<br><br>None of the review authors reported a conflict of interest. |
| **Date range (years) of included studies** | The ten included trials were published between 2005 and 2020. |
| **Number of primary studies included in the systematic review** | The review authors included ten randomised controlled trials.<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included ten randomised controlled trials: Caglar (2005), Caglar (2008), Caglar (2014), Cildir (2009), Javid (2020), Nagarajappa (2015), Pinto (2014), Srivastava (2016), Taipale (2012), Taipale (2013).<br><br>The excluded studies were not listed, but reasons for exclusion were reported. |
| **Country of origin of included studies** | Information pertaining to the countries of origin of the included trials was not provided. |
| **Appraisal instrument(s)** | Two investigators independently carried out the risk of bias assessment. Disagreements were resolved through discussion and consultation with a third review authors. The risk of bias was evaluated according to the Cochrane guidelines. The following seven domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias) |

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| | 5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias. |
| **Appraisal rating** | Overall, none of the included trials were categorised as having a low risk of bias. Eight trials were categorised as having a high risk of bias, and two trials were categorised as having an unclear risk of bias.<br><br>Five trials were categorised as having a low risk of bias for randomisation, and five trials were categorised as having an unclear risk of bias for randomisation.<br><br>Six trials were categorised as having a low risk of bias for outcome ascertainment, and four trials were categorised as having an unclear risk of bias for outcome ascertainment.<br><br>The GRADE approach for assessing the quality of the body of evidence was not used. However, the risk of bias in the included trials were mentioned as one of several limitations in the review.<br><br>Publication bias was not assessed. |
| **Method of analysis** | For continuous variables, the standardised mean difference was used instead of the mean difference since the measurement methods and measurement units of each study were different. For dichotomous variables, the risk ratio was used. The preventive effect of *Bifidobacterium* on dental caries was evaluated by the pooled standardized mean difference and risk ratio and their 95% confidence intervals. The review authors grouped and analysed continuous and dichotomous variables separately for each outcome.<br><br>In the meta-analysis, Cochrane's Q statistics and Higgins I-squared statistic ($I^2$) were used to detect the heterogeneity. A fixed-effect model was selected if the heterogeneity was not statistically significant ($I^2 < 50\%$). Conversely, in the case of $I^2 \geq 50\%$, a random-effects model was used. All the analyses were performed with Stata 16.0. Qualitative descriptions were performed if the data were not suitable for meta-analysis.<br><br>Sensitivity analyses were conducted when high heterogeneity was observed. |
| **Outcome(s) assessed** | Primary outcome 1: occurrence of deciduous tooth caries<br><br>Secondary outcome 1: *Streptococcus mutans* count in Saliva<br><br>Secondary outcome 2: *Streptococcus mutans* counts in dental plaque |

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| | Secondary outcome 3: *Lactobacillus* counts in saliva<br><br>Secondary outcome 4: *Lactobacillus* counts in dental plaque<br><br>Secondary outcome 5: adverse events<br><br>*Note*. The nature of the outcomes (i.e. primary or secondary) is not made explicit in the review. For the HRB's purposes they are considered primary and secondary outcomes as presented above. |
| **Results/findings** | **Primary outcome 1: Occurrence of deciduous tooth caries**<br>Data could not be pooled due to heterogenous outcomes. Neither of the two trials reporting this outcome showed a statistically significant difference in caries incidence between the test group and the control group. Both used 100mg/d or 300mg/d (different test and control groups receiving both), with an intake of $5x10^9$ (CFU/day), using slow-release pacifiers or tablets.<br><br>The first trial included 69 infants aged 1 to 2 months at baseline with an average intervention duration of 14.9 months. The trial assessed outcomes at 8 months and 2 years of age. The deciduous teeth of both groups had a decayed, missing and filled (dmf) score of 0 upon assessment.<br><br>The second trial, conducted by the same authors, followed up 61 of the same children and evaluated them when they were four years old. The results showed that the incidence of enamel caries (ICDAS code 2-3) was higher in the test group compared to the control, but the increase was not statistically significant.<br><br>**Secondary outcome 1: *Streptococcus mutans* count in Saliva**<br><u>Continuous variables:</u><br>There was no statistically significant difference in *Streptococcus mutans* counts between the *Bifidobacterium* group and control group (SMD -0.32, 95% CI -0.67 to 0.04, P = 0.08; *4 trials; 208 participants; $I^2$ = 38%; high and unclear risk of bias trials).<br><br>*Note*. One of the pooled trials was conducted using a sample of orthodontic patients (Pinto 2014) and as such, this finding is not usable.<br><br><u>Dichotomous variables:</u><br>There was no statistically significant difference in *Streptococcus mutans* counts between the *Bifidobacterium* group and control group (RR 0.53, 95% CI 0.17 to 1.66, p = 0.28; *3 trials; 137 participants; $I^2$ = 70.1%; unclear and high risk of bias trials). Since heterogeneity was present, the review authors conducted a sensitivity analysis which indicated that the data from one trial was the source of heterogeneity. After excluding it from the meta-analysis, |

the result was still not statistically significant (RR 0.30, 95% CI 0.07 – 1.20, p = 0.09; *2 trials; 95 participants), demonstrating that *Bifidobacterium* could not effectively inhibit *Streptococcus mutans*.

*Note*. One of the pooled trials was conducted using a sample of orthodontic patients (Cildir 2009) and as such, this finding is not usable.

**Secondary outcome 2: *Streptococcus mutans* counts in dental plaque**
Data could not be pooled in a meta-analysis. One trial was conducted using a sample of orthodontic patients and therefore the findings were excluded.

The second cross-design trial involving 104 healthy participants aged 8–10 also showed no statistically significant difference in *Streptococcus mutans* counts in the dental plaque of the *Bifidobacterium* group compared to the control group. This trial had an overall high risk of bias.

**Secondary outcome 3: Lactobacillus counts in saliva**
Continuous variables:
A fixed-effects meta-analysis showed no statistically significant difference in *Lactobacillus* counts between the *Bifidobacterium* group and the control group (SMD -0.07, 95% CI -0.39 to 0.26, p = 0.69; *3 trials; 148 participants; $I^2$ = 0%; high risk of bias trials).

*Note*. One of the pooled trials was conducted using a sample of orthodontic patients (Pinto 2014) and as such, this finding is not usable.

Dichotomous variables:
A fixed-effects meta-analysis showed no statistically significant difference in *Lactobacillus* counts between the *Bifidobacterium* group and the control group (RR 0.87, 95% CI 0.59 to 1.29, p = 0.50; *3 trials; 137 participants, $I^2$ = 0%; high and unclear risk of bias trials).

*Note*. One of the pooled trials was conducted using a sample of orthodontic patients (Cildir 2009) and as such, this finding is not usable.

**Secondary outcome 4: Lactobacillus counts in dental plaque**
The one trial evaluating this outcome was conducted using a sample of orthodontic patients and the findings were therefore excluded.

**Secondary outcome 5: Adverse events**
Five of the ten included trials reported no local or systemic adverse reactions in either the test or the control group. Two trials conducted by the same author and examining the same participants reported that two subjects in the test group suffered from gastrointestinal discomfort, with one in the control group reporting gastrointestinal discomfort. There was no significant difference in the incidence of adverse events between the two groups. The other three trials (one of which was conducted using a sample of

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| | orthodontic patients and therefore not usable) did not report whether adverse events occurred. |
| **Significance/direction** | Available evidence demonstrates that *Bifidobacterium* is neither effective in reducing *Streptococcus mutans* and *Lactobacillus* counts in the saliva or dental plaque nor in reducing the occurrence of caries in deciduous teeth. Therefore, *Bifidobacterium* is not a competent probiotic candidate to prevent dental caries. Further high-quality RCTs using the initiation of dental caries as the endpoint are required to verify these conclusions in the future. |
| **Heterogeneity** | The review author described several limitations in the present review, of which included heterogeneity of the included trials in intervention duration, vehicle, and dosage. Most meta-analyses conducted in the review showed no significant heterogeneity, except in the *Streptococcus mutans* count in Saliva assessment, which was satisfied by removing one trial in the sensitivity analysis. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |

| Parameter | Lam *et al.* (2020) |
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| **First Author and year of publication** | Lam *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To systematically assess randomized controlled trials and summarize the evidence on the effectiveness of different sealants in prevention and arrest of the pit and fissure occlusal caries in primary molars of children (p1). |
| **Participants (characteristics and numbers)** | Primary (first and second molars); sealants, resin, glass-ionomer; combined intervention.<br><br>Baseline caries were reported in all included trials. Five of the trials included participants with primary molars with sound occlusal surfaces or with no signs of caries or cavitation.<br><br>A total of 980 participants and 3,526 molars with sound occlusal surfaces, incipient active or non-cavitated occlusal carious lesions were included in the review. The age of the children recruited in the included trials ranged from 18 months to 8 years. Information pertaining to the sex of included participants was not reported. |

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| **Setting/context** | The trials were conducted in China (1 trial), Denmark (1 trial), Greenland (1 trial), India (1 trial), Kuwait (1 trial), Turkey (1 trial), and the United Kingdom (1 trial).<br><br>Two trials were conducted in outreach settings, wherein the participants were examined and treated at their respective schools. Five trials were performed in clinical settings, wherein participants were enrolled from their schools or public dental clinics. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was any type of pit and fissure sealant placed in any primary molars. The control teeth or control groups were those that did not receive sealant or received professional topical fluoride application alone. Resin-based sealant groups were considered as the control when comparing the efficacy of the resin-based sealant with other sealant types. Alternatively, when making a comparison between conventional sealants and new types of sealants or caries-preventive or caries arrest measures, the conventional types of sealants were used as the control group.<br><br>For primary outcomes, the review authors were interested in comparing eight interventions:<br>1. Resin-based sealant versus no sealant (no included trial made this comparison)<br>2. Glass-ionomer/resin-modified glass-ionomer sealant versus no sealant<br>3. New types of fissure sealants versus no sealant (no included trial made this comparison)<br>4. Resin-based sealant versus glass-ionomer sealant<br>5. Resin-based sealant versus other new sealants<br>6. Autopolymerised resin-based sealant versus light-curing resin-based sealant<br>7. Fissure sealants with topical fluoride application versus topical fluoride application alone, and<br>8. Fissure sealants compared with other types of caries preventive and caries arrest measures.<br><br>For secondary outcomes, the review authors grouped and analysed the following intervention types:<br>1. Direct head-to-head comparison of sealant retention rate<br>2. Resin-based sealant pooled retention rate, and<br>3. Glass-ionomer sealant pooled retention rate. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials (CENTRAL) |

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| | • Ovid Embase<br>• Ovid MEDLINE, and<br>• Web of Science.<br><br>Searches of the databases were performed from inception to March 2018. A hand search was conducted, and reference lists of the included studies and relevant previous systematic reviews were screened for additional studies. Only studies with full text available in English were included.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements at the screening stage were resolved through consultation with a third review author (disagreement resolution at the extraction stage was not reported).<br><br>There was no mention of a protocol being prepared or published, and no registration number was provided.<br><br>No sources of funding were declared for the review. The review authors also declared no conflicts of interest. |
| **Date range (years) of included studies** | The seven included trials were published between 1998 and 2015. |
| **Number of primary studies included in the systematic review** | The review author included seven randomised controlled trials. Six trials used a split-mouth design, and one trial used a parallel-group design. Follow-up periods varied and ranged from 6 months to 3 years.<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included seven randomised controlled trials: Bakhshandeh (2015), Honkala (2015), Ünal (2015), Ren (2011), Ganesh (2006), Chadwick (2005), Hotuman (1998).<br><br>The excluded studies were not listed, but reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in China (1 trial), Denmark (1 trial), Greenland (1 trial), India (1 trial), Kuwait (1 trial), Turkey (1 trial), and the United Kingdom (1 trial). |
| **Appraisal instrument(s)** | Risks of bias of each included trial were assessed based on the five domains and the signalling questions mentioned in the revised Cochrane risk of bias tool for randomized trials (RoB 2.0) Each trial report was evaluated in 5 domains of bias with signalling questions used to |

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| | formulate the judgment regarding the overall risk of bias. The five domains assessed in each trial were:<br>1. Bias arising from the randomisation process<br>2. Bias due to deviation from intended interventions<br>3. Bias due to missing outcome data<br>4. Bias in the measurement of outcome, and<br>5. Bias in selection of reported result.<br><br>As recommended by RoB 2.0 for split-mouth studies, bias arising from the timing of identification and recruitment of individual participants was also assessed. This domain was evaluated as a subdomain under the randomisation process domain. |
| **Appraisal rating** | Overall, all seven included trials were categorised as having a high risk of bias. Blinding could not be achieved because outcome assessors can easily identify subjects from sealant groups with visual examination, while different types of sealants can be differentiated by the investigators via tactile speculation. Therefore, six of the seven trials that only used visual and tactile examinations were rated as of high risk of bias for outcome ascertainment. The only trial which also used bitewings as an adjunct to outcome assessment was rated as of low risk of bias for outcome ascertainment.<br><br>No trials were categorised as having low risk of bias for randomisation. One trial was categorised as having high risk of bias for randomisation, and the remaining six trials were categorised as having unclear risk of bias for randomisation.<br><br>Two review authors independently graded the certainty in the evidence for each outcome, adopting the GRADE approach. The quality of evidence was assessed with reference to the overall risk of bias, imprecision, inconsistency, indirectness, or publication bias. Overall, the quality of evidence in the review was graded as low to very low primarily due to risk of bias, indirectness, and imprecision.<br><br>The review authors had planned to generate funnel plots and assess publication bias according to the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions. However, no meta-analysis conducted included more than 10 studies. |
| **Method of analysis** | When evaluating the primary outcome, categorical data of caries increment in both intervention and control groups were extracted in all included reports. When evaluating the secondary outcome, the total number of fully retained and partially retained events was grouped as one |

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| | variable and compared with the total number of sealants placed. The pooled retention rate of each sealant was calculated in the meta-analysis.<br><br>In trials using split-mouth design, both intervention and control measures are performed on different teeth inside the mouth of the same subject. Findings from split-mouth trials that compared sealant versus non-sealant, or sealant versus another type of sealants, were used as a single effect estimate.<br><br>Stata, version 13.1, was used to perform the meta-analysis. Meta-analysis with fewer than 5 trials was handled with a fixed-effects model, while the random-effects model was adopted for analysis with more studies.<br><br>For the following two comparisons (reported above under Description of Intervention), caries incidence and caries progression were reported together as a single outcome:<br>1. Fissure sealants with topical fluoride application versus topical fluoride application alone, and<br>2. Fissure sealants compared with other types of caries preventive and caries arrest measures.<br><br>Therefore, subgroup analyses were conducted to evaluate the treatment effects for sealants placed on sound occlusal surfaces (ICDAS code 0), incipient occlusal carious lesions (ICDAS code 1-2), occlusal surfaces with localized enamel break down and without clinical signs of dentinal involvement (ICDAS code 3), and non-cavitated occlusal carious lesion progressed to the outer one-third of the dentine (ICDAS code 4), if available. For the purposes of this umbrella review, only the subgroup analyses that relate to caries incidence will be discussed.<br><br>The amount of heterogeneity among studies was quantified using the $I^2$ statistic, and the level of significance of the statistical heterogeneity was set at $P < .05$ and calculated using a Chi-square test. Heterogeneity was determined as substantial when $I^2 > 60\%$ and $P < .05$. |
| **Outcome(s) assessed** | Primary outcome 1: Caries incidence (defined as the diagnosis of new carious lesions established from sound occlusal surfaces leading to localized enamel breakdown on the occlusal surface (ICDAS code 3), and change in decayed, missing, and filled teeth or surfaces (dmft or dmfs) index in primary molars)<br><br>Secondary outcome 1: Sealant retention<br><br>*Note*. Both outcomes are identified in the review as presented here. |

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| **Outcome(s) excluded from umbrella review** | Primary outcome: Caries increment on the occlusal surface of primary molars.<br><br>This outcome was excluded by the HRB as measures included both measures of caries incidence and caries progression. |
| **Results/findings** | **Primary outcome 1: Caries incidence**<br><u>Comparison 1: Resin-based sealant versus no sealant:</u><br>No trials reported this comparison.<br><br><u>Comparison 2: Glass-ionomer/resin-modified glass-ionomer sealant versus no sealant:</u><br>The results from one trial showed no statistically significant difference in the number of carious occlusal surfaces between the experimental (glass-ionomer sealant) and control group (no sealant) at 12-months follow-up (OR 0.79, 95% CI 0.50 – 1.25; P = 0.31; 1 trial; 508 participants; 2032 teeth; very low certainty of evidence).<br><br><u>Comparison 3: New types of fissure sealants versus no sealant:</u><br>No trials studied the comparison between new sealants, for instance, amorphous calcium phosphate (ACP)-containing resin-based sealant (ACP-RBS) and fluoride-containing sealants (F-RBS), and controls with no sealant placed. Hence, no outcome could be assessed.<br><br><u>Comparison 4: Resin-based sealant versus glass-ionomer sealant:</u><br>Only results from one trial were used due to methodological limitations in the other trial that evaluated this comparison.<br><br>The results from a single trial showed significantly lower caries incidence rate in the experimental group compared to the control group at 6-months follow-up (OR 3.90, 95% CI 1.06 to 14.4, p = 0.041; 1 trial; 89 participants; 356 teeth; low certainty of evidence). However, at 18-months follow-up there was no statistically significant difference in incidence rate between the two groups (OR 1.92, 95% CI 0.68 to 5.40).<br><br><u>Comparison 5: Resin-based sealant versus other new sealants:</u> One trial compared conventional resin-based sealant (RBS) with two other newly developed sealants, including ACP-RBS (amorphous calcium phosphate-RBS) and F-RBS (fluoride-RBS). There was no statistically significant difference in caries incidence between RBS and F-RBS at 24-months follow-up (OR 12.2, 95% CI 0.65 to 226.97, p = 0.93; 1 trial; 75 participants; 150 teeth; low certainty of evidence). No caries developed at 24 months in both the groups comparing RBS with ACP-RBS and F-RBS with ACP-RBS; therefore, no difference was found between these 2 comparisons.<br><br><u>Comparison 6: Auto-polymerised resin-based sealant versus light-curing resin-based sealant:</u> |

There was no statistically significant difference in caries incidence between the experimental and control group at 24-months follow-up (OR 0.58, 95% CI 0.13 – 2.55, p = 0.466; 1 trial; 52 participants; 102 teeth; low certainty of evidence).

Comparison 7: Fissure sealants with topical fluoride application versus topical fluoride application alone:
Results from one trial show significantly lower caries incidence rate in the light-cured resin-based sealant + 5% NaF varnish group compared to the 5% NaF varnish alone group at 1-years follow-up (OR 0.52, 95% CI 0.29 to 0.96, p = 0.034; 1 trial; 147 participants; 529 teeth; low certainty of evidence). However, at 2-years follow-up, there was no statistically significant difference in caries incidence between the two groups (OR 0.54, 95% 0.23 to 12.78, p = 0.702; 147 participants; 10 teeth; low certainty of evidence).

Comparison 8: Fissure sealants compared with other types of caries-preventive measures:
One trial indirectly compared the effect of resin infiltration with sealant. The trial contained three treatment arms: resin infiltration and topical fluoride varnish, resin-based sealant and fluoride varnish, and topical fluoride varnish alone.

The results showed no difference was found in caries prevention between the resin-based sealants plus fluoride varnish group, compared with the resin infiltration plus fluoride varnish group at 24 months follow-up (OR, 3.57; 95% CI, 0.11-111.71; P = 5.584).

In subgroup analyses, no significant difference in caries incidence was found between the resin-based sealants + fluoride varnish group compared to the fluoride varnish alone group when the baseline caries level was below ICDAS code 3 (OR 0.54; 95% CI, 0.02-12.78; P = 702) at 24 months follow-up. Similarly, no significant difference in caries incidence was found between the resin-based sealants + topical fluoride varnish group and the resin infiltration + fluoride varnish group when the baseline caries level was below ICDAS code 3 (OR 0.127, 95% CI 0.00 to 3.52, p = 0.22; 1 trial; 47 participants; 8 teeth; very low certainty of evidence) at 24-months follow-up.

**Secondary outcome 1: Sealant retention**
Direct head-to-head comparison of sealant retention rate: Analyses showed the retention rate of glass-ionomer sealant significantly outweighed the retention rate of resin-based sealant at 6 months after placement (OR 0.29, 95% CI 0.17 to 0.53; 2 trials; 189 participants; 556 teeth; certainty of evidence not reported). However, at 18 months, the situation was reversed, with significantly more retained resin-based sealant than glass-ionomer sealant (OR 1.49, 95% 1.04 to 2.12; 2 trials; 189 participants; 556 teeth; certainty of evidence not reported).

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| | One trial involving 50 participants and 100 teeth found no significant difference in retention rate among RBS, F-RBS and ACP-RBS.<br><br>Another trial involving 51 participants and 102 teeth found no significant difference in retention rate between auto-polymerised RBS and light-curing RBS.<br><br><u>Resin-based sealant pooled retention rate:</u><br>Five trials involving 422 participants provided the data for the calculation of retention rate of RBS. The pooled retention rates of RBS were calculated to be 89.79% (95% CI, 86.14%-92.97%) at 6 months (3 trials), 86.81% (95% CI 83.62%- 89.70%) at 12 months (3 trials), and 85.94% (95% CI, 82.13%-89.38%) at 18 months (4 trials).<br><br>However, owing to the nature of the observational data included, high risk of overall bias of all reports included, and considerable heterogeneity associated (6 months: $I^2$ = 94.29%, 12 months: $I^2$ = 87.49%, and 18 months: $I^2$ = 90.72%), the certainty in the evidence was judged to be very low.<br><br><u>Glass-ionomer sealants pooled retention rate:</u><br>Three trials evaluating a total of 644 participants reported the retention rate of GIS. The overall retention rate of GIS at 6 months was 94.85% (95% CI, 94.15% to 96.00%) (2 trials). However, the retention rate dropped considerably to 20.18% (95% CI, 17.91% to 22.54%) when evaluated at 18 months (3 trials).<br><br>The certainty in evidence was graded as very low because of the inclusion of observational data, high risk of overall bias, and substantial heterogeneity (6 months: $I^2$ = 72.50%, and 18 months: $I^2$ = 78.61%). |
| **Significance/direction** | There are currently insufficient well-controlled randomized controlled clinical trials to determine the benefits of pit and fissure sealants to prevent occlusal caries in primary molars.<br><br>The review identified no currently available evidence regarding the effectiveness of different sealants in preventing pit and fissure caries in primary molars in children and adolescents compared with no sealants. Limited evidence was also found in suggestion of any superiority among different types of sealants or with other kinds of caries-preventive measures.<br><br>The high risks of bias associated with a majority of the identified studies placed the validity of the current findings uncertain.<br><br>High-quality clinical trials are required in the future to generate reliable evidence. |

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| **Heterogeneity** | Most of the results could not be pooled for data synthesis and meta analysis in multiple outcomes because of limited relevant studies identified, as well as heterogeneity of the study design, participants, clinical settings, treatment modalities for comparison, and evaluation time points.<br><br>Significant heterogeneity was observed in the secondary outcome assessments which was unexplained; however, the certainty of evidence was downgraded due to the inconsistencies. |
| **Summary for GRADE assessment for HRB report** | The review authors graded evidence from the following comparisons in primary outcome 1 as low: resin-based sealants versus glass-ionomer sealants (downgraded twice for very high risk of bias), resin-based sealants versus fluoride-containing sealant (downgraded twice due to high risk of bias and imprecision), auto-polymerized resin-based sealant versus light-curing resin-based sealant (downgraded twice due to high risk of bias and imprecision), and resin-based sealant plus topical fluoride varnish versus topical fluoride varnish alone (downgraded twice due to high risk of bias and imprecision).<br><br>The review authors graded evidence from the following comparisons in primary outcome 1 as very low: glass-ionomer/resin-modified glass-ionomer sealant versus no sealant (downgraded three times for very high risk of bias and indirectness) and resin-based sealant plus topical fluoride varnish versus resin infiltration plus topical fluoride varnish (downgraded three times for high risk of bias, indirectness, and imprecision).<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Li *et al.* (2020) |
| **First Author and year of publication** | Li *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To accurately evaluate the efficacy of first permanent molars caries management between fluoride sealant and fluoride varnish (p1).<br><br>*Note*. This review was coded under “sealants” only, rather than both “sealants” and “fluoride varnish”. The HRB authors considered the fluoride varnish groups as the comparator groups. |

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| **Participants (characteristics and numbers)** | Permanent (first molars); sealants, resin, combined.<br><br>Baseline caries were reported in all included trials using ICDAS codes. Six trials reported ICDAS scores of 0 and two trials reported ICDAS scores between 0-3.<br><br>A total of eight trials involving 3,289 participants and 6,878 first permanent molars were included in this review. The age of participants ranged from 6 to 9 years. Two trials did not report on sex. Of the six trials that did report on sex, the % female ranged from 48% to 53%. |
| **Setting/context** | Information pertaining to the countries of origin and setting of the included trials was not provided. |
| **Description of Interventions/ phenomena of interest** | For a trial to be included, the intervention had to contain fluoride sealant and fluoride varnish. In the fluoride sealant group, either resin-based sealant or glass-ionomer sealant could be used. Of the eight included trials, six used resin-based sealants and two used glass-ionomer-based sealants. In the fluoride varnish group, fluoride varnish application must have been biannually. The procedures of fluoride sealant and fluoride varnish should have rigorously followed standard protocols of manufacturers.<br><br>Each trial consisted of at-least two arms, comprising the two different interventions (fluoride sealant and fluoride varnish). In trials with only two arms, one of the interventions would have acted as the control. In addition, five trials included a third arm which acted as the "standard" control. Of these five, one used water as the control, three used blanks as controls, and one used oral health education as the control. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials (CENTRAL) (2018)<br>• MEDLINE via OVID (1948 to February 2018)<br>• PUBMED (1960 to February 2018)<br>• Embase (1984 to February 2018)<br>• CNKI (2018), and<br>• The World Health Organisation International Clinical Trials Registry Platform.<br><br>The search was restricted to articles written in English or Chinese. The reference lists of relevant articles were checked for additional studies. The following journals were also searched:<br>• Journal of Dental Research<br>• Journal of Dentistry |

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| | • International Journal of Paediatric Dentistry<br>• European Journal of Paediatric Dentistry, and<br>• Community Dentistry and Oral Epidemiology.<br><br>There was no mention of a protocol being prepared or published, and no registration number was provided.<br><br>Four review authors independently screened and evaluated the titles and abstracts and full texts of all potentially relevant articles. Three review authors independently performed data extraction. Disagreements at the screening stage were resolved through consensus and if necessary, consultation with an alternative investigator (disagreement resolution at the extraction stage was not reported).<br><br>The review was supported by the National Natural Science Foundation of China, the preeminent youth fund of Sichuan province, and the Sichuan Province Science and Technology Innovation Team Program.<br><br>None of the review authors reported a conflict of interest. |
| **Date range (years) of included studies** | The eight included trials were published between 1984 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included eight randomised controlled trials. Of these eight trials, one trial used a split-mouth design, and the remaining seven trials used a parallel-group design. Follow-up periods ranged from 23 months to 36 months.<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included eight randomised controlled trials: Liu (2012), Bravo (1996), Raadal (1984), Chestnutt (2017), Salem (2014), Bravo (1997), Tagliaferro (2011), Ji (2007).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | Information pertaining to the countries of origin was not provided. |
| **Appraisal instrument(s)** | The Cochrane “risk of bias” instrument was used to assess the risk of bias. This evaluation was performed by three independent reviewers. Disagreements between estimators were resolved by discussion until consensus was reached. The following seven domains were assessed in each included trial:<br>1. Random sequence generation (selection bias) |

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| | 2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias.<br><br>The risk of bias was classified into three categories:<br>• Low risk of bias if all domains were marked as "low risk"<br>• Moderate risk of bias if no domain was marked as "high risk" but at least one was coded as "unclear risk", and<br>• High risk of bias if one or more domains were marked as "high risk". |
| **Appraisal rating** | Overall, only one of the included trials were categorised as having low risk of bias. One trial was categorised as having an unclear risk of bias, and the remaining six trials were categorised as having a high risk of bias.<br><br>Five trials were categorised as low risk of bias for randomisation, two trials were categorised as having high risk of bias randomisation, and one trial was categorised as having unclear risk of bias for randomisation.<br><br>Five trials were categorised as low risk of bias for outcome ascertainment, one trial was categorised as high risk of bias for outcome ascertainment, and two trials were categorised as high risk of bias for outcome ascertainment.<br><br>The GRADE approach for assessing the quality of the body of evidence was not used.<br><br>Publication bias was not assessed. |
| **Method of analysis** | Statistical analysis was carried out utilizing Review Manager 5.1. Heterogeneity was assessed via the $I^2$ statistic. If there was considerable or substantial heterogeneity ($I^2 > 50\%$), a random-effects model was adopted; otherwise, a fixed-effects model was used.<br><br>The results of intervention effect were presented as relative risk (RR) utilizing 95% confidence intervals (CIs). All tests were 2-tailed, and $P \leq 0.05$ was considered statistically significant.<br><br>Subgroup analyses were conducted when high heterogeneity was observed in the meta-analyses. A sensitivity analysis was conducted excluding the one trial that used a split-mouth design. |

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| **Outcome(s) assessed** | Primary outcome 1: caries incidence<br><br>Primary outcome 2: DMFS increment<br><br>*Note*. The nature of the outcomes (i.e. primary or secondary) is not made explicit in the review. For the HRB's purposes both are considered primary outcomes as presented above. |
| **Results/findings** | **Primary outcome 1: Caries incidence**<br>Three layers of caries incidence were examined.<br><br><u>Caries incidence of enrolled children:</u><br>There was no statistically significant difference in caries incidence in children between the fluoride sealant group and fluoride varnish (22,600 ppm F) group at 2-3 years follow-up (RR 1.12, 95% CI 0.60 to 2.09, p = 0.72; 2 trials; 1,072 participants; $I^2$ = 59%; high and unclear risk of bias trials). Both trials used resin-based sealants in the intervention group.<br><br>The outcome in both pooled trials was caries incidence.<br><br><u>Caries incidence of first permanent molars:</u><br>There was no statistically significant difference in caries incidence in first permanent molars between the fluoride sealant group and fluoride varnish group at 2-3 years follow-up (RR 1.29, 95% CI 0.95 to 1.75, p = 0.10; 6 trials; 6,878 molars; $I^2$ = 76%; high and unclear risk of bias trials). Five out of six trials resin-based sealants in the intervention group, one used glass-ionomer based sealants in the intervention group.<br><br>A subgroup analysis was conducted excluding one trial because of its high risk of bias and substantial contribution to heterogeneity of this outcome. Results showed that exclusion of this trial did not change overall effect but significantly reduced heterogeneity (RR 1.05, 95% CI 0.91 to 1.22, p = 0.48, 5 trials; $I^2$ = 0%).<br><br>A sensitivity analysis was conducted excluding the RCT with a split-mouth design. Results from the analysis showed still no statistically significant difference in caries incidence in first permanent molars between the fluoride sealant group and fluoride varnish group at 2-3 years follow-up (RR 1.29, 95% CI 0.88 to 1.87, p = 0.19; 5 trials; $I^2$ = 80%).<br><br>The outcomes in the pooled trials were caries incidence in 4 trials, DMFS in 1 trial and both caries incidence and DMFS in 1 trial.<br><br><u>Caries incidence of first permanent molar's occlusal surfaces:</u> There was no statistically significant difference in caries incidence in first permanent molar's occlusal surfaces between the fluoride sealant group and fluoride varnish group at 2-3 years follow-up (RR 1.33, 95% CI 0.83 to 2.11, p = 0.23; 4 |

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| | trials; 6,551 first permanent molars; $I^2$ = 85%; high and unclear risk of bias trials). All four trials used resin-based sealants in the intervention group.<br><br>A subgroup analysis was conducted excluding one trial because of its high risk of bias and substantial contribution to heterogeneity of this outcome. Results showed that exclusion of this trial did not change overall effect but significantly reduced heterogeneity (RR 0.98, 95% CI 0.82 to 1.16, p = 0.78, 3 trials; $I^2$ = 0%).<br><br>The outcomes in the pooled trials were caries incidence in 2 trials, DMFS in 1 trial and both caries incidence and DMFS in 1 trial.<br><br>**Primary outcome 2: DMFS increment**<br>There was no statistically significant difference in DMFS increment of occlusal surfaces in children between the fluoride sealant and fluoride varnish group at 2 years follow-up (MD = 0.13, 95% CI -0.09 to 0.34, p = 0.25; 1,030 participants, 3 trials; $I^2$ = 85%; high and low risk of bias trials). Two out of three trials used resin-based sealants in the intervention group, one used glass-ionomer-based sealants in the intervention group.<br><br>A subgroup analysis was conducted excluding one trial because of its high risk of bias and substantial contribution to heterogeneity of this outcome. Results showed that exclusion of this trial did not change overall effect and only slightly reduced heterogeneity (MD 0.04, 95% CI -0.15 to 0.23, p = 0.70; 2 trials; $I^2$ = 83%). |
| **Significance/direction** | Compared with fluoride varnish, fluoride sealants were not significantly associated with higher caries incidence or more DMFS increment in 6–9 years old children at 2–3 years follow-up.<br><br>The available evidence showed that biannual application of fluoride varnish is no more effective at preventing caries in first permanent molars than flourish sealant at two to three years follow-up. These findings do not support routine recommendation of fluoride sealant over fluoride varnish. Future choices between these two skills may rely on technique sensitivity, accessibility and cost of these two treatments in the local community. |
| **Heterogeneity** | High heterogeneity was observed in all main meta-analyses. Following subgroup analysis excluding trials suspected to be contributing to the high heterogeneity, the overall effects did not change but heterogeneity was reduced markedly for the primary outcomes. However, the source of the heterogeneity in the excluded trials in the subgroup analysis were not adequately explained. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |

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| **References to previously published versions** | N/A |
| Parameter | Marghalani *et al.* (2017) |
| **First Author and year of publication** | Marghalani *et al.* (2017) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effectiveness of xylitol in reducing dental caries in children compared to no treatment, a placebo, or preventive strategies (p103). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (mixed); topical other chemicals, xylitol.<br><br>Baseline caries were not reported in any included trial.<br><br>The review included healthy paediatric patients aged 0 to 18 years. The included trials involved a total of 5,965 participants, with ages ranging from six months to 14 years. One trial involved 6- to 35-month-olds, two trials involved 3- to 6-year-olds, and seven trials involved 7- to 14-year-olds. Information pertaining to the sex of included participants was not reported. |
| **Setting/context** | The trials were conducted in Belize (2 trials), Costa Rica (2 trials), Estonia (1 trial), Finland (2 trials), Lithuania (1 trial), Sweden (1 trial), and the USA (1 trial).<br><br>Eight trials were conducted in a community-based setting, and two trials were conducted in a clinic-based setting. |
| **Description of Interventions/ phenomena of interest** | The invention of interest was xylitol products (all forms, dosages, and frequencies), with an intervention duration of at least 12 months. The control groups received either no treatment, placebo, or preventative strategies such as sealants, toothbrushing with fluoride toothpaste, or fluoride varnish.<br><br>Among included trials, the vehicle for xylitol delivery included gum, dentifrice, lozenges, and wipes. The frequency of xylitol consumption ranged from three to five times a day, except for the trials examining dentifrices containing xylitol, which was used two times a day. Two trials did not report the daily dose of xylitol. However, in the remaining eight trials the daily dose of xylitol ranged from 2.5g to 10.67g. Control groups consisted of no gum, a placebo, or preventative strategies such as sealants, toothbrushing with fluoride dentifrice, or fluoride varnish. No trials were included that had other sugar alcohols as a control group. There were two trials with a minimum of |

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| | one-year follow-up, three with a minimum of two years, and five with a minimum of three years. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• MEDLINE via PubMed<br>• Thomson Reuters Web of Science, and<br>• Cochrane Central Register of Controlled Trials.<br><br>Databases were searched for all review articles and clinical trials published from 1 January 1995 to 26 September 2016 that were restricted to the English language. The review authors also conducted hand searches using reference lists of previously published articles to identify any additional eligible trials.<br><br>There was no mention of a protocol being published, and a registration number was not provided. However, the review authors mentioned that title and abstract screening was conducted consulting the review protocol.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements during screening were resolved by discussion with a third reviewer. Disagreement resolution in the data extraction phase was not described.<br><br>Funding sources and conflicts of interest were not provided. |
| **Date range (years) of included studies** | The 10 included trials were published between 1995 and 2012. |
| **Number of primary studies included in the systematic review** | The review authors included 10 randomised and nonrandomised controlled trials. Five trials were randomised, and five trials were nonrandomised. Of the randomised controlled trials, three were cluster randomised. Follow-up periods ranged from one to three years.<br><br>Funding sources of the included trials were not reported; however, five trials were categorised as having a high risk of bias in the domain of 'other bias/funding'. |
| **Types of studies included** | The review authors included 10 randomised and nonrandomised controlled trials: Alanen (2000a), Alanen (2000b), Kavori (2003), Machiuskiene (2001), Makinen (1995), Makinen (1996), Sintes (1995), Sintes (2002), Stecken-Blicks (2008), and Zhan (2012).<br><br>Studies that were excluded at full-text screening and their reasons for exclusion were reported. |

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| **Country of origin of included studies** | The trials were conducted in Belize (2 trials), Costa Rica (2 trials), Estonia (1 trial), Finland (2 trials), Lithuania (1 trial), Sweden (1 trial), and the USA (1 trial). |
| **Appraisal instrument(s)** | The Cochrane Collaboration's tool was used for the assessment of the risk of bias of the included trials. The following domains were assessed in each included trial by two review authors:<br>1. Random sequence generation<br>1. Allocation concealment<br>2. Blinding of participants and personnel<br>3. Blinding of outcome assessment<br>4. Incomplete outcome data<br>5. Selective reporting, and<br>6. Other biases/funding.<br><br>A summary assessment for risk of bias was provided for each trial. Each trial was characterized as:<br>• Low risk of bias if all domains were determined to have low risk of bias<br>• Unclear risk of bias if at least one domain was determined to have unclear risk of bias, and<br>• High risk of bias if at least one domain was determined to have high risk of bias.<br><br>Any discrepancies were resolved through discussion. |
| **Appraisal rating** | Overall, all included trials were assessed as having a high risk of bias. High risk of bias was frequently found in the domains of random sequence generation, blinding of participants and personnel, and funding.<br><br>Five trials were categorised as having a low risk of bias for randomisation, and five trials were categorised as having a high risk of bias randomisation.<br><br>Six trials were categorised as having a low risk of bias for outcome ascertainment, one trial was categorised as having an unclear risk of bias for outcome ascertainment, and three trials were categorised as having a high risk of bias for outcome ascertainment.<br><br>The quality of evidence was evaluated using the GRADE approach. For all analyses, the quality of evidence was determined to be very low. This was primarily due to the high risk of bias and inconsistency (heterogeneity) observed in the included trials. |

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| | Publication bias was not assessed and was noted as one of the limitations of this systematic review. |
| **Method of analysis** | The review authors used mean difference and the 95 percent confidence interval as the effect size measure between xylitol and control groups. The weighted mean difference was used if<br>caries measure was reported on the same scale and the standardized mean difference was used if different scales were reported. Standardised mean difference is the mean difference in the caries index score between the xylitol and the control groups divided by the pooled standard deviation. When pre-intervention measures were reported, adjustments were made in the baseline differences. When necessary, standard errors or confidence intervals were converted to standard deviations.<br><br>Random-effect models were used due to expected heterogeneity because of variation in treatment protocols and subject populations. $I^2$ and chi-square test for heterogeneity were used to detect trial heterogeneity. Revman 5.2 software was used to perform statistical analyses.<br><br>A subgroup analysis was carried out including only the randomised controlled trials. Additional subgroup analyses compared the effect of various xylitol doses. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment using mean number of decayed, missing, and filled primary and permanent surfaces/teeth (dmfs/t and DMFS/T)<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Caries increment**<br>The main analysis showed a significantly lower caries increment in the xylitol group compared to the control group at at least 1 year follow-up (SMD -0.97, 95% CI -1.39 to -0.55, $p < 0.001$; 10 trials; 5,965 participants; $I^2 = 98\%$; very low certainty of evidence). A sensitivity analysis was conducted excluding one trial that showed a caries incidence reduction by almost 11 times more than any other included trial. The effect size was reduced but results still showed a significantly lower caries increment in the xylitol group (SMD -0.28, 95% CI -0.46 to -0.10, $p = 0.002$; 9 trials; 5,781 participants; $I^2 = 86\%$, very low certainty of evidence). 6/10 trials involved xylitol gum, 2/10 involved xylitol-containing toothpaste, 1/10 trials involved xylitol lozenges, and 1/10 trials involved xylitol wipes. The dose of xylitol in gum was 2.5g/day (1 trial), 2.9g/day (1 trial), 4.3-8.5g/day (1 trial), 5g/day (2 trials) and 10.67g/day (1 trial). The dose of xylitol in toothpaste 10% (2 trials). The dose of xylitol provided from lozenges was 2.5g/day (1 trial). The dose of xylitol provided from wipes was 4.2g/day (1 trial). |

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| | The subgroup analysis of the five randomised controlled trials showed a small effect of xylitol on reducing dental caries, however the results were not statistically significant (SMD -0.24, 95% CI -0.48 to 0.01, p = 0.06, 5 trials; 2,739 participants; $I^2$ = 80%; very low certainty of evidence).<br><br>Additional subgroup analyses were conducted comparing the effect of a lower concentration of xylitol (< 3 grams per day) and a higher concentration of xylitol (> 4 grams per day). For the lower concentration analysis, there were no significant difference in caries increment between the low-dose xylitol group and the control group (SMD -0.17, 95% CI -0.60 to 0.25, p = 0.42; 3 trials; 819 participants; $I^2$ = 82%; very low certainty of evidence). For the high concentration analysis, results showed a lower caries increment in the high-dose xylitol group compared to the control group, however, the result was not statistically significant (SMD -0.54, 95% CI -1.14 to 0.05, p = 0.07; 4 trials; 1,565 participants; $I^2$ = 92%; very low certainty of evidence). |
| **Significance/direction** | Available evidence of randomised controlled trials shows a small potential benefit of xylitol at reducing caries incidence in children. In addition, results showed the effect of xylitol may be greater with higher xylitol doses (greater than four grams a day). This potential effect of dosage is observational, as dose was not randomized in the included trials.<br><br>Overall, the evidence was very low certainty, and the effect sizes observed may not be clinically important. Therefore, future well-conducted clinical trials are recommended in order to generate conclusive evidence. |
| **Heterogeneity** | The review authors described the ten trials that met the inclusion criteria as rather heterogenous, in that the experimental groups had various daily doses and various forms of xylitol delivery. Furthermore, the length of the studies, follow-up periods, comparison groups, population age, baseline caries risk of the children, and clinical dental caries definition varied considerably among the trials. The review authors attempted to reduce the high heterogeneity observed by subgroup analyses based on randomisation and xylitol dose; however, even after these procedures, heterogeneity was still high and subsequently mandates interpretation of the results with great caution. It also downgraded the quality of the evidence. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the overall quality of evidence as very low, downgraded due to the high risk of bias and inconsistency (heterogeneity) seen in the studies.<br><br>The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |

| Parameter | Pagano *et al.* (2020) |
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| **First Author and year of publication** | Pagano *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To verify whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures.<br><br>To determine whether laser use was safe for the dental pulp vitality, and moreover whether participants assessed as acceptable this intervention (p2). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate for caries incidence outcome, mixed for secondary outcomes); laser, combined intervention.<br><br>Participants, irrespective of age and gender, with sound primary and/or permanent teeth (without caries or other treatments such as fillings, prosthetic manufactures or orthodontic brackets and/or bands), who had undergone laser prophylaxis (primary prevention) interventions on enamel coronal surfaces, were considered.<br><br>In the nine* included trials, 269 individuals were recruited, and 1,628 teeth were evaluated. The number of participants in each trial varied from 12 to 51. In five trials, the treatments were carried out in children, and in the remaining four trials that treatments were carried out in young adults. Five trials did not report the ratio of males to females. In the other four trials, the proportion of females to males, in percentage, ranged from 7/20 to 15/16 (35% to 94% females).<br><br>*One trial was described in two publications (Nammour *et al.* 2003 and Nammour *et al.* 2005). |
| **Setting/context** | The trials were conducted in Australia (1 trial), Belgium (1 trial), Brazil (3 trials), India (1 trial), Turkey (2 trials), and the USA (1 trial).<br><br>Seven trials were conducted in university dental clinics. The setting of the remaining two trials was not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention group was any laser application (specific to increasing the resistance against demineralisation of enamel) alone or in combination with any traditional prophylactic intervention (TPI). The control group was no treatment, placebo alone, placebo in combination with any TPI, or any TPI alone. |

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| | In all nine included trials, the lasers were employed with sub-ablative parameters, with a low level of fluency ranging from 10 J/cm$^2$ to 85 J/cm$^2$. In three trials, the $CO_2$ laser was adopted; in two trials, the neodymium- doped yttrium aluminium garnet (Nd:YAG) laser was used; in one trial, the argon (two publications) laser was employed; in one trial, the erbium- doped yttrium aluminum garnet (Er:YAG) laser was used; and in the remaining two trials the erbium, chromium: yttrium scandium gallium garnet (Er,Cr:YSGG) laser was used.<br><br>To support the use of laser prophylactic interventions, other interventions were adopted (Raucci-Neto 2015, Zezell 2009) in the included trials such as 1.23% acidulated phosphate fluoride gel or foam, enamel pit and fissure resin sealant (Walsh 1996), and 5% fluoride varnish (Brugnera 1997). |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Medline (via PubMed)<br>• Embase<br>• Web of Science, and<br>• Cochrane Library.<br><br>The search of the databases was carried out in December 2019. No restrictions were placed on language.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion and, where necessary, consultation with a third review author.<br><br>The review author state that the review protocol was prepared, however, it was not registered in PROSPERO.<br><br>The review was funded by the National Centre for Disease Prevention and Control.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The nine included trials were published between 1996 and 2005. |
| **Number of primary studies included in the systematic review** | The review authors included seven randomised controlled trials and two controlled clinical trials. All trials had a split- mouth design where both intervention and control groups were represented by teeth located in opposite sides of single dental arcs rather than in different patients. |

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| | The funding sources of the included trials were not reported. |
| **Types of studies included** | The review authors included seven randomised controlled trials and two controlled clinical trials: Brugnera (1997), Durmus (2017), Goodis (2004), Karaman (2013), Kumar (2016), Nammour (2003 and 2005), Raucci-Neto (2015), Walsh (1996), and Zezell (2009).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Belgium (1 trial), Brazil (3 trials), India (1 trial), Turkey (2 trials), and the USA (1 trial). |
| **Appraisal instrument(s)** | In the included trials, the risk of bias was independently assessed by two researchers. Disagreements were resolved by consultation with a third review author. The Cochrane Handbook for Systematic Reviews of Interventions was used as a tool for assessing the risk of bias. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias), and<br>6. Selective reporting (reporting bias).<br><br>The risk of bias judgement for each outcome was expressed in three degrees: low risk of bias, unclear risk of bias, and high risk of bias. |
| **Appraisal rating** | Overall, none of the included trials were assessed as having a low risk of bias. Eight trials were assessed as having a high risk of bias, and one trial was assessed as having an unclear risk of bias.<br><br>One trial was categorised as having a low risk of bias for randomisation. Seven trials were categorised as having an unclear risk of bias for randomisation, and one trial was categorised as having a high risk of bias for randomisation.<br><br>Six trials were categorised as having a low risk of bias for outcome ascertainment. Three trials were categorised as having an unclear risk of bias for outcome ascertainment.<br><br>The review authors describe several limitations of the present review, one of which included the unclear and high risk of bias of all included trials, rendering the degree of confidence in the results as low. Another limitation described was the limited number of studies found for each tested laser |

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| | (with a small sample of enrolled participants), which casted doubts on the results' precision.<br><br>Publication bias was not assessed as no meta-analyses were conducted. |
| **Method of analysis** | The effectiveness and safety of laser prophylactic intervention was calculated for dichotomous data using risk ratio with a 95% CI, while for continuous data the mean difference with 95% CI was calculated.<br><br>Due to the high heterogeneity of type of lasers and outcome measures, the review authors did not perform meta- analyses and instead presented the results in a narrative way. |
| **Outcome(s) assessed** | Primary outcome 1: Caries incidence (number of cases of new caries)<br><br>Secondary outcome 1: Sealant retention<br><br>Secondary outcome 2: Adverse events<br><br>Secondary outcome 3: Patient discomfort<br><br>*Note*. Primary outcome 1 is identified as a primary outcome in the review. Secondary outcomes 1 and 2 are identified as primary outcomes in the review, but for the HRB's purposes are considered secondary outcomes. Secondary outcome 3 is identified as a secondary outcome in the review. |
| **Results/findings** | **Primary outcome 1: Caries incidence (number of cases of new caries)**<br>Four trials reported this outcome. Three trials were carried out on permanent teeth (molar and premolars), while one trial considered only primary molars.<br><br><u>Permanent teeth:</u><br>The results of one trial showed that when a laser was used alone ($CO_2$ laser), it was not effective in reducing caries incidence compared with a control group of untreated teeth at 4-years follow-up (RR 0.89, 95% CI 0.40 to 1.97, p = 0.77; 1 trial; 28 participants; 112 first molars).<br><br>Conversely, when laser was combined with TPIs, it was shown to be effective, as demonstrated by two trials. In the first of these trials, when $CO_2$ laser was combined with the sealants compared with a control group of untreated teeth, results showed a statistically significant reduction in caries incidence at 4 years follow-up, with a preventable fraction of 78% (RR 0.22, 95% CI 0.05 to 0.94, p = 0.02; 1 trial; 28 participants; 112 first molars). Similarly, in the second trial, when Er:YAG laser was combined with sealants (compared with the same sealants used alone), results also showed a statistically significant reduction in caries incidence at 18-months follow-up, |

with a preventable fraction of 56% (RR 0.44, 95% CI 0.20 to 0.97, p = 0.03; 1 trial; 51 participants; 204 first molars).

In another trial, when Nd:YAG laser was combined with acidulated phosphate fluoride gel (compared to the fluoride gel used alone), results showed a statistically significant reduction in caries incidence at 1 year follow-up, with a preventable fraction of 61% (RR 0.39, 95% CI 0.22 to 0.71; 1 trial, p = 0.001; 1 trial; 33 participants; 242 premolars and lower molars).

Primary teeth:
In one trial, four different interventions were used: (1) Nd:YAG laser alone, (2) Nd:YAG laser + fluoride gel, (3) Nd:YAG laser + fluoride variant, and (4) sealant. The control groups were (1) fluoride varnish, (2) fluoride gel, and (3) no treatment. Only when laser was used alone (compared to no treatment), results showed a statistically significant reduction in caries incidence in first and second primary molars at 1 year follow-up, with mean values of 70% (RR 0.30, 95% CI 0.11 to 0.78, p = 0.004; 1 trial; 35 participants; 416 first and secondary primary molars). No statistical information was provided for the other 4 intervention arms.

**Secondary outcome 1: Sealant retention**
Four trials reported this outcome. Sealant retention was assessed by comparing two different types of enamel etching, laser light irradiation (laser etching) and traditional acid gel apposition (acid etching). Two types of comparisons were performed: (1) laser etching combined with acid etching versus acid etching alone and (2) laser etching versus acid etching.

Comparison 1: Laser etching combined with acid etching versus acid etching alone:
In two trials, laser light combined with acid gel resulted in better etching than acid gel used alone in terms of sealant retention. In one trial, when $CO_2$ laser in addition to acid gel was used, a reduction from 19 (n = 19/28) to 12 (n = 12/28) detachments were found at 4 years follow-up, although the reduction was not statistically significant (RR = 0.63, 95% CI 0.38 to 1.04, p = 0.059; 1 trial; 28 participants; 112 permanent first molars). Similarly, when Er:YAG laser in addition to acid gel was used, a 46% detachment reduction from 35 (n = 35/84) to 19 (n = 19/84) was found at 18-months follow-up, and this reduction was statistically significant (RR 0.54, 95% CI 0.34 to 0.87; 1 trial; 51 participants; 204 permanent first molars). The duration of these trials ranged from 18 months to 24 months.

Comparison 2: Laser etching versus acid etching:
Three trials made this comparison (N = 86), with duration ranging from 1 year to 3 years. There was no statistically significant difference between the laser light etching and the acid etching with regard to sealant retention in any of the three trials.

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| | In the first trial, in which ER,CR:YSGG laser was used, 9 out of 56 sealant fillings were detached in the intervention group (laser etching), while 8 out of 56 in the control group (acid etching) were detached. There was no statistically significant difference between groups (RR 0.87, 95% CI 0.37 to 2.06).<br><br>In the second trial, where again Er,Cr:YSGG was used, in both acid and laser etching groups, the same number of detachments (78/100) were found.<br><br>In the third trial, similar to the other two, 2 sealant fillings out of 96 were detached in the laser etching group, while 4 out of 74 were detached in the acid etching group, with no significant difference (RR 0.39, 95% CI 0.07 to 2.05, p = 0.24).<br><br>**Secondary outcome 2: Adverse events**<br>Two trials investigated dental pulp health after laser irradiation. A total of 44 participants, aged 15–38 years,<br>were enrolled in the two trials and 174 permanent molars and premolars (including third molars) were examined by clinical evaluation (symptomatology) as well as with electrical and thermal pulp vitality tests. Control radiographs were also taken in one of the two trials. In the two trials, there was only one case of reversible pulpitis 3 days after treatment.<br><br>**Secondary outcome 3: Patient discomfort**<br>In the only trial reporting this outcome, both Er,Cr:YSGG laser and orthophosphoric acid were equally well accepted by patients (p=1). The Visual Analogue Scale mean score measuring the patients' discomfort resulted in very low for both laser or acid etching procedures, with the same value of 0.33 (SD=2.22). |
| **Significance/direction** | Lasers used at sub-ablative energy level in combination with TPIs resulted in an increased caries prevention effectiveness compared with TPIs alone or to untreated teeth. Laser combined with a TPI, indeed, reduces the incidence of caries by reinforcing enamel, and moreover it reduces the detachment of sealant fillings from the dental enamel surfaces. Conversely, when the laser was used alone, it did not improve enamel resistance against caries or sealants retention.<br><br>However, results should be taken with caution due to the limited number of studies (with few participants) included in the review and the evident risk of bias discovered in all outcomes considered in this review. High quality methodological studies are required to obtain a more thorough knowledge of all topics considered in this study. |
| **Heterogeneity** | Due to the high heterogeneity of type of lasers and<br>outcome measures, the review authors did not perform meta- analyses and instead presented the results in a narrative way. |

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| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Gupta *et al.* (2020b) |
| **First Author and year of publication** | Gupta *et al.* (2020b) |
| **Objectives (exact review question(s) and page number)** | To compare the effectiveness of combined therapy using topical fluoride along with an antimicrobial agent (Povidone Iodine/Chlorhexidine/Xylitol/Triclosan/Cetylpyridinium Chloride) versus topical fluoride monotherapy in preventing dental caries among 1- to 16-year-old children (p630). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (dentition not made explicit, coded as mixed); combined intervention.<br><br>Baseline caries was reported in two out of 16 included trials. Both trials reported baseline scores above 0.<br><br>The total number of participants included in the review was approximately 6,003. The ages of participants ranged from 2 to 16 years. Information pertaining to the sex of participants was not reported.<br><br>The total number of participants in the 14 (out of 16) included trials that inform this umbrella review was 5,793. |
| **Setting/context** | Information pertaining to the countries of origin and setting of the included trials was not provided. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was topical fluoride combined with an antibacterial agent such as povidone iodine, chlorhexidine, xylitol, triclosan, or cetylpyridinium chloride. The control group was topical fluoride alone. Only trials with identical fluoride exposure in terms of dosage, delivery vehicle and fluoride concentration in the two groups were included.<br><br>Among included trials, eight trials were included that used chlorhexidine as the antibacterial agent; five trials used xylitol as the antibacterial agent; two trials used povidone iodine as the antibacterial agent; and one trial used triclosan as the antibacterial agent. No trials were included that used cetylpyridinium chloride as the antibacterial agent. |

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| | In the chlorhexidine group, variations in dosage and form of chlorhexidine application were observed. In included trials, it was used in concentrations of 0.12% solution, 0.12% gel, 1% gel, and varnish. In the xylitol group, xylitol was used in various forms, such as chewing gum, toothpaste, and gummy bears. In the povidone iodine group, povidone iodine was used in solution form and foam form. Finally, in the triclosan group, a mouthwash containing 0.3% triclosan was used. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Web of Science<br>• EBSCOhost<br>• Scopus, and<br>• Cochrane Library.<br><br>The databases were searched for articles published until May 2020. Additional records were manually searched from cross-references. Grey literature was searched in OpenGrey and TRIP databases.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion and consensus.<br><br>The review protocol was registered with PROSPERO (ID: CRD42019145136).<br><br>The source of funding for the review was not provided.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 16 included trials were published between 1995 and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included 16 randomised controlled trials. Of these, two were cluster randomised. Follow-up periods were outcome specific and ranged from one week to three years.<br><br>Funded sources of the included trials were not provided. |
| **Types of studies included** | The review authors included 16 randomised controlled trials: Petersson (1998), Duarte (2008), Ribeiro (2008), Martinez (2012), Pukallus (2013), Sundell (2013), Paul (2014), Naidu (2016), Zhan (2006), Xu (2009), Perala (2016), Sintes (1995), Sintes (2002), Campus (2009), Chi (2014), and Lee (2015). |

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| | The results of 14 randomised controlled trials informed the outcomes of interest to this umbrella review: Petersson (1998), Ribeiro (2008), Martinez (2012), Pukallus (2013), Sundell (2013), Paul (2014), Zhan (2006), Xu (2009), Perala (2016), Sintes (1995), Sintes (2002), Campus (2009), Chi (2014), and Lee (2015).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | Information pertaining to the countries of origin was not provided. |
| **Appraisal instrument(s)** | Risk of bias was assessed based on the Cochrane's Collaboration Tool (Higgins et al. 2011). Two review authors assessed the risk of bias in included trials. Disagreements were resolved after consulting other review authors. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias. |
| **Appraisal rating** | Overall, only one of the included trials was assessed as having a low risk of bias, and two trials were assessed as having an unclear risk of bias. The remaining 13 trials were assessed as having a high risk of bias. Of the 14 trials relevant to this umbrella review, one trial was categorised as low risk of bias, one trial was categorised as being at unclear risk of bias, and 12 trials were categorised as being at high risk of bias.<br><br>Six trials were at categorised as being at low risk of bias for randomisation, three trials were categorised as being at high risk of bias for randomisation, and seven trials were categorised as being at an unclear risk of bias for randomisation. Of the 14 trials relevant to this umbrella review, five were at low risk of bias for randomisation, seven were at unclear risk of bias for randomisation, and two were at high risk of bias for randomisation.<br><br>Ten trials were categorised as being at low risk of bias for outcome ascertainment, three trials were categorised as being at high risk of bias for outcome ascertainment, and three trials were categorised as being at an unclear risk of bias for outcome ascertainment. Of the 14 trials relevant to this umbrella review, nine were at low risk of bias for outcome |

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| | ascertainment, two were at unclear risk of bias for outcome ascertainment, and three were at high risk of bias for outcome ascertainment.<br><br>Overall, the quality of evidence was judged to be low for primary outcomes and very low with respect to the secondary outcomes. The quality of evidence was assessed with reference to risk of bias, imprecision, inconsistency, indirectness and publication bias. The certainty of the evidence was downgraded due to unclear/ high risk of bias. Moreover, the trials were assessed to exhibit serious concerns with respect to 'indirectness' due to the variability in the treatment regimen and follow-up period. Furthermore, the quality of the evidence for the secondary outcome was downgraded due to 'imprecision' owing to the small sample sizes in the included trials.<br><br>Publication bias was assessed; however, the results of this assessment were not reported. |
| **Method of analysis** | For quantitative analysis, only those trials that reported outcomes as continuous data could be pooled. Owing to variability in reporting of the outcome variables, results from all the trials could not be pooled. Because of the different scales used to record the primary and secondary outcomes among the included trials, standardised mean difference with 95% Confidence Interval statistic was used in Review Manager Version 5.4 for the quantitative analysis. A p-value of less than 0.05 was considered as statistically significant. Sub-group analysis was carried out for individual antibacterial agents (Chlorhexidine, Povidone-Iodine, Triclosan and Xylitol).<br><br>The data of the two experimental administering chlorhexidine gel and the three experimental groups administering chlorhexidine varnish were combined to form one representative experimental group to avoid double counting of the comparator group in the respective trials.<br><br>Due to the observed clinical heterogeneity across the included trials with respect to the intervention regimen, there exists variability in the measured intervention effects and thus a random effects model using the Inverse variance method was applied. Statistical heterogeneity was quantified using $I^2$ statistic, where $I^2$ values over 50% indicated moderate to high heterogeneity. |
| **Outcome(s) assessed** | Primary outcome 1: mean increment in dental caries seen at a minimum follow-up period of one year in the combined therapy (TF and antibacterial agent) versus TF monotherapy<br><br>Secondary outcome 1: mean salivary *Streptococcus mutans* counts |

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| | Secondary outcome 2: mean salivary *Lactobacillus* counts<br><br>*Note*. All outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Caries increment**<br>Of the 11 trials reporting caries increment as an outcome, only five contributed data to the meta-analysis. Overall, there was a significant difference in the primary outcome between the experimental and control groups favouring combined therapy (SMD − 0.12, 95% CI − 0.2 to − 0.04, p = 0.004; 4,442 participants; 5 trials; $I^2$ = 20%; low certainty of evidence). However, this result was driven by two studies on topical fluoride + xylitol combined therapy by the same authors.<br><br>The precise outcome measure varied; mean number of decayed surfaces (ds) in 1 trial, incidence of caries (unspecified) in 2 trials, and mean increment of Decayed and Filled Surfaces (DFS) in 2 trials.<br><br>The dose and form of fluoride and antimicrobial agents were 0.304% fluoride toothpaste + 0.12% chlorhexidine gel (1 trial), 250 ppm fluoride toothpaste + 1% chlorhexidine gel (1 trial), 1.23% APF gel + 2ml povidone-iodine (1 trial), and toothpaste containing 1100 ppm fluoride + 10% xylitol (2 trials). Follow up periods were 1 year (1 trial), 2 years (2 trials), 30 months (1 trial), and 3 years (1 trial).<br><br>*Note*. 2/5 included trials involved complex interventions (in addition to FT + xylitol, oral health education + dietary counselling was provided in 1 trial, and oral prophylaxis + restorative therapy was provided in another trial).<br><br>Results from sub-group analyses that were carried out for individual antibacterial agents are presented below.<br><br><u>Comparison 1: Chlorhexidine + TF versus TF alone:</u><br>Pooled data from two trials found no statistically significant difference in caries incidence between the combined therapy group and the topical fluoride monotherapy group at 2 ears follow-up (SMD 0.13, 95% CI -0.14 to 0.41; 2 trials; 207 participants; $I^2$ = 0%; high risk of bias trials).<br><br><u>Comparison 2: Povidone Iodine + TF versus TF alone:</u><br>One trial found no statistically significant difference in caries incidence between the combined therapy group and the topical fluoride monotherapy group at 1 year follow-up (SMD -0.09, 95% CI -0.99 to 0.82; 1 trial; 19 participants; unclear risk of bias).<br><br><u>Comparison 3: Xylitol + TF versus TF alone:</u><br>Pooled data from two trials found a statistically significant difference in caries incidence between the combined therapy group and the topical fluoride monotherapy group at three years and 30 months follow-up (SMD - |

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| | 0.14, 95% CI -0.21 to -0.07; 2 trials; 4,216 participants; $I^2$ = 0%; high risk of bias trials).<br><br>Comparison 4: Triclosan + TF versus TF alone:<br>No trials comparing these interventions reported this outcome.<br><br>**Secondary outcome 1: *Streptococcus mutans* counts**<br>Of the nine trials reporting *Streptococcus mutans* counts as an outcome, five contributed data to the meta-analysis. Overall, there was no statistically significant difference in *Streptococcus mutans* counts between the combined therapy group and TF monotherapy group (SMD -0.11, 95% CI -0.33 to 0.10, p = 0.30; 5 trials; 356 participants; $I^2$ = 0%; very low certainty of evidence).<br><br>Results from sub-group analyses that were carried out for individual antibacterial agents are presented below.<br><br>Comparison 1: Chlorhexidine + TF versus TF alone:<br>One trial found no statistically significant difference in *Streptococcus mutans* counts between the combined therapy and monotherapy groups (SMD -0.42, 95% CI -1.06 to 0.23, p = 0.2; 1 trial; 55 participants; very low certainty of evidence).<br><br>Comparison 2: Povidone Iodine + TF versus TF alone:<br>Pooled data from two trials showed no statistically significant difference in *Streptococcus mutans* counts between the combined therapy and monotherapy groups (SMD -0.10, 95% CI -0.57 to 0.37, p = 0.69; 2 trials; 70 participants; $I^2$ = 0%; very low certainty of evidence).<br><br>Comparison 3: Xylitol + TF versus TF alone:<br>One trial found no statistically significant difference in *Streptococcus mutans* counts between the combined therapy and monotherapy groups at three-months follow-up (SMD -0.02, 95% CI -0.33 to 0.29; 1 trial; 165 participants; very low certainty of evidence).<br><br>Comparison 4: Triclosan + TF versus TF alone:<br>One trial found no statistically significant difference in *Streptococcus mutans* counts between the combined therapy and monotherapy groups at 15-day's follow-up (SMD -0.19, 95% CI -0.67 to 0.29, p = 0.44; 1 trial; 66 participants; very low certainty of evidence).<br><br>**Secondary outcome 2: *Lactobacillus* counts**<br>None of the trials reporting this outcome could be included in the quantitative synthesis. Results were not described narratively. |
| **Significance/direction** | The pooled analysis significantly favours combined use of TF with an antibacterial agent over TF use alone in preventing dental caries among 1- to |

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| | 16-year-old children, the results need to be interpreted with caution since this result is driven by two studies on Xylitol conducted on the same study population. The collective available evidence shows topical fluoride in combination with an antibacterial is no more effective than topical fluoride alone at preventing dental caries and limiting *Streptococcus mutans* build-up. However, in light of the low-quality evidence generated, further research is very likely to have an important impact on the estimate. There is a need to conduct well-designed trials to guide future evidence-based preventive strategies for the management of dental caries among children. |
| **Heterogeneity** | Due to the observed clinical heterogeneity across the included trials with respect to the intervention regimen, a random effects model was used where meta-analysis were conducted. Although appropriate method of analysis was used to counter the clinical heterogeneity present across the studies, the review authors state that such variability might have brought some inconsistencies in the results. The certainty of the evidence was downgraded for due to unclear/ high risk of bias (primary outcome) and due to 'imprecision' owing to the small sample sizes in the included studies (secondary outcome). |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as low for the primary outcome and very low for the secondary outcome.<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Zhang *et al.* (2020) |
| **First Author and year of publication** | Zhang *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To summarize and synthesize the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries (p506). |
| **Participants (characteristics and numbers)** | Permanent dentition; topical fluoride, solution, varnishes, gels, mouthrinses, toothpaste, combined intervention.<br><br>Baseline caries were not reported in any included trial.<br><br>Participants included adults of any age. Trials focussing on special population groups, such as life-threatening diseases or conditions that significantly affect salivary gland function, were excluded. |

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| | The nine included trials involved a total of 4,030 participants. The mean age of participants ranged from approximately 49 years to 83 years. Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | The trials were conducted in Canada (1 trial), Hong Kong (3 trials), the Netherlands (1 trial), Sweden (1 trial), the United Kingdom (1 trial), and the United States (2 trials).<br><br>Information pertaining to the settings of the included trials was not provided. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was professionally or self-applied topical fluorides. Professionally applied fluorides included those for clinical use, such as NaF varnish, SDF solution, and acidulated phosphate fluoride (APF) gel. Self-applied topical fluorides included fluoride toothpaste and mouthrinse available in stores. Comparison groups included different concentrations or content of fluoride, placebo, and blank (no special intervention) control. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• MEDLINE (via ProQuest)<br>• PubMed<br>• Embase (via Ovid)<br>• Scopus, and<br>• Cochrane Library.<br><br>There were no restrictions on language or date of publication. The references of previous reviews and the included papers were searched for any additional studies.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements during screening were resolved by discussion with a third reviewer. Disagreement resolution in the data extraction phase was not described.<br><br>The review protocol was submitted for registration in the PROSPERO database (provisional number: 128903).<br><br>This review was funded by the Tam Wah Ching endowed professorship of the University of Hong Kong.<br><br>None of the review authors declared a conflict of interest. |

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| **Date range (years) of included studies** | The nine included trials were published between 1987 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included nine controlled clinical trials. Duration of the trials ranged from 1 year to 4 years. For both professionally applied and the self-applied fluoride trials, the most frequent follow-up time was 2 to 3 years.<br><br>The funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included nine controlled clinical trials: Li (2017), Zhang (2013), Tan (2010), Paraskevas (2004), Wyatt (2004), Fure (1998), Wallace (1993), Jensen (1988), and Ripa (1987).<br><br>A list of excluded studies and the reasons for exclusion were provided in an appendix. |
| **Country of origin of included studies** | The trials were conducted in Canada (1 trial), Hong Kong (3 trials), the Netherlands (1 trial), Sweden (1 trial), the United Kingdom (1 trial), and the United States (2 trials). |
| **Appraisal instrument(s)** | Cochrane risk of bias tool (RoB 2.0) was used to evaluate the included clinical trials. The following domains were assessed in each included trial:<br>1. Randomisation process<br>2. Deviations from intended interventions<br>3. Missing outcome data<br>4. Measurement of outcome, and<br>5. Selection of reported results.<br><br>An overall judgement of low risk, some concerns, and high risk was assigned to each included trial. The highest level in the domains was assigned as the overall risk of bias.<br><br>Certainty in the evidence for each comparison between interventions was assessed by the GRADE approach. |
| **Appraisal rating** | Overall, six trials were categorised as having a low risk of bias. The remaining three trials were categorised as having some concerns. Among the three trials with some concerns, the bias arose from the randomisation process.<br><br>All trials were categorised as having a low risk of bias in measurement of the outcome. |

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| | For direct comparison of two interventions, the certainty of evidence was assessed with reference to risk of bias, inconsistency, indirectness, imprecision, and publication bias. For indirect comparisons, the certainty of evidence was assessed with reference to intransitivity, imprecision, and the lowest-certainty ratings for the direct comparison. For the certainty of evidence in the network meta-analysis, the lower level of certainty in the direct and indirect comparisons was adopted.<br><br>Overall, certainty in the evidence ranged from very low to moderate. In 8 out of the 15 professionally applied fluoride comparisons, the certainty was moderate. These were all direct comparisons. For self-applied topical fluorides, only the direct comparison of 0.05% NaF mouth rinse with control reached the moderate level of evidence. The level of evidence of the other comparisons was downgraded mainly due to serious issues of risk of bias, imprecision, and indirectness.<br><br>The review authors had planned to assess publication bias using the funnel plot technique. However, as the number of included trials in the meta-analysis was smaller than 10, this assessment was not conducted. |
| **Method of analysis** | The software package Stata (version 16.0, StataCorp, College Station) was used. Two network meta-analyses were conducted, one on professionally applied and one on self-applied fluorides, using a frequentist fixed-effects approach. Because the number of included trials was relatively small in contrast to the interventions compared within the network meta-analysis, it was not feasible to yield a robust estimate for the heterogeneity variance. Stata issued a warning and suggested the use of a fixed-effect model. |
| **Outcome(s) assessed** | Primary outcome 1: Root caries increment, measured by both decayed root (D-root), and decayed and filled root (DF-root)<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Root with new caries/caries experience**<br><u>Professionally applied topical fluorides:</u><br>Five arms were included in the network meta-analysis of professional applied topical fluoride, and all five interventions were more effective than the control in preventing root caries:<br>1. Annual application of 38% SDF solution (Mean -0.68, 95% CI -0.99 to -0.38)<br>2. Annual application of 38% SDF followed by potassium iodide (KI) (2.36 mol/L) (Mean -0.59, 95% CI -0.94 to -0.23)<br>3. Annual application of 38% SDF solution and oral health education (OHE) (Mean -0.85, 95% CI -1.23 to -0.47) |

4. Quarterly application of 5% NaF varnish (Mean -0.67, 95% CI -1.22 to -0.12), and
5. Semiannual application of 1.2% APF gel (Mean -0.64, 95% CI -1.27 to -0.01).

There were no statistically significant differences between the intervention groups.

A 2-year follow-up was chosen for the NMA of the effectiveness of professionally applied topical fluorides because the clinical trials lasted for at least 2 years.

Self-applied topical fluorides:
Seven arms of interventions were included, and three were more effective in preventing root caries compared to the control:

1. Daily use of 0.05% NaF mouthrinse (NS)
2. Daily use of 0.2% NaF mouthrinse (S)
3. Daily use of 1100 – 1500 ppm fluoride toothpaste (S)
4. Daily use of 1100 – 1500 ppm fluoride toothpaste + toothpaste rinsing slurry (NS)
5. Daily use of 1100 – 1500 ppm fluoride toothpaste + 1.66mg NaF tablets (NS)
6. Daily use of 1100 – 1500 ppm fluoride toothpaste + AmF/$SnF_2$ mouthrinse (250 ppm amine/stannous Fluoride) (NS), and
7. Daily use of 1100 – 1500 ppm fluoride toothpaste + 0.05% NaF mouthrinse (250 ppm F) (S).

Daily use of 0.2% NaF mouthrinse was more effective than 0.05% NaF mouth rinse. Meanwhile, use of 1100 ppm to 1500 ppm fluoride toothpaste plus 0.05% NaF mouthrinse had lower root caries increment, compared to any of the following four interventions: 1100 ppm to 1500 ppm fluoride toothpaste, use of the fluoride toothpaste plus 1.66 mg NaF tablet, rinsing with toothpaste slurry, or using 0.05% NaF mouth rinse alone.

A 1-year follow-up was chosen for the NMA of the effectiveness of self-applied topical fluorides because 1 of the 6 studies only lasted for 1 year.

Overall, inconsistency tests showed that the results of the included trials on professionally applied fluorides (P = .094) and on self-applied fluorides (P = 0.450) were consistent. Differences between direct and indirect treatment comparison in each side were not significant (all P > 0.05).

Ranking of the fluoride interventions according to their probability of greater effectiveness in preventing root caries was shown in appendices. The order

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| | from highest to lowest probability of being the most effective in preventing root caries among the professionally applied fluorides was:<br>1. Annual application of 38% SDF solution plus oral health education (highest probability of being the most effective)<br>2. Annual application of 38% SDF solution<br>3. Quarterly application of 5% NaF varnish<br>4. Semiannual application of 1.2% APF gel, and<br>5. Annual application of 38% SDF followed by potassium iodide (lowest probability of being the most effective).<br><br>The order from highest to lowest probability of being the most effective in preventing root caries among the self-applied topical fluorides was:<br>1. 0.2% NaF mouthrinse (highest probability of being the most effective)<br>2. 1100 – 1500 ppm fluoride toothpaste + 0.05% NaF mouthrinse (250 ppm F).<br>3. 1100 – 1500 ppm fluoride toothpaste + 1.66mg NaF tablets<br>3. 1100 – 1500 ppm fluoride toothpaste + AmF/$SnF_2$ (250 ppm amine/stannous Fluoride) mouthrinse<br>5. 1100 – 1500 ppm fluoride toothpaste + toothpaste rinsing slurry<br>6. 1100 – 1500 ppm fluoride toothpaste, and<br>7. 0.05% NaF mouthrinse (lowest probability of being the most effective). |
| **Significance/direction** | All the professionally applied topical fluorides were shown to prevent root caries compared with a non-fluoride control. Among them, annually applied 38% SDF solution combined with oral health education is likely to be the most effective. Among the self-applied topical fluoride methods, 0.2% NaF mouth rinse is likely to be the most effective, followed by combined use of 1100 ppm to 1500 ppm fluoride toothpaste and 0.05% NaF mouth rinse, and 1100 ppm to 1500 ppm fluoride toothpaste. |
| **Heterogeneity** | Due to the limited number of included trials, room for the heterogeneity test was limited and thus a fixed-effect model was used in this review. However, the review authors stated that heterogeneity may exist and the results should be interpreted with this in consideration as the confidence intervals may be misleadingly underestimated. |
| **Summary for GRADE assessment for HRB report** | Overall, the evidence from direct comparisons on the effect of professionally-applied fluoride interventions was graded by the review authors as moderate. Downgrading occurred due to serious issues of imprecision. The certainty of evidence from indirect comparisons was graded as moderate (6/13 indirect comparisons), low (3/13 indirect comparisons) and very low (4/13 indirect comparisons). Downgrading |

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| | occurred due to serious issues of imprecision and/or risk of bias and/or indirectness.<br><br>The evidence from direct comparison on the effect of self-applied fluoride interventions was graded by the review authors as moderate (3/10 direct comparisons) and low (7/10 direct comparison). Downgrading occurred due to serious issues of imprecision and/or risk of bias. The certainty of evidence from indirect comparisons was graded as low (20/25 indirect comparisons) and very low (5/25 indirect comparisons). Downgrading occurred due to serious issues of risk of bias and/or indirectness.<br><br>The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Yu *et al.* (2021) |
| **First Author and year of publication** | Yu *et al.* (2021) |
| **Objectives (exact review question(s) and page number)** | To assess whether the combined use of professional fluoride application and regular fluoride toothpaste has additional benefit than using regular fluoride toothpaste alone for children under 16 (p3410). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate and mixed); combined intervention.<br><br>Baseline caries were reported in five of the six included trials. Of these five trials, two included participants who were caries free at baseline.<br><br>The six included trials involved a total of 5,034 participants, with ages ranging from 12 months to 8 years. In five trials, participants were no more than five years old at baseline and with primary dentition. In one trial, participants had mixed dentition. Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | The trials were conducted in Brazil (1 trial), Greece (1 trial), Sweden (1 trial), the UK (2 trials), and the USA (1 trial).<br><br>The settings of the included trials were not explicitly stated. |
| **Description of Interventions/ phenomena of interest** | The invention of interest was the combined use of professional fluoride application (with fluoride in any form (gels, varnishes, foams) or concentration) and regular fluoride toothpaste (≥ 1,000 ppm). The control of |

interest was self-applied regular fluoride toothpaste alone, with a fluoride concentration of 1,000 ppm or above.

In all trials, the fluoride concentration in the toothpaste was similar. Three trials had a concentration of 1450 ppm, one trial had a concentration of 1100 ppm, one trial had a concentration of 1000 ppm, and the remaining one trial had a concentration that ranged from 1000 to 1450 ppm. In two of the trials, toothbrushing was performed under supervision. Two trials reported a clear source of other fluorides, such as fluoridated milk or water. All professional fluoride applications used in the study groups was fluoride varnish. Five of the trials used fluoride varnish with 5% sodium fluoride, and the other used fluoride varnish with 0.9% difluorosilane. All the professional fluoride was applied every six months.

Tickle (2017) involved a combined intervention consisting of 5% NaF varnish, 1450ppm fluoride toothpaste, oral health education and dietary counselling, and the control group received oral health education and dietary counselling.

Agouropoulos (2014) involved a combined intervention consisting of 0.9% difluorosilane varnish, 1000ppm fluoride toothpaste, oral health education and supervised toothbrushing, and the control group received biannual application of placebo varnish, oral health education and supervised toothbrushing.

Oliveira (2014) involved a combined intervention consisting of 5% NaF varnish, 1450ppm fluoride toothpaste, oral health counselling and supervised toothbrushing, and the control group application of placebo varnish, oral health counselling and supervised toothbrushing.

Anderson (2016) involved a combined intervention consisting of 5% NaF varnish, 1000-1450ppm fluoride toothpaste, oral health education and dietary counselling, and the control group received usual care, oral health education and dietary counselling.

Hardman (2007) involved a combined intervention in which participants received 5% NaF varnish, 1450ppm fluoride toothpaste and usual care, and the control group received usual care.

Braun (2016) involved a combined intervention in which participants received % NaF varnish, 1100ppm fluoride toothpaste and oral health education, and the control group received usual care.

The review authors noted other background sources of fluoride (exposure to fluoridated water or milk where possible).

**Databases and sources searched**

The reviews authors searched the following sources:

- PubMed
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Embase, and
- Google Scholar.

No restrictions were placed on language or date of publication. In addition, the reference lists of eligible trials, as well as relevant reviews, were examined.

Manual searching was performed on the following ten dental journals:

- Journal of dental research
- Paediatric dentistry
- Journal of dentistry
- Journal of the American Dental Association
- Caries research
- International journal and paediatric dentistry
- Oral Health and preventive dentistry
- Journal of clinical paediatric dentistry, and
- American journal of dentistry.

All electronic and manual searches were last updated in February and March 2020, respectively.

The review protocol was registered with PROSPERO (ID: CRD42020165270). The review authors reported no important discrepancies between the protocol and the final report.

Two review authors independently and in duplicate screened the titles and abstracts of retrieved articles. Disagreements were resolved by discussion with two experts. It was not reported how full-texting screening was completed. Two review authors independently and in duplicate performed data extraction. Disagreements were resolved through discussion with a third review author.

The review was supported by 'The Hubei Provincial Natural Science Foundation and the Wuhan Young and Middle-aged Medical Talents Training Program.

None of the review authors declared a conflict of interest.

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| **Date range (years) of included studies** | The six trials were published between 2007 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included six randomised controlled trials. In three trials, randomisation was performed at the individual level and in three trials, randomisation was performed at the cluster level. Follow-up periods ranged from 12 to 36 months.<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included six randomised controlled trials: Tickle (2017), Agouropoulos (2014), Oliveira (2014), Anderson (2016), Hardman (2007), and Braun (2016).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Brazil (1 trial), Greece (1 trial), Sweden (1 trial), the UK (2 trials), and the USA (1 trial). |
| **Appraisal instrument(s)** | The Cochrane risk of bias tool was used to assess the risk of bias among included studies. Two reviewers assessed all trials independently and in duplicate. All discrepancies were resolved by discussion with two experts. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias.<br><br>Each domain was assessed as having a high, low, or unclear risk of bias. |
| **Appraisal rating** | Overall, no trials were categorised as having a low risk of bias. Four trials were categorised as having a high risk of bias, and two trials were categorised as having an unclear risk of bias.<br><br>All six trials were categorised as having a low risk of bias for randomisation.<br><br>Five trials were categorised as having a low risk of bias for outcome ascertainment, and one trial was categorised as having a high risk of bias for outcome ascertainment. |

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| | The certainty of evidence was assessed with reference to risk of bias, imprecision, inconsistency, indirectness, and publication bias. The reason for downgrading was primarily due to imprecision of results. Overall, the certainty of evidence was assessed to be moderate.<br><br>Publication bias would have been assessed through a funnel plot and Egger's test; however, no meta-analysis included more than 10 trials. |
| **Method of analysis** | The review authors summarised dichotomous data with risk ratios and continuous data with mean differences, together with the corresponding 95% confidence intervals. Data synthesis was conducted using Review Manager software. A random-effects model was applied to analyse pooled data. This was because the confidence interval of mean effect size was wider than that obtained from a fixed effects model, and consequently led to a more conservative interpretation. The number needed to treat (NNT) was calculated when the difference was statistically significant in the overall pooled effect.<br><br>Subgroup analyses were planned and conducted using a $chi^2$ test, where a $P < 0.1$ was considered statistically significant. The following comparisons were made:<br>1. Primary dentition versus mixed dentition versus permanent dentition at baseline<br>2. Different follow-up length (12 months versus 24 months versus 36 months), and<br>3. High caries risk at baseline versus low caries risk at baseline.<br><br>Two forms of sensitivity analyses were also carried out: removing studies with the shortest observed follow-up period (12 months) and removing studies where we imputed missing standard deviations. The review authors performed these meta-analyses using random-effects models. |
| **Outcome(s) assessed** | Primary outcome 1: increment of decayed (missing/extraction indicated) and filled surfaces/teeth (D(M/E)FS or D(M/E)FT in permanent teeth, continuous outcome)<br><br>Primary outcome 2: increment of decayed (missing/extraction indicated) and filled surfaces/teeth (d(m/e)fs or d(m/e)ft in primary teeth, continuous outcome)<br><br>Primary outcome 3: caries incidence<br><br>Secondary outcome 1: patient-reported outcomes (e.g. ease of use/quality of life)<br><br>Secondary outcome 2: fluoride-related adverse events |

*Note*. All outcomes are identified in the review as presented here.

**Results/findings**

**Primary outcome 1: Increment of D(M/E)FS or D(M/E)FT**
None of the included trials reported on this outcome.

**Primary outcome 2: Increment of d(m/e)fs or d(m/e)ft**
The d(m/e)fs increment pooled estimate of all six trials from the random-effects meta-analysis was -0.17 (MD) (95% CI – 0.60 to 0.26; P = 0.43; 5,034; participants; 6 trials; $I^2$ = 38%; moderate certainty of evidence) at 24-36 months follow-up, suggesting a non-significant effect in favour of the additional use of FV.

These trials involved the use of fluoride varnish (5% NaF in 5 trials, and 0.9% difluorosilane, applied every 6 months) + fluoride toothpaste (1000-1450 ppm) + additional active intervention components (oral health education and/or counselling in 5 trials, dietary counselling in 2 trials, supervised toothbrushing in 2 trials, and "usual care" in 1 trial) compared to control groups that all received every active intervention component with the exception of the fluoride varnish in 4 out of 5 trials with combined interventions (the control was "usual care" in 1 trial).

No evidence from subgroup analyses suggested that primary dentition or mixed dentition, low or high caries risk at baseline and different follow-up lengths could affect the caries prevention effect of additional use of FV.

**Primary outcome 3: Caries incidence**
Analyses showed there was no statistically significant difference in caries incidence in the primary dentition of children between the FV + RFT group and the RFT group alone (RR 0.91, 95% CI 0.80 to 1.05, p = 0.21; 4 trials; 4,477 participants; $I^2$ = 41%; moderate certainty of evidence) at 24-36 months follow-up.

All trials used 5% NaF varnish + fluoride toothpaste (1000-1450 ppm); oral health education/counselling was provided in 3 trials, dietary counselling was provided in 2 trials, supervised toothbrushing was provided in 1 trial, and "usual care" was provided in 1 trial.

**Secondary outcome 1: Patient-reported outcomes**
No included trials reported this outcome.

**Secondary outcome 2: Fluoride-related adverse events**
One trial reported no serious adverse effects following the varnish applications. In some cases, the smell of the varnish was unpleasant to the young children, but the problem was overcome using appropriate behaviour management.

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| | Another trial reported no serious effects after the varnish was applied. A few children vomited directly after application due to the smell, texture, or taste of the varnish.<br><br>One trial reported a mother felt bothered by the coloration of her child's teeth who belonged to the test group. In addition, one child in the control group complained of a burning sensation in her mouth on the day of application.<br><br>Lastly, one trial reported a small number of adverse reactions with a possible link to the varnish. However, all of these were minor and self-limiting, which suggested to the review authors that fluoride varnish is this young age group is safe. |
| **Significance/direction** | Available evidence suggests that fluoride varnish does not have significant additional caries-preventive benefit for children (under 8 years old) when provided as an adjunct to daily tooth brushing with regular fluoride toothpaste (≥ 1000 ppm). |
| **Heterogeneity** | The heterogeneity in the meta-analyses was moderate. This heterogeneity was not explained. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence for primary outcome 2 (dmfs increment) and primary outcome 3 (caries incidence) as moderate, both downgraded once for imprecision (none of the included trials evaluated primary outcome 1).<br><br>The HRB authors graded the certainty of evidence in this review as moderate. |
| **References to previously published versions** | N/A |
| Parameter | Xiao *et al.* (2019) |
| **First Author and year of publication** | Xiao *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To systematically review the scientific evidence relating to the association between prenatal oral health care, reduced carriage of *S. Mutans*, and early childhood caries prevention (p413). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate, but primary only for primary outcome); systemic fluoride, supplements; topical other chemicals, xylitol; combined intervention. |

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| | The participants in the review had no caries at baseline (the review included pregnant women, regardless of their dental caries to examine subsequent caries in their offspring).<br><br>The five included studies involved a total of approximately 2,017 pregnant women and 1,699 children. The ages of the children at follow-up ranged from 15 months to 5 years. Information pertaining to the sex of the children was not provided.<br><br>The total number of pregnant woman and children evaluated in the three (out of five) included studies that inform this umbrella review was approximately 1,368 and 1,094. |
| **Setting/context** | The studies were conducted in Australia (1 study), Germany (1 study), Japan (2 studies), and the USA (1 study).<br><br>All five studies were conducted in a medical setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was prenatal oral health care utilisation/intervention. The control group was women who did not receive prenatal oral health care.<br><br>Oral health care interventions were delivered from the prenatal through to the infant stage. The interventions included:<br>1. Fluoride-based intervention, where fluoride supplement intake was provided to pregnant women and their infant in a population that was not exposed to optimal water fluoridation<br>2. Primary-primary prevention, where all prophylactic measures were carried out in pregnant women in order to prevent the transmission of cariogenic bacteria and improve feeding behaviours after birth<br>3. Oral health education promotion in pregnant women, and<br>4. Xylitol gum chewing in pregnant women.<br><br>Based on the inclusion criteria of this umbrella review, findings in relation to oral health educational interventions were not extracted. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Embase<br>• Scopus<br>• Web of Science<br>• LILACS<br>• Cochrane Library, and |

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| | • ClinicalTrials.gov.<br><br>Database searches were conducted in May 2018.<br><br>Two review authors independently completed study selection in accordance with the inclusion/exclusion criteria. Disagreements were resolved by consensus between the two reviewers. It was not stated how many reviewers were involved in performing data extraction.<br><br>There was no mention of a protocol being prepared, and a registration number was not provided.<br><br>This study was supported in part by Jin Xiao's faculty start-up funds from the Eastman Institute for Oral Health, University of Rochester, and the National Institute for Dental and Craniofacial Research/National Center for Advancing Translational Sciences.<br><br>Information in relation to conflicts of interest of the review authors was not provided. |
| **Date range (years) of included studies** | The five included studies were published between 1997 and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included five studies in this review. Of these, three were randomised controlled trials, one was a prospective cohort study, and one was a nested case-control in a cohort study. The nested case-control did not meet the eligibility criteria for this umbrella review under study design and therefore the findings from this study were not extracted (Nakai, 2016). The outcomes in the five trials relevant to this umbrella review were assessed when children reached 15 months to 5 years of age.<br><br>Funding sources of the included studies were not provided. |
| **Types of studies included** | The review authors included three randomised controlled trials: Leverett (1997), Plutzer (2008), Nakai (2010); one prospective cohort study: Günay (1998); and one nested case-control study (Nakai, 2016).<br><br>The results of three (out of five) studies were relevant to this umbrella review: Leverett (1997), Nakai (2010), and Günay (1998).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | The studies were conducted in Australia (1 study), Germany (1 study), Japan (2 studies), and the USA (1 study). |
| **Appraisal instrument(s)** | Two methodologies were used to assess the quality of the selected studies. The first was the Cochrane's Collaboration's tool for assessing risk of bias in |

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| | randomised trials (Higgins et al., 2011). The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias.<br><br>The second method was the Adapted Downs and Black scoring (Downs and Black, 1998) that assesses the methodological quality of both randomised and nonrandomised studies of healthcare interventions. A total score of 26 represents the highest study quality. |
| **Appraisal rating** | The review authors stated that two randomised controlled trials were of high quality based on the Cochrane risk of bias assessment tool and Downs and Black scoring system. The other three studies showed moderate quality. However, based off graphical information provided in the review, no studies can be considered at an overall low risk of bias; three were at high risk of bias overall and two studies were at unclear risk of bias. Of the three studies relevant to this umbrella review, graphical information illustrates that two were at high risk of bias and one was at an unclear risk of bias.<br><br>Three studies were categorised as having a low risk of bias for randomisation, and two studies were categorised as having an unclear risk of bias for randomisation. Of the three studies relevant to this umbrella review, two were categorised as having a low risk of bias for randomisation, and one was categorised as having an unclear risk of bias for randomisation.<br><br>Three studies were categorised as having a low risk of bias for outcome ascertainment, and two studies were categorised as having an unclear risk of bias for outcome ascertainment. Of the three studies relevant to this umbrella review, two were categorised as having a low risk of bias for outcome ascertainment, and one was categorised as having an unclear risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | For the articles selected for quantitative analysis, the R package Metafor was used for meta-analysis. The odds ratios and 95% confidence intervals and p values were estimated using an unconditional generalized linear mixed effects model with random study effects. Children's age at study endpoint was used as a covariate. |

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| | Heterogeneity among the studies was evaluated using $I^2$ statistics and tested using the likelihood ratio test. A forest plot was created to summarize the meta-analysis study results. |
| **Outcome(s) assessed** | Primary outcome 1: Caries incidence, measured using DMFS/dmfs index<br><br>Secondary outcome 1: Salivary *Streptococcus mutans*<br><br>*Note*. The nature of the outcomes (i.e. primary or secondary) is not made explicit in the review. For the HRB's purposes the outcomes are considered primary and secondary outcomes as presented above. |
| **Results/findings** | **Primary outcome 1: Caries incidence**<br>Due to the heterogeneity in intervention type and study design, the findings of the meta-analysis performed by the review authors could not be extracted. Results are instead presented narratively.<br><br><u>Intervention 1: Fluoride-based intervention:</u><br>There was no statistically significant difference in caries incidence between the offspring of pregnant women who received the intervention (daily intake of tablet containing 1mg fluoride beginning with the 4th month of pregnancy until the end of pregnancy (approximately 6 months)) and the offspring of pregnant women who did not receive the intervention (no fluoride intake) when the children were assessed at 5 years of age (OR 0.94, 95% CI 0.57 to 1.56; 1 trial; 789 children; high risk of bias trial).<br><br>*Note*. This intervention also involved the use of a daily drop of fluoride water from birth to 2 years of age, followed by a daily 0.5-mg tablet from 2 to 3 years of age.<br><br><u>Intervention 2: Primary-primary prevention:</u><br>Caries incidence was lower in the offspring of pregnant women who received the intervention compared to the offspring of pregnant woman who did not receive the intervention when the children were assessed at 3 years of age (OR 0.04, 95% CI 0.00 to 0.68; 1 trial; 119 participants; high risk of bias trial).<br><br>Similarly, caries incidence was lower in the offspring of pregnant women who received the intervention compared to the offspring of pregnant woman who did not receive the intervention when the children were assessed at 4 years of age (OR 0.13, 95% CI 0.04 to 0.42; 1 trial; 92 participants; high risk of bias trial).<br><br>This intervention consisted of: Dental examination findings, individual preventive self-care oral health instruction, instruction on avoiding microbe transmission, caries etiology education, and referral for dental treatment if |

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| | needed (at first pregnancy visit), education about infection related to maternal-child caries transmission (at second pregnancy visit (>8 months gestational age), maternal oral exam and oral health instruction (after birth visit, 0-3 years), and offspring oral health instruction, teeth cleaning and topical fluoride and chlorhexidine varnish application (after birth, 3-4 years of age).<br><br>Intervention 3: Xylitol gum chewing:<br>No trials comparing this intervention reported this outcome.<br><br>**Secondary outcome 1: Salivary *Streptococcus mutans***<br>Intervention 1: Fluoride-based intervention:<br>No trials comparing this intervention reported this outcome.<br><br>Intervention 2: Primary-primary prevention:<br>One trial showed a significant difference in *S. mutans* reduction between the intervention and control groups: 100% of children in the intervention group remained *S. mutans* free by the age of 3 years, whereas only 38.5% of children in the control group remained *S. mutans* free by the age of 3 years. Moreover, mothers in the intervention group also showed a significant improvement in plaque index and reduction in *S. mutans* score.<br><br>Intervention 3: Xylitol gum chewing:<br>One trial showed that significantly more children in the xylitol chewing group remained *S. mutans* free at 9, 12, and 24 months. Furthermore, pre- and perinatal xylitol chewing by mothers delayed *S. mutans* carriage in children. The children's *S. mutans* acquisition age in the xylitol chewing group was 8.8 months later than that of the control group (mean age 20.8 vs. 12.0 months). |
| **Significance/direction** | This review reports a reduced early childhood caries incidence and *S. mutans* carriage in children whose mothers received pre-natal oral health care. Maintaining oral health during pregnancy may be a critical and promising step towards early childhood caries prevention. |
| **Heterogeneity** | The significant heterogeneity observed in intervention modalities, timing of the main outcome measurement, and study design restricted use of quantitative syntheses for the main outcome. In addition, where meta-analyses were conducted, data from randomised controlled trials and non-randomised epidemiological studies were combined and thus meaningful results were limited. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |

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| **References to previously published versions** | N/A |
| Parameter | Wright *et al.* (2016) |
| **First Author and year of publication** | Wright *et al.* (2016) |
| **Objectives (exact review question(s) and page number)** | To summarise the available evidence regarding the effect of dental sealants for the prevention of pit-and-fissure occlusal caries in primary and permanent molars on children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with another head-to-head comparison to inform the development of a joint evidence-based clinical practice guideline by the American Dental Association and the American Academy of Pediatric Dentistry (p631). |
| **Participants (characteristics and numbers)** | Permanent dentition (molars); sealants, glass-ionomer, hybrids, combined.<br><br>Seventeen trials included participants who were caries-free at baseline.<br><br>The review authors included trials that involved children, adolescents, and adults from the general population who did or did not have a history of carious lesions and who had either a sound occlusal surface or a non-cavitated carious lesion in primary and permanent molars. The 23 included trials involved a total of 9,349 children and adolescents, aged 3 to 16 years old. Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | The trials were conducted in Australia (1 trial), Brazil (5 trials), Canada (1 trial), China (3 trials), Colombia (1 trial), Egypt (1 trial), Germany (1 trial), India (2 trials), Spain (1 trial), Turkey (4 trials), and the United States (3 trials).<br><br>Seven trials were conducted within a school setting, six trials were conducted in dental school clinics, three trials were conducted in a healthcare centre setting, and two trials were conducted within private practice offices. The setting of the remaining four trials was either not clearly defined or not described. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was sealants. For this review, the review authors defined four categories of sealant materials:<br>• Resin-based sealants<br>• Glass-ionomer cements or glass-ionomer sealants<br>• Resin-modified glass-ionomer sealants, and |

- Polyacid-modified resins.

The review authors classified resin-modified glass-ionomer sealants as a subcategory of the glass-ionomer sealants category and polyacid-modified resins as a subcategory of the resin-based sealants category. Intervention was defined as any of the four types of sealant materials, irrespective of the application technique. Studies were excluded where the investigators used sealant material that were not commercially available at the time of this review. The comparison group was defined as any type of sealant material irrespective of the application technique, the nonplacement of sealants, or the use of fluoride varnishes. Therefore, the review authors compared six interventions:

1. Sealants versus non-use of sealants
2. Sealants versus fluoride varnishes
3. Glass-ionomer sealants versus resin-based sealants
4. Glass-ionomer sealants versus resin-modified glass-ionomer sealants
5. Resin-modified glass-ionomer sealants versus polyacid-modified resin sealants, and
6. Polyacid-modified resin sealants versus resin-based sealants.

**Databases and sources searched**

The review authors searched the following sources:

- MEDLINE (via PubMed)
- Embase
- LILACS
- Cochrane Central Register of Controlled Trials (CENTRAL), and
- ClinicalTrials.gov.

No restrictions were placed on language or publication status. Databases were searched from January 1971 to May 2013. In addition, MEDLINE and CENTRAL were searched from June 2013 to May 2016. The reference lists of included studies from previous systematic review were also screened for any additional studies.

Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion and, where necessary, a third review author acting as an arbiter.

There was no mention of a protocol being prepared or published.

The review was in part funded by the American Academy of Paediatric Dentistry.

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| | Multiple review authors reported disclosures. One author was a consultant for the American Dental Association Council on Scientific Affairs. In the past, this author had received funds from the National Institute of Dental and Craniofacial Research, Delta Dental, and Ivoclar Vivadent to conduct research focused on dental sealants. These grants ended before their engagement with the work involved in this manuscript.<br><br>Another author's previous continuing education lecture honoraria were provided by the following manufacturers of sealant materials: GC America, SDI, and Shofu, and their previous continuing education lecture honoraria were provided by the following dental manufacturers: Air Techniques, CariFree, GlaxoSmithKline, Ivoclar, Phillips, Solutionreach, Triodent, and Xlear.<br><br>Another author was the chair of the Children's Dental Health Project's sealant work group and has received funding from Children's Dental Health Project, Delta Dental of Wisconsin, Washington Dental Services Foundation, DentaQuest Foundation, Health Resource and Services Administration Maternal and Child Health Bureau, and the Healthier Wisconsin Partnership Program. This author served on the board of trustees of the American Dental Hygienists' Association.<br><br>None of the other authors reported any disclosures. |
| **Date range (years) of included studies** | The 23 included trials were published between 1976 and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included 23 randomised controlled trials. Fourteen trials used a split-mouth design, and nine trials used a parallel-group design. All trials included a follow-up period of at least two years.<br><br>Funding sources of the included trials were not provided. |
| **Types of studies included** | The review authors included 23 randomised controlled trials: Bojanini (1976), Richardson (1980), Houpt (1983), Mertz-Fairhurst (1984), Erdogan (1987), Arrow (1995), Bravo (1996), Splieth (2001), Pereira (2003), Gungor (2004), Pardi (2005), Ganesh (2006), Amin (2008), Barja-Fidalgo (2009), Baseggio (2010), Tagliaferro (2011), Antonson (2012), Chen (2012), Dhar (2012), Liu (2012), Chen (2013), Guler (2013), and Haznedaroglu (2016).<br><br>A list of excluded studies and the reasons for exclusion were not provided. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Brazil (5 trials), Canada (1 trial), China (3 trials), Columbia (1 trial), Egypt (1 trial), Germany (1 trial), India (2 trials), Spain (1 trial), Turkey (4 trials), and the United States (3 trials). |

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| **Appraisal instrument(s)** | Two reviewers independently assessed the risk of bias for each included trial by using the Cochrane risk of bias tool. Any disagreements were resolved by means of discussion until consensus was reached. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Masking of participants and personnel (performance bias)<br>4. Masking of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias)<br>7. Other bias.<br><br>For each domain, the review authors determined whether a trial had a high, low, or unclear risk of bias. The review authors considered randomisation sequence generation and allocation concealment to be the most important domains for the overall assessment of risk of bias. |
| **Appraisal rating** | Poor quality of reporting of the included studies prevented the review authors from conducting a complete assessment of the risk of bias. However, graphical information provided in the paper indicates that, overall, none of the included trials were categorised as being at low risk of bias. Nine trials were categorised as being a high risk of bias, and the remaining 14 trials were categorised as being at unclear risk of bias.<br><br>Eleven trials were categorised as having a low risk of bias for randomisation, ten trials were categorised as having an unclear risk of bias for randomisation, and two trials were categorised as having a high risk of bias for randomisation.<br><br>Nine trials were categorised as having a low risk of bias outcome ascertainment, ten trials were categorised as having an unclear risk of bias for outcome ascertainment, and four trials were categorised as having a high risk of bias for outcome ascertainment.<br><br>The certainty of evidence was assessed with reference to the risk of bias, imprecision, inconsistency, indirectness, and publication bias. Overall, the certainty of evidence was graded as very low to moderate. The review authors found moderate quality evidence for the outcome of caries incidence in the comparison of sealants versus the control without sealants. However, when making more specific comparisons, the review authors found the quality of evidence decreased to low or very low for most of the head-to-head sealant comparisons. The reasons for downgrading were primarily due to risk of bias, inconsistency, and imprecision. |

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| | Publication bias could not be assessed by means of a funnel plot due to the limited number of included trials per outcome. |
| **Method of analysis** | The outcomes caries incidence, lack of retention, and adverse events were analysed as dichotomous outcomes. For trials in which the investigators reported sealants as being fully retained, partially retained, and not retained, the review authors grouped the fully and partially retained events and compared them with the sealants that were not retained to create the estimate. Odds ratios and 95% confidence intervals were calculated for both outcomes.<br><br>The review authors conducted subgroup analysis to determine whether the trials whose investigators had enrolled participants with non-cavitated pit-and-fissure occlusal carious lesions, sound occlusal surfaces, and those who had both (that is, a population who had a mix of both sound occlusal surfaces and non-cavitated carious lesions) had different treatment effects. For the purposes of this umbrella review, only the results from the subgroup analysis involving sound occlusal surfaces will be described. The HRB is only interested in the findings of studies that are focussed on the prevention of caries initiation and not caries progression.<br><br>For all outcomes, the review authors grouped the trials into three categories according to the length of follow-up: 2 to 3 years, 4 to 7 years, and 7 or more years. |
| **Outcome(s) assessed** | Primary outcome 1: Caries incidence, defined as the identification of a new carious lesion on the occlusal surface of a primary or permanent molar that compromised dentin tissue<br><br>Secondary outcome 1: Lack of retention<br><br>Secondary outcome 2: Adverse effects<br><br>*Note*. Primary outcome 1 is identified as a primary outcome in the review. Secondary outcomes 1 and 2 are assumed to be primary outcomes in the review, but for the HRB's purposes are considered secondary outcomes. |
| **Results/findings** | **Primary outcome 1: Caries incidence**<br><u>Comparison 1: Sealants versus non-use of sealants:</u><br>The risk of developing new carious lesions was significantly lower in participants who received sealants compared to participants who did not receive sealants at 2-3 years follow-up (OR 0.22, 95% CI 0.16 to 0.32, $p < 0.00001$; 6 trials; 1,770 participants; $I^2 = 55\%$; moderate certainty of evidence). Participants who received sealants reduced their risk of developing new carious lesions by 76%. |

Similarly, the risk was also lower at 4-7 years follow-up (OR 0.21, 95% CI 0.10 to 0.44, p < 0.0001; 3 trials; 752 participants; $I^2$ = 77%; low certainty of evidence; risk reduced by 79%) and a follow-up period of 7 years or more (OR 0.15, 95% CI 0.08 to 0.27, p < 0.00001; 2 trials; 246 participants; $I^2$ = 50%; moderate certainty of evidence; risk reduced by 85%).

Comparison 2: Sealants versus fluoride varnishes:
The risk of developing new carious lesions was significantly lower in participants who received sealants compared to participants who received varnishes at 2-3 years follow-up (OR 0.19, 95% CI 0.07 to 0.47, p < 0.0004; 2 trials; 990 participants; $I^2$ = 87%; low certainty of evidence; risk reduced by approximately 73%).

Similarly, the risk was also lower in the sealant group at 4-7 years follow-up (OR 0.19, 95% CI 0.07 to 0.51, p < 0.0008; 2 trials; 472 participants; $I^2$ = 80%; low certainty of evidence; reduced risk by 81%) and a follow-up period of 7 years or more (OR 0.29, 95% CI 0.17 to 0.49, p < 0.00001; 1 trial; 242 participants; low certainty of evidence; reduced risk by 71%).

Comparison 3: Glass-ionomer sealants versus resin-based sealants:
There was no statistically significant difference in the risk of developing new carious lesions between participants who received glass-ionomer sealants and participants who received resin-based sealants at 2-3 years follow-up (OR 0.63, 95% CI 0.25 to 1.57, p < 0.0004; 9 trials; 3,007 participants; $I^2$ = 83%; very low certainty of evidence).

The results from one trial also show no statistically significant difference in risk between the two groups at 4-7 years follow-up (OR 0.41, 95% CI 0.12 to 1.37, p = 0.15; 1 trial; 96 participants; very low certainty of evidence).

Comparison 4: Glass-ionomer sealants versus resin-modified glass-ionomer sealants:
The results from one trial found no statistically significant difference in the risk of developing new carious lesions between participants who received glass-ionomer sealants and participants who received resin-modified glass-ionomer sealants at 2-3 years follow-up (OR 1.41, 95% CI 0.65 to 3.07, p = 0.38; 1 trial; 344 participants; very low certainty of evidence).

Comparison 5: Resin-modified glass-ionomer sealants versus polyacid-modified resin sealants:
The results from one trial found no statistically significant difference in the risk of developing new carious lesions between participants who received resin-modified glass-ionomer sealants and participants who received polyacid-modified resin sealants at 2-3 years follow-up (OR 0.44, 95% CI 0.11 to 1.82, p = 0.26; 1 trial; 186 participants; very low certainty of evidence).

Comparison 6: Polyacid-modified resin sealants versus resin-based sealants:

There was no statistically significant difference in the risk of developing new carious lesions between participants who received polyacid-modified resin sealants and participants who received resin-based sealants at 2-3 years follow-up (OR 1.01, 95% CI 0.48 to 2.14, p = 0.97; 2 trials; 322 participants; $I^2$ = 0%; very low certainty of evidence).

**Secondary outcome 1: Lack of retention**

Comparison 1: Sealants versus non-use of sealants:

The nature of this comparison did not allow the review authors to obtain information to compare the use versus the non-use of sealants.

Comparison 2: Sealants versus fluoride varnishes:

The nature of this comparison did not allow the review authors to obtain information to compare the use of sealants versus the use of varnishes.

Comparison 3: Glass-ionomer sealants versus resin-based sealants:

Sealant retention loss at 2-3 years follow-up was significantly greater in participants who received glass-ionomer sealants compared to participants who had received resin-based sealants (OR 5.62, 95% CI 1.26 to 25.07, p = 0.02; 9 trials; 3,007 participants; $I^2$ = 97%; low certainty of evidence)

Similarly, at 4-7 years follow-up, sealant retention loss was also significant greater in the glass-ionomer group compared to resin-based group (OR 7.97; 95% CI 2.19 to 29.01, p = 0.002; 1 trial; 96 participants; low certainty of evidence).

Comparison 4: Glass-ionomer sealants versus resin-modified glass-ionomer sealants:

The results from one trial found sealant retention loss at 2-3 years follow-up to be significantly greater in participants who received glass-ionomer sealants compared to participants who received resin-modified glass-ionomer sealants (OR 3.21, 95% CI 1.87 to 5.51, p < 0.0001; 1 trial; 344 participants; moderate certainty of evidence).

Comparison 5: Resin-modified glass-ionomer sealants versus polyacid-modified resin sealants:

The results from one trial found no statistically significant difference in sealant retention loss at 2-3 years follow-up between participants who received resin-modified glass-ionomer sealants and participants who received polyacid-modified resin sealants (OR 1.17, 95% CI 0.52 to 2.66, p = 0.70; 1 trial; 186 participants; very low certainty of evidence).

Comparison 6: Polyacid-modified resin sealants versus resin-based sealants:

There was no statistically significant difference in sealant retention loss at 2-3 years follow-up between participants who received polyacid-modified resin sealants and participants who received resin-based sealants (OR 0.87,

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| | 95% CI 0.12 to 6.21, p = 0.89; 2 trials; 322 participants; $I^2$ = 81%; very low certainty of evidence).<br><br>**Secondary outcome 2: Adverse effects**<br>The investigators of two trials sought to measure adverse events associated with the use of sealants. No adverse effects were discovered among participants. |
| **Significance/direction** | The review authors found moderate-quality evidence to suggest that the use of sealants compared with control groups that did not use sealants reduces the incidence of carious lesions in the occlusal surfaces of permanent molars by approximately 80% in children and adolescents. In addition, the review authors found low-quality evidence to suggest that the use of sealants compared with control groups that used fluoride varnishes reduces the incidence of carious lesions also by approximately 80%. However, with the available evidence, strong statements could not be made about the relative merits of each sealant material. |
| **Heterogeneity** | For most comparisons, the review authors downgraded the quality of evidence wherever heterogeneity was present in the analyses. For the sealants versus no sealant comparison, moderate heterogeneity was observed, however, the review authors did not downgrade the quality of evidence as the investigators of all the included trials reported the same direction of effect with an overlap of confidence intervals. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as moderate for the sealant vs no sealant comparison; low for the sealant vs fluoride varnish comparison; and very low for the glass-ionomer vs resin, glass-ionomer vs resin-modified glass-ionomer, resin-modified glass-ionomer sealants versus polyacid-modified resin sealants, and polyacid-modified resin sealants versus resin-based sealants comparisons.<br><br>The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Wierichs *et al.* (2015) |
| **First Author and year of publication** | Wierichs *et al.* (2015) |
| **Objectives (exact review question(s) and page number)** | To critically summarize and evaluate results of clinical studies investigating chemical agents to reduce initiation of root caries lesions (RCLs) or inactivate existing ones (p262). |

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| | *Note*. For the purposes of this umbrella review, the HRB is only interested in the findings from studies that are focussed on reducing initiation of root caries lesions. |
| **Participants (characteristics and numbers)** | Permanent dentition; topical fluoride, mouthrinses, varnishes; topical other chemicals, CHX; combined intervention.<br><br>Baseline caries were reported in 28 out of the 30 included trials.<br><br>The 30 included trials involved a total of 10,136 participants whose ages ranged from 20 to 101 years. Information pertaining to the sex of included participants was not provided.<br><br>The total number of participants in the 19 (out of 30) included trials that inform this umbrella review was 7,573. |
| **Setting/context** | The trials were conducted in Brazil (1 trial), Canada (1 trial), China (3 trials), Denmark (1 trial), Germany (1 trial), Hungary (1 trial), Israel (1 trial), the Netherlands (2 trials), Spain (1 trial), Switzerland (2 trials), Sweden (5 trials), the United Kingdom (3 trials), and the United States (9 trials). One trial was conducted in two different countries (Switzerland and Germany).<br><br>The settings of the included trials were not provided. |
| **Description of Interventions/ phenomena of interest** | The interventions of interest were preventive dental regimes (e.g., oral health instructions) and/or one or more chemical agents applied on one or more occasion by a dental professional or self-applied by the patient. The control was either negative (placebo treatment), positive (other intervention), or standard therapy.<br><br>Among the included trials, chemical agents included chlorhexidine (CHX), fluoride, and ozone. Interventions included varnishes, dentifrices, mouthrinses, ozone, solution/varnishes, and gels. Four comparisons were made that were relevant to the objectives of this umbrella review:<br>1. AmF/$SnF_2$-containing dentifrice (1400 ppm F) + AmF/$SnF_2$ rinse (250 ppm F) versus NaF-containing dentifrice (1400 ppm F) + NaF rinse (250 ppm F)<br>2. 225 – 900 ppm fluoride mouthrinse versus placebo mouthrinses<br>3. SDF varnish versus placebo varnish, and<br>4. Chlorhexidine varnish versus placebo varnish. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• EMBASE, and<br>• Cochrane Central Register of Controlled Trials (CENTRAL). |

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| | Grey literature was not evaluated. Articles published between January 1947 and May 2014 were searched. Language was restricted to English and German. Cross-referencing was performed to identify any additional potentially relevant studies.<br><br>The review authors independently reviewed the titles and abstracts of articles retrieved using the search strategy; however, it was not stated how many authors were involved in this process. Disagreements were resolved by discussion. It was not stated how data extraction was completed.<br><br>There was no mention of a protocol being prepared or published.<br><br>The review was funded by the authors and their institution.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 30 included trials were published between 1987 and 2013. |
| **Number of primary studies included in the systematic review** | The review authors included 29 randomised controlled trials and 1 nonrandomised controlled trial. Follow-up periods ranged from 5 to 60 months. The median follow-up time was 15 months. Eleven trials investigated both initiation of RCLs and the change of RCLs, 11 analysed the change of RCLs, and 8 studies initiation of RCLs.<br><br>The funding sources of the primary studies were not provided. However, 15 trials were reported to have a high risk of bias under the domain “sponsoring by manufacturer”. |
| **Types of studies included** | The review authors included 30 randomised and nonrandomised controlled trials: Baysan (2001), Ekstrand (2013), Hu (2013), Souza (2013), Banocy (1991), Paraskevas (2004), Fure (1998), Ripa (1987), Wallace (1993), Wyatt (2004), Baca (2009), Tan (2010), Zhang (2013), Baysan (2007), DePaola (1993), Fure (2009), Holmes (2003), Jensen (1988), Mojon (1998), Papas (2007), Papas (2008), Petersson (2007), Petersson (2011), Powell (1999), Ravald (1992), Schaeken (1991), Srinivasan (2013), Vered (2009), Wyatt (2007).<br><br>The results of 19 trials informed the outcomes of interest to this umbrella review: Ekstrand (2013), Banting (2000), Banocy (1991), Paraskevas (2004), Fure (1998), Ripa (1987), Wallace (1993), Wyatt (2004), Baca (2009), Tan (2010), Zhang (2013), Jensen (1988), Mojon (1998), Papas (2008), Powell (1999), Ravald (1992), Schaeken (1991), Vered (2009), Wyatt (2007).<br><br>A list of excluded studies and the reasons for exclusion were provided in an appendix. |

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| **Country of origin of included studies** | The trials were conducted in Brazil (1 trial), Canada (1 trial), China (3 trials), Denmark (1 trial), Germany (1 trial), Hungary (1 trial), Israel (1 trial), the Netherlands (2 trials), Spain (1 trial), Switzerland (2 trials), Sweden (5 trials), the United Kingdom (3 trials), and the United States (9 trials). One trial was conducted in two different countries (Switzerland and Germany). |
| **Appraisal instrument(s)** | Risk of bias assessment was performed according to guidelines outlined by the Cochrane Collaboration (Higgins et al. 2011). The following domains were assessed in each included trial:<br>1. Random sequence generation<br>2. Allocation concealment<br>3. Blinding of participants and personnel<br>4. Blinding of outcome assessment<br>5. Incomplete outcome data<br>6. Selective reporting<br>7. Sponsoring by manufacturer, and<br>8. Conflict of interest. |
| **Appraisal rating** | Overall, the review authors described five trials as having a very low risk of bias. However, based off tabular information provided in the review, all trials had at least one unclear or high risk of bias score, therefore, all trials should have been categorised as having an overall unclear or high risk of bias.<br><br>Fourteen trials were categorised as having a low risk of bias for randomisation. Of the 19 trials relevant to this umbrella review, nine were categorised as having a low risk of bias for randomisation, six were categorised as having an unclear risk of bias for randomisation, and four were categorised as having a high risk of bias for randomisation.<br><br>Twenty-five trials were categorised as having a low risk of bias for outcome ascertainment. Of the 19 trials relevant to this umbrella review, 16 were categorised as having a low risk of bias for outcome ascertainment, two were categorised as having an unclear risk of bias for outcome ascertainment, and one was categorised as having a high risk of bias for outcome ascertainment.<br><br>The certainty of evidence was assessed with reference to study design, risk of bias, publication bias, imprecision, inconsistency, and indirectness. The certainty of evidence for outcomes relevant to this umbrella review was assessed as low and very low. The reasons for downgrading were primarily due to risk of bias, publication bias, inconsistency, and imprecision. |

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| | Publication (reporting) bias was assessed by funnel plots (Egger et al. 1997). This bias was detected in four of the three intervention comparisons relevant to the umbrella review. |
| **Method of analysis** | The primary measures of effect between treatment and control groups were the mean differences for trials based on the same units and standardized mean differences for trials based on the same construct but different scales. Changes were calculated for the following outcomes: DMFRS/DFRS and RCI. A random effects model was used to calculate a pooled estimate of effect.<br><br>Meta-analyses were performed only for chemical agents with similar interventions and outcome measures investigated in more than one trial. |
| **Outcome(s) assessed** | Primary outcome 1: Initiation of new RCLs, measured either by change from baseline in Decayed, missing, filled root surfaces (DMFRS) or Root Caries Index (RCI), or the initiation of new RCLs<br><br>*Note*. This outcome is not explicitly identified as an outcome in the methods section but is identified as a primary outcome in the review aim and in the results section. It is there considered a primary outcome in the review and for the HRB's purposes.<br><br>*Note*. DMFRS as an outcome can relate to both caries initiation and caries progression. The HRB is only interested in the findings of studies that are focussed on the prevention of caries initiation. Therefore, data from studies where DMFRS was measured to describe a surface with (active) root caries developing to a fill or missing surface at follow-up, were not extracted. |
| **Results/findings** | **Primary outcome 1: Initiation of new RCLs**<br>Of these 19 trials reporting this outcome, only nine contributed data to the meta-analyses.<br><br><u>Comparison 1: AmF/$SnF_2$-containing dentifrice (1400 ppm F) + AmF/$SnF_2$ rinse (250 ppm F) versus NaF-containing dentifrice (1400 ppm F) + NaF rinse (250 ppm F):</u><br>The results from one trial found no statistically significant difference in the initiation of new RCLs between the two groups at 24 months follow-up (SMD 0.04, 95% CI -0.43 to 0.50, p = 0.88; 1 trial; 71 participants; low certainty of evidence).<br><br>The results from a second trial also found no statistically significant difference in change in root caries index between the two groups at 5 months follow-up (SMD 0.34, 95% CI -0.25 to 0.94, p = 0.26; 1 trial; 44 participants; low certainty of evidence.<br><br>Overall, results show no significant differences between intervention and control groups in change in root caries index/new RCLs at 5-24 months |

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| | follow-up (SMD 0.15, 95% CI -0.22 to 0.52, p = 0.42; 2 trials; 115 participants; low certainty of evidence)<br><br><u>Comparison 2: 225 – 900 ppm F versus placebo mouthrinses:</u><br>The initiation of RCLs was significantly lower in patients that rinsed with the fluoride (NaF) mouthrinse compared with those that rinsed with the placebo mouthrinse at 24 – 48 months follow-up (MD -0.18, 95% CI -0.35 to -0.01, p = 0.03; 4 trials; 1,206 participants; $I^2$ = 77%; low certainty of evidence).<br><br><u>Comparison 3: 38% SDF varnish versus placebo varnish:</u><br>The initiation of RCLs at 24 – 36 months follow-up was significantly lower in patients who received professionally applied 38% SDF varnish compared to those who received a placebo varnish (MD -0.33, 95% CI -0.39 to -0.28, p < 0.00001; 2 trials; 264 participants; $I^2$ = 87%; very low certainty of evidence).<br><br><u>Comparison 4: Chlorhexidine varnish versus placebo varnish:</u><br>The initiation of RCLs at 12 – 36 months follow-up was significantly lower in patients who received professional applied 1% or 10% chlorhexidine varnish compared to those that received placebo varnish (MD -0.67, 95% CI -1.01 to -0.32, p = 0.0002; 3 trials; 305 participants; $I^2$ = 8%; very low certainty of evidence). |
| **Significance/direction** | Based on meta-analyses, dentifrice containing 5,000 ppm F- and professionally applied CHX or SDF varnish may reduce the initiation of RCLs. However, results should be interpreted with caution due to the low numbers of clinical trials for<br>each agent, the high risk of bias within studies, and the limiting grade of evidence. |
| **Heterogeneity** | Heterogeneity was assessed via $I^2$ (Higgins and Thompson 2002). The quality of evidence for some comparisons was downgraded due to inconsistency of results among trials. However, there is little discussion regarding the potential impact of heterogeneity on the findings. |
| **Summary for GRADE assessment for HRB report** | The certainty of evidence was graded as low in relation to two outcomes: the use of AmF/SnF2-containing dentifrice plus AmF/SnF2-containing rinse, and fluoride mouthrinse. The certainty of evidence was graded as very low in relation to two outcomes: sodium diamine fluoride and chlorhexidine.<br><br>The HRB authors graded the quality of evidence in the review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Slot *et al.* (2011) |

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| **First Author and year of publication** | Slot *et al.* (2011) |
| **Objectives (exact review question(s) and page number)** | To systematically evaluate the current literature to determine the effect of the use of chlorhexidine varnish on root caries incidence and activity (p163).<br><br>*Note*. For the purposes of this umbrella review, the HRB is only interested in the findings from studies that are focussed on the effect of chlorhexidine varnish on root caries incidence. |
| **Participants (characteristics and numbers)** | Permanent dentition; combined intervention.<br><br>Baseline caries were reported in three out of six of the included trials.<br><br>The six included trials involved a total of 451 participants. Four trials reported the mean age, which ranged from 44.44 to 78.8 years. In the two trials that reported sex, the proportion of females to males, in percentages, were 63% and 65%.<br><br>Two trials involved elderly populations, one trial involved physically dependent patients, one trial involved xerostomia (dry mouth) patients, and two trials involved patients from a periodontal maintenance program (in one of these trials patients had undergone periodontal surgery). |
| **Setting/context** | The study countries were not provided. The study settings were not explicitly stated. However, two trials involved participants living in elderly institutions and two trials involved patients attending a periodontal maintenance programme. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was chlorhexidine varnish (CHX-V). The control group consisted of either a placebo, a control treatment, or fluoride varnish.<br><br>Among the included trials, three different concentrations of CHX were used in the varnishes: 1%, 10% and 40%. Some trials included more than one intervention arm, each consisting of different CHX-V concentrations. 1% CHX-V was used in 4 trials and 40% CHX-V was used in 2 trials.<br><br>In one trial, a two-staged application was performed; first 1ml of either the active varnish or a placebo was used, and this was followed by a second treatment with 1ml of polyurethane 29%, ethyl acetate 22%, and acetone 49%. Both varnishes contained Benzoin Sumatra U.S.P. 20% and Alcohol Dehydrated U.S.P. to volume, while the active treatment contained 10% custom-made CHX acetate.<br><br>Some trials included more than one control group. In two trials, the control group received no intervention; in one trial, the control group received a placebo varnish; in one trial, the control group received water; in one trial, |

the control group received water flavoured with eucalyptus oil; and in three trials, the control groups received fluoride varnish.

In the first trial, individualized oral hygiene instruction was provided to each participant, focusing on effective brushing with a manual toothbrush. Fluoride toothpaste was recommended. Before applications, a piece of gauze was used to clean and dry the teeth; the study agents were then applied onto the exposed root surfaces of participants in the respective groups by means of a disposable microbrush. The participants were instructed not to eat within half an hour after treatment. Applications of water were repeated every 12 months, and applications of CHX-V or fluoride varnish were repeated every 3 months. Participants received oral prophylaxis after baseline examination if necessary and oral health instruction.

In the second trial, 1% CHX-V was applied by a dentist with portable equipment following the manufacturer's instructions. Briefly, the teeth were cleaned with a toothbrush for 2–3 min. The teeth were then isolated from saliva with cotton rolls and dried with compressed air. A thin coat of varnish was then applied to all teeth and surfaces. The varnish was gently dried by air for 30 seconds. The subjects were instructed not to eat or drink for 3 hours, not to clean their teeth until the following day, and not to use dental floss for one week. Applications of CHX-V occurred twice in the first week and every 3 months thereafter. Participants received oral prophylaxis 30-45 days before the study commenced, and no oral health instruction.

In the third trial, 40% CHX-V or 1% CHX-V were applied to the root surface every 3 months after teeth cleaning and polished with a fluoride paste and a rubber cup. The teeth receiving the varnish were isolated with cotton rolls, quadrant by quadrant, and then dried with an air syringe. The respective agents were applied with a disposable microbrush. According to the manufacturer's instructions, the 40% CHX-V was left in place for 8 minutes and then removed with a rubber cup, polishing paste, and dental floss. After the 1% CHX-V application, subjects were instructed to avoid food and beverages for two hours. However, according to the manufacturer's instructions, after the 40% CHX-V application, the diet was not restricted.

In the fourth trial, there were two treatments with 1% CHX-V. Within 10 days, and then every 3 months for 18 months. The varnishes were applied by the same dental hygienist in accordance with the manufacturer's recommendation.

In the fifth trial, the 10% CHX-V was applied once weekly for 4 consecutive weeks after screening and testing, and then a single reapplication was performed after 6 months by a dental hygienist. The application was performed following a predetermined, but unspecified protocol. Participants

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| | did not receive oral prophylaxis but did receive oral health instruction at every visit.<br><br>In the sixth trial, the varnish was applied every 3 months after the periodontal check-up. The varnishes were applied on dried root surfaces with a small firm brush and with a blunt dental instrument. After treatment, the subjects were allowed to rinse with tap water. Then, excess varnish on the mucosa was removed with the blunt dental instrument. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• MEDLINE-PubMed<br>• Cochrane Central Register of Controlled Trials (CENTRAL), and<br>• EMBASE.<br><br>These databases were searched for studies conducted in the period up to and including 23 December 2010. Two review authors hand-searched the reference lists of all selected studies for potentially relevant studies.<br><br>Two review authors independently screened search results (title and abstract). It was not reported how disagreements were resolved. In addition, it was not made explicit how full-text screening and data extraction were completed, although it is likely that they were completed by same two reviewers.<br><br>There was no mention of a protocol being prepared or published.<br><br>The review was self-funded by the authors and their institutions.<br><br>None of the review authors reported a conflict of interest. |
| **Date range (years) of included studies** | The six included trials were published between 1991 and 2010. |
| **Number of primary studies included in the systematic review** | The review authors included six randomised controlled trials. Of these, five used a parallel-group design and one used a split-mouth design. Three trials were double-blinded, two trials were single-blinded, and one trial involved no blinding. The trial durations ranged from 1 year to 3 years.<br><br>Four of the six included trials reported sponsoring and funding. Two trials received non-industry funding. Another trial received non-industry funding, but industry supplied the intervention. One trial received industry funding. |
| **Types of studies included** | The review authors included six randomised controlled trials: Tan (2010), Baca (2009), Bizhang (2007), Johnson (2003), Banting (2000), and Schaeken (1991). |

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| | A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | The study countries were not provided. |
| **Appraisal instrument(s)** | Two review authors scored the methodological quality of the included studies. An assessment of the methodological study quality was performed as proposed by the RCT checklist of the Dutch Cochrane Center and was completed with quality criteria that were obtained from the CONSORT statement 2001 (CONSORT Group, 2009), Moher et al. (2001a, b, c) Needleman et al. (2005), the Jadad scale (Jadad et al. 1996), and the Delphi List (Verhagen et al. 1998). Criteria were designated to each domain of internal validity, external validity, and statistical methods.<br><br>The domains of internal validity included:<br>• Random allocation<br>• Allocation concealment<br>• Blinded to patient<br>• Blinding to examiner<br>• Blinding during statistical analysis<br>• Balanced experimental groups<br>• Reported loss to follow-up<br>• Number (%) of dropouts, and<br>• Treatment identical, except for intervention.<br><br>The domains of external validity included:<br>• Representative population group, and<br>• Eligibility criteria defined.<br><br>The domains of statistical validity included:<br>• Sample size calculation and power<br>• Point estimates<br>• Measures of variability presented for the primary outcome<br>• Include an intention-to-treat analysis<br>• Authors estimated risk of bias, and<br>• Level of evidence (CEBM).<br><br>If random allocation, defined eligibility criteria, blinding to patient and examiner, balanced experimental groups, an identical treatment between groups except for intervention, and report of follow-up were present, the |

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| | trial was classified as having a low risk of bias. If one of these six criteria was missing, the trial was considered to have a moderate potential risk of bias. If two or more of these criteria were missing, the trial was considered to have a high potential risk of bias. |
| **Appraisal rating** | According to the criteria above, the estimated potential risk of bias was low for one trial and moderate for five trials. The HRB notes that when applying the Cochrane risk of bias scoring system, all trials were at high and unclear risk of bias. All trials were categorised as having a low risk of bias for randomisation. Five trials were categorised as having a low risk of bias for outcome ascertainment and one was categorised as having a high risk of bias.<br><br>Two review authors rated the quality of the evidence and strength of recommendations on the following aspects: risk of bias of the individual studies, consistency and precision among the study outcomes, directness of the study results, and the detection of publication bias. The authors described the strength of the recommendation to use CHX-V as an effective anti-caries agent to be "weak". This was due to the data being inconsistent, the moderate risk of bias present, the precision being undeterminable to moderate, and the study results not being generalisable.<br><br>The risk of publication bias was assessed; however, the results were not reported. |
| **Method of analysis** | The review authors found that considerable heterogeneity was present in the study designs, characteristics, outcome variables, and results. Therefore, where appropriate, a random effects meta-analysis was performed, and weighted mean differences were calculated by means of the Review Manager 4.2 software. However, as only a few trials could be included in the quantitative analysis, a descriptive manner of data presentation was also used. |
| **Outcome(s) assessed** | Primary outcome 1: Root caries incidence, measured by decayed, missing and filled root surfaces (DMF-RS)<br><br>*Note*. This outcome is identified in the review as presented here (as a primary outcome). |
| **Results/findings** | **Primary outcome 1: Root caries incidence measured by decayed, missing and filled root surfaces (DMF-RS)**<br><u>Meta-analysis:</u><br>Of the five trials that reported root caries incidence, three contributed data to the meta-analysis. Root caries incidence was significantly lower in the chlorhexidine varnish group compared to the control/placebo group (MD -0.65, 95% CI -1.01 to -0.30; 3 trials; 356 participants; weak body of evidence). The follow-up periods for the three trials were 3 years, 1 year and |

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| | 13 months. Two trials evaluated 1% CHX-V in an elderly population and one trial used 10% CHX-V in xerostomia patients. The frequency of application was every 3 months in two trials, and twice in the first week followed by application at 1, 3, 6, 9, and 12 months in one trial.<br><br>*Note*. In one out of the three pooled trials, participants received oral health instruction at baseline, and in two out of the three pooled trials, participants received professional prophylaxis, either at baseline or every 3 months alongside the application of chlorhexidine varnish. One of the pooled trials involved the delivery of a complex intervention in which participants received oral health instruction + professional oral prophylaxis (both at baseline) + the application of chlorhexidine varnish.<br><br><u>Descriptive analysis:</u><br>Two trials involved participants from a periodontal maintenance programme. One trial, with two comparisons (CHX-V vs. both control and fluoride varnish), and two different concentrations of CHX-V (1% and 40%), showed no difference in effect. Another trial with 40% CHX-V showed a significant positive effect on root caries incidence ($p < 0.01$) as compared to the control.<br><br>One trial, involving a xerostomia population, showed a positive effect on root caries incidence ($p = 0.02$) with 10% CHX-V compared to the placebo.<br><br>Two trials measuring caries incidence involved geriatric populations. One trial testing 1% CHX-V observed a positive significant effect on root caries incidence ($p = 0.039$) as compared to a placebo varnish. In another trial, when comparing 1% CHX-V to a control, an effect on root caries incidence was observed ($p = 0.001$); however, when comparing 1% CHX-V to fluoride varnish, there was no significant difference in effect. |
| **Significance/direction** | Within the limitations of this review, it may be concluded that in the absence of regular professional tooth cleaning and oral hygiene instructions, CHX-V may provide a beneficial effect for patients in need of special care. However, the strength of this recommendation was graded as 'weak' for caries incidence. |
| **Heterogeneity** | The review authors stated considerable heterogeneity was present in the study designs, characteristics, outcome variables, and results. Therefore, a random effects model was used during the analysis. The strength of the recommendations put forth by the review authors was described as "weak" in part due to the inconsistency found in the results. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as "weak" (out of only two possible grades; strong or weak). |

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| | The HRB authors graded the certainty of evidence from this review as moderate. |
| **References to previously published versions** | N/A |
| Parameter | Santos *et al.* (2013) |
| **First Author and year of publication** | Santos *et al.* (2013) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effects of low and standard fluoride toothpastes on the prevention of caries in the primary dentition of preschoolers and moderate to severe forms of fluorosis in the permanent dentition (p383). |
| **Participants (characteristics and numbers)** | Primary (caries and fluorosis) and permanent (fluorosis only) dentition (separate); topical fluoride, toothpaste.<br><br>Baseline caries were reported in all included trials and ranged from 0 (2 trials) to 5.25.<br><br>Participants were children not older than seven years when the outcome caries was assessed. There was no age limit for the assessment of fluorosis. Studies whose participants had special general or oral health conditions were excluded.<br><br>The five included trials involved a total of 5,376 participants. Three trials reported the age of participants at baseline, which ranged from 1 to 4 years. Two trials reported the age of participants at the time of outcome assessment, which ranged from to 5 to 6 years. One trial involved participants who were 4 years of age; however, it was not stated whether this was the age at baseline or at final examination. Information pertaining to the sex of included participants was not clearly stated, but this information was extracted by the review authors. Supplemental information provided indicated that at least two trials contained equal numbers of males and females. |
| **Setting/context** | The trials were conducted in Brazil (1 trial), Germany (1 trial), Sweden (1 trial), and the UK (2 trial).<br><br>Three trials were conducted in a school setting and two trials were conducted in a community health setting. |
| **Description of Interventions/ phenomena of interest** | The interventions of interest were low (<600 ppm) and standard (1000 – 1500 ppm) fluoride toothpastes, irrespective of formulation. The comparison group was each other. Studies whose interventions included fluoride gel, |

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| | fluoride varnish, fluoride mouth rinse, chlorhexidine, xylitol or dental sealants were excluded. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• MEDLINE via PubMed<br>• EMBASE<br>• Web of Science<br>• LILACS, and<br>• BBO (Brazilian Library of Dentistry).<br><br>The databases were searched from date of online availability to January 2010. The electronic search was updated by one of the authors in March 2012, however, no additional studies were found.<br><br>Additional sources included a Brazilian database of thesis and dissertations (Banco de Teses CAPES), a Brazilian register of ethically approved projects involving human beings (SISNEP) and two international registers of ongoing trials (Current Controlled Trials and ClinicalTrials.gov). Meeting abstracts of the International Association for Dental Research and the European Organisation for Caries Research were also searched. Sixteen dental journals that were in the Cochrane Master List of Journals Being Searched were handsearched from the last date of the Cochrane Collaboration's hand search until June 2010. References of eligible trials and systematic and narrative reviews were checked for any additional potentially relevant studies. Finally, specialists in the field were contacted by e-mail.<br><br>Two reviewers read the titles and abstracts of all studies identified. Whenever there was not enough information<br>available, the full-text article was obtained. Two reviewers independently extracted the data using a data extraction form. Disagreements were resolved by consensus after consultation with a third review author.<br><br>There was no mention of a protocol being prepared or published.<br><br>Funding source of the review was not reported.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The five included trials were published between 1974 and 2010. |
| **Number of primary studies included in the systematic review** | The review authors included five randomised and nonrandomised controlled trials, with a follow-up period of at least one year. |

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| | The funding sources of the primary studies were not provided. |
| **Types of studies included** | The review authors included five randomised and nonrandomised controlled trials: Davies (2002), Gerdin (1974), Sonju-Clasen (1995), Vilhena (2010), and Winter (1989).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Brazil (1 trial), Germany (1 trial), Sweden (1 trial), and the UK (2 trial). |
| **Appraisal instrument(s)** | The Cochrane Collaboration's tool was used for assessing the risk of bias in included studies (Higgins and Altman, 2008). The following domains were assessed in each included trial:<br>1. Sequence generation<br>2. Allocation concealment<br>3. Blinding<br>4. Incomplete outcome data, and<br>5. Selective outcome reporting.<br><br>Each domain was classified as having low, high or uncertain risk of bias.<br><br>The review authors stated that non-blinding of participants of participants was unlikely to introduce bias; therefore, when only the outcome assessors were blinded, studies were considered as having low risk of bias. The studies were also considered to be free of selective outcome reporting when caries incidence was assessed at surface, tooth, and individual level.<br><br>Other possible sources of bias were:<br>• Losses to follow-up (low risk of bias when less than 20%)<br>• Diagnosis reliability (low risk of bias when good [Altman, 1991])<br>• Baseline balance (low risk of bias when data showed balance regarding age, gender, socioeconomic status and caries levels), and<br>• Contamination (low risk of bias when strategies to avoid contamination between groups were reported). |
| **Appraisal rating** | The overall risk of bias of each included trial was not provided. However, based on the Cochrane Collaboration's risk of bias instrument presented in the review, all trials had a high risk of bias.<br><br>Two trials were categorised as having a low risk of bias for randomisation, two had a high risk of bias for randomisation and one had an unclear risk of |

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| | bias for randomisation. All trials were categorised as having a low risk of bias for outcome ascertainment.<br><br>Publication bias was not measured due to the paucity of studies. |
| **Method of analysis** | Pooled relative risks and 95% confidence intervals were estimated to assess the proportion of children who developed caries in primary teeth and aesthetically objectionable fluorosis in permanent teeth.<br><br>For the cluster randomised trial, an external estimate of an intraclass correlation coefficient was used to obtain the design effect and then the effective sample size.<br><br>No meta-analyses of the difference in means were per formed as data regarding caries incidence at surface and tooth level were highly skewed.<br><br>Heterogeneity of studies was assessed by visual inspection of forest plots, $X^2$ test for heterogeneity and Higgins index ($I^2$). A random effects model was used in the presence of heterogeneity ($X^2$ with significance level < 0.10 and $I^2$ > 50%).<br><br>All analyses were carried out in Stata ® 11.1. The paucity of studies prevented the use of meta-regression to assess the influence of study characteristics on the treatment effect. |
| **Outcome(s) assessed** | Primary outcome 1: caries increment, measured as change in damaged, missing and filled surfaces (dmfs)<br><br>Primary outcome 2: caries increment, measured as change in damaged, missing and filled teeth (dmft)<br><br>Primary outcome 3: Proportion of children developing caries<br><br>Secondary outcome 1: Proportion of children developing fluorosis<br><br>*Note*. Primary outcomes 1-3 are identified in the review as primary outcomes. Primary outcome 4 is identified as a primary outcome, but for the HRB's purposes is considered a secondary outcome. |
| **Results/findings** | **Primary outcome 1: caries increment (dmfs)**<br>Four trials reported caries incidence at surface level. All measures were smaller than twice the SD, indicating that the data were highly skewed, which prevented the calculation of weighted mean difference. There were no significant differences found between the use of low fluoride (<600 ppm) and standard fluoride (1000-1500 ppm) toothpastes in any of the trials (p > 0.05; 3,014 participants; 4 trials; narrative synthesis). |

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| | **Primary outcome 2: caries increment (dmft)**<br>Four trials reported caries incidence at tooth level. All measures were smaller than twice the SD, indicating that the data were highly skewed, which prevented the calculation of a pooled weighted mead difference. There were no significant differences found between the use of low F and standard F toothpastes in three of the trials ($p > 0.05$; 2,485 participants; 3 trials; narrative synthesis). One trial showed that children using low F toothpaste had a significant increase in the mean incidence of caries at tooth level compared to those using standard F toothpastes ($p > 0.02$; 2,362 participants; 1 trial).<br><br>**Primary outcome 3: Proportion of children developing caries**<br>The proportion of children developing caries in primary teeth was higher in the low fluoride toothpaste group compared to the standard fluoride toothpaste group (RR 1.13, 95% CI 1.07 to 1.20; 4,634 participants; 3 trials; $I^2 = 0\%$).<br><br>**Secondary outcome 1: Proportion of children developing fluorosis**<br>Low fluoride toothpastes did not significantly decrease the risk of aesthetically objectionable fluorosis in the upper anterior permanent teeth (RR 0.32, 95% CI 0.03 to 2.97; 1,968 participants; 2 trials; $I^2 = 76.3\%$). |
| **Significance/direction** | No evidence was found to support the use of low fluoride toothpastes by preschoolers as they increased the risk of caries in the primary dentition and did not decrease the<br>risk of aesthetically objectionable fluorosis in upper per-<br>manent anterior teeth. |
| **Heterogeneity** | Heterogeneity of studies was assessed by visual inspection of<br>forest plots, χ 2 test for heterogeneity and Higgins index. A random effects model was used in the presence of heterogeneity.<br><br>No statistical heterogeneity was observed for the dental caries analysis; however, significant heterogeneity was observed for the fluorosis analysis. This heterogeneity was not explained. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence as low. |
| **References to previously published versions** | N/A |
| Parameter | James *et al.* (2010) |

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| **First Author and year of publication** | James *et al.* (2010) |
| **Objectives (exact review question(s) and page number)** | To summarise the evidence of the effectiveness of chlorhexidine varnish at preventing caries in the permanent and primary teeth of children and adolescents compared to placebo or no treatment, using data from randomised controlled trials only.<br><br>To summarise the evidence of the caries-preventive effectiveness of chlorhexidine varnish compared to fluoride varnish (p334). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); topical other chemicals, CHX.<br><br>Baseline caries were reported in all included trials. Four trials exclusively included participants who were caries-free at baseline.<br><br>The 12 included trials involved a total of 2,934 participants. The age of included participants ranged from 4 to 18 years. Information pertaining to the sex of included participants was not provided. Most of the trial participants were considered at moderate to high risk of developing dental caries. |
| **Setting/context** | The study countries and study settings were not reported.<br><br>The review authors noted in the discussion that the three trials that showed a significant effect for the use of chlorhexidine varnish were all conducted in developing countries; two in China and one in Thailand. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was chlorhexidine varnish. The comparison group was either a placebo, no treatment, or a fluoride varnish.<br><br>For the comparison between chlorhexidine varnish and fluoride varnish, only parallel-group trials were included, as a carry-over effect for fluoride varnish in split-mouth trials cannot be ruled out. Trials where chlorhexidine varnish explicitly formed part of a combined intervention with other preventive methods were excluded.<br><br>The concentration of CHX was 1% (6 trials, permanent teeth), 10% (1 trial, permanent teeth), and 40% (4 trials for permanent teeth and 1 trial for primary teeth). Application frequency was once every 2 weeks (1 trial), 1-2 months (2 trials), 3 months (4 trials), 4 months (1 trial) and 6 months (4 trials). All trials included some exposure to fluoride (either water, toothpaste or mouthrinse. However, this was existing fluoride exposure, rather than part of any intervention. |
| **Databases and sources searched** | The review authors searched the following sources: |

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| | • MEDLINE<br>• EMBASE, and<br>• Cochrane Central Register of Controlled Trials.<br><br>The search was conducted in December 2009 and updated on 19 March 2010. Language was restricted to English. The reference lists of previously published reviews were also searched; however, no additional relevant studies were identified.<br><br>There was no mention of a protocol being prepared or published, however, the review authors stated the inclusion criteria for the review were decided a priori.<br><br>Two review authors independently screened search results; it was not specified whether this applied to title and abstract screening, full-text screening, or both. Data was extracted from the included trials by one review author and verified by another review author. It was not reported how disagreements in relation to both screening and extraction were resolved.<br><br>The review was supported in funding by the Health Research Board (HRB), Ireland.<br><br>Conflicts of interest were not reported. |
| **Date range (years) of included studies** | The 12 included trials were published between 1995 and 2008. |
| **Number of primary studies included in the systematic review** | The review authors included 12 randomised and quasi-randomised controlled trials. Of these, eight had a parallel-group design and four had a split-mouth design. The duration of the trials ranged from 1 to 3 years, except for one trial where the duration of the intervention was dependent on the treatment time with fixed orthodontic appliances (median duration 21 months). One trial evaluated the effect 3 years after the termination of a 2-year trial.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 12 randomised and quasi-randomised controlled trials: Baca (2003), Ersin (2008), Forgie (2000), De Soet (2002), Fennis-le (1998), Jenatschke (2001), Petersson (2000), Du (2006), Bratthall (1995), Haukali (2003), Rodrigues (2008), Zhang (2006).<br><br>The review authors included a list of excluded studies; however, they did not provide a specific reason for why each was excluded beyond stating that they did not meet the inclusion criteria. |

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| **Country of origin of included studies** | The study countries were not reported. |
| **Appraisal instrument(s)** | The risk of bias of the included trials was assessed independently by two authors using the 'risk of bias' assessment tool described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (Higgins and Deeks, 2009). Any areas of disagreement were resolved by discussion. Each trial was assessed overall as having a 'high'. 'low', or 'unclear' risk of bias. |
| **Appraisal rating** | Graphical information in relation to risk of bias was not provided. Overall, four trials were categorised as having a low risk of bias, four trials were categorised as having an unclear risk of bias, and four trials were categorised as having a high risk of bias.<br><br>The review authors stated that sequence generation and allocation concealment were poorly reported in the majority of the included trials; only four reported sufficient information to assess the method of randomisation. Of these four, only three were judged to have adequate randomisation. Other reasons the quality of evidence was reduced included balance imbalances in MS counts and caries levels, high or unexplained losses to follow-up, lack of assessment of intra-examiner reliability, and small sample sizes.<br><br>Publication bias was not measured. |
| **Method of analysis** | It was originally envisaged by the review authors that the results of the included trials would be presented graphically in a forest plot, and that parallel-group and split-mouth trials would be considered separately to take account of potential differences in effect due to study design. However, due to missing data and variation in the reporting of outcomes, this approach was not possible. Therefore, it was decided to present a narrative summary of the results in which parallel-group and split-mouth trials were considered separately. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment measured using the decayed, missing, and filled surface index (DMFS/dmfs)<br><br>Secondary outcome 1: Adverse events<br><br>*Note*. Both outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Caries increment measured using decayed, missing, and filled surface index (DMFS/dmfs)**<br><u>Comparison 1: Chlorhexidine varnish compared to placebo or no treatment in permanent teeth:</u><br>Six parallel-group trials assessed the effectiveness of |

chlorhexidine varnish compared to placebo or no treatment for preventing caries in permanent teeth. None found a statistically significant difference in caries increment in the chlorhexidine varnish groups compared to placebo or control ($p > 0.05$; 1,471 participants; one low risk of bias, three unclear risk of bias, and one high risk of bias trial). Follow-up periods ranged from 2-3 years. CHX % was 1% (3 trials), 10% (1 trial) and 40% (2 trials), applied every 1-2 months (1 trial), 3 months (3 trials), or 6 months (2 trials).

Four split-mouth trials assessed the effectiveness of chlorhexidine varnish (three tested against placebo or no treatment using caries free pairs of molars and one used quadrants of the mouth as the unit of randomisation and included teeth that were not all caries-free at baseline).

- Two trials, which had no-treatment control groups, reported results in favour of chlorhexidine varnish (1% and 40% chlorhexidine) compared to a placebo varnish or a control. One of those trials assessed the effect of 1% chlorhexidine varnish for preventing caries on the occlusal surfaces of first permanent molars (PF 25%, 95% CI 1% to 49%, $p = 0.04$; 1 trial; 305 participants; high risk of bias), and on the other assessed the effect of 40% chlorhexidine varnish for preventing caries on the occlusal surfaces of first and second permanent molars ($p < 0.001$; 1 trial; 502 participants; low risk of bias).
- The two other trials reported no significant difference in caries increment between the teeth that received 1% chlorhexidine varnish compared to the teeth that received placebo varnish (2 trials; 142 participants; one high risk of bias and one low risk of bias trial). One trial assessed the effect of chlorhexidine varnish for preventing caries on the occlusal surfaces of first permanent molars and one trial assessed the effect of chlorhexidine varnish for preventing caries at the approximal surfaces of premolar and molar teeth in 2 quadrants of the mouth.

<u>Comparison 2: Chlorhexidine varnish compared to placebo or no treatment in primary teeth:</u>

One trial evaluated the caries-preventive effect of chlorhexidine varnish in primary teeth. The double-blind cluster randomised placebo-controlled trial involved 6-monthly applications of 40% chlorhexidine varnish in children with low background exposure to fluoride. Although the overall 2-year caries increment in primary molars was quite low, a statistically significant reduction in the caries increment in dentine was reported for children in the treatment group (mean dmfs molar 1.0 versus 1.6; $p = 0.036$; 334 participants; low risk of bias), suggesting a 37.3% reduction in caries increment over 2 years.

<u>Comparison 3: Chlorhexidine varnish compared to fluoride varnish in permanent teeth:</u>

One trial compared the caries-preventive effect of chlorhexidine varnish directly with that of fluoride varnish. The single-blind, randomised controlled trial compared the effectiveness of 3-monthly 1%

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| | chlorhexidine-thymol varnish applications with 3-monthly 0.1% fluoride varnish applications in a group of 180 Swedish adolescents with background exposure to topical fluoride applications. The caries increment after 3 years was mostly in enamel and was slightly higher in the treatment group, but not statistically significantly (mean DMFS approximal 3.08 versus 2.81 respectively, no p value reported; 180 participants; unclear risk of bias).<br><br>**Secondary outcome 1: Adverse events**<br>No adverse effects were reported in any of the included trials. Three trials reported that the chlorhexidine varnish (1 and 10%) was well tolerated by the trial participants. Two trials reported dropouts due to the taste of the varnish. Dropouts were minimal (2 participants) for one of these trials involving 13-year-old children and 1% chlorhexidine-thymol varnish. The second trial reported that 13 participants aged 4–5 years (4% of the participants at baseline) objected to the taste of the varnish (40% chlorhexidine) and refused to be examined. |
| **Significance/direction** | Evidence regarding the effectiveness of chlorhexidine varnish for preventing caries is inconclusive. Further well-conducted randomised trials are required before chlorhexidine varnish can be recommended for caries prevention. |
| **Heterogeneity** | The review authors decided to present a narrative summary of the results due to the variation in reporting of outcomes. They noted that heterogeneity was assessed informally by examination of the summary of results tables presented in the paper. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the overall certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Chou *et al.* (2021) |
| **First Author and year of publication** | Chou *et al.* (2021) |
| **Objectives (exact review question(s) and page number)** | To determine how effective oral screening (including risk assessment) performed by a primary care clinician is in preventing dental cares in children younger than age 5 years.<br><br>To determine the harms of oral health screening performed by a primary care clinician in children younger than age 5 years. |

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| | To determine how effective referral by a primary care clinician to a dental health care professional is in preventing dental caries in children younger than age 5 years.<br><br>To determine how effective preventive interventions (dietary fluoride supplements, topical fluoride application, silver diamine fluoride, or xylitol) is in preventing dental caries in children younger than age 5 years.<br><br>To determine the harms of specific oral health interventions to prevent dental caries in children younger than age 5 years (parental or caregiver/guardian oral health education, referral to a dental health care professional, and preventive interventions) (p6). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (assumed primary only for primary outcomes); attendance for dental assessment, scheduled primary care appointments; systemic fluoride, supplements; topical fluoride, solution; topical other chemicals, xylitol; combined intervention.<br><br>The 33 included studies involved a total of 106,694 children. The age of participants ranged from 0 to 4 years at baseline. Of the 21 studies that reported sex, % female ranged from 36% to 56%.<br><br>The total number of participants analysed in the 22 (out of 33) included studies that inform this umbrella review was approximately 11,979.<br><br>For the 15 trials evaluating topical fluoride, five trials reported the proportion of children with caries at baseline, which ranged from 17 to 100 percent. Seven of the fifteen trials enrolled children who were caries-free at baseline. The trials with the highest proportion of children with caries at baseline (72% and 100%) were conducted in Aboriginal communities in Canada and Australia. Fourteen of the fifteen trials evaluated children classified as being at higher risk, based on low socioeconomic status, high community prevalence of caries, high baseline caries burden, or low rates of oral health behaviours (e.g., tooth brushing with fluoride toothpaste).<br><br>For the two trials evaluating xylitol, baseline caries prevalence was 6% and 7%, the proportion of children that brushed their teeth daily was 79% and 68%, respectively. One of the trials involved children who were of low socioeconomic status.<br><br>Information pertaining to participant characteristics in the remaining five trials relevant to this umbrella review was not available.<br><br>*Note*. Although some trials were not adequately described in relation to intervention, population, and follow-up periods, the HRB authors assumed, given the age range of the population samples, that all outcomes related to primary dentition. |

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| **Setting/context** | The studies were conducted in Australia (1 study), Brazil (1 study), Canada (1 study), Chile (1 study), China (2 studies), Greece (1 study), Iran (3 studies), Kosovo (1 study), Scotland (2 studies), Sweden (3 studies), the UK (1 study), and the USA (10 studies). For six studies, the country of origin was not reported. Studies conducted in Kosovo, Iran, China, and the Aboriginal communities (Canada and Australia) were not classified as "very high" on the human development index; the other trials were conducted in "very high" human development index countries.<br><br>Seven studies were conducted in a medical setting, five studies were conducted in a preschool or day-care setting, four studies were conducted in a community setting, three studies were conducted in dental clinics, and one study was conducted in a dental/public health clinic. The setting of one study was unclear, and the setting of 12 studies was not reported. |
| **Description of Interventions/ phenomena of interest** | Interventions of interest were referral to a dentist by a primary care clinician, and preventive treatments including dietary fluoride supplementation, topical fluoride application (varnish, foam, or gel), xylitol, and silver diamine fluoride. The comparison for each was either no intervention or a placebo.<br><br>Five trials evaluated the effectiveness of dietary fluoride supplementation. One trial evaluated the effect of 0.25mg fluoride drop or chews. The remaining four trials did not specify the concentration or method of administration of the fluoride.<br><br>Fifteen trials evaluated the effects of topical fluoride application: five from an earlier version of the review and ten additional trials (in 12 publications) for this update. Fourteen trials evaluated fluoride varnish and one trial evaluated fluoride administered as a foam. Fluoride varnish was most commonly administered as 5% sodium fluoride varnish; however, single trials also evaluated 1.5% ammonium fluoride, 0.2 ml 0.9 difluorosilane fluoride varnish, and 1.23% acidulated phosphate fluoride foam. Topical fluoride was administered every 6 months in all trials except two in which varnish was administered every 3 or 4 months. One trial evaluated fluoride varnish every 6 or 12 months. Topical fluoride was administered by a dental health professional in all 15 trials in which this information was reported. Three of the trials did not describe provision of oral health education. In the remaining 12 trials, oral health education was provided in addition to the randomised intervention. The duration of follow up ranged from 1 to 3 years.<br><br>Two trials evaluated the effects of xylitol. One trial compared xylitol tablets which were administered as one 0.5mg tablet at bedtime for 6 months, followed by two tablets daily. The other trial compared xylitol wipes which were administered to teeth three times per day for 1 year. |

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| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials (through April, 2021)<br>• Cochrane Database of Systematic Reviews (through April, 2021), and<br>• Ovid MEDLINE (2013 through April, 2021).<br><br>Language was restricted to English. The reference lists of relevant articles and systematic reviews were also searched for any additional potentially relevant studies. A final search was conducted on 23 July 2021.<br><br>At least two review authors evaluated each study to determine inclusion eligibility. One review author performed data extraction, which was reviewed for completeness and accuracy by another team member. It was not reported how disagreements were resolved.<br><br>There was no mention of a protocol being prepared or published.<br><br>The review was funded by AHRQ (Agency for Healthcare Research and Quality).<br><br>Conflicts of interest were not reported. |
| **Date range (years) of included studies** | The 33 included studies were published between 1967 and 2020. |
| **Number of primary studies included in the systematic review** | The review authors included 33 studies (reported in 37 publications) in this update. Of the 33 studies, 19 were randomised controlled trials, four were nonrandomised controlled trials, nine were observational studies, and one was a systematic review. The results from the observational studies, the systematic review, and one randomised controlled trial were not relevant to the objectives of this umbrella review. Alas, the results of 22 randomised and nonrandomised controlled trials informed the outcomes of interest to this umbrella review.<br><br>Of the randomised controlled trials, five were cluster randomised and thirteen were individually randomised.<br><br>Nineteen of the 33 studies were funded by non-commercial organisations (e.g. government funding bodies, academic sources, or other not-for-profit foundations). Two were partially funded by commercial organisations. One received free supplies from a commercial organisation, and two reported no external funding. Sources of funding were not reported for the remaining nine studies. |
| **Types of studies included** | The review authors included 33 studies (reported in 37 publications): Pierce (2002), Serwint (1993), MacRitchie (2012), Agouropoulos (2014), Anderson |

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| | (2016), Anderson (2017), Frostell (1991), Jiang (2005), Jiang (2014), Latifi-Xhemajili (2019), Lawrence (2008), McMahon (2020), Memarpour (2015), Memarpour (2016), Munoz-Millan (2018), Oliverira (2014), Dos Santos (2016), Slade (2011), Tickle (2016), Tickle (2017), Weintraub (2006), Beil (2012), Beil (2014), Blackburn (2017), Kranz (2014a), Kranz (2014b), Sen (2016), Oscarson (2006), Zhan (2012), Ismail (2008), Hamberg (1971), Hennon (1972), Hu (1998), Lin (2000), Margolis (1967), Margolis (1975).<br><br>The results of 22 studies (reported in 26 publications) informed the outcomes of interest to this umbrella review: Agouropoulos (2014), Anderson (2016), Anderson (2017), Frostell (1991), Jiang (2005), Jiang (2014), Latifi-Xhemajili (2019), Lawrence (2008), McMahon (2020), Memarpour (2015), Memarpour (2016), Munoz-Millan (2018), Oliverira (2014), Dos Santos (2016), Slade (2011), Tickle (2016), Tickle (2017), Weintraub (2006), Oscarson (2006), Zhan (2012), Hamberg (1971), Hennon (1972), Hu (1998), Lin (2000), Margolis (1967), Margolis (1975).<br><br>A list of excluded studies and the reasons for exclusion were provided in an appendix. |
| **Country of origin of included studies** | The studies were conducted in Australia (1 study), Brazil (1 study), Canada (1 study), Chile (1 study), China (2 studies), Greece (1 study), Iran (3 studies), Kosovo (1 study), Scotland (2 studies), Sweden (3 studies), the UK (1 study), and the USA (10 studies). For six studies, the country of origin was not reported. |
| **Appraisal instrument(s)** | Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies using criteria developed by the United States Preventive Services Task Force (USPSTF). Evidence was rated as “good,” “fair,” or “poor” as per USPSTF criteria, depending on the seriousness of the methodological shortcomings. For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus.<br><br>For randomised controlled trials, the quality rating was assessed with reference to:<br>1. Randomisation<br>2. Allocation concealment<br>3. Groups similar at baseline<br>4. Outcome assessors masked<br>5. Care providers masked<br>6. Patient masked<br>7. Intention-to-treat analysis<br>8. Patients with missing data analysed |

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| | 9. Acceptable levels of overall attrition and between-group differences in attrition<br>10. Post randomisation exclusions<br>11. Avoidance of selective outcomes reporting, and<br>12. Adjusted for cluster correlation.<br><br>For all key questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual. Evidence was rated "good", "fair", or "poor" based on study quality, consistency of results between studies, precision of estimates, study limitations, risk of reporting bias, and applicability.<br><br>It was not reported how the quality of the four included nonrandomised controlled trials was assessed. |
| **Appraisal rating** | Overall, six studies were judged to be of "good" quality, and 22 studies were judged to be of "fair" quality. The quality rating of the remaining five studies was not reported. Of the 22 trials relevant to this umbrella review, three were judged to be of "good" quality and 14 were judged to be of "fair" quality. The quality rating of the remaining five trials was not reported, presumably because they were completed in older versions of the review.<br><br>The HRB notes that, according to Cochrane's Collaboration tool, three out of the 17 relevant trials containing a risk of bias assessment had a low risk of bias, four trials had an unclear risk of bias, and 10 trials had a high risk of bias.<br><br>For the 17 relevant controlled trials that involved a quality assessment, 14 were judged to have adequate randomisation, one was judged to have unclear randomisation, and in two randomisation was not reported. Outcome assessors were masked in 12 trials, and not masked in two trials. Masking of outcome assessor was unclear in three trials.<br><br>Graphical and statistically methods were not used to assess publication bias due to diversity in populations, settings, and outcomes, and substantial statistical heterogeneity. |
| **Method of analysis** | The review authors performed a random effects meta-analysis using the profile likelihood model to summarise the effects of topical fluoride versus placebo or no fluoride on likelihood of developing caries (dichotomous outcome) or caries burden (continuous outcome, measured based on the number of<br>decayed, missing, or filled teeth [dmft] or surfaces [dmfs]). Effects on caries burden were based on mean difference in followup caries index if available; otherwise difference in change from baseline caries index (caries increment) was used. Adjusted differences were utilized when reported. For caries |

burden, the review authors used dmfs when available and otherwise used dmft. Data for dentin caries were used if available; otherwise data for any (enamel or dentin) caries were used. The review authors combined arms of comparable interventions within the same study in the primary analysis, so each study was represented once in a meta-analysis, in order to avoid overweighting.

For cluster randomized trials, treatment differences that accounted for the intracluster correlation were used, if reported. Otherwise, the review authors corrected for clustering using the intracluster correlation by calculating the design effect and the effective sample sizes before combining with individually randomized trials. If the intracluster correlation was not reported, the review authors imputed it based on the intracluster correlation reported in the other cluster trials.

The review authors conducted prespecified study-level subgroup analyses on the following factors:

- Use of cluster design (yes or no)
- Varnish frequency (every 4, 6, or 12 months)
- Trial conducted in very high human development index (HDI) setting (yes or no, based on a United Nations Development Programme HDI score of 0.800 or higher for the country or geographic setting)
- Trial conducted in preschool or daycare setting (yes or no)
- Trial conducted in high-risk population (yes or no; high-risk defined as high baseline caries, high community caries burden, low socioeconomic status, or low rates of oral health behaviors [e.g., brushing with fluoridated toothpaste]), mean age (<2 vs. ≥2 years),
- Enrolment restricted to caries-free children at baseline (yes or no)
- Adequate water fluoridation (yes or no; adequate fluoridation defined as ≥0.7 parts per million [ppm] F)
- Use of additional oral health measures (yes or no; additional oral health measures defined as education and/or provision of toothbrush and toothpaste)
- Follow-up duration (1 vs. <1 year), and
- Risk of bias (fair vs. good).

A sensitivity analysis was also conducted excluding a trial that used acidulated phosphate fluoride foam instead of fluoride varnish.

For all meta-analyses, statistical heterogeneity was assessed using the Cochran Q-test and $I^2$ statistic. All meta-analyses were conducted using Stata/SE 16.1.

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| **Outcome(s) assessed** | Primary outcome 1: Caries increment, measured as the number of decayed, missing, or filled teeth [dmft] or surfaces [dmfs]<br><br>Primary outcome 2: Caries incidence (presented as 'caries development' in the review)<br><br>Secondary outcome 1: Harms<br><br>*Note*. The nature of the outcomes (i.e. primary or secondary) is not made explicit in the review (assumed all are of equal importance). For the HRB's purposes, the outcomes are considered primary and secondary outcomes as presented above. |
| **Results/findings** | **Primary outcome 1: Caries increment, measured as the number of decayed, missing, or filled teeth [dmft] or surfaces [dmfs]**<br><u>Intervention 1: Oral screening (including risk assessment) performed by a primary care clinician):</u><br>No included trials reported this outcome.<br><br><u>Intervention 2: Referral by a Primary Care Clinician to a Dental Health Care Professional:</u><br>No included trials reported this outcome.<br><br><u>Intervention 3: Dietary fluoride supplementation:</u><br>The results from one randomised trial with 140 participants found use of 0.25mg fluoride drops of chews in Taiwanese children with cleft lips were associated with a decrease in caries incidence compared to no fluoride supplementation. The percent reduction in caries incidence ranged from 52 to 72% for dmft and from 51 to 81 percent for dmfs.<br><br>In four nonrandomised trials (2,273 participants), the reduction in caries incidence versus no fluoride supplementation ranged from mean dmft reduction of 32% to 69%. Two of these trials with extended follow-up found dietary fluoride supplementation was associated with decreased caries incidence at 7 to 10 years of age (reductions ranged from 33% to 80%).<br><br>*Note*. The above five trial were conducted in settings with water fluoridation levels below 0.6 ppm F associated.<br><br>*Note*. Most of the trials included in the review reported on combined interventions. However, the details of the interventions tested in the above 4 trials were not adequately described. The possibility of these trials including combined interventions is undetermined.<br><br><u>Intervention 4: Topical fluoride application:</u> |

In a meta-analysis, topical fluoride was associated with a decreased caries increment compared to a placebo or no topical fluoride at 1-3 years follow-up (MD -0.94, 95% CI -1.74 to -0.34; 13 trials; 5,733 participants; $I^2$ = 86%).

Results favoured topical fluoride in all sub-group analyses which included analyses stratified according to use of cluster randomization, application frequency, classification as very high human development index setting, preschool setting, mean age, enrolment restricted to caries-free children at baseline, adequate community water fluoridation, provision of additional oral health measures, risk of bias, and duration of follow-up. Results were also similar when the trial that evaluated fluoride foam was excluded from the analysis, leaving only trials of fluoride varnish in the meta-analysis.

The type of fluoride and concentration of fluoride varied greatly. Six trials used 5% NaF varnish, one trial used 1.23% APF foam, one trial used 0.9% Difluorsilane varnish, one trial used 1.5% ammonium fluoride varnish, one trial used 50mg/mL Durphat toothpaste, one trial used 0.5mL Profluorid varnish, one trial used a varnish consisting of 22,600 ppl fluoride, and the type of varnish was not specified in the last trial. The frequency of application was 6 months in 11 trials, 4 months in one trial, and 3 months in one trial.

*Note*. 12/13 of these trials involved complex combined interventions, many with multiple active components. The most common additional intervention components were parental oral health education (8 trials, OHE provided at different intervals), parental toothbrushing training/instruction (3 trials; frequency of training/instruction varied), the provision of toothbrushes and fluoride toothpaste (4 trials; fluoride concentration and frequency of provision varied), and supervised toothbrushing (3 trials, supervision frequency varied).

Intervention 5: Silver Diamine Fluoride*:*
No included trials reported this outcome.

Intervention 6: Xylitol:
The results from one randomised controlled trial (115 participants) found xylitol tablets after 2 years were associated with a lower dmfs increment compared to no xylitol (one 0.5 mg tablet at bedtime for 6 months, followed by two tablets daily). However, the difference was not statistically significant (mean percent reduction 52%, mean dmfs reduction 0.42). The review authors do not describe any additional intervention arms to indicate that this trial delivered a combined intervention, and note that water is not fluoridated in Sweden, the setting of the trial.

The results of another small randomised controlled trial found xylitol wipes (two at a time, three times per day (estimated

daily dosage 4.2 g) every 3 months for 1 year) were associated with markedly decreased risk of having incident caries versus placebo, though the difference was not statistically significant (5% [1/22] vs. 32% [7/22], RR 0.14, 95% CI 0.02 to 1.07). In an on-treatment analysis of 37 children who completed the study, xylitol was associated with decreased risk of incident caries versus placebo (5% vs. 40%, p=0.03) and deceased dmfs increment (0.05 vs. 0.53, p=0.01). The precise follow-up period was not specified. The review authors do not describe any additional intervention arms to indicate that this trial delivered a combined intervention but note that water is fluoridated in San Francisca (1.0mg/l).

**Primary outcome 2: Caries incidence**

Intervention 1: Oral screening (including risk assessment) performed by a primary care clinician):

No included trials reported this outcome.

Intervention 2: Referral by a primary care clinician to a dental health care professional:

No included trials reported this outcome.

Intervention 3: Dietary fluoride supplementation:

No included trials reported this outcome.

Intervention 4: Topical fluoride application:

In a meta-analysis, topical fluoride was associated with decrease likelihood of caries incidence compared to a placebo or no topical fluoride at 1-3 years follow-up (RR 0.80, 95% CI 0.66 to 0.95; 12 trials; 8,177 participants; $I^7$ = 79%). Definitions for incident caries included any caries lesion or development of ICDAS 5 to 6 (distinct dentine cavity) lesions.

*Note*. 10/12 of these trials involved complex combined interventions, many with multiple active components. The most common additional intervention components were parental oral health education (8 trials, OHE provided at different intervals), parental toothbrushing training/instruction (3 trials; frequency or training/instruction varied), the provision of toothbrushes and fluoride toothpaste (3 trials; fluoride concentration and frequency of provision varied), and supervised toothbrushing (3 trials, supervision frequency varied).

*Note*. These findings will not be used in data synthesis because some of the included trials tested caries progression rather than caries initiation.

Intervention 5: Silver Diamine Fluoride:

No included trials reported this outcome.

Intervention 6: Xylitol:

The results from one small randomised controlled trial found xylitol wipes (two at a time, three times per day (estimated
daily dosage 4.2 g) every 3 months) were associated with a markedly decreased risk of caries incidence compared to placebo wipes. However, the difference was not statistically significant (5% [1/22] vs. 32% [7/22], RR 0.14, 95% CI 0.02 to 1.07; 44 participants). In an on-treatment analysis of 37 children who completed the study, xylitol was associated with decreased risk of incident caries versus placebo (5% vs. 40%, p=0.03). The precise follow-up period was not specified.

**Secondary outcome 2: Harms**

Intervention 1: Oral screening (including risk assessment) performed by a primary care clinician):

No included trials reported this outcome.

Intervention 2: Referral by a primary care clinician to a dental health care professional:

No included trials reported this outcome.

Intervention 3: Dietary fluoride supplementation:

No trial reported risk of dental fluorosis associated with early childhood ingestion of dietary fluoride supplements.

Intervention 4: Topical fluoride application:

Five trials reported adverse events associated with fluoride varnish.

One trial reported one child with an allergy to lanolin experienced an adverse event.

One trial that followed children for four years reported no difference in the risk of fluorosis associated with the use of fluoride varnish compared with placebo (27% vs. 35%, p=0.44). There was also no difference in aesthetically objectionable fluorosis (4.8% vs. 8.3%, p=0.48). No other trial reported risk of fluorosis. However, the degree of systemic exposure following application of fluoride varnish is believed to be low.

One trial reported no difference in the rate of adverse events between fluoride varnish and no fluoride varnish (7.2% vs. 5.9%; RR 1.22, 95% CI 0.80 to 1.85).

Two trials reported child complaints about varnish odour, with one reporting a few children vomited directly after application.

Intervention 5: Silver Diamine Fluoride:

No included trials reported this outcome.

Intervention 6: Xylitol:

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| | Trials of xylitol did not report rates of diarrhoea, and either did not report adverse events or stated none were reported. |
| **Significance/direction** | Dietary fluoride supplementation and fluoride varnish appear to be effective at preventing caries outcomes in higher risk children younger than 5 years of age, though findings appear most applicable to higher risk children. Dietary fluoride supplementation in early childhood is associated with risk of enamel fluorosis, which is usually mild. More research is needed to understand the accuracy of oral health examination and caries risk assessment by primary care clinicians and primary care referral for dental care. |
| **Heterogeneity** | The substantial heterogeneity observed in analyses were listed as one of the limitations of the review. Results were consistent in prespecified stratified analyses based on factors related to study design, population characteristics, intervention characteristics, and setting, though stratification did not explain the heterogeneity. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | Chou R, Cantor A, Zakher B, et al. Preventing dental caries in children <5 years: systematic review updating USPSTF recommendation. Pediatrics. 2013 Aug;132(2):332-50. doi: 10.1542/peds.2013-1469. PMID: 23858419.<br><br>Chou R, Cantor A, Zakher B, et al. Prevention of Dental Caries in Children Younger Than 5 Years Old: Systematic Review to Update the U.S. Preventive Services Task Force<br>Recommendation. Evidence Synthesis No. 104. AHRQ Publication No. 12-05170-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014. |
| Parameter | Antonio *et al.* (2011) |
| **First Author and year of publication** | Antonio *et al.* (2011) |
| **Objectives (exact review question(s) and page number)** | To assess the overall caries preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria (p118). |
| **Participants (characteristics and numbers)** | Permanent dentition; topical other chemicals, polyols; combined intervention.<br><br>There were no restrictions on study population. The three included trials involved a total of 947 participants. The age of participants at baseline |

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| | ranged from 10 to 27 years. Information pertaining to the sex of included participants was not provided.<br><br>In two out of the three included trials, the participant sample were deemed representative of the entire population. The representativeness of the sample in the remaining trial was undetermined.<br><br>In two out of three included trials, the population samples were assessed by the original trial authors as being at high risk of caries. The remaining trial included participants at all levels of caries. |
| **Setting/context** | The trials were conducted in Estonia (1 trial), Kuwait (1 trial), and Sweden (1 trial).<br><br>Two trials were conducted in a community setting, and one trial was conducted in a non-institutionalised setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was xylitol products in the form of candies or lozenges. Control groups could be participants who had not received any kind of intervention, a placebo (e.g. sorbitol), or any preventive procedures (such as sealants, supervised tooth brushing with fluoride dentifrices, oral health instructions). Trials in which the experimental group was also exposed to products other than candies or lozenges containing xylitol (such as chewing gum and chlorhexidine), were excluded.<br><br>In the first trial, the intervention group received either 49% xylitol/maltitol candies or 49% xylitol/polydextrose candies (2 candies in the morning, 3 candies after lunch and 3 candies before the children left school). Participants in the control group were given no additional prevention outside routine local measures.<br><br>The intervention group in the second trial received 49% xylitol candies (1 xylitol candy, 3 times every school day). Participants in both the intervention and control groups received oral health education, supervised toothbrushing, sealant application, and restorative care.<br><br>In the third trial, the intervention group received either 42.2% xylitol lozenges or lozenges with 42.2% xylitol plus 0.025% sodium fluoride (2 tablets, 3 times a day). Participants in the control group received oral health education and fluoride varnish application (2 or 3 times/year. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Ovid MEDLINE (1956 to November 2009)<br>• PubMed (1950 to November 2009)<br>• ISI WEB of SCIENCE (1945 to November 2009) |

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| | • Latin Americans and Caribbean Health Science (LILACS Literature) (1982 to November 2009), and<br>• Cochrane Library (accessed in the first week of November 2009).<br><br>Hand searching and Related Articles link searched were performed in the selected studies by analysing title and abstracts.<br><br>There was no mention of a protocol being prepared or published.<br><br>Two review authors independently screened search results (titles and abstracts in electronic and hand searches, and full-text screening), and performed data extraction. Disagreements during screening were resolved through discussion with a third reviewer. It was not reported how disagreements at the data extraction phase were resolved.<br><br>Sources of funding and conflicts of interest were not provided. |
| **Date range (years) of included studies** | The three included trials were published between 2000 and 2008. |
| **Number of primary studies included in the systematic review** | The review authors included three controlled trials: two randomised controlled trials and one clinical controlled trial. Follow-up periods ranged from 1.5 to 3 years.<br><br>The unit of randomisation was either the individual (2 trials) or the school (1 trial). Funding sources of the primary studies were not provided. |
| **Types of studies included** | The review authors included three controlled trials: Alanen (2000), Honkala (2006), and Stecksen-Blicks (2008).<br><br>A list of excluded studies and the reasons for exclusion were provided in supplemental material. |
| **Country of origin of included studies** | The trials were conducted in Estonia (1 trial), Kuwait (1 trial), and Sweden (1 trial). |
| **Appraisal instrument(s)** | The methodological quality of the studies was assessed by focusing on the following issues adapted from Chambrone et al (2008):<br>• Method of randomization<br>• Allocation concealment<br>• Initial assembly ofcomparable or control group<br>• Calibration of examiners, and<br>• Blinding. |

The method of randomization was considered good when random number tables, tossed coin, or shuffled cards were used; fair when other methods were used, such as alternative assignment (e.g., date of birth, street address); and undetermined when the method of randomization was not described.

Allocation concealment was classified as good when the examiners or subjects were kept unaware of the randomization sequence; fair when other methods were used, such as alternative assignment; and undetermined when the method was not reported.

Classification of initial assembly of comparable or control groups was considered good when the groups contained randomly assigned subjects; fair when the subjects were assigned on the basis of returned permission slip or when schools, classrooms, or households were used as units of randomization instead of the subjects; and undetermined when the groups were not explained. Blinding as regards the type of intervention used in the study, as well as examiner calibration, was assessed as “yes,”, “no,” or “undetermined.”

For a study to be considered adequate, it needed to contain at least two items classified as good and the examiners needed to be blinded and calibrated. Unclear studies needed to contain at least one item classified as good and their examiners could be either blinded or calibrated or when the study did not meet the requirement of items classified as good, but the examiners were blinded and calibrated. Studies were considered inadequate when not a single item was considered good, and there was no blinding, even if the examiners were calibrated, or vice versa, considering the last two criteria. The studies classified as inadequate were excluded from the present systematic review.

Another form was completed to categorize the risk of bias of each study using the answers “yes,”, “no,” and “undetermined” to the following questions (on study conduct bias):

- “Was the sample representative of the entire population?”
- “Was the selection of all subjects random?”
- “Were the examiners blinded to assess outcome?”
- “Did the study show confounding factors such as the presence of additional caries preventive strategies such as diet counselling and patient education?”, and
- “Was the frequency of dropouts or exclusion similar between groups?”

Each review authors classified the study as:

- A – low risk of bias when the answer was “yes” to all questions

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| | • B – moderate risk of bias when the answer was “yes” to at least three questions, and<br>• C – high risk of bias when the answer was “no” or “undetermined” to two or more questions.<br><br>All questions were answered for each selected study, and the evaluation was performed by two reviewers then cross-checked by a third reviewer. |
| **Appraisal rating** | Quality assessment of the included studies showed that they were all categorised as unclear. In addition, all studies were considered to have a high risk of bias.<br><br>Two trials were considered to have an “undetermined” method of randomisation, and one trial was considered to have a “fair” method of randomisation. In addition, one trial was considered to have a low risk of bias for outcome ascertainment and two trials were considered to have an “undetermined” risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | The caries preventive effect of xylitol candies and lozenges was expressed by the prevented fraction. Results were presented narratively.<br><br>The heterogeneity of the studies was evaluated by the Compare 2 statistical test (WinPepi program). P values were obtained by comparing the statistics of the studies using the chi-square test. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment decayed, missing and filled surfaces (DMFS) and whole teeth (DMFT)<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Caries increment (DMFS and/or DMFT)**<br>The first trial (wherein the intervention group received either 49% xylitol/maltitol candies or 49% xylitol/polydextrose candies, and the control group received no additional preventive measure outside of routine local measures) did not carry out any statistical tests but did report the lowest 3-year increment in caries in the xylitol candies groups when compared with the control group.<br><br>The second trial (wherein the intervention group received 49% xylitol candies and both the intervention and control groups received oral health |

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| | education, supervised toothbrushing, sealant application, and restorative care) showed that DMFS and DMFT indices were significantly lower in the 49% xylitol candies group (1 xylitol candy, 3 times every school day) compared to the control group at 1.5-year follow-up ($p < 0.001$) (n = 126, analysed n = approx. 106 (16.6% dropout)).<br><br>Conversely, the third trial (wherein the intervention group received either 42.2% xylitol lozenges or lozenges with 42.2% xylitol plus 0.025% sodium fluoride lozenges, and the control group received oral health education and application for fluoride varnish 2 or 3 times per year) found no statistically significant differences between both the 42.2% xylitol lozenges group and 42.2% xylitol + 0.025% sodium fluoride lozenges (2 tablets, 3 times a day) compared to the control group ($p > 0.05$), considering the 2-year incidence of proximal enamel lesions and total proximal DMFS scores. |
| **Significance/direction** | The findings of the analysed studies suggest that although the use of xylitol-based candies and lozenges could reduce caries incidence in a wide segment of the population, their use did not seem to be effective on proximal surfaces. However, the current data should be interpreted with caution because they are based on results retrieved from only three studies, all of which were classified as "unclear" according to the quality criteria applied by the review authors.<br><br>Moreover, the review did not show homogeneity of the selected studies. This research demonstrates the need for well-designed randomised clinical studies with adequate control groups and high compliance by the subjects. |
| **Heterogeneity** | No meta-analysis was conducted. The review authors described the selected studies as having a lack of homogeneity. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | CADTH (2016) extraction |
| **First Author and year of publication** | CADTH (2016) |
| **Objectives (exact review question(s) and page number)** | To review the evidence with respect to clinical effectiveness, |

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| | specifically caries prevention, and cost effectiveness of dental sealants and preventative resins when applied to permanent teeth of children and adolescents (p2).<br><br>The HRB is only interested in the findings on the clinical effectiveness of sealants for caries prevention and so excluded the cost effectiveness aspect of this study. |
| **Participants (characteristics and numbers)** | Permanent dentition; sealants, resins, glass-ionomer, combined; combined intervention.<br><br>Children (age 0 to 14 years) with permanent teeth were included.<br><br>Only four of the 10 included studies measured caries prevention and met the inclusion criteria for this umbrella review. These four randomised controlled trials involved a total of 1,656 participants. In one trial the age of participants was 10 years. The mean age of participants in the other three trials ranged from 6.4 to 6.8 years.<br><br>Information pertaining to the sex of included participants was not reported.<br><br>Two trials involved children from low socioeconomic backgrounds. |
| **Setting/context** | The trials included were from China, Finland, USA, Italy, Latvia, France, Brazil, Philippines, and Portugal with one trial each.<br><br>The four randomised controlled trials were conducted In Brazil (1 trial), France (1 trial), Latvia (1 trial), and the Philippines (1 trial).<br><br>All four trials were conducted within a school setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was dental sealants and preventive resins. The comparison group was no dental sealant or preventive resin use. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Cochrane Library<br>• University of York Centre for Reviews and Dissemination (CRD) databases<br>• ECRI Institute, and<br>• Canadian and major international health technology agencies. |

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| | A focused internet search was also conducted. Language was restricted to English. Articles published between 1 January 2011 and 29 September 2016 were considered.<br><br>One review author screened search results (title and abstract, and full-text screening).<br><br>It was not reported how data extraction was completed.<br><br>There was no mention of a protocol being prepared or published.<br><br>Sources of funding and conflicts of interest were not provided. |
| **Date range (years) of included studies** | The ten included studies were published between 2011 and 2016.<br><br>The four relevant trials were published between 2012 and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included ten studies. Of these, four were systematic reviews, four were randomised controlled trials, one was a retrospective cohort study, and one was an evidence-based clinical practice guideline. Only the results of the randomised controlled trials were relevant to the objectives of this umbrella review.<br><br>One randomised controlled trial had a split-mouth design, and one was a cluster randomised trial. Follow-up periods ranged from 1 to 3 years.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included ten studies: Wright (2016), Hou (2015), Ahovuo-Saloranta (2013), Leo (2016), Kalnina (2016), Muller-Bolla (2013 and 2016), Hilgert (2015), Monse (2012), Baldini (2011), and ADA/AAPD (2016).<br><br>The results of four randomised control trials informed the outcomes of interest to this umbrella review: Kalnina (2016), Muller-Bolla (2013 and 2016), Hilgert (2015), and Monse (2012).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials included were from China, Finland, USA, Italy, Latvia, France, Brazil, Philippines, and Portugal with one trial each.<br><br>The four randomised controlled trials were conducted In Brazil (1 trial), France (1 trial), Latvia (1 trial), and the Philippines (1 trial). |
| **Appraisal instrument(s)** | The Cochrane Collaboration's tool for assessing risk of bias |

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| | was used to critically appraise the randomised controlled trials. The following domains were assessed in each included trial:<br>• Random sequence generation<br>• Allocation concealment<br>• Blinding of participants<br>• Blinding of outcome assessment<br>• Incomplete outcome data, and<br>• Selective reporting.<br><br>The AMSTAR checklist was used to critically appraise the systematic reviews... The Newcastle-Ottawa Quality Assessment Scale was used for non-randomized trials and the AGREE II instrument for appraisal of guidelines. |
| **Appraisal rating** | Overall, the included trials were judged to be good (3 trials), fair (3 trials), and poor (4 trials).<br><br>The four randomised controlled trials were judged to have a high risk of bias. Three of the four were of poor quality and one was of fair quality.<br><br>One trial was categorised as having a low risk of bias for randomisation, while the remaining three trials were categorised as having a high risk of bias for randomisation. Similarly, one trial was categorised as having a low risk of bias for outcome ascertainment, while the remaining three trials were categorised as having a high risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | Results were described narratively. |
| **Outcome(s) assessed** | Primary outcome 1: Caries prevention (incidence of caries (1 trial), new carious lesions (3 trials), caries prevention on PFM (1 trial)<br><br>*Note*. The specific outcomes reported in this review are not explicitly stated, but rather discussed as they are presented in the individual reviews. The stated outcome in the methods section is “clinical effectiveness”, and new caries was the only outcome relevant to this umbrella review that was reported in the included trials. For the HRB’s purposes, this outcome is considered a primary outcome. |
| **Results/findings** | **Primary outcome 1: New caries**<br>One trial found that sealant application to permanent pre-molars compared to a control (no sealant) did not prevent new caries at 12 months follow-up (0% vs. 3.5%, p = 0.106; 1 trial; 122 children; poor quality trial). |

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| | Similarly, one trial found a reduction in new carious lesions in permanent first molars that received a resin-based sealant compared to those that received no sealant at 1-year follow-up (OR 0.26, 95% CI 0.14 to 0.49; 1 trial; 276 children from low SES background; fair quality trial). The findings were consistent at 3 years follow-up (OR 0.38, 95% CI 0.28 to 0.52).<br><br>One trial found no difference in the development of cavitated dentine lesions between high-risk occlusal surfaces of permanent first molars that received composite resin or atraumatic restorative treatment-high-viscosity glass-ionomer cement (ART-GIC) compared to supervised tooth brushing over 3 years of follow-up (P=0.59; 1 trial; 242 children from low SES backgrounds; low quality trial).<br><br>*Note*. Participants in this trial had exposure to fluoridated water. However, this was background fluoride exposure, rather than part of the intervention of interest.<br><br>Lastly, one trial found a significant reduction in new D3 (enamel or dentin) caries at 18 months with the single application of atraumatic restorative treatment (ART) glass-ionomer sealant on permanent first molars compared to no treated permanent first molars in both those with daily brushing at school ($p < 0.01$) and those without ($p < 0.001$) (1 trial; 1,016 participants; low quality trial). |
| **Significance/direction** | Overall, the review authors concluded there exists good quality evidence that demonstrates caries reduction when dental sealants are applied to permanent molars in children and adolescents compared to no dental sealant application.<br><br>Dental sealants when applied to PFM demonstrated consistent and durable benefit for caries prevention in children and adolescents, but that optimal timing of application and clinical efficacy on other tooth groups remained somewhat unclear. |
| **Heterogeneity** | No meta-analyses were conducted. |
| **Summary for GRADE assessment for HRB report** | It is stated on page 6 of the report that the review authors used GRADE to assess the certainty of the evidence supporting their recommendations, which were generated by deliberation and consensus of the guideline panel. However, the results of this assessment were not reported on in the manuscript.<br><br>The HRB authors graded the certainty of evidence in this review as low. |

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| **References to previously published versions** | N/A |
| Parameter | Cagetti *et al.* (2012) |
| **First Author and year of publication** | Cagetti *et al.* (2012) |
| **Objectives (exact review question(s) and page number)** | To determine the effectiveness of fluoridated food in caries prevention (p2). |
| **Participants (characteristics and numbers)** | Permanent and primary dentition (separate); systemic fluoride, milk, salt, and sugar.<br><br>Baseline caries were not reported in any included trial.<br><br>The three included trials involved a total of 978 participants. The mean age of participants ranged from 3.5 to 11–19 years. Of the two trials that reported sex, the proportion of females in the study groups were 53% and 54%.<br><br>One trial involved children at high risk of caries who were residents of two orphanages. |
| **Setting/context** | One trial was conducted in Indonesia. The study countries of the other two trials were not reported.<br><br>One trial was conducted in an orphanage. Another trial took place in a pre-school. The setting of the other trial was not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of Interest was fluoridated food. The control groups were not specified.<br><br>Among the included trials, two investigated the caries-prevention effect of milk fluoridation on primary teeth, and one investigated the effect of sugar fluoridation in permanent teeth.<br><br>In one trial assessing the effect of fluoridated milk, the intervention group consumed 200ml of fluoridated milk a day for a period of 21 months. The control group was not indicated.<br><br>In the second trial, children in the intervention group received 150ml of milk supplemented with 2.5mg of fluoride per litre for lunch, while the control group received standard milk for 21 months. |

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| | In the single trial assessing the effect of fluoridated sugar, the intervention group used a sugar containing 10 ppm of fluoride and were followed for 18 months. The control group was not described. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Medline (1 January 1966 to 31 March 2011)<br>• Embase (1973 to 31 March 2011), and<br>• Cochrane Library.<br><br>The search was restricted to papers written in English.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening). Disagreements during screening were resolved through discussion. When resolution was not possible, the other two review authors were consulted.<br><br>It was not reported how data extraction was completed.<br><br>There was no mention of a protocol being prepared or published.<br><br>The source of funding was not reported.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The three included trials were published in 2002, 2003, and 2009. |
| **Number of primary studies included in the systematic review** | The review authors Included three clinical trials. It was not clear whether these were randomised or nonrandomised trials. Intervention length ranged from 18 to 21 months.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included three clinical trials: Bian (2003), Stecksen-Blicks (2009), and Mulyani (2002).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | One trial was conducted in Indonesia. The study countries of the other two trials were not reported. |
| **Appraisal instrument(s)** | The quality and relevance of each trial were graded as follows: high, medium or low using a study-quality checklist. External validity, internal validity and study precision were analysed to obtain an overall assessment of quality. The assessment was used as a basis for the discussion between two |

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| | examiners to grade the studies. In the case of disagreement, the review authors discussed the paper until a consensus was found.<br><br>The scientific evidence was assessed following the Swedish Council on Health Technology Assessment (SBU) criteria. The evidence was scored high when similar conclusions were obtained by at least two independent trials of high quality; medium when similar conclusions were supported by one trial of high quality or by at least two trials of medium quality; finally, the scientific evidence was defined as low when similar conclusions were achieved by at least two trials of medium quality. |
| **Appraisal rating** | Overall, two trials were graded as medium quality and one trial was graded as low quality.<br><br>The scientific evidence derived from the two papers on the effectiveness of fluoridated milk in the reduction of caries increment was scored low. The scientific evidence regarding fluoridated sugar was not possible to assess. The reasons for downgraded were not provided. |
| **Method of analysis** | Results were described narratively. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment using decayed, missing, and filled primary and permanent surfaces/teeth (dmfs/t and DMFS/T, respectively)<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Caries increment**<br><u>Intervention 1: Milk fluoridation:</u><br>The results of one trial found caries increment was lower in children who consumed 200ml of fluoridated milk per day (2.5mg of fluoride per litre) compared to children in the control group at 21 months follow-up (MD -0.9 dmft, $p < 0.001$; 1 trial; 664 participants), with a prevented fraction of 69%.<br><br>Similarly, the results of another trial found caries increment was lower in children who consumed 150ml of fluoridated milk per day (2.5mg of fluoride per litre) compared to children who consumed standard milk at 21 months follow-up (MD -1.3 dmfs, 1 trial; 186 participants) with a prevented fraction of 75%.<br><br>The scientific evidence derived from the two trials on the effectiveness of fluoridated milk was graded as low.<br><br><u>Intervention 2: Salt fluoridation:</u><br>No included trials assessed the effectiveness of this intervention.<br><br><u>Intervention 3: Sugar fluoridation:</u> |

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| | One trial found caries increment was lower in children who consumed fluoridated sugar (10 ppm of fluoride) compared to children in the control group at 18 months follow-up (MD -1.17 DMFS; 128 participants; low certainty of evidence). In this trial, fluoridated sugar was used as an ingredient in tea and porridge. |
| **Significance/direction** | Literature on the effectiveness of fluoridation in foods in caries prevention is scant and most studies have been conducted in children. There is low quality evidence that the use of milk fluoridation is effective in reducing the caries increment. The scientific evidence regarding fluoridated salt and sugar was scant. |
| **Heterogeneity** | No meta-analyses were conducted. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence a low for outcomes related to milk and sugar fluoridation. Specific reasons for downgrading were not provided. It is noted that the two trials reporting on the effectiveness of milk fluoridation were each awarded a quality appraisal of "medium", but that the combined body of scientific evidence of a given outcome was defined as "low" when similar conclusions were achieved by at least two studies of medium quality.<br><br>The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Carvalho *et al.* (2010) |
| **First Author and year of publication** | Carvalho *et al.* (2010) |
| **Objectives (exact review question(s) and page number)** | To assess whether there is evidence that professional application of fluoride varnish reduces the incidence of dental caries in primary dentition in children of up to six years of age (p2). |
| **Participants (characteristics and numbers)** | Primary dentition; topical fluoride, varnishes; combined intervention.<br><br>The population of interest was children of up to six years of age, regardless of their caries experience at the start of the study (initial dmfs ≥ 0).<br><br>The eight included trials involved a total of 2,501 children (2,135 at the end of the studies), aged six months to five years. |

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| | The seven trials that inform this review included a total of 2,378 children. Baseline caries were reported in all included trials. One trial involved participants who were caries-free at baseline.<br><br>Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | The trials were conducted in China (1 trial), Poland (1 trial), Sweden (4 trials), and the United States (2 trials).<br><br>The study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was the application of topical fluoride in the form of a varnish, in any quantity, concentration or application interval, using any application technique.<br><br>Among commercially existing products, the fluoride varnish Duraphat® (5% NaF) was used in seven studies and Fluor Protector® (1% Difluorsilano) was used in a single study. No study used a placebo in the control group. In all of the clinical trials analyzed, except one, the varnish was applied to all of the primary teeth. In the one exception, only the caries lesions present on the upper incisors were treated.<br><br>In five studies, the application of fluoride varnish took place every six months, and in two, the interval between applications was four and three months, respectively. In the most recent study, there were two test groups: one received yearly applications and the other received 6-month applications.<br><br>In all clinical trials analysed, except one, the varnish was applied to all the primary teeth. In the one exception, only the caries lesions present on the upper incisors were treated. The HRB is only interested in the findings on caries prevention, rather than treatment and so the results from this trial were excluded.<br><br>In two trials, it was reported that participants were exposed to water supplies with adequate fluoride levels. In three trials, it was mentioned that most of the children regularly used fluoridated toothpaste. In one trial, 27% of the participants regularly used fluoride tablets. In another trial, the participants a low concentration fluoridated toothpaste (0.025% sodium fluoride - NaF) supplied by the researchers. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• BBO<br>• LILACS<br>• Medline, and |

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| | • Cochrane Library.<br><br>Language was restricted to English, Spanish and Portuguese. Articles published up to December 2008 were included.<br><br>There was no mention of a protocol being prepared or published.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening). Disagreements during screening were resolved through consensus.<br><br>It was not reported how data extraction was completed.<br><br>Funding sources and conflicts of interest were not reported. |
| **Date range (years) of included studies** | The eight included trials were published between 1979 and 2006. |
| **Number of primary studies included in the systematic review** | The review authors included eight randomised controlled clinical trials. Two of these were cluster randomised trials. Follow-up periods ranged from 9 to 30 months and 75% of the trials covered a period of 24 months.<br><br>In five trials, the application of fluoride varnish took place every six months, and in two, the interval between applications was four and three months, respectively. In the most recent trial, there were two test groups: one received yearly applications and the other received 6-month applications.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included eight randomised controlled trials: Weintraud (2006), Chu (2002), Autio-Gold (2001), Twetman (1996), Frostell (1991), Petersson (1985), Grodzka (1982), and Holm (1979).<br><br>The results of seven trials informed the outcomes of interest to this umbrella review: Weintraub (2006), Autio-Gold (2001), Twetman (1996), Frostell (1991), Petersson (1985), Grodzka (1982), and Holm (1979).<br><br>A list of excluded studies and the reasons for exclusion were not reported. |
| **Country of origin of included studies** | The trials were conducted in China (1 trial), Poland (1 trial), Sweden (4 trials), and the United States (2 trials). |
| **Appraisal instrument(s)** | Jadad's scale was used to assess the quality of the included trials. This instrument was used to assign ratings to the trials, which varied from zero to five, based on the following criteria: method of randomisation, method of blinding and description of withdrawals and dropouts. |

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| **Appraisal rating** | Overall, assessment of the quality of the clinical trials, using Jadad's scale, showed that most of them presented problems in terms of their design. One trial was judged to have a score of "4", two trials had a score of "2", three trials had a score of "1", and two trials had a score of "0".<br><br>Of the included trials, only three used masking of the examiners. Two trials were described as being double-blind, however, one reported that they were unable to maintain the masking of parents and children throughout the study. Two trials made no mention of the use of blinding, and one trial resorted to masking of the children's parents.<br><br>Intra-examiner and inter-examiner reliability were measured in three studies and the Kappa coefficient values reported were in a range of 0.71 to 0.96.<br><br>Of the three trials that mentioned using a randomisation process, only one adequately described how the process was carried out. This trial also adequately described how the assignment concealment was done. The other trials reported that randomisation was used but did not describe how it was done. In two trials, the intervention was assigned by school or health centre.<br><br>The rate of loss to follow-up was reported in all trials, but many did not report the reasons why such losses occurred.<br><br>Publication bias was not measured. |
| **Method of analysis** | Results were described narratively. |
| **Outcome(s) assessed** | Primary outcome 1: Incidence of caries, given the presence of a cavitated lesion in primary dentition (decayed, missing and filled surfaces (dmfs) prevented fraction)<br><br>Secondary outcome 1: Adverse events<br><br>*Note*. Primary outcome 1 is identified as a primary outcome in the review. The nature of secondary outcome 1 (primary or secondary) is not explicitly stated in the review (assumed to be secondary given that it is not listed alongside the primary outcome when first identified). For the HRB's purposes is considered a primary outcome. |
| **Results/findings** | **Primary outcome 1: Incidence of caries**<br>Results from one trial found that mean caries increment was lower in participants who received annual or 6-monthly application of 5% NaF varnish compared to participants in the control group who received oral health counselling (dmfs prevented fraction 58%; MD -1.00, $p \leq 0.01$; 132 participants). |

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| | Results from four additional trials found caries increment was lower in participants who received fluoride varnish compared to participants in the control group who received no treatment. All p values were < 0.05. Samples sizes ranged from 123 to 816. The mean difference in dmfs between the intervention and control groups ranged from -1.64 to -0.46. The prevented fractions ranged from 30%-63%<br><br>One trial found caries increment (dmfs) was lower in the test group (5% NaF varnish applied every 6 months) compared to the no treatment group at 2 years follow-up. However, the result was not statistically significant (p > 0.1; 248 participants).<br><br>An additional trial also found dmfs increment was 15% lower in the test group (5% NaF varnish applied every 6 months + 0.025% sodium fluoride toothpaste, n = 88 at the end of the study) compared to a control group that received oral health counselling (n = 85 at the end of the study) at 24 months follow-up. However, no p value was provided (MD -0.30; 173 participants) (27% of the participants regularly used fluoride tablets).<br><br>**Secondary outcome 1: Adverse events**<br>One trial mentioned that no side effects were observed, such as gingival tissue damage. |
| **Significance/direction** | Available evidence suggests that fluoride varnish is capable of reducing the incidence of caries in the primary teeth of children six years of age or younger. However, the results provide no conclusive scientific evidence in this respect. It was not possible to conclude whether the magnitude of the fluoride varnish effect is related to previous caries experience. It is recommended that well designed, randomised clinical trials be conducted along this line of investigation.<br><br>The follow-up is recommended by the review authors: well designed, randomized clinical trials should be conducted along this line of investigation, as such clinical trials should seek to assess whether there is an ideal interval for applying the varnishes, taking into consideration the cost-benefit ratio; whether the magnitude of the beneficial effect of fluoride varnish is associated with prior caries experience; and what magnitude of additional benefit is derived from the application of fluoride varnish in populations exposed to fluoridated water and toothpastes. Moreover, it is important to investigate whether fluoride varnishes are, in fact, well accepted by children and their parents, and whether they cause side effects. |
| **Heterogeneity** | The review authors stated that there was no homogeneity between the trials concerning: previous caries experience of the subjects, the type of treatment administered to the control group, the children's exposure to other sources of fluoride, and the interval between varnish applications. |

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| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in the review as low. |
| **References to previously published versions** | N/A |
| Parameter | de Sousa *et al.* (2019) |
| **First Author and year of publication** | de Sousa *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To assess the effectiveness of fluoride varnish (FV) in reducing dentine caries at the patient, tooth, and surface levels as well as caries-related hospitalizations in preschoolers (p502).<br><br>To assess the effectiveness of fluoride varnish in reducing the risk of developing new dentine caries lesions and caries-related hospitalisations in pre-schoolers and to assess whether its effectiveness is influenced by baseline caries levels (p503). |
| **Participants (characteristics and numbers)** | Primary dentition; topical fluoride, varnishes; combined intervention.<br><br>The population of interest was children up to 71 months of age (pre-schoolers).<br><br>The total number of children randomised was 16,877, and 13,658 were included in the analyses. The proportion of caries-free children at baseline caries from 0% to 100%. Mean baseline dmfs and dmft varied from 0 to 22.8 surfaces and from 0 to 6.57 teeth, respectively. The age of participants ranged from 6 months to 5 years at baseline.<br><br>Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | The trials were conducted in Australia (1 trial), Brazil (1 trial), Canada (1 trial), Chile (1 trial), China (3 trials), Germany (1 trial), Greece (1 trial), Iran (2 trials), Ireland (1 trial), Poland (1 trial), Scotland (1 trial), Sweden (4 trials), and the United States (2 trials).<br><br>The study settings were not provided. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was fluoride varnish, alone or associated with an oral health programme, compared to placebo, usual care, or no intervention.<br><br>There are five different comparisons: |

1. FV versus placebo
2. Usual care
3. No intervention, and
4. Two comparisons where FV was associated with an oral health program and distribution of toothpaste.

*Note*. 13/20 included trials reported on combined interventions, including fluoride varnish + oral health education (5 trials), fluoride varnish + oral health education + supervised toothbrushing (2 trials), fluoride varnish + dietary counselling (3 trials), fluoride varnish + dietary counselling + supervised toothbrushing (1 trial), fluoride varnish + dietary counselling + fluoride toothpaste (2 trials; 500ppm F in 1 trial and 1450 ppm F in the other).

**Databases and sources searched**

The review authors searched the following sources:

- Cochrane Central Register of Controlled Trials
- MEDLINE via PubMed
- Web of Science
- EMBASE
- SCOPUS
- LILACS
- BBO
- Open Grey
- EThOS
- New York Academy of Medicine (GreyLit Report)
- Banco de Teses CAPES
- Current Controlled Trials
- ClinicalTrials.gov
- EU Clinical Trials Register
- Australia New Zealand Clinical Trials Registry, and
- Registro Brasileiro se Ensaios Clinicos.

Meeting abstracts of the International Association for Dental Research (2001–2018) and the European Organisation for Caries Research (1998–2018) were also searched. There were no language restraints.

References of eligible trials and systematic and narrative reviews on the subject were checked for any additional potentially relevant studies. There

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| | were no language restraints. Hand searching was performed in nine dental journals and two medical journals:<br>• Caries Research<br>• Community Dentistry & Oral Epidemiology<br>• European Archives of Paediatric Dentistry<br>• International Journal of Paediatric Dentistry<br>• Journal of the American Dental Association<br>• Journal of Dental Research<br>• Journal of Dentistry of Children<br>• Journal of Public Health Dentistry<br>• Paediatric Dentistry<br>• Paediatrics, and<br>• The Journal of Paediatrics.<br><br>All electronic and hand searches were last updated in July and August 2018, respectively.<br><br>It is not reported how screening was performed.<br><br>Two review authors independently performed data extraction. Disagreements were resolved through discussion with a third review author.<br><br>The review protocol was registered with PROSPERO (ID: CRD42016048599).<br><br>The review was funded in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brasil (CAPES). One of the authors received financial support from the Brazilian National Research Council.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 20 included trials were published between 1979 and 2018. |
| **Number of primary studies included in the systematic review** | The review authors included 20 randomised controlled trials. Of these, 14 were individually randomised and six were cluster randomised. Follow-up periods ranged from 12 to 36 months, with most trials using a follow-up period of 24 months.<br><br>Funding sources of the primary studies were not provided. |
| **Types of studies included** | The review authors included 20 randomised controlled trials: Agouropoulos (2014), Anderson (2016), Borutta (2006), Braun (2016), Chu (2002), Frostell |

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| | (1991), Grodzka (1982), Holm (1979), Jiang (2014), Lawrence (2008), McMahon (2018), Memarpour (2015), Memarpour (2016), Munoz-Millan (2018), Oliveira (2014), Petersson (1998), Slade (2011), Tickle (2017), Weintraub (2006), and Yang (2008).<br><br>The results of two trials did not contribute data to any quantitative analysis (Borutta 2006 and Frostell 1991).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Brazil (1 trial), Canada (1 trial), Chile (1 trial), China (3 trials), Germany (1 trial), Greece (1 trial), Iran (2 trials), Ireland (1 trial), Poland (1 trial), Scotland (1 trial), Sweden (4 trials), and the United States (2 trials). |
| **Appraisal instrument(s)** | The Cochrane risk of bias tool was used to assess the quality of included studies. The following domains were assessed in each included trial:<br>• Random sequence generation<br>• Allocation concealment<br>• Blinding of participants and personnel<br>• Blinding of outcome assessment<br>• Incomplete outcome data<br>• Selective reporting<br>• Baseline balance, and<br>• Diagnosis reliability. |
| **Appraisal rating** | Overall, only one study had low risk of bias in all domains assessed. The older studies had a poorer performance, especially regarding selection bias. They also had more domains assessed as unclear risk of bias, which emphasizes a poorer reporting of these studies. Studies published in the last 10 years tended to have more domains assessed as low risk of bias. We could not assess the risk of bias of one of the studies included in a meta-analysis because we only had access to the abstract; the authors were contacted, but they were not able to provide the necessary information.<br><br>Thirteen trials were categorised as having a low risk of bias for randomisation, four trials were categorised as having an unclear risk of bias for randomisation, and two trials were categorised as having a high risk of bias for randomisation.<br><br>Thirteen trials were categorised as having a low risk of bias for outcome ascertainment, three trials were categorised as having an unclear risk of bias |

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| | for outcome ascertainment, and three trials were categorised as having a high risk of bias for outcome ascertainment.<br><br>Publication bias was investigated using funnel plot and Egger's regression. The funnel plot showed asymmetry among the trials, and Egger's regression coefficient was –1.60 (95% CI –2.44, –0.75). The p value for the null hypothesis test of no small-study effects was 0.001. |
| **Method of analysis** | Meta-analyses at the individual level were performed using relative risk, and at the tooth and surface levels using prevented fraction and weighted mean difference. The number needed to treat (NNT) for an additional beneficial outcome was derived from the pooled RR and the median caries incidence in the control groups.<br><br>Due to the heterogeneity observed, a random-effects model was used, and prediction intervals were estimated. The Fieller method was used to calculate the 95% confidence intervals for the prevented fractions.<br><br>For the meta-analyses of the weighted mean differences, either the final dmfs/dmft or the net increment was used, depending on the data reported in the included studies. In two trials, there were two fluoride varnish intervention groups, and they were combined according to Higgins and Deeks [2011]. To assess whether baseline caries levels could influence the effectiveness of fluoride varnish, the review authors performed a meta-regression using the relative risk as the outcome variable and the mean baseline dmfs as the potential effect modifier.<br><br>All analyses were carried out in STATA 13.1. |
| **Outcome(s) assessed** | Primary outcome 1: Proportion of children developing new dentine caries lesions<br><br>Primary outcome 2: decayed, missing, and filled surfaces (dmfs)<br><br>Primary outcome 3: decayed, missing, and filled teeth (dmft)<br><br>Secondary outcome 1: Adverse events<br><br>*Note*. Primary outcomes 1-3 are identified as primary outcomes in the review. The nature of secondary outcome 1 (primary or secondary) is not explicitly stated in the review (assumed secondary given the wording in the review text). For the HRB's purposes is considered a secondary outcome. |
| **Results/findings** | **Primary outcome 1: Proportion of children developing new dentine caries lesions**<br>Overall, the proportion of children developing new caries was lower in those that received fluoride varnish compared to those that did not at 12-36 |

months follow-up (RR 0.88, 95% CI 0.81 to 0.95; 16 trials, 10 involving combined interventions; 9,373 participants; $I^2$ = 75.5%, p = .000). However, the findings were not statistically significant when the review authors considered the prediction intervals.

The interventions consisted of fluoride varnish (5% NaF in 13 trials, 0.1% difluorosiline in 2 trials, and 0.9% difluorosiline in 1 trial) applied at 6-month intervals in 15 trials (a 3-month interval in 1 trial) and were compared to no varnish at 12-36 months follow-up (16 trials; 10 included combined interventions), equating to a 12% reduced risk.

Comparison 1: Fluoride varnish versus placebo:
There was no difference in the proportion of children developing new caries between those who received flourish varnish and those who received a placebo (RR 0.86, 95% CI 0.72 to 1.03; 6 trials; 1,347 participants; $I^2$ = 34.7%, p = 0.18).

Comparison 2: Fluoride varnish versus usual care:
The proportion of children developing caries was lower in children who received fluoride varnish compared to those who received usual care (RR 0.84; 95% CI 0.72 to 0.98; 2 trials, 1 involving a combined intervention; 3,686 participants; $I^2$ = 0%, p = 0.74).

Comparison 3: Fluoride varnish versus no intervention:
The proportion of children developing caries was lower in children who received fluoride varnish compared to those who received no intervention (RR 0.85; 95% CI 0.73 to 0.98; 6 trials, 5 involving combined interventions; 2,701 participants; $I^2$ = 86.9%, p = .000).

Comparison 4: Fluoride varnish + oral health advice + community health promotion + 500 ppm fluoride toothpaste versus no intervention:
There was no difference in the proportion of children developing caries between the two groups (RR 1.00, 95% CI 0.94 to 1.06; 1 trial; 543 participants).

The group that received a combined intervention received 5% NaF varnish applied every 6 months + oral health education + dietary counselling + 500 ppm fluoride toothpaste compared to no intervention.

Comparison 5: Fluoride varnish + oral health advice + 1450 ppm fluoride toothpaste versus oral health advice:
There was no difference in the proportion of children developing caries between the two groups at 36 months follow-up (RR 0.87, 95% CI 0.81 to 0.95; 1 trial; 1,096 participants).

The group that received a combined intervention received 5% NaF varnish applied every 6 months + oral health education + dietary counselling + 1450

ppm fluoride toothpaste compared to oral health education + dietary counselling.

The results of all comparisons were not statistically significant when the prediction intervals were considered. The prediction interval for the pooled RR was 0.68 to 1.14, meaning that given the current data, the relative risk of a future trial may be as low as 0.68 and as high as 1.14.

The results of the meta-regression showed that an increase in one unit of mean baseline dmfs led to a 1% increase in RR (95% CI 0.99, 1.02), which was not statistically significant. In addition, adjusted $R^2$ showed that baseline caries levels explained 25.87% of between-study variance. This information was provided in an appendix.

**Primary outcome 2: Decayed, missing, and filled surfaces (dmfs)**
Overall, dmfs scores were lower in those who received fluoride varnish compared to those who received any control (WMD -0.77, 95% CI -1.23 to -0.31; 11 trials; 6,644 participants). The prevented fraction was 24.15 (95% CI 12.91, 35.38).

The interventions consisted of fluoride varnish (5% NaF in 8 trials, 0.1% difluorosiline in 2 trials, and 0.9% difluorosiline in 1 trial) applied at 6-month intervals in 9 trials (3-month intervals in 2 trials) compared to the control groups at 24-36 months follow-up (11 trials; 7 included combined interventions), equating to a 24% reduction in dmfs with the use of fluoride varnish.

Comparison 1: Fluoride varnish versus placebo:
Analyses showed dmfs scores were lower in those who received fluoride varnish compared to those who received a placebo (WMD -0.71, 95% CI -1.09 to -0.33; 4 trials; 742 participants).

Comparison 2: Fluoride varnish versus usual care:
Results found one trial found no difference in dmfs scores between those that received fluoride varnish and those that received usual care (MD 0.10, 95% CI -0.05 to 0.25; 1 trial; 2,536 participants).

Comparison 3: Fluoride varnish versus no intervention: Analyses showed dmfs scores were lower in those who received fluoride varnish compared to those who received no intervention (WMD -1.01, 95% CI -1.77 to -0.25; 6 trials; 2,700 participants).

Comparison 4: Fluoride varnish + oral health advice + community health promotion + 500 ppm fluoride toothpaste versus no intervention:
Results from one trial found significantly lower dmfs scores in those that received the intervention compared to those that received no intervention

at 24 months follow-up (MD -2.30, 95% CI -3.86 to -0.74; 1 trial; 666 participants).

The group that received a combined intervention received 5% NaF varnish applied every 6 months + oral health education + dietary counselling + 500 ppm fluoride toothpaste compared to no intervention.

**Primary outcome 3: Decayed, missing, and filled teeth (dmft)**
Overall, there was no difference in dmft scores between those who received fluoride varnish compared to those who received any control (WMD -0.30, 95% CI -0.70 to 0.09; 5 trials; 877 participants).

The interventions consisted of fluoride varnish (5% NaF in 4 trials and 0.1% difluorosiline in 1 trial) applied at 6-month intervals and were compared to control groups at months 24-36 months follow-up (5 trials; 2 included combined interventions), equating to a 31% reduction in dmft with the use of fluoride varnish.

Comparison 1: fluoride varnish versus placebo:
Analyses showed there was no different in dmft scores between that received fluoride varnish and those that received a placebo (WMD -0.34; 95% CI -0.93 to 0.25; 3 trials; 666 participants).

Comparison 2: fluoride varnish versus no intervention:
Results from one trial found no difference in dmft scores between those that received flourish varnish and those that received no intervention (MD -0.42, 95% CI -1.09 to 0.25; 1 trial; 151 participants).

Comparison 3: Fluoride varnish + oral health advice versus oral health advice:
Results from one trial found no difference in dmft scores between those that received flourish varnish + oral health advice and those that just received oral health advice (MD -0.12, 95% CI -0.60 to 0.36; 1 trial; 151 participants).

The group that received a combined intervention received 5% NaF varnish + oral health education + dietary counselling compared to a control group that received placebo water-based coloured solution + oral health education + dietary counselling, at 12 months follow-up.

**Secondary outcome 1: Adverse events**
Adverse events associated with fluoride varnish applications were provided in an appendix. Adverse events included vomiting, unpleasant smell, burning sensation, and dissatisfaction with tooth appearance after application. Only one trial actively investigated long-term adverse events. The participants of this study were recruited five years after the trial ended to assess dental fluorosis incidence; there was no significant difference between those who had received fluoride varnish and those who had received placebo varnish.

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| **Significance/direction** | At the surface level, the results showed a statistically significant difference favouring fluoride varnish. Overall, the lower increment of caries in the varnish group was of one surface per child or less. This difference is possibly clinically irrelevant. At the tooth level, no significant difference was observed between children who received fluoride varnish and those who did not. Finally, at the individual level, the meta-analysis showed that the risk of developing new dentine caries lesions was reduced by 12% among the children who received fluoride varnish when compared to those who did not. This was a rather modest benefit as many the children developed new dentine caries lesions, regardless of fluoride varnish use.<br><br>The review authors concluded that fluoride varnish showed a modest and uncertain anticaries effect in pre-schoolers. Cost-effectiveness analyses are needed to assess whether fluoride varnish should be adopted or abandoned by dental services. |
| **Heterogeneity** | Due to the high clinical and statistical heterogeneity observed among trials, the review authors used a random-effects model and estimated prediction intervals.<br><br>Statistical heterogeneity was discussed for tooth and surface level analyses. For individual-level analyses, significant heterogeneity was observed for the fluoride varnish versus no intervention comparison. This heterogeneity was not explained.<br><br>Results from the meta-regression showed that baseline caries levels explained a small percentage of between-study variance, which means that other factors besides baseline caries levels led to heterogeneous treatment effects among the trials included in the review. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Dos Santos *et al.* (2018) |
| **First Author and year of publication** | Dos Santos *et al.* (2018) |

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| **Objectives (exact review question(s) and page number)** | To assess the effects of supervised toothbrushing on caries incidence in children and adolescents (p3). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate); Dental hygiene, supervised toothbrushing; combined intervention.<br><br>The population of interest was children and adolescents up to 18 years of age.<br><br>Participants in the four included trials were 2 to 14 years of age. One trial included only pre-school children. The risk of caries varied among participants.<br><br>Information pertaining to the number of and the sex of included participants was not reported. |
| **Setting/context** | The trials were conducted in Brazil (1 trial), Germany (1 trial), Jordan (1 trial), and the United States (1 trial).<br><br>All trials were conducted within a school setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was supervised toothbrushing. The control group included those that did not receive supervised toothbrushing but were exposed to a toothpaste with the same fluoride concentration as the test group.<br><br>In the included trials, toothbrushing was performed with no fluoride toothpaste, 500 ppm fluoride toothpaste, and 1000 ppm fluoride toothpaste.<br><br>In one trial, 30 minutes oral hygiene instruction sessions and practical demonstration and application of toothbrushing technique on five consecutive school days and repeated twice a year by a dental hygienist and a research assistant. In addition, daily school-supervised toothbrushing by a research assistant was also provided with 500 ppm (6.3-year-olds) or 1000 ppm fluoride toothpaste (11.7-year-olds). The control group received only 30 minutes oral hygiene instruction sessions on five consecutive school days and repeated twice a year by a dental hygienist and a research assistant.<br><br>In the second trial, the test group received daily supervised toothbrushing by a dental assistant with 1000 ppm fluoride toothpaste. The control group received no intervention, but all children received an oral hygiene kit containing a toothbrushing, a 1000 ppm fluoride toothpaste, plaque-disclosing toothpaste and dental floss. They were instructed on how to use these devices and were encouraged to brush their teeth twice daily. |

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| | In the third trial, the test group received intensive daily dental hygiene in kindergarten provided by special personnel with 500 ppm fluoride toothpaste. Families were supplied with free toothbrushes and toothpaste. The control group received instruction for cleaning the teeth, three to four times a year. Families were supplied with free toothbrushes and 500 ppm fluoride toothpaste.<br><br>In the fourth trial, the test group received daily school-supervised toothbrushing by the school faculty with non-active toothpaste. The study population was supplied with toothbrushes and non-active (no fluoride) toothpaste. The control group received no intervention, but the study population was supplied with toothbrushes and non-active (no fluoride) toothpaste. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials<br>• Medline via PubMed<br>• WEB OF SCIENCE<br>• EMBASE<br>• LILACS<br>• BBO<br>• Open Grey<br>• ETHoS<br>• Banco de Teses CAPES<br>• Current Controlled Trials, and<br>• ClinicalTrials.gov.<br><br>All electronic searches were last updated in July 2017. Meeting abstracts of the International Association for Dental Research (2001–2016) and the European Organisation for Caries Research (1998–2016) were also searched. References of eligible trials and systematic and narrative reviews on the subject were checked for any additional potentially relevant studies. There were no language restrictions. Handsearching was also performed in sixteen dental journals:<br>• Acta Odontologica Scandinavica<br>• Archives of Oral Biology<br>• British Dental Journal<br>• Caries Research<br>• Community Dental Health |

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| | • Community Dentistry & Oral Epidemiology<br>• European Archives of Paediatric Dentistry<br>• European Journal of Oral Sciences<br>• International Dental Journal<br>• International Journal of Paediatric Dentistry<br>• Journal of the American Dental Association<br>• Journal of Clinical Pediatric Dentistry<br>• Journal of Dental Research<br>• Journal of Dentistry for Children<br>• Journal of Public Health Dentistry, and<br>• Pediatric Dentistry.<br><br>The review protocol was registered with PROSPERO (ID: CRD42014013879).<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements during extraction were resolved by a third review author. Disagreement resolution at the screening phase was not reported.<br><br>The funding source of the review was not reported.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The four included trials were published 1978, 2006, 2015, and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included four randomised and quasi-randomised controlled trials. Follow-up periods ranged from 21 months to 4 years.<br><br>One trial was funded by the toothpaste company providing the toothpaste for the trial. The funding sources of the remaining three trials was not reported. |
| **Types of studies included** | The review authors four randomised and quasi-randomised trials: Al-Jundi (2006), Hilgert (2015), Pieper (2016), and Spears (1978).<br><br>HRB excluded the findings from one trial due to the uncertainty of the results (Al-Jundi 2006). The review authors could not determine how the statistical analyses in the primary study were performed; therefore, they recalculated the results based on the raw data provided in the paper. Their findings differed from those reported in the study. |

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| | The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Brazil (1 trial), Germany (1 trial), Jordan (1 trial), and the United States (1 trial). |
| **Appraisal instrument(s)** | The risk of bias was assessed using the Cochrane's Collaboration tool. The following domains were assessed in each included trial:<br>• Random sequence generation<br>• Allocation concealment<br>• Blinding of participants and personnel<br>• Blinding of outcome assessment<br>• Incomplete outcome data<br>• Selective reporting<br>• Diagnosis reliability, and<br>• Baseline balance. |
| **Appraisal rating** | Overall, no included trials had a low risk of bias. All trials were categorised as having a high risk of bias. Blinding of participants and personnel was not feasible due to the nature of the intervention.<br><br>No trials were categorised as having a low risk of bias for randomisation. Two trials were categorised as having an unclear risk of bias for randomisation and two trials were categorised as having a high risk of bias for randomisation.<br><br>One trial was categorised as having a low risk of bias for outcome ascertainment. Two trials were categorised as having an unclear risk of bias for outcome ascertainment and one trial was categorised as having a high risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | No meta-analysis was performed due to substantial clinical heterogeneity among the included studies and differences in the reporting of data that prevented the calculation of pooled estimates.<br><br>Results were instead described narratively. |
| **Outcome(s) assessed** | Primary outcome 1: Proportion of caries-free children / proportion who developed new carious lesions |

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| | Primary outcome 2: Number of decayed, missing and filled teeth (dmft/DMFT)<br><br>Primary outcome 3: Number of decayed, missing and filled surfaces (dmfs/DMFS)<br><br>Primary outcome 4: Cumulative survival rates<br><br>*Note*. The overall outcome in the review is the incidence of caries at dentine level in primary or permanent dentition assessed by any caries index. For the HRB's purposes, the four above measures of caries incidence were extracted as primary outcomes. |
| **Results/findings** | **Primary outcome 1: Proportion of caries-free children**<br><u>Comparison 1: Supervised toothbrushing + 500 ppm fluoride toothpaste versus oral hygiene instruction:</u><br>One trial found the proportion of caries-free children in the intervention group to be 68.3% and in the control group to be 64% at 27-29 months follow-up (**primary dentition**). A P value was not provided. Families in both the intervention and control groups were supplied with free toothbrushes and toothpaste. This intervention in this trial consisted of intensive daily dental hygiene in kindergartens provided by special personnel with 500 ppm F toothpaste. The control group received instruction for cleaning the teeth, three to four times a year. All families were supplied with free toothbrushes and toothpaste.<br><br>The results from another trial reported that the proportion of caries-free children in the intervention group (14.0%) was significantly higher than in the control group (9.4%) at 4 years follow-up (**primary dentition**). The intervention in this second trial consisted of 30-min oral hygiene instruction sessions + practical demonstration + application of toothbrushing technique on five consecutive school days and repeated twice a year by a dental hygienist and a research assistant + daily school-supervised toothbrushing by a research assistant with 500 ppm (6.3-year-olds) or 1000 ppm F toothpaste (11.7-year-olds). The comparison group received 30-min oral hygiene instruction sessions on five consecutive school days and repeated twice a year by a dental hygienist and a research assistant.<br><br><u>Comparison 2: Supervised toothbrushing + 1000 ppm fluoride toothpaste versus oral hygiene instruction:</u><br>One trial (the same trial as the previous result reported) reported that the proportion of caries-free children in the intervention group (43.6%) was significantly higher than in the control group (33%) at 4 years follow-up (**permanent dentition**). |

Comparison 3: Daily school-supervised toothbrushing with non-active toothpaste versus no intervention:
No trials included in the review made this comparison for this outcome.

Comparison 4: Daily school-supervised toothbrushing + 1000 ppm fluoride toothpaste versus no intervention:
No trials included in the review made this comparison for this outcome.

**Primary outcome 2: Number of decayed, missing/extracted and filled teeth (d(m/e)ft/DMFT)**
Comparison 1: Supervised toothbrushing + 500 fluoride toothpaste versus oral hygiene instruction:
The same trial as in primary outcome 1 (comparison 1) found the mean dmft increment to be lower in the intervention group compared to the control group at 27-29 months follow-up (MD -0.21, p = 0.043).

Comparison 2: Supervised toothbrushing + fluoride toothpaste versus oral hygiene instruction:
The results from the second trial as in primary outcome 1 indicated significantly lower deft scores (SD) post-intervention in the intervention group (4.6 (3.2)) compared to the control group (5.25 (3.2), P = 0.001) at 4 years follow-up. The intervention group in this trial received 500 ppm fluoride toothpaste.

The results from the second trial as in primary outcome 1 also indicated significantly lower DMFT scores (SD) post-intervention in the intervention group (1.7 (1.9)) compared to the control group (2.0 (1.9), P = 0.001) at 4 years follow-up. The intervention group in this trial received 1000 ppm fluoride toothpaste.

Comparison 3: Daily school-supervised toothbrushing with non-active toothpaste versus no intervention:
One trial found the incremental change in DMFT in the test group to be 0.92 and in the control group to be 0.93 at 21 months follow-up. No p value was provided as no statistical approach was used to compare the results because, according to the authors, the differences observed were deemed to be of no significance.

Comparison 4: Daily school-supervised toothbrushing + 1000 ppm fluoride toothpaste versus no intervention:
No trials included in the review made this comparison for this outcome.

**Primary outcome 3: Number of decayed, missing and filled surfaces (dmfs/DMFS)**
Comparison 1: Supervised toothbrushing + 500 fluoride toothpaste versus oral hygiene instruction:

The same trial as in primary outcome 1 (comparison 1) found the mean dmfs increment to be lower in the intervention group compared to the control group at 27-29 months follow-up (MD -0.47, p = 0.042).

Comparison 2: Supervised toothbrushing + 1000 ppm fluoride toothpaste versus oral hygiene instruction, permanent teeth:
No trials included in the review made this comparison for this outcome.

Comparison 3: Daily school-supervised toothbrushing with non-active toothpaste versus no intervention:
The same trial as in primary outcome 2 (comparison 3) found the incremental change in DMFS in the test group to be 1.55 and in the control group to be 1.18 at 21 months follow-up. No p value was provided as no statistical approach was used to compare the results because, according to the authors, the differences observed were deemed to be of no significance.

Comparison 4: Daily school-supervised toothbrushing + 1000 ppm fluoride toothpaste versus no intervention:
No trials included in the review made this comparison for this outcome.

**Primary outcome 4: Cumulative survival rates**
Comparison 1: Supervised toothbrushing + 500 fluoride toothpaste versus oral hygiene instruction:
No trials included in the review made this comparison for this outcome.

Comparison 2: Supervised toothbrushing + 1000 ppm fluoride toothpaste versus oral hygiene instruction, permanent teeth:
No trials included in the review made this comparison for this outcome.

Comparison 3: Daily school-supervised toothbrushing with non-active toothpaste versus no intervention:
No trials included in the review made this comparison for this outcome.

Comparison 4: Daily school-supervised toothbrushing + 1000 ppm fluoride toothpaste versus no intervention, **permanent** dentition:
Results from one trial showed that the cumulative survival rate of occlusal first permanent molar surfaces with no dentine caries was 94.8% in the test group and 92.1% in the control group at 3 years follow-up (p = 0.43). No information regarding the increment of caries or the proportion of children who developed new caries lesions in both groups was available in this trial.

*Note*. Sample sizes were not reported in the review. While participants in the control group did not receive the intervention, they did receive an oral hygiene kit containing a toothbrush, a 1000 ppm fluoride toothpaste, plaque-disclosing toothpaste and dental floss. They were instructed on how to use these devices and were encouraged to brush their teeth twice daily.

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| **Significance/direction** | There is no conclusive evidence regarding the effectiveness of supervised toothbrushing on caries incidence.<br><br>The review found conflicting results regarding the effects of supervised toothbrushing on caries incidence. Among the four included studies, two reported (but only one of these actually showed) some beneficial effect of providing children with school-supervised toothbrushing.<br><br>There is no conclusive evidence that supervised toothbrushing increases the anticaries benefit provided by F toothpastes. For supervision during toothbrushing to be widely recommended and adopted, high-quality trials with proper control groups should confirm whether caries could be reduced further by supervising children when they are brushing their teeth with F toothpaste. |
| **Heterogeneity** | No meta-analysis was performed due to the clinical heterogeneity among the included studies and differences in the reporting of data. The review authors stated that there was great variation regarding children's age, fluoride content of the toothpaste, baseline caries levels and the way caries incidence was reported.<br><br>No meta-analysis was performed due to substantial clinical heterogeneity among the included studies and differences in the reporting of data that prevented the calculation of pooled estimates. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Figuero *et al.* (2017) |
| **First Author and year of publication** | Figuero *et al.* (2017) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systemically health patients (pS117).<br><br>To report the evidence on the effect of mechanical and/or chemical plaque control in the simultaneous management of gingivitis and caries (pS116).<br><br>*Note*. Some results presented in the text of this review are not consistent with results presented in the review tables. This, in addition to the limited |

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| | information provided in the review regarding the nature of the interventions and the findings, has resulted in the HRB not using this review in the evidence synthesis. |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (mixed); topical fluoride, toothpaste, mouthrinses; topical other chemicals, CHX; combined intervention.<br><br>The population of interest was systemically healthy patients.<br><br>The age of participants at baseline ranged from 3 to 61 years. However, schoolchildren aged 6 to 16 years were the most frequently selected populations in the included studies.<br><br>The sample size at baseline for both test and control groups ranged from 16 to 574 participants. The corresponding values for the final examinations were from 16 to 383 participants. The total number of participants included was 4,880.<br><br>Of the 12 studies that reported gender, 11 studies included both females and males, and one study included females only.<br><br>Of the total studies, two were excluded from consideration for this review due to nature of their study design, one was excluded due to the nature of the intervention, and two were excluded due to the nature of the outcomes. The number of participants in the included studies was 4,418. |
| **Setting/context** | The studies were conducted in Brazil (2 studies), Denmark (2 studies), Germany (2 studies), Greece (1 study), Norway (2 studies), Russia (1 study), Sweden (9 studies), Switzerland (1 study), Tanzania (2 studies), the UK (3 studies), and the United States (2 studies).<br><br>Twenty studies were conducted in a university, three studies were conducted within a public health service, and two studies were conducted in a private practice. One study took place in both a public health service and university and one study took place in a both a private practice and university. |
| **Description of Interventions/ phenomena of interest** | The interventions of interest were (i) mechanical plaque control procedures with or without the additional use of fluoride and/or (ii) chemical plaque control formulations adjunctive to oral hygiene procedures with or without prophylaxis. The comparison group was any mechanical or chemical plaque control regime (positive control) or placebo (negative control) or no control regime.<br><br>In the included studies, the specific interventions being evaluated were:<br><u>Mechanical plaque control:</u> |

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| | 1. Professional tooth-cleaning (e.g., flossing, prophylactic paste, topical fluorides)<br>2. Motivational programmes and oral health instructions (e.g., supervised toothbrushing)<br>3. Self-performed tooth-cleaning (e.g., toothbrushing)<br><br><u>Chemical plaque control:</u><br>4. Chlorhexidine (mouth rinses, gels, toothpastes)<br><br>Under the motivational programmes and oral health instructions intervention group, one trial was evaluating the effect of experimental oral hygiene education. This was not an intervention of interest to HRB and therefore the findings were therefore excluded from extraction (Angelopoulou, 2015). |
| **Databases and sources searched** | The review authors searched the following sources:<br>• MEDLINE via PubMed,<br>• Cochrane Central Register of Controlled Trials.<br><br>A protocol registration number was not provided; however, the review authors mentioned a protocol was developed in advance of the conduction of the review.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved by discussion and, where necessary, consultation with a third review author.<br><br>The review was self-funded by the ETEP (Etiology and Therapy of Periodontal Diseases) Research Group, University Complutense, Madrid, Spain, and by the Catholic University of Louvain (UCL), Faculty of Medicine and Dentistry, Brussels, Belgium and by the University of Campinas (UNICAMP), Piracicaba Dental School, Piracicaba, Brazil.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 27 included studies were published between 1973 and 2015. |
| **Number of primary studies included in the systematic review** | The review authors included 27 studies (reported in 32 publications). Of these, 15 were randomised controlled trials, 10 were clinical controlled trials, and two were prospective case series. The case series did not fit the inclusion criteria for this umbrella review and the findings therefore were excluded from extraction (Petersen 1989 and Chambrone 2011). Of the |

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| | clinical trials, 24 had a parallel-group design and one had a split-mouth design. Follow-up periods ranged from 3 to 240 months.<br><br>Of the clinical trials, twelve trials received public funding, three trials received industry funding, one trial received both public and industry funding, and one trial was self-funded. The funding source of the remaining eight trials was unclear. |
| **Types of studies included** | The review authors included 27 studies (reported in 32 publications): Chambrone (2011), Petersen (1989), Lindhe (1973), Axelsson (1974), Lindhe (1975), Axelsson (1977), Hamp (1978), Kjaerheim (1980), Ashley (1981), Klimek (1985), Ekstrand (2000), Hamp (1982), Hamp (1984), Horowitz (1976), Horowitz (1977), Horowitz (1980), Axelsson (1981), Alexlsson (1975), Zickert (1982), Fischman (1977), Melsen (1980), van Palenstein Helderman (1997), Zanin (2007), Mbawalla (2013), Angelopoulou (2015), Willershausen (2001), Murray (1980), Andlaw (1975), Lang (1982), Johanssen (1975), Axelsson (1976), and Emilson (1982).<br><br>The results of 24 studies (reported in 29 publications) were relevant to the objectives of this umbrella review: Lindhe (1973), Axelsson (1974), Lindhe (1975), Axelsson (1977), Hamp (1978), Kjaerheim (1980), Ashley (1981), Klimek (1985), Ekstrand (2000), Hamp (1982), Hamp (1984), Horowitz (1976), Horowitz (1977), Horowitz (1980), Axelsson (1981), Alexlsson (1975), Zickert (1982), Fischman (1977), Melsen (1980), van Palenstein Helderman (1997), Zanin (2007), Mbawalla (2013), Willershausen (2001), Murray (1980), Andlaw (1975), Lang (1982), Johanssen (1975), Axelsson (1976), and Emilson (1982).<br><br>A list of excluded studies and the reasons for exclusion were provided in an appendix. |
| **Country of origin of included studies** | The studies were conducted in Brazil (2 studies), Denmark (2 studies), Germany (2 studies), Greece (1 study), Norway (2 studies), Russia (1 study), Sweden (9 studies), Switzerland (1 study), Tanzania (2 studies), the UK (3 studies), and the United States (2 studies).<br><br>The relevant studies were conducted in Brazil (1 study), Denmark (1 study), Germany (2 studies), Norway (2 studies), Russia (1 study), Sweden (9 studies), Switzerland (1 study), Tanzania (2 studies), the UK (3 studies), and the United States (2 studies). |
| **Appraisal instrument(s)** | Two review authors carried out the quality assessment. Disagreements were resolved by discussion until a consensus was reached. The Cochrane Collaboration's risk of bias tool was employed to assess the risk of bias in the included randomised controlled trials and controlled clinical trials. The following domains were assessed in each included trial: |

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| | • Random sequence generation<br>• Allocation concealment<br>• Blinding of participants and personnel<br>• Blinding of outcome assessment<br>• Incomplete data outcome<br>• Reporting bias, and<br>• Other potential sources of bias (e.g. funding)<br><br>The Newcastle-Ottawa Scale was used to assess the risk of bias in observational studies.<br><br>The quality of assessment for each intervention was rated into high, moderate, low, and very low level of evidence, according to Needleman *et al.* (2005). |
| **Appraisal rating** | The overall risk of bias of the included trials was not provided. However, based off information presented in an appendix, it appeared none of the clinical trials had an overall low risk of bias. It appeared eleven trials had an unclear risk of bias, and the remaining fourteen trials had a high risk of bias.<br><br>Two trials were categorised as having a low risk of bias for randomisation, six trials were categorised as having a high risk of bias for randomisation, and 17 trials were categorised as having an unclear risk of bias for randomisation.<br><br>Nineteen trials were categorised as having a low risk of bias for outcome ascertainment, two trials were categorised as having a high risk of bias for outcome ascertainment, and four trials were categorised as having an unclear risk of bias for outcome ascertainment.<br><br>Publication bias was evaluated using the Egger's linear regression method. There was no evidence of publication bias among the included studies for the main common outcome (standardised plaque). |
| **Method of analysis** | Mean values of all outcomes were directly pooled with weighted mean differences and 95% confidence intervals. In the case of plaque, due to the high variability of indexes found in the litera ture, standardized weighted mean differences were calculated (difference in the mean outcome between groups/standard deviation of outcome among participants). Study-specific estimates were pooled, and the random-effect model results were presented. STATA intercooled software was used to perform all analyses. Statistical significance was defined as a $p < 0.05$.<br><br>The statistical heterogeneity among studies was assessed using the Q test as well as the $I^2$ index. STATA (StataCorp LP, Lakeway Drive, College Station, TX, |

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| | USA) intercooled software was used to perform all analyses. Statistical significance was defined as a p <0.05.<br><br>A sensitivity analysis of the meta-analysis results was performed. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment<br><br>Secondary outcome 1: Plaque levels<br><br>*Note*. The nature of primary outcome 1 in the review (primary or secondary) is not explicitly stated, although the wording of the text could imply it is a secondary outcome. For the HRB's purposes, it is considered a primary outcome. Secondary outcome 1 is identified as the primary outcome of the review, but for the HRB's purposes it is considered a secondary outcome. |
| **Results/findings** | **Meta-analyses**<br><br>**Secondary outcome 1: Plaque levels**<br>Comparison 1: Professional tooth cleaning + oral health instruction versus unspecified control:<br>Analyses showed plaque levels were lower in those that received professional tooth cleaning + oral health instruction compared to the control group (WMD 1.29, 95% CI 0.45 to 2.14, p = 0.003; 4 trials; 2,351 participants; $I^2$ = 68.5%; moderate certainty of evidence).<br><br>Comparison 2: fluoride applications (toothpastes and rinses, containing sodium fluoride and monofluorophosphate) versus unspecified control:<br>Analyses showed no difference in plaque levels from those that received fluoride applications compared to those in the control group (WMD 0.15, 95% CI -0.14 to 0.43, p = 0.323; 4 trials; 935 participants; $I^2$ = 82.7%; moderate certainty of evidence).<br><br>**Primary outcome 1: Caries increment**<br>Comparison 1: Professional tooth cleaning + oral health instruction versus unspecified control:<br>No trials using this comparison reported on caries increment.<br><br>Comparison 2: fluoride applications (toothpastes and rinses, containing sodium fluoride and monofluorophosphate) versus unspecified control:<br>Analyses showed caries increment was significantly lower in the test group compared to the control (WMD 1.16; 95% CI 0.15 to 2.17, p = 0.025; 5 trials; 2,641 participants; $I^2$ = 83.7%; moderate certainty of evidence).<br><br>**Descriptive results**<br>There are 26 individual comparisons, all listed narratively below. |

**Secondary outcome 1: Plaque levels**

Comparison 1: Professional tooth cleaning (5% monoflurophosphate (MFP) prophylactic paste) + flossing versus toothbrushing with 0.2% sodium fluoride (NaF) solution + mouthrinsing with 0.2% NaF solution:

Six controlled trials (total participants = 1968, all permanent dentition) from Scandinavian countries reported significant reductions in plaque scores at the end of study periods ($p < 0.001$) (Lindhe 1973, Axelsson 1974, Lindhe 1974, Axelsson 1977, Hamp 1978, Kjaerheim 1980) (limited information available).

Comparison 2: Professional tooth cleaning (5% monoflurophosphate (MFP) prophylactic paste) + flossing versus no intervention:

Two trials, one conducted in Germany and the other in Russia (total participants = 862, mixed dentition) reported both significant (Ekstrand 2000: $p < 0.001$) and non-significant differences in plaque scores at the end of the study periods. (Klimek 1985 and Ekstrand 2000) (limited information available).

Comparison 3: Professional tooth-cleaning (fluoride-free prophylactic paste) versus oral hygiene instructions:

One trial in the UK using schoolchildren (total participants = not reported, all permanent dentition) reported significant reductions in plaque score at the end of the intervention ($p < 0.001$) (Ashley 1981) (limited information available).

Comparison 4: Professional tooth-cleaning (with fluoride toothpaste or mouthrinse) OR professional tooth-cleaning followed by fluoride varnish application versus each other, and by frequency of treatment:

In one trial (total participants = 290, all permanent dentition) when the intervals of professional tooth-cleaning increased from once a month to once every 3 months in test groups did not report any significant differences in plaque scores (Zickert 1982) (limited information available).

Comparison 5: Professional tooth-cleaning (with fluoride toothpaste and mouthrinse) versus fluoride mouthrinse alone:

In one trial (total participants = 146, all permanent dentition), professional tooth-cleaning performed every 3 weeks, every month, or every 6 months had significant effects on plaque scores over a 3-year period ($p < 0.001$) (Hamp 1982) (limited information available).

Comparison 6: Professional tooth-cleaning (with fluoride toothpaste and mouthrinse) versus fluoride varnish:

In one trial (total participants = 132, all permanent dentition), professional tooth-cleaning intervals according to the individual needs did not have a significant effect on plaque scores compared to fluoride varnish treatment every 6 months (Hamp 1984) (limited information available).

Comparison 7: Professional tooth-cleaning (0.4% monoflurophosphate (MFP) and 0.1% sodium fluoride (NaF) prophylactic paste) + oral health instruction or not combined with oral health instruction (no comparator):

One trial (total participants: 104, mixed dentition) reported no significant differences in plaque scores (Axelsson 1981) (limited information available).

Comparison 8: Motivation programmes/oral health instruction (individualized supervised toothbrushing) versus control group:

Three trials reported on this comparison (total participants = 1410, all permanent dentition). One showed a significant difference in plaque scores in the test group compared to control in one trial (Horowitz 1980: Group 1 MD = -0.88 (0.63) ($p < 0.01$), Group 2 MD = 0.30 (0.74) (not significant)), but there was no improvement in plaque scores in the other two trials (Horowitz 1976: MD = 0.06 (0.82) (not significant), Horowitz 1977: MD = 0.0 (0.63) (not significant)) (Horowitz 1976, 1977, 1980) (limited information available).

Comparison 9: Motivation programmes/oral health instruction (supervised toothbrushing) versus N/A (no control group):

One trial involving children in Tanzania from a low socioeconomic background (total participants = 550, all permanent dentition) reported no significant difference in the outcome of plaque scores (MD = -4.3 (2.5) (not significant)) (Van Palenstein Helderman 1997) (limited information available).

Comparison 10: Motivational programmes/oral health instruction + topical fluoride/fluoride rinses versus:

"The addition of topical fluoride application or fluoride rinses had no effect either on plaque or gingival scores, or on caries increment (Fischman et al. 1977, Melsen & Agerbaek 1980)."

Two trials (total participants = 164+, all permanent dentition) reported no significant effect on plaque scores (Fischman 1977 and Melsen 1980) (limited information available).

Comparison 11: Manual self-performed toothbrushing (0.8% monoflurophosphate (MFP) toothpaste) versus manual self-performed toothbrushing (non-fluoride toothpaste):

Trials (total participants: 1799, all permanent dentition) reported no significant differences in plaque scores, with contradictory results (Murray 1980 and Andlaw 1975) (limited information available).

Comparison 12: Mouth rinse (0.1% or 0.2% chlorhexidine (CHX)) versus placebo:

One trial (total participants = 232, all permanent dentition), involving children took place over 6 months, reported significant reductions in plaque scores compared to the control group ($p < 0.05$) (Lang 1982) (limited information available).

Comparison 13: Professional tooth-cleaning + toothpaste (0.4% or 1% chlorhexidine (CHX)) versus placebo:

One trial involving dental students (total participants = 58, dentition not reported) found no significant differences in plaque scores between the groups (Johanssen 1975) (limited information available).

Comparison 14: Gel (0.5% chlorhexidine (CHX)) + rinse (2% monoflurophosphate (MFP) solution) versus gel (0.5% chlorhexidine (CHX)) + toothpaste (0.8% monoflurophosphate (MFP)):

Two trials (total participants = 588, all permanent dentition) reported no significant differences in plaque index, except for in one test group for Emilson 1982 (Axelsson 1976 and Emilson 1982) (limited information available).

**Primary outcome 1: Caries increment**

Comparison 15: Professional tooth cleaning (5% monoflurophosphate (MFP) prophylactic paste) + flossing versus toothbrushing (0.2% sodium fluoride (NaF) solution) + mouthrinsing (0.2% NaF solution):

Six trials from Scandinavian countries (total participants = 1969, all permanent dentition) reported significant differences in caries increment (Lindhe 1973: not reported, Axelsson 1974: Group 1 MD = 0.27 Group 2 MD = 0.27 Group 3 MD = 0.17, Lindhe 1975: Group 1 MD = 0.33 Group 2 MD = 0.54 Group 3 MD = 0.5, Hamp 1978: MD = 5.9, Kjaerheim 1980: Group 1 MD = 0.22 Group 2 MD = 0.29 Group 3 MD = 1.32) ($p < 0.001$) in all but Axelsson 1977 at the end of the study periods (Lindhe 1973, Axelsson 1974, Lindhe 1974, Axelsson 1977, Hamp 1978, Kjaerheim 1980) (limited information available).

Comparison 16: Professional tooth cleaning (5% monoflurophosphate (MFP) prophylactic paste) + flossing versus no intervention:

Two trials, one conducted in Germany and the other one in Russia (total participants = 862, mixed dentition) reported significant reduction in caries increment (Klimek 1985: MD = 2.71, Ekstrand 2000: not reported) ($p < 0.001$) at the end of the study periods (Klimek 1985 and Ekstrand 2000) (limited information available).

Comparison 17: Professional tooth-cleaning (fluoride toothpaste/rinse) OR professional tooth-cleaning followed by fluoride varnish application versus each other and by frequency of treatment (once every 2 weeks up to once every year):

A group of trials (total participants = 568, permanent dentition) reported no significant differences in caries increment were observed when the intervals of professional tooth-cleaning increased from once a month to once every 3 months in the test groups (Zickert 1982: Group 1 MD = 0.9 Group 2 MD = 2.5 Group 3 MD = 0.6 (not significant), Hamp 1982: Group 1 MD = 1.0 Group 2 MD = 1.2 Group 3 MD = 2.0 ($p < 0.05$)). Caries increment was not

significantly different for a 6-month interval than for monthly prophylaxis sessions (Hamp 1984: Group 1 MD = 1.3 Group 2 MD = 2.3 (not significant)) (Zickert 1982, Hamp 1982, Hamp 1984) (limited information available).

Comparison 18: Professional tooth-cleaning (0.4% monoflurophosphate (MFP) and 0.1% sodium fluoride (NaF) prophylactic paste) + oral health instruction versus oral health instruction alone:

One trial (total participants: 104, mixed dentition) did not report significant differences in caries increments (Axelsson 1981) (limited information available).

Comparison 19: Motivation programmes + oral health instruction (individualized supervised toothbrushing) versus unspecified control group:

Two trials (total participants = 1137, mixed dentition) reported no significant differences in caries increment in the test groups (Zanin 2007: MD = 8, Mbwalla 2013: MD = 0.7 (not significant)) compared to the control groups (Zanin 2007 and Mbwalla 2013) (limited information available).

Comparison 20: Motivation programmes + oral health instruction (supervised toothbrushing) versus N/A (no control group):

One trial involving childrenin Tanzania from a low socioeconomic background (total participants = 550, all permanent dentition) reported no significant differences in the outcome of caries increment (Van Palenstein Helderman 1997) (limited information available).

Comparison 21: Motivational programmes/oral health instruction + topical fluoride/fluoride rinses versus:

Two trials (total participants = 164+, all permanent dentition) reported no significant differences (Fishman 1977: not reported, Melsen 1980: Group 1 MD = 2.85 Group 2 MD = 1.83 (not significant)) on caries increment (Fishman 1977 and Melsen 1980) (limited information available).

Comparison 22: Manual self-performed tooth-cleaning versus powered toothbrush self-performed tooth-cleaning:

One trial (total participants = 130, all permanent dentition) reported that there were no significant differences in caries increment in children (Willerhausen 2001) (limited information available).

Comparison 23: Manual self-performed toothbrushing (0.8% monoflurophosphate (MFP) toothpaste) versus manual self-performed toothbrushing (non-fluoride toothpaste):

Trials (total participants: 1799, all permanent dentition) reported significant reductions in caries increment (Murray 1980: Group 1 MD = 4.22 Group 2 MD = 4.72, Andlaw 1975: MD = 7.14 ($p < 0.001$)) for the test group (Murray 1980 and Andlaw 1975) (limited information available).

Comparison 24: Mouth rinse (0.1% or 0.2% chlorhexidine (CHX)) versus placebo:

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| | One trial, involving children took place over 6 months (total participants = 232, all permanent dentition) reported no significant differences for caries increment (Lang 1982: Group 1 MD = 0.93 Group 2 MD = 0.71 Group 3 MD = 0.89 (not significant)) between the groups (Lang 1982) (limited information available).<br><br><u>Comparison 25: Professional tooth-cleaning + toothpaste (0.4% or 1% chlorhexidine (CHX)) versus placebo:</u><br><br>One trial (total participants = 58, dentition not reported) involving dental students found no significant differences in caries increment between groups (Johanssen 1975) (limited information available).<br><br><u>Comparison 26: Gel (0.5% chlorhexidine (CHX)) + rinse (2% monoflurophosphate (MFP) solution) versus gel (0.5% chlorhexidine (CHX)) + toothpaste (0.8% monoflurophosphate (MFP)):</u><br><br>Two trials (total participants = 588, all permanent dentition) reported both significant (Axelsson 1976: Group 2 MD = 0.3 Group 3 MD = 0.4 Group 4 MD = 0.3 Group 5 MD = 0.4 Group 6 MD = 0.4, Emilson 1982: Group 1 MD = 1.3 ($p < 0.001$) and non-significant (Axelsson 1976: Group 1 MD = 4.3, Emilson 1982: Group 2 MD = 5.7 Group 3 MD = 8.4 (not significant)) differences in caries index (Axelsson 1976 and Emilson 1982) (limited information available). |
| **Significance/direction** | Reductions in plaque scores may be obtained by mechanical plaque control. The combined use of chemical agents with mechanical plaque control in the management of caries is still limited in evidence. The indication of either intervention<br>should be based on individual needs and risk assessment.<br><br>*Note*. Some results presented in the text of this review are not consistent with results presented in the review tables. This, in addition to the limited information provided in the review regarding the nature of the interventions and the findings, has resulted in the HRB not using this review in the evidence synthesis. |
| **Heterogeneity** | The limited number of studies available for meta-analysis, with some comparisons coming from the same studies, resulted in a high degree of heterogeneity. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the overall certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |

| Parameter | Hendre *et al.* (2017) |
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| **First Author and year of publication** | Hendre *et al.* (2017) |
| **Objectives (exact review question(s) and page number)** | To provide a systematic review of the evidence regarding the effectiveness of silver diamine fluoride in arresting or preventing root caries in older adults (p412).<br><br>*Note*. The HRB is only interested in the findings on prevention and so excluded the caries arrest aspect of this study. |
| **Participants (characteristics and numbers)** | Permanent dentition; combined intervention.<br><br>The population of interest was adulted aged 18 years or older either institutionalised or living in a community dwelling.<br><br>The three included trials involved a total of 655 participants, and approximately 541 were evaluated in analyses. The mean age of participants in two of the included trials was 72.2 years 78.8 years. In the other trial, the age of participants ranged from 60 to 89 years.<br><br>The total number of participants in the two (out of 3) included trials that inform this umbrella review was 572 at baseline, and the total number evaluated was 474.<br><br>Information pertaining to the sex of participants in the included trials was not provided. |
| **Setting/context** | All three included trials were conducted in Hong-Kong.<br><br>One trial was conducted in residential and nursing homes, and two trials were conducted in community-dwelling centres. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was the effect of silver diamine fluoride (SDF) on root caries compared to other preventive agents or placebo.<br><br>Three trials were included in the review; however, only two trials informed the outcomes that were of interest to this umbrella review.<br><br>Of these two trials, one investigated the effect of 38% silver diamine fluoride. The effectiveness of annual application of SDF was compared with four quarterly applications of 5% sodium fluoride varnish (NaF), 1% chlorhexidine varnish (CHX) and a placebo. Each group received oral hygiene instruction (OHI). |

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| | The second trial also investigated the effect of annual application of SDF. Participants in this trial were randomly assigned to three groups who received one of the following:<br>1. Annual application of 38% SDF on root caries and on sound exposed root surfaces with oral hygiene instruction (SDF + OHI) (*Note*. For the purposes of this review the caries arrest aspect was excluded)<br>2. SDF application and oral hygiene instruction supplemented with tailored biannual oral hygiene education (SDF + OHI + OHE), and<br>3. Oral hygiene instruction and placebo, the control group. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• PubMed Clinical Queries<br>• EMBASE<br>• American Dental Association's Evidence-Based Dentistry Website<br>• Cochrane library<br>• Web of Science<br>• Journal of the American Dental Association repository, and<br>• Google Scholar.<br>These sources were searched for articles published from 1946 to November 2015. Monthly reruns of search terms in PubMed were conducted through August 2016. Bibliographies of the selected manuscripts were subsequently hand-searched. Language was restricted to English.<br><br>It was not reported how screening and data extraction were performed.<br><br>There was no mention of a protocol being prepared or published.<br><br>The review was supported by an unrestricted honorarium from the American Dental Association's National Elder Care<br>Advisory Committee (NECAC) of the Council on Access, Prevention and Interprofessional Relations (CAPIR).<br><br>Conflicts of interest were not reported. |
| **Date range (years) of included studies** | The included trials were published in 2010, 2013, and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included three randomised controlled trials. The duration of the trials were 2 years, 30 months, and 3 years. The relevant included trials lasted for 2 years and 3 years. |

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| | The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included three randomised controlled trials: Tan (2010), Zhang (2013), and Li (2016).<br><br>The results of two trials informed the outcomes that were of interest to this umbrella review: Tan (2010) and Zhang (2013).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | All three included trials were conducted in Hong- Kong. |
| **Appraisal instrument(s)** | The critical appraisal worksheet for randomised controlled trials from the Oxford Centre for Evidence-based Medicine (CEBM 2005) provided the framework to assess the quality and risk of bias of the selected articles. All four authors recorded their findings in an assessment table and discussed disagreements until achieving consensus. The appraisal worksheet was slightly modified: Question 3b was added to the therapy appraisal for clinical trials to gauge inter-examiner calibration. |
| **Appraisal rating** | Using the quality assessment framework, one trial met all CEMB criteria while two trials met 8 out of the 9 criteria. The review authors stated all three trials exhibited a low degree of bias.<br><br>All three trials were categorised as having a randomised assignment of subjects. In addition, all three trials had a double-masked (blinded) study design.<br><br>Publication bias was not measured. |
| **Method of analysis** | Results were described narratively. |
| **Outcome(s) assessed** | Primary outcome 1: Caries prevention: mean number of new root caries surfaces and root surfaces prevented fractions<br><br>*Note*. The overall outcome in the review is the prevention of root caries in older adults assessed by several caries indices. For the HRB's purposes, the above measure was extracted as the primary outcome as reported in the trials relevant to this umbrella review. |
| **Results/findings** | **Primary outcome 1: Mean number of new root caries surfaces and root surfaces prevented fractions**<br>Trial one (Tan 2010): OHI + water (control group) versus OHI + CHX (group 2 – intervention group) versus OHI + NaF (group 3 - intervention group) versus OHI + SDF (group 4 – intervention group |

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| | All three intervention groups had significantly lower mean number of new root caries surfaces than the control group at 3 years follow-up ($p < 0.001$). The mean number of new root caries surfaces, compared to the control group, was 0.70, 0.90, and 1.10 for SDF, NaF and CHX varnish, respectively. The prevented fraction calculated, compared to placebo and oral health instruction, was 71%, 64%, and 57% for 38% SDF varnish (annual application), 5% NaF varnish (four quarterly) and 1% CHX varnish, respectively, at 3 years follow-up ($p < 0.001$; 1 trial; 203 participants).<br><br>The number needed to treat for preventing new caries was 2.5, 3.1 and 3.2 for SDF, NaF and CHX varnish, respectively.<br><br><u>Trial two (Zhang 2013): OHI + placebo (water) (group 1 – control) versus OHI + SDF (group 2 – intervention) versus OHI + SDF + OHE (group 3 – intervention)</u><br>This trial involved OHI + placebo (control), annual application of 38% SDF on sound exposed root surfaces + OHI, and annual application of 38% SDF on sound exposed root surfaces + OHI + tailored biannual OHE.<br><br>The mean number of new root caries surfaces were 0.70, 1.00 and 1.33, respectively, for the (SDF + OHI + OHE), (SDF + OHI) and (OHI + P) groups ($P < 0.05$). The prevented fraction calculated was 25% for (SDF + OHI) group and 47% for (SDF + OHI + OHE) group, using the control group as the reference group.<br><br>SDF + OHI had a significantly better effect on prevention of root caries than OHI alone ($p < 0.05$; 1 trial; 227 participants). In addition, more improvement was seen by adding OHE to SDF + OHI ($p < 0.05$).<br><br>For number needed to treat, to prevent one new root caries surface, the (SDF + OHI) and (SDF + OHI + OHE) groups required treating of 3.03 and 1.59 patients, respectively. |
| **Significance/direction** | Available evidence supports the use of silver diamine fluoride for the prevention of root caries in older adults. |
| **Heterogeneity** | No meta-analyses were conducted. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as moderate. |
| **References to previously published versions** | N/A |
| Parameter | Hujoel (2013) |

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| **First Author and year of publication** | Hujoel (2013) |
| **Objectives (exact review question(s) and page number)** | To conduct a systematic review of controlled clinical trials (CCTs) assessing the impact of vitamin D on dental caries prevention. |
| **Participants (characteristics and numbers)** | Permanent and primary teeth (mixed); other systemic chemicals, vitamin D.<br><br>There were no restrictions on participant characteristics.<br><br>The 24 included trials involved a total of 2,827 children and young adults.<br><br>The age of participants ranged from 2 years to 16 years, with a weighted mean age of 10 years.<br><br>Fifteen trials enrolled both females and males, four trials enrolled either exclusively females or males, and five trials did not specify the gender enrolled.<br><br>Caries counts were reported at patient level in one trial, at tooth level in ten trials, and at surface level in 13 trials. The caries data were based on permanent teeth in 11 trials, primary teeth in 2 trials, permanent and primary teeth in 8 trials, and unspecified teeth in 3 trials. |
| **Setting/context** | The trials were conducted in Austria (1 trial), Canada (4 trials), New Zealand (1 trial), Sweden (1 trial), the United Kingdom (6 trials), and the United States (11 trials).<br><br>Thirteen trials were conducted in institutional settings, five trials were conducted in school-based settings, four trials were conducted in hospital-based settings, and two trials were conducted in practice-based settings. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was vitamin D. The 24 included trials reported a total of 28 vitamin D efficacy estimates: 17 vitamin $D_3$ efficacy estimates (median dose 800 IU), 15 vitamin $D_2$ estimates (median dose 3,750 IU) and 6 UV radiation estimates (4 delivering erythemal doses, 2 using full-spectrum fluorescent lighting).<br><br>The control intervention most closely approximating a placebo was selected for estimating vitamin D efficacy. For instance, “milk” or “olive oil” was selected for estimating the efficacy of “milk-vitamin D mixtures” or “cod-liver oil,” and not a “no-milk” or “treacle” control group.<br><br>Trial duration lasted from 6 to 36 months. “The median duration of follow-up was 12 months, and the median sample size was 101 children” p92. |

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| **Databases and sources searched** | The review author searched the following sources:<br>• JSTOR<br>• PubMed<br>• Web of Science, and<br>• Cochrane Central Register of Controlled Trials.<br>Three reference works on dental caries were searched for citations on the topic. There were no date restrictions for the searches.<br><br>There was no a priori protocol or registration of a protocol.<br><br>As there was only one review author, it was presumed screening and data extraction were performed by one individual.<br><br>There were no external funding sources for this review.<br><br>The review author did not declare any conflicts of interest. |
| **Date range (years) of included studies** | The 24 included trials were published between 1924 and 1989. |
| **Number of primary studies included in the systematic review** | The review authors included 24 clinically controlled trials. Eleven trials were randomised at a cluster level and 13 were randomised at an individual level.<br><br>The median duration of follow-up was 12 months, and the median sample size was 101 children.<br><br>Caries counts were reported at patient level in one trial, a tooth level in ten trials, and a surface level in 13 trials.<br><br>Thirteen of the included trials received industry funding. |
| **Types of studies included** | The review authors included 24 clinically controlled trials: Mellanby (1924), Mellanby (1926), McKeag (1930), Hubbell (1932), Schoenthal (1933a), Schoenthal (1933b), Jameson (1933), Day (1934), Anderson (1934), MRC (1936a), MRC (1936b), MRC (1936c), McBeath (1937a), McBeath (1937b), McBeath (1937c), McBeath (1937d), Jundell (1938), Goll (1939), Brodsky (1941), McBeath (1942), Strean (1945a), Strean (1945b), Mayron (1975), and Hargreaves (1989).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | The trials were conducted in Austria (1 trial), Canada (4 trials), New Zealand (1 trial), Sweden (1 trial), the United Kingdom (6 trials), and the United States (11 trials). |

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| **Appraisal instrument(s)** | Quality was quantified using a 21-item questionnaire and content-specific measures such as method of treatment assignment, setting, clinician blinding, use of placebo, commercial funding source, loss to follow-up, and study duration. Biased assignment was defined as present when trial investigators purposefully made the comparison groups different on at least one characteristic, such as baseline caries severity or health awareness. Baseline comparability was assessed based on reported caries prevalence at baseline. A trial was labelled as partially commercially funded if it received vitamin D preparations or UV equipment free, or if investigators were employed by commercial companies. These risk of bias measures were related to treatment effectiveness using the methods described in the Cochrane handbook (Section 9.6.4). |
| **Appraisal rating** | The quality score ranged from 6 to 21, with a mean of 14.8 (standard deviation, 4.0). Common potential sources of bias included the lack of examiner blinding (19 of 24), the lack of placebos (14 of 24), and partial funding by commercial companies (13 of 24). Based off graphical information provided in the review, the quality score break was as follows:<br>• Score of 21 – one trial<br>• Score of 20 – four trials<br>• Score of 18 – one trial<br>• Score of 17 – two trials<br>• Score of 16 – two trials<br>• Score of 15 – four trials<br>• Score of 14 – two trials<br>• Score of 13 – one trial<br>• Score of 12 – three trials<br>• Score of 10 – two trials<br>• Score of 8 – one trial<br>• Score of 6 – one trial<br><br>Random assignment was performed for three trials.<br><br>Publication bias was assessed using the Egger's statistics and a funnel plot. Results suggested the presence of publication bias. The funnel plot was asymmetrical and the statistical measure assessing publication bias was highly significant (Egger's statistic: $P < 0.001$). |
| **Method of analysis** | Relative incidence rates and their naive standard errors were estimated using Poisson regression methods. The numerator of the incidence rate was the sum of the incident caries events. The denominator of the incidence rate was the sum of the time at risk. |

The time at risk for each surface or tooth was calculated as follows for a CCT of t years duration: t years when the surface or tooth remained caries free during the CCT, t/2 years when the tooth or surface erupted during the CCT and remained caries free, t/2 years when the tooth or surface developed a cavity during the CCT, and t/4 years when the surface or tooth erupted during the CCT and developed a cavity before the end of the CCT. When no information was provided on whether caries onsets occurred on erupting or erupted teeth, the caries onsets were assumed to have occurred on erupted teeth.

The number of caries-free surfaces or teeth at baseline was calculated as the difference between the number of erupted and carious surfaces or teeth. For studies in which the number of sound surfaces or teeth at baseline was not reported, it was imputed based on eruption patterns, tooth counts, or caries status at baseline.

To take into account the within-patient correlation of caries onsets, robust standard errors were estimated using one of three methods. For one trial reporting data on individual patients, the robust standard error was estimated using Poisson regression models for correlated data. For trials reporting the necessary data to calculate a mean difference in caries counts (D) and a standard error of the mean difference (SE), the robust standard error ofthe relative rate (RR) was estimated as RR/(D/SE). When the P value associated with D/SE was less than or equal to 0.0001, D/SE was set equal to 4.01 to improve the robustness of the findings.

For trials in which only caries count and no measures of variability were reported, the robust standard error was estimated as the naïve standard error multiplied by a scale factor of 2.1. This scale factor is a number reflecting the magnitude of the within-patient correlation of caries events. The estimate of 2.1 was derived from two large clinical trials in which the typical scale factor for primary teeth and permanent teeth was 1.9 (range, 1.7–2.3) and 2.2 (range, 1.9–3.2), respectively. Differences in baseline caries severity across the compared groups were evaluated using logistic regression models.

Due to the significant heterogeneity in the vitamin D effect sizes, random effect models were used to estimate summary relative risks. The heterogeneity of the studies was evaluated using the Q statistic and the $I^2$ statistic. The trial characteristics specified in the risk of bias section were related to the magnitude of the treatment effect by means of meta-regression models. Following PRISMA guidelines, specific sensitivity and subgroup analyses were performed to assess the robustness of the

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| | conclusions. All analyses were completed using SAS 9.2 and STATA 11.2 meta-analysis software. |
| **Outcome(s) assessed** | Primary outcome 1: Incidence of caries<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Incidence of caries**<br><u>Comparison 1: Any vitamin D supplementation versus unspecified control:</u><br>Overall, pooled data showed supplemental dietary vitamin D and UV radiation to be protective against caries (RR 0.53; 95% CI 0.43 to 0.65, p < 0.0001; 24 trials; 2827 participants).<br><br>The median dose of vitamin D2 supplementation in the included trials was 3,750 IU and the median dose of vitamin D3 was 800 IU. Either erythemal or full-spectrum fluorescent lighting was used in the trials that examined UV radiation.<br><br>Retrospective exploration suggested that biased treatment assignment was a significant determinant of the heterogeneity. The $I^2$ statistic decreased from 72% to 49% when trials with biased treatment assignment were excluded from analysis.<br><br><u>Comparison 2: Vitamin D3 versus no supplement:</u><br>The relative caries risk was significantly lower in those that received dietary vitamin D3 compared to those who received no supplement (RR 0.51, 95% CI 0.40 to 0.65, p < 0.0001; 12 trials; 594 participants).<br><br><u>Comparison 3: Vitamin D2 versus no supplement:</u><br>The relative caries risk was significantly lower in those that received dietary vitamin D2 compared to those who received no supplement (RR 0.64, 95% CI 0.48 to 0.86, p < 0.0031; 15 trials; 675 participants).<br><br><u>Comparison 4: UV therapy versus no therapy:</u><br>The relative caries risk was significantly lower in those that received UV therapy compared to those who received no UV therapy (RR 0.36, 95% CI 0.17 to 0.78, p < 0.0088; 6 trials; 138 participants).<br><br>All relative risks exhibited significant overall heterogeneity (Q = 134.4 on 38 df, p < 0.0001). Deletion of one CCT from the analysis led to significant differences favouring UV therapy and vitamin D3 over vitamin D2.<br><br>Study characteristics that significantly decreased vitamin D effectiveness included low study quality (P < 0.005), conduct of CCT in a school (P < 0.017), biased assignment of vitamin D (P < 0.003), assignment of vitamin D to patients rather than to a cluster of patients (P < 0.041), a mean age over |

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| | 12.5 years (P < 0.050), and trials conducted before 1950 (P < 0.050). Study characteristics that had no impact on vitamin D effectiveness included the use of placebo (P < 0.646), blinding of examiners (P < 0.450), partial commercial funding (P < 0.630), patient dropout (P < 0.811), trial duration (P < 0.200),<br>country of conduct (P < 0.204), dose of daily vitamin D supplementation (P < 0.816), and the delivery of vitamin D with a mineralising diet (P < 0.565). Exclusion of trials with variation in carbohydrate intakes in one of the experimental arms did not impact the overall conclusions of this report. |
| **Significance/direction** | Available evidence suggests that supplemental vitamin D was associated with a 47% reduced risk of caries. No robust differences could be identified between the effects of UV therapy and nutritional supplementation with either vitamin D2 or vitamin D3. Retrospective analyses suggested that vitamin D supplementation was ineffective after the age of 13 years, particularly for girls, suggesting that growth and variations in body fat may influence the effectiveness of the fat-soluble vitamin D in caries prevention. It can be concluded with low certainty (using the criteria for certainty established<br>by the US Physician Services Task Force) that vitamin D in childhood may reduce the incidence of dental caries. |
| **Heterogeneity** | The heterogeneity of the studies was evaluated using the Q statistic and the $I^2$ statistic.<br><br>The relative rate estimates of the 24 CCTs exhibited significant heterogeneity (P < 0.0001). The $I^2$ statistic decreased from 72% to 49% when CCTs with biased treatment assignment were eliminated from analysis. Consequently, limiting the systematic review to high-quality studies led to findings of higher vitamin D effectiveness and less heterogeneity between studies.<br><br>The review authors note that heterogeneity was in part explained by factors such as study setting and age of enrolled children. |
| **Summary for GRADE assessment for HRB report** | It is unclear whether the review authors graded the certainty of evidence. In the conclusion it is stated, “It can be concluded with low certainty (using the criteria for certainty established by the US Physician Services Task Force) that vitamin D in childhood may reduce the incidence of dental caries” (p94).<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Jørgensen *et al.* (2016) |

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| **First Author and year of publication** | Jørgensen *et al.* (2016) |
| **Objectives (exact review question(s) and page number)** | To review and summarise the available literature on the prevention of caries in early childhood through biofilm engineering with probiotic bacteria (p127). |
| **Participants (characteristics and numbers)** | Primary teeth; topical other chemicals, probiotics; combined intervention.<br><br>The seven included trials involved a total of 1,715 children, whose ages ranged from 0 to 6 years. Information pertaining to the sex of included participants was not provided. One trial involved children from a low socioeconomic background.<br><br>The total number of participants in the 2 (out of 7) included trials that inform this umbrella review was 386. |
| **Setting/context** | The seven included trials were published in Sweden, Finland, and Chile.<br><br>Two trials took place in municipal day-care centres. One trial took place in a nursery school. The remaining four trials did not report their setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was any administration route for live probiotic bacteria. The control group received a placebo, no treatment, or best clinical practice.<br><br>Of the seven trials included in the review, only two were relevant to the objectives of this umbrella review.<br><br>The first trial evaluated the effect of daily serving (weekdays) of milk (1.5 dl) containing *Lactobacillus rhamnosus* LB21 on caries incidence over 21 months. In addition, 0.5 ppm fluoride was added to the experimental milk which the control group was given a milk without both fluoride and probiotic bacteria.<br><br>In the second trial, probiotic lozenges containing three streptococcus-derived strains were given to the children. The control group received a placebo. The duration of the intervention was 1 year. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Cochrane Library, and<br>• Trip database. |

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| | The databases were searched through January 2016. Reference lists were hand searched for additional potentially relevant studies.<br><br>Two review authors independently assessed selected articles and performed data extraction. It was not reported how disagreements were resolved.<br><br>There was no mention of a protocol being prepared or published.<br><br>The review was funded by the author's academic institution.<br><br>Two review authors declared no conflicts of interest. Two review authors received tuition fees from the industry to attend an academic institution. |
| **Date range (years) of included studies** | The seven included trials were published 2001 and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included seven double-blinded randomised controlled trials. Of these, two were cluster randomised and five were (presumed to be) individually randomised. Follow-up periods ranged from 7 months to 9 years.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included seven double-blind randomised controlled trials: Taipele (2013), Hasslof (2013), Stensson (2014), Nase (2001), Stecksen-Blicks (2009), Hedayati-Hajikand (2015), and Rodriguez (2016).<br><br>The results of two trials informed the outcomes of interest to this umbrella review: Stecksen-Blicks (2009) and Hedayati-Hajikand (2015).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | The seven included trials were published in Sweden, Finland, and Chile. |
| **Appraisal instrument(s)** | Two authors not involved in the studies independently assessed the quality of the selected publications according to predetermined criteria.<br><br>The criteria of Cochrane handbook for interventions was used and the risk of bias for each paper was graded as "low", "moderate", or "high". The following domains were assessed in each included trial:<br>1. Selection bias<br>2. Performance bias<br>3. Detection bias<br>4. Attrition bias, and |

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| | 5. Reporting bias. |
| **Appraisal rating** | Overall, five of the included trials were assessed as having a high risk of bias, while two were assessed as having a moderate and moderate/low risk of bias. Of the two trials relevant to this umbrella review, two were at high risk of bias.<br><br>The most common concern was high attrition bias, followed by performance bias and selection bias. Thus, the quality of bias was rated as low or very low.<br><br>Two trials were categorised as having a low risk of selection bias, four trials were categorised as having an unclear risk of selection bias, and one trial was categorised as having a high risk of selection bias. Of the two trials relevant to this umbrella review, one was categorised as having a low risk of selection bias and one was categorised as having a high risk of selection bias.<br><br>Four trials were categorised as having a low risk of detection bias, one trial was categorised as having an unclear risk of bias detection bias, and two trials were categorised as having a high risk of detection bias. Of the two trials relevant to this umbrella review, one had a low risk of bias detection bias and one had a high risk of detection bias.<br><br>Publication bias was not measured. |
| **Method of analysis** | Due to heterogeneity and paucity of included studies, a narrative synthesis was performed. The effect size was estimated from the caries prevalence figures and expressed as prevented fraction (control event rate minus the experimental event rate, divided with the control event rate, expressed as percent). The number needed to treat (NNT) was calculated as 1/ARR (absolute risk reduction). |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment (decayed, missing and filled surfaces (dmfs) prevented fraction)<br><br>*Note*. This outcome is identified in the review as presented here (as a primary outcome). |
| **Outcome(s) excluded from umbrella review** | Primary outcome: Development of new cavitated caries lesions.<br><br>This outcome was assessed using the International Caries Detection and Assessment System (ICDAS) classification 5-6. It was not clear whether the review authors assessed progression from non-cavitated caries lesions (e.g. ICDAS 3) to cavitated caries lesions (ICDAS 5-6) or from sound tooth surfaces (ICDAS 0) to cavitated caries lesions. |
| **Results/findings** | **Primary outcome 1: Caries increment** |

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| | <u>Comparison 1: fluoridated milk containing Lactobacillus rhamnosus versus non-fluoridated milk without probiotic bacteria:</u><br>The caries increment of decayed, extracted and filled surfaces was significantly reduced in the test group (dmfs = 0.3) compared to the control group (dmfs = 1.6) at 21 months follow-up ($p < 0.05$; 1 trial; 248 participants). In addition, the proportion of caries-free children was 77% in the test group compared with 56% in the control group. The fluoridated / non-fluoridated milk was consumed 5 days/week over 21 months.<br><br><u>Comparison 2: Streptococcus-based probiotic lozenges versus placebo:</u><br>There were significantly fewer new caries lesions (ds 0.2) in the probiotic group compared with the placebo group (ds = 0.8) at 12 months follow-up ($p < 0.05$; 1 trial; 138 children living in a low SES community; effective sample size of approx. 110 as the dropout was 20%). The presence of caries was 24% in the test group following intervention compared with 47% in the placebo group. However, the review authors noted that the results were obtained in spite of the fact that approximately 80% of the families reported supervised toothbrushing twice daily and despite a far from optimal compliance with the probiotic lozenges. |
| **Significance/direction** | Available evidence suggests that probiotic supplements are better than placebo in preventing early childhood caries. However, the quality of the evidence was low or very low and further translational research is needed to investigate this preventative approach. |
| **Heterogeneity** | Due to heterogeneity and paucity of included studies, a narrative synthesis was performed. |
| **Summary for GRADE assessment for HRB report** | It is stated on page 127 of the report that the review authors used GRADE to assess the certainty of the evidence. However, the results of this assessment were not reported on in the manuscript.<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Oliveira *et al.* (2018) |
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| **First Author and year of publication** | Oliveira *et al.* (2018) |
| **Objectives (exact review question(s) and page number)** | The objective of this systematic review is to perform a qualitative and quantitative synthesis of the scientific evidence on the effect of SDF for preventing and arresting dental caries on exposed root surfaces of adults (p3). |

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| | *Note*. The HRB is only interested in the findings on caries prevention and so excluded the caries arrest aspect of this study. |
| **Participants (characteristics and numbers)** | Permanent dentition; combined intervention.<br><br>The population of interest was adults of any age with exposed root surfaces at the beginning of the study.<br><br>The three trials randomised 895 elderly people and analysed 544, 712 and 460 subjects at 12, 24 and 30 or more months of follow-up, respectively. The participants had similar mean ages (from 72.1 to 78.8 years) and low caries experience (mean baseline decayed and filled root surfaces ranged from 1.1 to 2.1). Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | All three included trials were conducted in Hong Kong.<br><br>The settings of the included trials were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was topical silver diamine fluoride solution (any concentration or frequency) applied by any health care worker in any setting. The comparison group received either no intervention, a placebo, or any cariostatic agent or dental restorative material.<br><br>All three included trials used silver diamine fluoride (SDF) at a 38% concentration and compared it to a placebo (water or tonic water). In addition, in all trials, the test and control groups received individualised oral hygiene instruction making this a review of combined interventions. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials<br>• EMBASE<br>• MEDLINE via PubMed<br>• SCOPUS<br>• Web of Science<br>• LILACS<br>• BBO, and<br>• SciELO.<br><br>The databases were searched in April 2016. There was no date of publication restrictions. It is mentioned that Japanese and Chinese studies were included, among other unspecified languages. |

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| | Five registries of ongoing trials (i.e., ClinicalTrials.gov, Brazilian Register of Clinical Trials, EU Clinical Trials Register, ISRCTN registry and Current Controlled Trials and Australian New Zealand Clinical Trials Register) and the Brazilian database of thesis and dissertations were also searched. All searches were updated in July 2017. Cross-referencing from narrative reviews on the subject was used to identify additional articles.<br><br>The review protocol was registered with PROSPERO (ID: CRD42016036963).<br><br>After training, two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction with a pilot tested data extraction form. Disagreements were resolved through discussion with a third review author.<br><br>None of the review authors declared a conflict of interest.<br><br>The review was partially supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health, and partially funded through a Patient-Centred Outcomes Research Institute Award. |
| **Date range (years) of included studies** | The three included trials were published in 2010, 2013 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included three randomised controlled trials. Two trials had two intervention groups: one compared yearly SDF applications with or without the inclusion of a<br>biannual oral health education program to a placebo; another compared yearly SDF applications followed or not by a potassium iodide application to a placebo. One trial also compared yearly SDF applications to quarterly applications of 1% chlorhexidine varnish and 5% sodium fluoride varnish.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included three randomised controlled trials: Li (2017), Tan (2010), and Zhang (2013).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | All three included trials were conducted in Hong Kong. |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias for all included trials by using the Cochrane risk of bias tool. Disagreements were resolved by discussion with a third review author.<br>The following domains were assessed in each included trial: |

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Balanced groups at baseline (selection bias), and
8. Reliability of measurements (misclassification bias).

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| **Appraisal rating** | The review authors described the three included trials as soundly designed, conducted, and reported. Overall, HRB notes that using the Cochrane's Collaboration tool all trials had an unclear risk of bias.<br><br>In one trial, all domains, except for allocation concealment, had a low risk of bias. The other two trials had six domains with low risk of bias and two domains with unclear risk of bias.<br><br>All three trials had a low risk of bias for randomisation and outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | The review authors used the fixed-effect model to obtain pooled estimates of caries increment as weighted mean differences since the estimate of between-studies variance under the random-effects model has poor precision when the number of studies is very small.<br><br>Heterogeneity of studies was assessed by the Chi-square ($\chi^2$) test for heterogeneity and Higgins index ($I^2$). The studies in the meta-analyses were grouped according to the duration of their follow-up in: 12 months, 24 months and 30 months or more. The difference in caries increments regarding the comparisons between SDF and other active treatments (i.e., chlorhexidine varnish and sodium fluoride varnish) could not be pooled because there was only one study for each comparison. When there was more than one SDF intervention group per study they were combined into a single group. All analyses were carried out in Stata® 14 and followed the procedures described in the Cochrane Handbook for Systematic Reviews of Interventions.<br><br>We also calculated prevented fractions (mean caries increment in control minus mean caries increment in intervention groups divided by mean caries increment in control) for the comparison between SDF and placebo. Confidence intervals of PFs were estimated by using Fieller's method. |

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| **Outcome(s) assessed** | Primary outcome 1: Difference in mean caries increment and prevented fraction (i.e., mean number of decayed or filled root surfaces minus baseline mean number of decayed or filled root surfaces - DFRS) between the SDF and control groups<br><br>Secondary outcome 1: Adverse events<br><br>*Note*. Both outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Difference in mean caries increment and prevented fraction**<br>Analyses showed that annual 38% SDF applications + OHI significantly decrease the new number of new root caries lesions compared to a placebo at 24 months follow-up (WMD -0.56; 95% CI -0.77 to -0.36; 3 trials; 712 participants; $I^2$ = 61.5%). The same result was found at 12 months follow-up (WMD -0.48, 95% CI -0.69 to -0.27; 2 trials; 544 participants; $I^2$ = 89.9%) and 30 months or more of follow-up (WMD -0.80, 95% CI -1.19 to -0.42; 2 trials; 460 participants; $I^2$ = 74%). The prevented fraction for root caries prevention ranged from 50.30% to 68.35% depending on duration of follow-up.<br><br>In one trial, when SDF was compared to SDF followed by potassium iodide no significant difference was observed in caries increment after 30 months of follow-up (effective sample size of 257).<br><br>In another trial with an effective sample size of 227, only the test group that received a biannual oral health education co-intervention had a significantly lower new caries increment in comparison to the placebo group. Therefore, the review authors performed a sensitivity analysis excluding this group from the overall comparison between SDF and placebo. The pooled WMD changed slightly from -0.56 to -0.54 (95% CI -0.75, -0.33).<br><br>One trial made a comparison between SDF and fluoride varnish or chlorhexidine varnish. Chlorhexidine varnish had a significantly higher preventive effect than SDF at 12 months of follow-up but there were no significant differences between SDF and FV at any of the follow-up periods analysed (i.e., 12, 24 or 36 months (effective sample sizes were 247 (12 months), 227 (24 months), and 203 (36 months))) or between SDF and CHX varnish at 24 months follow-up or more.<br><br>*Note*. The review authors reported that participants in all trials had exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest.<br><br>**Secondary outcome 1: Adverse events**<br>Two trials reported that the interventions were well accepted by the elders. In one trial, 3.5% of all participants complained about the black staining of |

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| | their treated root surfaces. In another, only two elders, both in the SDF group, raised the same complaint (additional information provided by one of the authors). |
| **Significance/direction** | Limited evidence with low risk of bias indicates that SDF is significantly more effective in preventing the development of new carious lesions when compared to placebo.<br><br>Yearly 38% SDF applications to exposed root surfaces of elderly people are effective against dental caries initiation and progression. The preventive effect of SDF for root caries is similar to that of 5% sodium fluoride and 1% chlorhexidine varnishes. Further research is needed to replicate these findings and to determine the best frequency and interval of SDF applications. Given the potential of SDF for both prevention and arrest of dental caries, its low cost and simplicity of application, future studies in elderly populations should consider the impact of SDF on satisfaction with dental care, quality of life and the cost benefit of using SDF in lieu of more complex treatments at this stage of life. |
| **Heterogeneity** | Moderate to considerable statistical heterogeneity was encountered when weighted mean differences were pooled. The review authors found this difficult to explain since relevant clinical and methodological variations among the studies were not apparent.<br><br>The change of the effect measure has been suggested as an alternative to deal with heterogeneity. 12 When pooled PF were estimated no heterogeneity was observed and results were consistent with those obtained through meta-analyses of WMD confirming the effectiveness of SDF for the prevention of root caries. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Poorni *et al.* (2019) |
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| **First Author and year of publication** | Poorni *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To review the published literature with the purpose of knowing the importance of using various probiotic Streptococcus strains as a preventive and therapeutic method for dental caries management. |

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| **Participants (characteristics and numbers)** | Unspecified dentition (coded as mixed); topical other chemicals, probiotics.<br><br>There are five included trials, with which only two are relevant to current HRB interests. The two relevant trials involved a total of 159 participants. Information pertaining to the age and gender of included participants was not reported. |
| **Setting/context** | The study countries and settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was probiotic *Streptococcus* strains. The control group received a placebo or no treatment. Among the two relevant included clinical trials, one administered the probiotics in the form of two lozenges each day for three months. The other trial administered the probiotic in the form of dissolving oral tablets taken once a day for three months. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed/Medline<br>• Scopus<br>• EBSCOhost<br>• Embase, and<br>• ScienceDirect.<br><br>Two preliminary searches were conducted in January 2018. All papers from 1989 to December 2017 were considered for the present review. Manual searches were also performed. Language was restricted to English.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion with a third review author.<br><br>There was no mention of a protocol being prepared or published.<br><br>The review received no financial support or sponsorship.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The two relevant included trials were published in 2013 and 2015. |
| **Number of primary studies included in the systematic review** | The review authors included two non-randomised clinical trials and three in vitro studies in the review. For the purposes of this umbrella review, HRB is interested only in the findings of in vivo studies and therefore the findings from in vitro studies were excluded.<br><br>The funding sources of the primary studies were not reported. |

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| **Types of studies included** | The review authors included two clinical trials: Di Pierro (2015) and Burton (2013).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The study countries were not reported. |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of included trials. Disagreements were resolved by discussion and, where necessary, consultation with a third review author. Each trial was assessed using the evaluation method described in the Cochrane Handbook for Systematic Reviews.<br><br>The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias.<br><br>Each domain was classified as having a low, high, or unclear risk of bias. |
| **Appraisal rating** | Overall, the two included trials were categorised as having a high risk of bias.<br><br>Both trials had a high risk of bias for randomisation and outcome ascertainment.<br><br>Publication bias was not mentioned. |
| **Method of analysis** | Results were described narratively. |
| **Outcome(s) assessed** | Primary outcome 1: Development of new dental caries<br><br>Secondary outcome 1: *S. Mutans* count<br><br>*Note*. Both outcomes are presented as primary outcomes in the review. However, for the HRB's purposes, secondary outcome 1 is considered a secondary outcome. |
| **Results/findings** | **Primary outcome 1: Development of new dental caries** |

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| | The results of one trial with 83 participants found the use of *salivarius* M18 in lozenges (2 lozenges per day for 3 months) increases the chance of avoiding new dental caries development in children compared to a placebo (limited information reported).<br><br>**Secondary outcome 1: *S. Mutans* count**<br>In one trial with 76 participants, cell-culture analyses of sequential saliva samples showed no differences in *S. mutans* counts between the intervention (*salivarius* M18 in in dissolvable oral tablets, once per day for 3 months) and no treatment control group (limited information reported). |
| **Significance/direction** | There was insufficient evidence to determine the effectiveness of probiotic Streptococcus strains as a method for dental caries prevention.<br><br>Within the limitations of the systematic review, it can be concluded that, the two included clinical studies on the use of probiotic Streptococcus strains for caries prevention had high risk of bias. |
| **Heterogeneity** | Among the included trials, differences were observed in the form of probiotic, probiotic dosage, and outcomes assessed. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Rethman *et al.* (2011) |
| **First Author and year of publication** | Rethman *et al.* (2011) |
| **Objectives (exact review question(s) and page number)** | To present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States (p7). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (separate and mixed); topical other chemicals, CHX, calcium phosphate agents, antimicrobial agents, xylitol, polyols; other systemic chemicals, sialagogues; combined intervention.<br><br>The number of participants is not specified in the report. The 66 studies involved participants between the ages of 9 months to 101 years. Twenty-seven studies specifically recruited high-risk patients which was defined as subjects with incipient or cavitated lesions, prior caries experience, or those |

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| | with high salivary or plaque *Streptococcus Mutans* scores. Information pertaining to the sex of included participants was not reported.<br><br>Three trials involved orthodontic patients. For the purposes of this umbrella review, the HRB is not interested in this population group and so the results from these studies were excluded. |
| **Setting/context** | The studies were conducted in Argentina (1 study), Australia (1 study), Belize (2 studies), Brazil (1 study), Canada (2 studies), China (3 studies), Costa Rica (2 studies), Estonia (2 studies), Finland (6 studies), Germany (3 studies), Hong Kong (1 study), Hungary (1 study), India (2 studies), Italy (1 study), Lithuania (1 study), Kuwait (1 study), Madagascar (1 study), Marshall Islands (1 study), Netherlands (3 studies), New Zealand (1 study), Puerto Rico (2 studies), Scotland (1 study), Serbia (1 study), Spain (2 studies), Surinam (1 study), Sweden (13 studies), the United Kingdom (2 studies), the United States (5 studies), Venezuela (2 studies) and one study was conducted in both the United States and Canada.<br><br>The study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The interventions of interest were non-fluoride caries preventative agents requiring professional application or prescription, or over-the-counter agents likely to be used upon the recommendation of a dentist.<br><br>Studies in which the experimental arm had other co-interventions (fluoride/oral health instructions etc.) in which the control arm did not were excluded. In addition, studies without a concurrent control group or studies with sucrose as the control were excluded.<br><br>The included trials evaluated the effect of the following non-fluoride agents:<br>1. Sucrose-free polyol chewing gums (e.g. xylitol, sorbitol)<br>2. Xylitol candy, lozenge, syrup<br>3. Xylitol dentifrice<br>4. Triclosan<br>5. Iodine<br>6. Chlorhexidine varnish<br>7. Chlorhexidine/thymol varnish<br>8. Chlorhexidine mouth rinses<br>9. Chlorhexidine gels<br>10. Calcium and/or phosphate agents with and without casein derivatives<br>11. Sialagogues, and<br>12. Use of non-fluoride agents in mother to prevent caries in children. |

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| **Databases and sources searched** | One review author searched the following sources:<br>• MEDLINE via PubMed, and<br>• Cochrane library.<br>The references of selected articles were also searched to identify any additional potentially relevant studies. Articles published between 1966 to April 2010 were considered for inclusion. A final search was conducted in March 2011.<br><br>There was no specific mention of a protocol being published; however, the authors stated that most of the inclusion and exclusion criteria were set a priori.<br><br>Two review authors independently screened search results. Disagreements were resolved by two additional review authors. It was not reported how data extraction was completed.<br><br>The review was in part funded by the Centres for Disease Control and Prevention.<br><br>Five review authors had disclosures to report which included some affiliations with the industry. |
| **Date range (years) of included studies** | The 66 included studies were published between 1972 and 2010. |
| **Number of primary studies included in the systematic review** | The review authors included 51 randomised controlled trials and 15 nonrandomised studies. The randomised controlled trials included 42 trials randomised individually and 9 trials that were cluster randomised. The nonrandomised studies were a mixture of 8 clinical control trials allocated individually and 7 clinical control trials allocated by groups. The duration of the studies ranged from 10 months to 12 years.<br><br>The review authors mentioned that most studies failed to report funding sources. |
| **Types of studies included** | The review authors included 66 studies (reported in 71 published articles): Finn (1978), Richardson (1972), Szoke (2001), Beiswanger (1998), Peng (2004), Glass (1983), Machiulskiene (2001), Makinen (1995), Makinen (1996), Kandelman (1990), Petersen (1999), Alanen (2000a), Kovari (2003), Isokangas (1988), Alanen (2000b), Alanen (2000c), Honkala (2006), Stecksen (2008), Oscarsen (2000), Milgrom (2009), Sintes (2002), Sintes (1995), Acevedo (2005), Acevedo (2008), Papas (2008), Silva (2001), Kolmakow (1991), Morgan (2008), Hay (2002), Rao (2009), Andersson (2007), Xu (2009), Zhan (2006), Lopez (2002), Simratvir (2010), Du (2006), Forgie (2000), Fennis-le (1998), de Soet (2002), Jenatschke (2001), Schaeken (1991), |

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| | Lindquist (2006), Petti (2006), Lundstrom (1987), Gisselsson (1994), Gisselsson (1998), Emilson (1976), Keltjens (1990), Wyatt (2004), Wyatt (2007), Spets-Happonen (1991), Luoma (1978), Petersson (2000), Petersson (1998), Splieth (2000), Ogaard (2001), Plotzitza (2005), Baca (2002), Baca (2004), Twetman (1999), Baca (2009), Brailsford (2002), Tan (2010), Isokanga (2000), Kohler (1994), Dasanayake (2002), and Bergel (2010).<br><br>The results of 55 included studies were relevant to the objectives of this umbrella review: Finn (1978), Richardson (1972), Szoke (2001), Beiswanger (1998), Peng (2004), Glass (1983), Machiulskiene (2001), Makinen (1995), Makinen (1996), Kandelman (1990), Petersen (1999), Alanen (2000a), Kovari (2003), Isokangas (1988), Alanen (2000b), Alanen (2000c), Honkala (2006), Stecksen (2008), Oscarsen (2000), Milgrom (2009), Sintes (2002), Sintes (1995), Acevedo (2005), Acevedo (2008), Papas (2008), Silva (2001), Hay (2002), Rao (2009), Xu (2009), Zhan (2006), Du (2006), Forgie (2000), Fennis-le (1998), de Soet (2002), Schaeken (1991), Lindquist (2006), Petti (2006), Gisselsson (1994), Gisselsson (1998), Emilson (1976), Keltjens (1990), Wyatt(2004), Wyatt (2007), Spets-Happonen (1991), Luoma (1978), Petersson (2000), Petersson (1998), Splieth (2000), Plotzitza (2005), Baca (2002), Baca (2004), Baca (2009), Tan (2010), Isokanga (2000), Kohler (1994), Dasanayake (2002), and Bergel (2010).<br><br>A list of excluded studies and the reasons for exclusion were provided in an appendix. |
| **Country of origin of included studies** | The studies were conducted in Argentina (1 study), Australia (1 study), Belize (2 studies), Brazil (1 study), Canada (2 studies), China (3 studies), Costa Rica (2 studies), Estonia (2 studies), Finland (6 studies), Germany (3 studies), Hong Kong (1 study), Hungary (1 study), India (2 studies), Italy (1 study), Lithuania (1 study), Kuwait (1 study), Madagascar (1 study), Marshall Islands (1 study), Netherlands (3 studies), New Zealand (1 study), Puerto Rico (2 studies), Scotland (1 study), Serbia (1 study), Spain (2 studies), Surinam (1 study), Sweden (13 studies), the United Kingdom (2 studies), the United States (5 studies), Venezuela (2 studies) and one study was conducted in both the United States and Canada. |
| **Appraisal instrument(s)** | The Downs and Black instrument was used to assess the quality of included studies. The questions in the instrument addressed five separate domains including reporting, external validity, bias, confounding and statistical power. All panel members participated in an orientation through a conference call to standardise the application of the critical appraisal instrument. Along with a copy of the instrument, each panel member received five to six studies to review. Independent from the panel member, one author duplicated the review and critical appraisal across all included studies. This ensured appraisal by two independent reviewers and standardised application of the instrument by all reviewers. Following the critical appraisal, a composite |

score was developed for each study based on a standardized rating scale as follows:

- Reporting (range 1 - 10):
  - >9 = Good
  - 8–7 = Fair
  - <6 = Poor
- Internal validity including bias, confounding and power (range 1 – 14):
  - >12 = Good
  - 11–10 = Fair
  - <9 = Poor.

During the panel meeting, all panel members reviewed and extensively discussed results from each study.

The level of certainty of the evidence was graded as high, moderate or low based on a standardised grading system (adapted from the United States Preventive Services Task Force system).

**Appraisal rating**

The review authors judged 10 studies to be of good quality, 23 studies to be of fair quality, and 22 studies to be of poor quality. The quality rating of the remaining studies was not reported.

The review authors separately measured reporting and internal validity. For reporting, 12 studies were judged to be good quality, 29 studies were of fair quality, and 25 studies were of poor quality. For internal validity, 13 studies were judged to be good quality, 24 were fair quality, and 29 were of poor quality.

Randomisation and outcome bias were not individually reported.

Publication bias was not measured.

**Method of analysis**

The panel adapted a set of rules published in a recent Cochrane review of caries trials to select outcome data from each study for subsequent analysis. Specifically, the panel chose data on tooth surfaces level over data on tooth level; data for "all surface types combined" over data for “specific types" only; data for "all erupted and erupting teeth combined" over data for "erupted" only, and this over data for "erupting" only"; data from "clinical and radiological examinations combined" over data from "clinical" only, and this over "radiological" only; DMFS scores over DFS or DS; data for “dentinal/cavitated” caries lesions over data for "all stages" over data for “enamel/non-cavitated” lesions; net caries increment data over crude (observed) increment data; and follow up nearest to three years (often the one at the end of the treatment period) over all other lengths of follow up. Further, DMFS data was chosen over defs data unless otherwise stated.

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| | For studies that evaluated more than one relevant treatment arm, the review authors combined the raw results (the numbers, mean DMF increments and standard deviations) from all parallel arms in order to obtain an estimate of treatment effect. When possible, they imputed missing standard deviations that were not reported using linear regression of log (standard deviations) on log (mean caries) increments.<br><br>Meta-analysis was used to synthesize the results when multiple papers were included in the review. Like the summary estimate used in the Cochrane review of caries trials, the panel selected "prevented fraction" (PF) as the measure of treatment effect. PF is the difference in DMF increment scores between the groups that received the experimental treatment and those who received a comparison or no active treatment divided by the average number of DMF scores in people who received a comparison or no active treatment.<br><br>Random-effects meta-analyses were conducted throughout to generate forest plots using RevMan 5 software. The panel used a random-effects model to overcome some of the limitations of heterogeneous data and graded the level of certainty based on these considerations. The $I^2$ statistic generated by RevMan quantified the statistical heterogeneity. |
| **Outcome(s) assessed** | Primary outcome 1a: Caries increment (the number of new decayed, missing or filled surfaces or teeth (dmft and dmfs) experienced by each treatment group in primary dentition)<br><br>Primary outcome 1b: Caries increment (the number of new decayed, missing or filled surfaces or teeth (DMFT and DMFS) experienced by each treatment group in permanent dentition)<br><br>Primary outcome 1c: Caries increment (the number of new decayed, missing or filled surfaces or teeth (dmft/DMFT and dmfs/DMFS) experienced by each treatment group in mixed dentition)<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1a: Caries increment (the number of new decayed, missing or filled surfaces or teeth in primary dentition (dmft and dmfs)**<br><br><u>Intervention 1: Sucrose-free polyol chewing gums (e.g. xylitol, sorbitol, combinations) versus no gum:</u><br>None of the included trials reported on the effect of this intervention in primary dentition. |

Intervention 2: Xylitol candy, lozenge, syrup:
Two trials evaluated the effect of xylitol candy/lozenges/syrup on caries increment in primary dentition. However, the findings were only presented for one (the results of the other trial were analysed in a meta-analysis along with trials evaluating permanent dentition).

The trial evaluated the effect of xylitol candy/lozenges/syrup on the caries increment in primary dentition among children in the Marshall Islands, comparing 8g of xylitol syrup a day (intervention) to 2.67g of xylitol syrup a day (control). The concentration of xylitol in these trials was not reported. At 10 months follow up, the review authors reported a statistically significant difference in favour of xylitol syrup (good quality evidence). The review authors concluded that there is insufficient evidence that xylitol syrup prevents caries in children under 2 years of age. Limited information reported.

Intervention 3: Xylitol + fluoride dentifrice:
None of the included trials reported on the effect of this intervention on caries increment in primary dentition in primary dentition.

Intervention 4: Triclosan:
No included trials assessed the effectiveness of this intervention in primary dentition.

Intervention 5: Iodine:
Four of the included trials reported on the effect of 10% povidone-iodine on coronal caries compared to fluoride foam or saline after one application. However, the overall effect could not be determined due to differences in the outcome measures reported (varying in caries prevention and caries progression).

Intervention 6: Chlorhexidine varnish:
One included trial assessed the effect of chlorhexidine varnish on caries increment in primary teeth, however this trial was included in a meta-analysis with other trials assessing permanent dentition and could not be separated. This intervention therefore is reported in mixed dentition.

Intervention 7: Chlorhexidine-thymol varnish:
None of the included trials reported on the effect of this intervention in primary dentition.

Intervention 8: Chlorhexidine mouthrinses:
One trial examined the effect of chlorhexidine mouthrinse on caries increment in primary dentition. However, results were described through meta-analysis which pooled trials that examined primary and permanent dentition separately. This intervention therefore is reported in mixed dentition.

Intervention 9: Chlorhexidine gels:

Only one trial evaluated the use of chlorhexidine gels on caries increment in primary dentition. The trial, conducted in high-risk patients, compared a professionally applied 1% chlorhexidine gel using trays (applied for 3 consecutive days every 3 months) with no gel application. After 18 months, there were no significant differences in dft increment between intervention arms (poor quality evidence).

*Note*. The review authors reported that participants in this trial also had exposure to fluoride toothpaste. However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest.

Intervention 10: Calcium and/or phosphate agents with and without casein derivatives:

None of the included trials reported on the effect of this intervention on caries increment in primary dentition.

Intervention 11: Sialogogues*:*

None of the included trials reported on the effect of this intervention in primary dentition.

Intervention 12: Use of non-fluoride agents in mothers to prevent caries in children:

Three trials evaluated the use of non-fluoride agents in mothers to prevent caries in children's primary teeth. A meta-analysis for the three studies evaluating the effect of this intervention was not possible. Follow-up periods ranged from 4-7 years. Concentrations of intervention agents include: 65% xylitol and 1-40% chlorhexidine.

One randomised controlled trial evaluating xylitol gum (6-7 g/day, gum chewed 4 times per day from 3 months postpartum to 24 months postpartum) and 40% chlorhexidine varnish (applications at 6, 12, and 18 months postpartum) (combined intervention) compared to fluoride varnish reported that use of xylitol gum significantly lowered the incidence of caries (measured by the increment of decayed, missing and filled (dmf) teeth) in children at 5 years follow-up (poor quality evidence).

The second controlled trial evaluating 1% chlorhexidine gel (applied up to 3 years post-partum) plus a preventive programme reported a statistically significant reduction in caries experience (measured by the increment of decayed, extracted and filled (defs) teeth) in children compared to a control group that received a preventive programme only at 7 years follow-up (poor quality evidence). The nature of the preventive programme was unspecified, but the authors noted that a regular caries preventive program includes routine and periodic examination by a dentist, patient education, dietary

advice and appropriate use of professional and home fluoride products and dental sealants.

Another RCT evaluating 10% chlorhexidine varnish (4 weekly applications 6 months after delivery, following by a single application every once every 6 months) reported nonsignificant differences in caries increment (measured by the decayed and filled (dfs) index) in children compared to a control group at 4 years follow-up (fair quality evidence).

Overall, authors concluded that there is insufficient evidence that use of xylitol gum, chlorhexidine varnish or gel, or calcium supplementation in mothers lowers incidence of caries in children.

**Primary outcome 1b: Caries increment (the number of new decayed, missing or filled surfaces or teeth in permanent dentition (DMFT and DMFS)**

Intervention 1: Sucrose-free polyol chewing gums (e.g. xylitol, sorbitol, combinations) versus no gum:

Of the 15 randomised and non-randomised trials that assessed this intervention, only the nine trials contributed data to the meta-analysis. The results of the other six trials (two of which include primary dentition, four focus on permanent) are not reported. In most trials, gum chewing was conducted under supervised conditions. Frequency of gum chewing was between 2 and 6 times per day with a duration of chewing ranging from 10 to 20 minutes. The concentration of sorbitol (10 trials) ranged from 50-70%, xylitol (10 trials) ranged from 4.3-65%, mannitol (3 trials) ranged from 4-70%, and carbamide (2 trials) was 2.3%. Follow-up periods were 2 years (4 trials), 2.5 years (1 trial), 3 years (3 trials), and 40 months (1 trial).

There was a significant reduction in caries in permanent teeth when sucrose-free polyol gum were used compared to no gum chewing (PF -39.30; 95% CI -57.14 to -21.45, $p < 0.00001$; 9 trials; 5,144 participants; $I^2 = 95\%$; moderate certainty of evidence). The preventive effect, however, was not the same for all types of polyols. Subgroup analyses showed that xylitol only gum had the highest caries reduction effect (PF -63.88, 95% CI -85.25 to -42.10, $p < 0.00001$; 4 trials; 848 participants; $I^2 = 91\%$), followed by gums with a combination of polyols (PF -36.03; 95% CI -62.91 to -9.15, $p = 0.009$; 6 trials; 3,498 participants; $I^2 = 96\%$), and sorbitol only (PF -6.59; 95% CI -21.44 to 8.26, $p = 0.38$; 798 participants; $I^2 = 0\%$).

Confidence in the summary estimate was limited because several of the trials were cluster or group-randomised typically by classroom or school followed by analyses that were based on the number of subjects included in the study (i.e. unit of analysis error). A statistically significant reduction with the use of sucrose-free polyol gums compared to no gum chewing was maintained after adjusting for these errors.

However, when the non-randomised studies were excluded and adjustments were made within the subset of studies with unit of analysis errors, the result in favour of sucrose-free polyol gum became statistically nonsignificant.

Intervention 2: Xylitol candy, gum, lozenge, syrup:
One trial evaluated the use of 422mg xylitol candies (2 candies 3x/day) on the caries increment (DMFS approximal only) compared to conventional care (including fluoride varnish) in the permanent dentition of high-risk participants. This trial specifically enrolled high-risk patients and reported nonsignificant differences between the groups after 2 years (low quality evidence).

Intervention 3: Xylitol + fluoride dentifrice:
The effect of this intervention could not be adequately determined due to additional components besides xylitol being added to the dentifrice.

Intervention 4: Triclosan:
No included trials assessed the effectiveness of this intervention.

Intervention 5: Iodine:
Four of the included trials reported on the effect of 10% povidone-iodine (one application) on coronal caries. However, these trials appear to focus on caries arrest or reduction in caries progression.

Intervention 6: Chlorhexidine varnish:
The pooled results include 4 trials that assessed solely permanent dentition and 1 trial that assessed primary dentition. The findings were to be presented in mixed dentition. However, one of the pooled trials was a trial involving orthodontic patients. Therefore, this finding will not be used in the evidence synthesis for this umbrella review.

Intervention 7: Chlorhexidine-thymol varnish:
A single trial that evaluated the efficacy of 1:1 chlorhexidine/thymol varnish on root caries incidence (RCI) showed a statistically significant reduction in the incidence of caries with the use of chlorhexidine/thymol varnish (at 1, 3, 6, 9, and 12 months) compared to placebo at 1 year follow-up. This trial was considered moderate certainty evidence.

*Note*. Participants in this trial had exposure to fluoridated water. However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest.

Another single trial that evaluated the efficacy of 1:1 chlorhexidine/thymol varnish on root caries incidence (RCI) showed a significant reduction in root caries incidence (RCI) following the application of 1:1 chlorhexidine/thymol

varnish + oral health instruction every 3 months compared to oral health instruction alone at 3 years follow-up.

Intervention 8: Chlorhexidine mouthrinses:
Analyses showed no statistically significant difference in new caries (measured via DMFS increment in three trials, and incidence rate in one trial) between those received a 0.05-0.12% chlorhexidine rinse and those that received a control (PF -13.08; 95% CI -29.08 to 2.91, p = 0.11; 4 trials; 1,252 participants; $I^2$ = 0%; high certainty of evidence). Follow-up periods for included trials ranged from 2-5 years. Frequency of application ranged from every day for two trials, every day for 5 days every third week for another trial, and daily for one month then weekly for 5 months in the final trial. The concentration of chlorhexidine was 0.12% in two trials and 0.05% in one trial. Chlorhexidine concentration was not reported in one trial.

A subgroup analysis found no statistically significant difference in caries incidence between those that received a chlorhexidine rinse and that those received either a placebo or no rinse (PF -11.73; 95% CI -28.77 to 5.31; 3 trials; 1,184 participants; $I^2$ = 0%).

*Note*. One of the pooled trials delivered a combined intervention involving mouthrinse consisting of CHX + fluoride followed by brushing twice a day with toothpaste having the same composition as rinse.

*Note*. In 3/4 pooled trials, participants were reported to have exposure to fluoride (toothpaste or varnish). However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest.

Intervention 9: Chlorhexidine gels:
Five trials reported on the effect of chlorhexidine gel on caries increment in permanent dentition. A meta-analysis was not possible due to the different delivery methods used. Concentrations of chlorhexidine ranged from 0.5-1%. Follow-up periods ranged from 1-3 years.

Two studies conducted in the general population compared professional flossing with 1% chlorhexidine gel to flossing with placebo gel in reduction of D(E)FS increment. Both trials applied the intervention 4 times a year. Both trials reported favourable results for approximal lesions at 3 years follow-up (fair quality evidence).

*Note*. In both trials, participants were reported to have exposure to fluoride (water, toothpaste, tablets and/or mouthrinse). However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest.

*Note*. In both trials, participants received professional flossing prior to application of CHX gel, presumably as a preparation measure for the gel.

One study also conducted in the general population compared brushing at home with 0.5% gel compared to brushing with a placebo gel, with no specified frequency of application. A nonsignificant difference was found between intervention arms in Decayed Surfaces (DS) at 1 year follow-up (fair quality evidence).

One study conducted in high-risk patients compared 1ml of 1% chlorhexidine gel (5 minutes for 2 days in a row every 3 months) to fluoride varnish. A nonsignificant difference was found between the groups in DFS scores.

*Note*. In this trial, participants were reported to have some exposure to fluoride (water and mouthrinse). However, this was considered background fluoride exposure, rather than part of the intervention of interest.

Finally, a study conducted in adults and elderly participants compared initial application of 5% chlorhexidine gel followed by daily 1% Chlorhexidine gel + 0.1% NaF compared to 0.1% NaF gel alone. A nonsignificant difference was found between the groups in relation to Root Caries Index (RCI) at 18 months follow-up (poor quality evidence).

Overall, in children aged 3-15 years, and adults and elderly, there is insufficient evidence that professionally applied 1% chlorhexidine gel reduces the incidence of caries.

<u>Intervention 10: Calcium and/or phosphate agents with and without casein derivatives:</u>
A meta-analysis was not possible due to differences in composition of the products, varying delivery mechanisms and differing study designs. Five trials evaluated the use of calcium and/or phosphate agents with/without casein derivatives on permanent dentition. Follow-up periods ranged from 1-2 years. Concentrations of intervention agents are not reported.

One trial compared the combined use of DiCalciumphosphate dihydrate + 0.243% NaF dentifrice (twice daily) with 0.243% NaF dentifrice and concluded that the addition of dicalcium phosphate dihydrate improved anticaries efficacy (lower increment of DMFS) at 2 years follow-up (limited information provided) (fair quality evidence).

*Note*. Participants in this trial were exposed to fluoridated water (low levels of fluoride). However, this was considered background fluoride exposure rather than part of the intervention of interest.

One trial compared the combined use of a dicalcium phosphate dihydrate + NaF dentifrice (twice daily for 60 seconds) with NaF toothpaste (1100 ppm

fluoride) in cancer radiation patients and found a stronger root caries reduction (lower DMFS) in the treatment group compared to the control group at 12 months follow-up (limited information provided) (good quality evidence).

*Note*. This trial was not included in the evidence synthesis because the population sample were a sample of cancer radiation patients.

One trial on arginine bicarbonate/calcium phosphate toothpaste (3 times daily) compared to a fluoride toothpaste reported a statistically significant reduction in caries (lower DMFS) at 1 year follow-up, although the difference was less in magnitude at 2 years (poor quality evidence).

*Note*. The review authors noted that participants in this trial had exposure to fluoridated salt. However, this was considered background fluoride exposure rather than part of the intervention of interest.

One study evaluated calcium phosphate in mouthrinses (rinse 3x/day) on patients with salivary gland dysfunction and reported a nonsignificant difference in caries increment between the test rinse and fluoride rinse (limited information provided) (fair quality evidence).

One study compared a dentifrice containing casein phosphopeptide (twice per day for 5 minutes for 12 months) to a fluoride-containing dentifrice and a placebo. This study concluded that the caries prevention efficacy (measured by the increment of Decayed Surfaces (DS)) of the dentifrice containing casein phosphopeptide was like that of the fluoride dentifrice and both were more efficacious than the placebo at 2 yeas follow-up (limited information provided) (good quality evidence).

Overall, authors concluded that there is insufficient evidence from clinical trials that use of agents containing calcium and/or phosphates with or without casein derivates lowers incidence of either coronal or root caries.

Intervention 11: Sialogogues*:*
No included trials assessed the effectiveness of this intervention.

Intervention 12: Use of non-fluoride agents in mothers to prevent caries in children:
No included trials assessed the use of non-fluoride agents in mothers to prevent caries in children's permanent dentition.

**Primary outcome 1c: Caries increment (the number of new decayed, missing or filled surfaces or teeth in mixed dentition (dmft/DMFT and dmfs/DMFS)**

Intervention 1: Sucrose-free polyol chewing gums (e.g. xylitol, sorbitol, combinations) versus no gum:
None of the included trials reported on the effect of this intervention on caries increment in mixed dentition.

Intervention 2: Xylitol candy, lozenge, syrup:
Of the five studies that assessed xylitol candies/syrup, three contributed data to the meta-analysis (1 conducted on primary dentition and 2 on permanent dentition). The analysis found xylitol candies/tablets were more effective at reducing the incidence of caries compared to a control (no candy or tablets) (PF -79.93; 95% CI -142.96 to -16.91; 3 trials; 548 participants; $I^2$ = 95%; low certainty of evidence). Follow-up periods were 1.5 years, 2 years and 3 years. The concentration of xylitol was 49% in the 2 trials that reported on candy (3 per day), and 0.48g xylitol tablet (one per day for 6 months and then 2 per day). In one of the trial participants were reported to have exposure to fluoride toothpaste. However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest. It was reported in two trials that participants received other preventive measures as part of routine care.

The review authors concluded that in children reporting caries experience, consumption of xylitol containing lozenges or hard candy reduces incidence of coronal caries.

A meta-analysis comparing the efficacy of xylitol gum with sorbitol gum directly found xylitol gum was more efficacious in reducing incidence of caries at 24 months-40 months follow-up (SMD -0.47, 95% CI -0.83 to -0.10, p = 0.003; 3 trials; 728 participants; $I^2$ = 83%) (mixed primary and permanent dentition; DMFS in two trials and lesion onset per subject" in primary dentition in one trial). The number of pieces of gum chewed was 5 times per day in 1 trial, 3-5 times per day in 1 trial, and 10 times per day in 1 trial. Concentrations of xylitol were 589mg per day in 1 trial, 10.42-10.67mg per day in 1 trial, and 3.3g per day in 1 trial.

Intervention 3: Xylitol + fluoride dentifrice:
None of the included trials reported on the effect of this intervention on caries increment in mixed dentition.

Intervention 4: Triclosan:
None of the included trials assessed the effectiveness of this intervention in mixed dentition.

Intervention 5: Iodine:
Results could not be determined due to differences in outcome measures reported in the studies.

Intervention 6: Chlorhexidine varnish:

The pooled results include 4 trials that assessed solely permanent dentition and 1 trial that assessed primary dentition. However, one of the pooled trials was a trial involving orthodontic patients. Therefore, this finding will not be used in the evidence synthesis for this umbrella review.

Intervention 7: Chlorhexidine-thymol varnish:
Of the 6 studies that evaluated this intervention, 5 contributed data to the meta-analysis. The analysis found no statistically significant difference in caries incidence between those that received a 1:1 chlorhexidine/thymol varnish and those that received a control. However, one of the pooled trials was a trial involving orthodontic patients. Therefore, this finding will not be used in the evidence synthesis for this umbrella review.

A subgroup analysis of 2 trials (neither of which involved orthodontic patients) found no statistically significant difference in caries incidence between those that received a 1:1 chlorhexidine/thymol varnish applied every 3 months (for 1 year in 1 trial and 2 years in the other) and those that received no varnish (PF -16.25, 95% CI 46.55 to 14.06, p = 0.29; 2 studies; 228 participants; $I^2$ = 0%). One of the pooled trials reported on mixed dentition and the other reported on primary dentition.

Intervention 8: Chlorhexidine mouthrinses:
None of the included trials assessed the effectiveness of this intervention in mixed dentition.

Intervention 9: Chlorhexidine gels:
None of the included trials assessed the effectiveness of this intervention in mixed dentition.

Intervention 10: Calcium and/or phosphate agents with and without casein derivatives:
One trial compared a sugarless confection (mints) with arginine bicarbonate/calcium carbonate (2 mints, twice daily). The trial reported a statistically significant reduction in caries (DMFS and defs) at 12 months (limited information provided) (fair quality evidence).

*Note*. Participants in this trial had exposure to fluoride toothpaste and salt fluoridation. However, this was considered existing/background fluoride exposure, rather than part of the intervention of interest.

Intervention 11: Sialogogues*:*
None of the included trials reported on the effect of this intervention on caries increment in mixed dentition.

Intervention 12: Use of non-fluoride agents in mothers to prevent caries in children:

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| | Only one trial evaluated the use of non-fluoride agents (calcium supplementation, 2 g/day) in mothers to prevent caries in the mixed dentition of children compared to a control group at 12 years follow-up. The trial reported a 27% reduction in risk of developing caries (fair quality evidence). No P value was reported. |
| **Significance/direction** | The following recommendations may be considered as adjuncts to dietary counselling and a regular caries preventive program offered to patients at higher risk for caries:<br>• WEAK RECOMMENDATION: Advise parents and caregivers of children 5 years or older, that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 - 20 minutes after meals may reduce incidence of coronal caries<br>• IN FAVOR: Apply 1:1 mixture of chlorhexidine/thymol varnish every three months to reduce the incidence of root caries<br>• AGAINST: Applying 10 – 40 percent chlorhexidine varnish alone or in combination with fluoride for prevention of coronal caries is not recommended<br>• AGAINST: Using 0.12 percent chlorhexidine rinse alone or in combination with fluoride for prevention of coronal or root caries is not recommended<br>• WEAK RECOMMENDATION: Advise parents and caregivers of children 5 years or older, that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 - 20 minutes after meals may reduce incidence of coronal caries<br>• IN FAVOR: Apply 1:1 mixture of chlorhexidine/thymol varnish every three months to reduce the incidence of root caries<br>• AGAINST: Applying 10 – 40 percent chlorhexidine varnish alone or in combination with fluoride for prevention of coronal caries is not recommended<br>• AGAINST: Using 0.12 percent chlorhexidine rinse alone or in combination with fluoride for prevention of coronal or root caries is not recommended<br>• EXPERT OPINION: Advise adults, that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 – 20 minutes after meals may reduce incidence of coronal caries<br>• EXPERT OPINION: Advise parents and caregivers of children 5 years or older, that the daily use of xylitol-containing lozenges or hard candy that are dissolved slowly in the mouth after meals may reduce incidence of coronal caries (5-8 grams/day divided into two to three doses) |

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| | • EXPERT OPINION: Applying 0.5 to 1.0 percent chlorhexidine gel alone or in combination with fluoride for caries prevention of coronal or root caries is not recommended<br>• EXPERT OPINION: Applying 1:1 mixture of chlorhexidine/thymol varnish alone or in combination with fluoride for prevention of coronal caries is not recommended |
| **Heterogeneity** | Significant heterogeneity was observed in most meta-analyses confirming clinical or methodological differences amongst studies. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence as low (consumption of xylitol candy/lozenges/syrup, CHX-thymol varnish in children), moderate (sucrose-free polyol chewing gum, CHX varnish, CHX-thymol varnish in adults) and high (CHX mouthrinse). Several of the outcomes were graded on analyses involving both primary and permanent dentition pooled together rather than analysed separately. As such, the certainty of evidence for some outcomes under primary and permanent dentition when analysed separately was not reported.<br><br>The HRB authors graded the certainty of evidence in the review as very low. |
| **References to previously published versions** | N/A |

| Parameter | Zhang *et al.* (2019) |
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| **First Author and year of publication** | Zhang *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To assess the clinical effects of laser preparation compared to other types of chemical or mechanical preparation of the tooth surfaces used in fissure sealant placement.<br><br>The research aimed to systematically retrieve and analyse clinical studies assessing the effects of laser preparation compared to other tooth surface pre-treatment methods used in fissure sealant placement (p2). |
| **Participants (characteristics and numbers)** | Primary and permanent teeth (planned separate, permanent for primary outcome 1 and secondary outcome 1; unclear dentition for secondary outcome 2, coded as mixed); combined intervention.<br><br>The population of interest was patients who were caries-free and had untreated premolars and/or molars and/or primary molars suitable for pit- and fissure-sealing. |

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| | The five included trials involved a total of 201 participants (39 participants had dropped out by the final follow-up). The age of participants ranged from 6 to 38 years. Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | The trials were conducted in Australia (1 trial), Bulgaria (1 trial), India (1 trial), and Turkey (2 trials).<br><br>The study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was the use of lasers as a pre-treatment method for pit-and-fissure sealing. The comparison group included the use of any other mechanical or chemical preparation for pit-and-fissure sealing, such as acid-etching, enameloplasty or air abrasion.<br><br>Out of the five included trials, two used erbium, chromium: yttrium-scandium-galium garnet (Er, Cr: YSGG) lasers alone, one used a carbon dioxide laser, and two used Er: YAG laser combined with acid etching. All of them used acid-etching as the only comparator.<br><br>The power of the carbon dioxide laser was 5W and that of the erbium lasers ranged from 0.7W to 2.0 W. Two trials reported that the exposure time depended on the time needed to guide the laser beam evenly across the pits and fissures to be irradiated, one did not report exposure time, and the exposure time in the remaining study ranged from 7 to 10 seconds. One study reported that the energy density was 67 J/cm2 and one reported a power density of 530.5 W/cm2. The laser application methods were similar, presenting small differences in the tip-to-tissue distance, tip diameters and angles. The carbon dioxide system was not water-cooled, while the erbium laser systems were equipped with water-cooled systems.<br><br>Follow-up duration ranged from 12 to 36 months, except for one study without a follow-up. Two studies reported drop-out rates according to the follow-up periods. One reported a 17.65% drop-out rate and two reported 0%.<br><br>Two studies performed pit-and-fissure sealants on the first permanent molars, two were performed on the permanent premolars and molars, and one was performed on any intact teeth without caries on the occlusal surface. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Pubmed<br>• Scopus<br>• MEDLINE via OVID |

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| | • Embase via OVID<br>• Cochrane library<br>• ClinicalTrials.gov (www.clinicaltrials.gov)<br>• International Standard Randomised Controlled Trail Number (ISRCTN) registry (www.isrctn.com), and<br>• OpenGrey.<br><br>The databases were searched from inception to January 2019. Language was restricted to English. The reference lists of included articles were also manually searched to identify any additional potentially relevant studies.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved through discussion with a third review author.<br><br>There was no mention of a protocol being prepared or published.<br><br>The review was supported in funding by the National Natural Science Foundation of China and the Innovation and Collaborative Project of Sichuan Science and Technology Agency.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The five included trials were published between 1996 and 2018. |
| **Number of primary studies included in the systematic review** | The review authors included five randomised controlled trials. Of these, three used a split-mouth design and two used a parallel-group design. Follow-up periods ranged from 12 to 36 months, except for one study with no follow up.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included five randomised controlled trials: Durmus (2017), Karaman (2013), Kumar (2016), Shindova (2018), Walsh (1996).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Bulgaria (1 trial), India (1 trial), and Turkey (2 trials). |
| **Appraisal instrument(s)** | The risk of bias in the included trials was assessed according to the Cochrane Handbook for Systematic Reviews of<br>Interventions. Two review authors independently assessed and scored the trials to identify any potential sources of systematic bias. The related risk of |

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| | bias for each domain was rated at three levels: low risk, high risk, or unclear risk. The following domains were assessed in each included trial:<br>• Random sequence generation (selection bias)<br>• Allocation concealment (selection bias)<br>• Blinding of participants and personnel (performance bias)<br>• Blinding of outcome assessment (detection bias)<br>• Incomplete outcome data (attrition bias)<br>• Selective reporting (reporting bias), and<br>• Other bias.<br><br>The comprehensive methodological quality of a trial was classified as low risk of bias (six domains assessed as low risk), moderate risk of bias (one or more domains assessed as unclear risk) or high risk of bias (one or more domains assessed as high risk). Disagreements between the authors were resolved through discussion and, if needed, by consultation with another author. |
| **Appraisal rating** | Overall, all the included trials had a high risk of bias. All trials had a high risk of performance bias (blinding of participants and personnel).<br><br>One trial was categorised as having a low risk of bias for randomisation, and four trials were categorised as having an unclear risk of bias for randomisation.<br><br>Four trials were categorised as having a low risk of bias for outcome ascertainment and one trial was categorised as having a high risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | Statistical heterogeneity was assessed using a Chi-squared test and the Higgins index ($I^2$). Heterogeneity was considered statistically significant for $P < 0.1$. Meta-analyses were performed when there was little clinical heterogeneity. A random-effects model was used for $I^2 > 50\%$ and a fixed-effect model was used for $I^2 \leq 50\%$. Odds ratios and their corresponding 95% confidence intervals were calculated. The statistical significance of the hypothesis test was set at a $\alpha = 0.05$ (two-tailed z tests). All analyses were performed using<br>Revman 5.3 software. The data were summarised qualitatively when a meta-analysis could not be performed.<br><br>Retention rates reflected completely retained sealants. The retention rates were reported according to the different follow-up times in all the studies, ranging from 3 months to 24 months. |

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| **Outcome(s) assessed** | Primary outcome 1: Incidence of caries<br><br>Secondary outcome 1: Retention rate<br><br>Secondary outcome 2: Adverse events (including dental anxiety)<br><br>*Note*. All outcomes are presented as primary outcomes of interest in the review. For the HRB's purposes, the outcomes as presented above are in line with what is are considered primary and secondary outcomes in this umbrella review. |
| **Results/findings** | **Primary outcome 1: Incidence of caries**<br>In one trial with 16 participants, the incidence of caries on permanent premolars and molars in both the Er, Cr: YSGG laser group and the acid etching (control) group prior to application of a light-cure, low-viscosity, fluoride-releasing sealant was 0% at 2 years follow-up.<br><br>Another trial with 51 (9 drop-puts at follow-up) participants reported that the incidence of caries was 10% in the Er: YAG laser plus acid etching group and 22% in the acid-etching only group at 18 months follow-up. However, the difference was not statistically significant.<br><br>**Secondary outcome 1: Retention rate**<br>At 3 months follow-up, there was no significant difference in retention rates between acid-etching and laser preparations (OR 2.78; 95% CI 0.87 to 8.91; 2 trials; 350 teeth; $I^2$ = 0%). This result was similar to those obtained at 6 months (OR 1.22, 95% CI 0.69 to 2.16; 3 trials; 458 teeth; $I^2$ = 0%), 9 months (OR 1.15, 95% CI 0.63 to 2.10; 1 trial; 172 teeth), 12 months (OR 1.05, 95% CI 0.61 to 1.80; 1 trial; 433 teeth), 18 months (OR 0.82, 95% CI 0.23 to 2.85; 1 trial; 112 teeth) and 24 months (OR 0.87, 95% CI 0.31 to 2.45; 1 trial; 112 teeth).<br><br>One trial involving 168 teeth used Er: YAG laser combined with acid etching in the intervention group. The sealant retention rate was significantly higher at 12 (OR 0.39, 95% CI 0.19 to 0.80) and 18 months (OR 0.41, 95% CI 0.21 to 0.80) compared to the acid-etched group, while there were no significant differences in retention rates between these two preparation methods at the 3- (OR 0.47, 95% CI 0.14 to 1.64) and 6-month (OR 0.55, 95% CI 0.23 to 1.43) follow-ups.<br><br>**Secondary outcome 2: Adverse events (including dental anxiety)**<br>One trial subjectively and objectively evaluated dental anxiety when lasers were used to pretreat the dental surface in the process of pit-and-fissure sealing. The authors did not find any significant differences between the initial and final subjective scores for dental anxiety between the Er: YAG laser combined with acid etching conditioning group and the acid etching group. |

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| **Significance/direction** | The present limited evidence suggests that lasers could be an effective pre-treatment method. The retention rate was like that of conventional acid etching. However, the included studies had an overall high risk of bias and more rigorously designed research is needed.<br><br>In summary, our meta-analysis and systematic review demonstrated that laser preparation was a safe, effective and highly acceptable method of enamel preparation before sealant placement. The retention rate of pit-and-fissure sealants after laser preparation alone was comparable to that of acid-etching preparation. Furthermore, laser preparation used as a supplementary method to conventional acid-etching enhanced the retention rate of sealants. However, the current study exhibited an overall high risk of bias. Further research with a better study design is required to provide more reliable evidence for clinical application. |
| **Heterogeneity** | No significant heterogeneity was observed in the analyses. The heterogeneity between studies was 0%. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |

| Parameter | Wang *et al.* (2017) |
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| **First Author and year of publication** | Wang *et al.* (2017) |
| **Objectives (exact review question(s) and page number)** | To assess the effect of non-fluoride agents on the prevention of dental caries in primary dentition (p1). |
| **Participants (characteristics and numbers)** | Primary dentition; topical other chemicals, CHX, calcium phosphate agents, antimicrobial agents, xylitol; combined intervention.<br><br>Studies in which participants had carious lesions in the primary dentition or mixed dentition (outcome reported on primary teeth) at the start of the study were considered for inclusion in this review, irrespective of the baseline caries experience. The inclusion age range of participants was 0–12 years old. All carious lesions (including ICDAS 1 and 2) were included. Studies in which participants had systemic disease were excluded. |

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| | The 14 included studies involved a total of 4,269 participants. All participants were described as healthy by the review authors. The age of participants ranged from 0 to 11 years, and the sample sizes of the studies ranged from 37 to 1,306 children. Information pertaining to the sex of the included participants was not provided.<br><br>The total number of participants in the 13 (out of 14) included trials that inform this umbrella review was 4,193. |
| **Setting/context** | The study countries and study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was non-fluoride agents, such as arginine, chlorhexidine, xylitol, casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) and bioactive glass in any modality that were compared with placebos and/or fluoride were included. No restrictions were implemented regarding the dose, frequency, duration or method of non-fluoride agent administration.<br><br>Five chemical agents, namely arginine, CPP-ACP, chlorhexidine, triclosan and xylitol were investigated in these included studies. One trial reported the topical application of arginine mint confection. Seven trials investigated the efficacy of chlorhexidine. Of these, four were in the form a 1–40% chlorhexidine varnish and three were in the form of a 0.12% - 1% chlorhexidine gel varnish. Three trials reported the effect of xylitol in the form of a tablet, wipe and gummy bear. And finally, one assessed the effect of a 0.3% triclosan varnish. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Medline via PubMed<br>• Web of Science<br>• EMBASE<br>• CENTRAL (Cochrane Library)<br>• CBM (Chinese Biological Medical) database<br>• CNKI (Chinese National Knowledge Infrastructure) database<br>• ClinicalTrial.gov<br>• OpenGrey, and<br>• World Health Organization's International Clinical Trial Registry Platform.<br><br>The reference lists of related papers and review articles were also searched to identify any additional potentially relevant studies. No restrictions were placed on language or year of publication. All searches were first conducted on 25 December 2015 and updated on 16 December 2016. |

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| | Two review authors independently screened search results (title and abstracts) and performed data extraction. Disagreements were resolved by discussion and consultation with a third review author.<br><br>The review was not registered before data collection.<br><br>The review was supported in funding by the National Natural Science Foundation of China.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 14 included trials were published between 1994 and 2015. |
| **Number of primary studies included in the systematic review** | The review authors included 14 randomised controlled trials. The duration of the studies ranged from 3 to 36 months.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 14 randomised controlled trials: Acevedo (2006), Gisselsson (1994), Tai (2003), Baca (2004), Du (2006), Amorim (2008), Plonka (2013), Pukallus (2013), Sitthisettapong (2012), Memarpor (2015), Cao (2007), Oscarson (2006), Zhan (2012), and Lee (2015).<br><br>The results of 13 randomised controlled trials were relevant to the objectives of this umbrella review: Acevedo (2006), Gisselsson (1994), Tai (2003), Baca (2004), Du (2006), Plonka (2013), Pukallus (2013), Sitthisettapong (2012), Memarpor (2015), Cao (2007), Oscarson (2006), Zhan (2012), and Lee (2015).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | The study countries were not reported. |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of the included studies using the evaluation method recommended by the Cochrane Handbook for Systematic Reviews for Interventions 5.1.0. The following domains were assessed in each included trial:<br>1. Random sequence generation<br>2. Allocation concealment<br>3. Blinding<br>4. Completeness of outcome data<br>5. Selective outcome reporting, and |

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| | 6. Other biases.<br><br>Each domain was classified as having either a low, high, or unclear risk of bias. Thus, the overall level of risk for each study was subsequently classified as low (all quality items were met), unclear (unclear risk of bias for one or more domain), or high (high risk of bias for one or more domain). |
| **Appraisal rating** | Overall, only one trial was categorised as having a low risk of bias. Three trials had an unclear risk of bias, and the remaining ten trials were scored as having a high risk of bias. Of the 13 trials relevant to this umbrella review, one had a low risk of bias, three had an unclear risk of bias, and nine had a high risk of bias.<br><br>Six trials were categorised as having a low risk of bias for randomisation, seven trials were categorised as having an unclear risk of bias for randomisation, and one trial was categorised as having a high risk of bias for randomisation. Of the 13 trials relevant to this umbrella review, six had a low risk of bias for randomisation, six had an unclear risk of bias for randomisation, and one had a high risk of bias for randomisation.<br><br>Eleven trials were categorised as having a low risk of bias for outcome ascertainment, two trials were categorised as having an unclear risk of bias for outcome ascertainment, and one trial was categorised as having a high risk of bias for outcome ascertainment. Of the 13 trials relevant to this umbrella review, eleven had a low risk of bias for outcome ascertainment, one had an unclear risk of bias for outcome ascertainment, and one had a high risk of bias for outcome ascertainment.<br><br>Publication bias was not statistically measured. |
| **Method of analysis** | Meta-analyses were not performed due to the significant heterogeneity among the included studies. Instead, results were described narratively. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment (dmfs/dmft/defs)<br><br>Primary outcome 2: Change in the proportion of participants developing new caries on primary teeth<br><br>Secondary outcome 1: Side effects<br><br>*Note*. All outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Caries increment (dmfs/dmft/defs)**<br><u>Intervention 1: Arginine confection + fluoride toothpaste versus control confection + fluoride toothpaste:</u><br>One high risk of bias trial with 195 participants found arginine-containing mint confection + fluoride toothpaste, 4 times per day, significantly reduced |

caries development in primary molars compared with placebo after 6 months (mean test defs = 0.95, mean control defs = 1.29) and 12 months (mean test defs = 0.81, mean control defs = 1.09). No P value was reported.

Intervention 2: Chlorhexidine versus placebo or no treatment:
Four trials with a total of 2,010 participants showed that chlorhexidine had caries-reducing potential in primary teeth at 2-3 years follow-up (one trial used 1% CHX gel applied 4 times per year, 2 trials used 40% CHX varnish applied every 6 months, and 1 trial used 1% CHX-thymol varnish applied every 2 months). 1 trial reported on defs scores, 1 trial reported on def scores and/or dmfs-molar scores, 1 trial reported on dmft and dmfs scores, and 1 trial reported on dmfs-molar scores.

Intervention 3: CPP-ACP versus fluoride varnish/toothpaste or placebo*:*
One high risk of bias trial with 122 participants (albeit the combined sample size of the three groups analysed in these comparisons was 91 (30 in the CPP-ACP group, 29 in the fluoride varnish group, and 32 in the no treatment group)) reported that the application of CPP-ACP mousse twice per day over a 12-month period was associated with smaller increase in dmft index compared with no treatment or fluoride varnish: test 1 (CPP-ACP) mean dmft = 0.17, control mean dmft = 2, test 2 (fluoride varnish) mean dmft = 0.3, control mean dmft = 2. The statistical significance was not reported.

Intervention 4: Xylitol versus placebo or no treatment:
One study with 118 participants evaluated products containing low doses of xylitol (0.5-1.0 g/ tablet) and found no difference in cariostatic activity (assessed via dmfs and number of children with new caries) at 24 months of follow-up.

Another trial involving 260 participants found the consumption of xylitol gummy bears (7.8 g/d) twice per day did not provide additional benefit (assessed via dmfs) beyond regular hygiene at 30 months follow-up.

Intervention 5: Triclosan varnish versus no treatment
One trial with 561 participants found that 0.3% triclosan varnish twice per year was more effective than a blank control in reducing caries incidence for children aged 2-5 years old during its one-year follow-up period (test mean dmft 1.34, control mean dmft 1.72; test mean dmfs 1.47, control mean dmfs 2.11).

**Primary outcome 2: Change in the proportion of participants developing new caries on primary teeth**

Intervention 1: Arginine confection + fluoride toothpaste versus control confection + fluoride toothpaste:
No trials assessing this intervention reported this outcome.

Intervention 2: Chlorhexidine versus placebo or no treatment:
One trial with 542 participants showed that the combined use of 0.12% chlorhexidine gel applied once daily and twice daily toothbrushing with fluoride toothpaste had no caries-reducing potential in primary teeth compared to no gel + compared to twice daily toothbrushing with fluoride toothpaste at 24 months follow-up. The number of infants with caries was 4/180 (2%) in the test group and 3/188 (2%) in the control group.

Another trial with 119 infants showed that the combined use of 0.12% chlorhexidine gel applied once daily and twice daily toothbrushing with low-dose fluoride toothpaste had limited caries-reducing potential in primary teeth at 24 months follow-up compared to twice daily toothbrushing with low-dose fluoride toothpaste. The number of infants with caries was 3/61 (5%) in the test group and 4/58 (7%) in the control group.

Intervention 3: CPP-ACP versus fluoride varnish/toothpaste or placebo:
One trial with 542 participants (531 completed) showed that the combined use of 10% CPP-ACP paste applied once daily and twice daily toothbrushing with fluoride toothpaste had a slight (albeit unlikely significant) caries-reducing potential in primary teeth compared to twice daily toothbrushing with fluoride toothpaste at 24 months follow-up. The number of infants with caries was 2/163 (1%) in the test group and 3/188 (2%) in the control group (there was another test group which brought the total number of participants to 531 (542 commenced, 531 at follow-up).

Intervention 4: Xylitol versus placebo or no treatment:
One low risk of bias trial with 37 participants found the number of participants with caries was lower among those who used xylitol wipes (4.2g/d) compared to those who received placebo wipes (1/20 in test group compared to 6/17 in control group).

Intervention 5: Triclosan varnish versus no treatment
No trials assessing this intervention reported this outcome.

**Secondary outcome 1: Side effects**
Intervention 1: Arginine confection + fluoride toothpaste versus control confection + fluoride toothpaste:
No trials assessing this intervention reported this outcome.

Intervention 2: Chlorhexidine versus placebo or no treatment:
Four trials presented information on the side effects of chlorhexidine varnish and gel. No serious side effects were reported during the 24-month observation period.

Intervention 3: CPP-ACP versus fluoride varnish or placebo:
One trial found the use of 10% CPP-ACP paste to have no adverse effects. Another study of CPP-ACP paste failed to provide information on side

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| | effects; however, the author was contacted by email and confirmed that no extra calculus formation had occurred on the primary teeth in their experimental group.<br><br>Intervention 4: Xylitol versus placebo or no treatment:<br>In a 12-month trial of xylitol wipes, no side effects (including allergy, flatulence and diarrhoea) were reported by the parents. In another trial, no major side effects from the xylitol-containing gummy bears intervention were reported.<br><br>Intervention 5: Triclosan varnish versus no treatment<br>No trials assessing this intervention reported this outcome. |
| **Significance/direction** | Available evidence suggests chlorhexidine and CPP-ACP may be more effective than placebo in preventing caries in primary dentition, but their efficacy relative to fluoride is still unclear. Arginine-containing mint confection and 0.3% triclosan varnish were found to reduce caries development in primary teeth but the evidence was at high risk ofbias. High quality randomised controlled trials are needed to make a definitive recommendation. |
| **Heterogeneity** | No meta-analyses were conducted due to the significant heterogeneity observed among included studies. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Twetman *et al.* (2021) |
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| **First Author and year of publication** | Twetman *et al.* (2021) |
| **Objectives (exact review question(s) and page number)** | To explore the preventive effect of probiotic supplements on the development of early childhood caries (p231). |
| **Participants (characteristics and numbers)** | Primary dentition; topical other chemicals, probiotics.<br><br>The population of interest was infants, toddlers and preschool children between the ages of 0 to 6 years. |

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| | The nine included trials involved a total of 2,363 preschool children with ages ranging from three weeks to six years. The number of participating children per trial ranged from 42 to 595 with a median value of 248. One trial involved participants who had active caries. This trial was excluded for the purposes of this review as it was focussed on treatment and not prevention. Information pertaining to the sex of included participants was not provided.<br><br>The total number of participants in the 7 (out of 9) included trials that inform this umbrella review was 1,663. |
| **Setting/context** | The trials were conducted in Chile (2 trials), Columbia (1 trial), Finland (2 trials), Sweden (2 trials), and Thailand (2 trials).<br><br>Seven trials were conducted in a day-care setting and two trials were conducting in a home setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was live probiotic bacteria delivered in the form of milk or tablets/lozenges. The control group was the intake of placebo milk, placebo tablets/lozenges or treatment as usual.<br><br>Among the included trials, six investigations utilised various *Lactobacillus* strains, one tested a single *Bifidobacterium* strain, one relied on a mix of *Streptococcus* strains, and in one a mix of genera was used. In seven trials, the vehicle for administration was milk served in day-care settings, while two studies relied on tablets given via pacifiers or crushed and mixed with food. The frequency of administration ranged from once daily to 3 times/week.<br><br>The authors note that the risk of bias assessment raised questions concerning the sample selection and sample size, study performance and attrition, which lowered the certainty of evidence. For example, the study by Stecksén-Blicks and co-workers (2009) was flawed by the addition of 2.5 mg/kg fluoride in the probiotic milk. No other instances of combined interventions were noted. However, as this one combined intervention was provided as an example, there is a possibility that other trials included in the review involved the delivery of combined interventions. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Google Scholar<br>• Cochrane Oral Health Group's Trials Register, and<br>• www.clinicaltrials.gov.<br><br>The databases were searched up to 15 January 2021. The reference lists of all accepted papers and systematic reviews were hand-searched for possible additional references. Language was restricted to English. |

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| | Two review authors independently screened search results (title and abstracts) and performed data extraction. Disagreements were resolved by consensus.<br><br>The review protocol was not pre-registered in a publicly accessible database.<br><br>The funding source(s) of the review was not reported.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The nine included trials were published between 2001 and 2021. |
| **Number of primary studies included in the systematic review** | The review authors included nine randomised controlled trials. Of these, five were randomised on an individual level and four were randomised on a cluster level. The duration of the trials ranged from 6 months to 2 years.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included nine randomised controlled trials: Hedayati-Hajikand (2015), Nase (2001), Pahumunto (2018), Piwat (2020), Rodriguez (2016), Sandoval (2021), Stecksen-Blicks (2009), Taipale (2013), and Villavicencio (2018).<br><br>The results of seven trials informed the outcomes of interest to this umbrella review: Hedayati-Hajikand (2015), Pahumunto (2018), Piwat (2020), Rodriguez (2016), Sandoval (2021), Stecksen-Blicks (2009), and Villavicencio (2018).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | The trials were conducted in Chile (2 trials), Columbia (1 trial), Finland (2 trials), Sweden (2 trials), and Thailand (2 trials). |
| **Appraisal instrument(s)** | The authors assessed the risk of bias independently according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). Disagreements were solved with a consensus discussion. The following domains were assessed in each included trial:<br>1. Selection bias<br>2. Performance bias<br>3. Detection bias<br>4. Reporting bias<br>5. Attrition bias, and |

6. Other bias.

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| **Appraisal rating** | Overall, no trial was assessed as having a low risk of bias. Two trials were assessed as having a moderate risk of bias and seven trials were assessed as having a high risk of bias. The most common shortcomings were attrition bias, selection bias and performance bias. Of the 7 trials relevant to this umbrella review, two were assessed as having a moderate risk of bias and five were assessed as having a high risk of bias.<br><br>Three trials were categorised as having a low risk of selection bias, three trials were categorised as having an unclear risk of selection bias, and three trials were categorised as having a high risk of selection bias. Of the 7 trials relevant to this umbrella review, three trials were categorised as having a low risk of selection bias, two trials were categorised as having an unclear risk of selection bias, and two trials were categorised as having a high risk of selection bias. It was not possible to isolate the risk of randomisation from allocation concealment.<br><br>All trials were categorised as having a low risk of detection bias (outcome ascertainment).<br><br>Publication bias could not be measured since less than 10 primary studies were included. |
| **Method of analysis** | The review authors applied unadjusted dichotomous data (new caries vs no new caries) to calculate the risk ratio with<br>95% confidence intervals for each separate study. Mean differences with 95% confidence intervals were calculated for continuous data. Data was thereafter pooled in a random effects model using the Review Manager 5.3 tool. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment (decayed, missed and filled primary teeth (dmft) or surfaces (dmfs)<br><br>Secondary outcome 1: Adverse events<br><br>*Note*. Primary outcome 1 is identified as a secondary outcome in the review (the primary outcome identified in the review is listed below under "outcome(s) excluded"). For the HRB's purposes, it is considered a primary outcome. The nature of secondary outcome 1 (primary or secondary) is not made explicit in the review (assumed secondary as this outcome is not listed alongside the other outcomes in the review but presented only in the results). For the HRB's purposes, it is considered a secondary outcome. |
| **Outcome(s) excluded from umbrella review** | Primary outcome: Incidence of caries on a subject level. |

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| | As the incidence of caries was defined as "the proportion of individuals with new or progressing caries lesions", the new caries could not be distinguished from the progressing caries, and this outcome was therefore excluded. |
| **Results/findings** | **Primary outcome 1: Increment of caries on tooth or surface level**<br>The mean number of new decayed teeth/tooth surfaces was significantly lower in the probiotic test group compared to the control group at 6-24 months follow-up (MD -0.57, 95% CI -0.91 to -0.23, p = 0.0010; 7 trials; 1,331 teeth/surfaces; $I^2$ = 32%). The mean number of new decayed tooth/surfaces ranged from 0.2 to 5.5.<br><br>*Note*. The seven trials varied in relation to the type of bacteria, the dose/frequency, and mode of delivery (tablets and milk). 6/7 trials used probiotic milk (2 used 50 powder milk once per day, 3 used 150ml powder or fresh milks on weekdays, and 1 used 200ml powder milk on weekdays). 1/7 trials used probiotic tablets (1 per day).<br><br>*Note*. At least one of these included trials (Stecksén-Blicks 2009) delivered a combined intervention involving 2.5 mg/kg fluoride in probiotic milk. However, there is a possibility that more than one trial delivered a combined intervention, as this information was not described in-depth in the review.<br><br>**Secondary outcome 1: Adverse events**<br>No included trials reported this outcome. |
| **Significance/direction** | The review authors demonstrated a small but statistically significant preventive effect of probiotic supplements on early childhood caries. However, the certainty of this finding was low due to heterogeneity and inconsistencies across the trials. Further long-term randomised controlled trials with low risk of bias are required in order to answer the research question with a higher certainty. |
| **Heterogeneity** | The review authors described the certainty of evidence as low due to risk of bias, heterogeneity, and inconsistencies across the studies. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Subbiah & Gopinathan (2018) |
| **First Author and year of publication** | Subbiah & Gopinathan (2018) |

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| **Objectives (exact review question(s) and page number)** | To evaluate the scientific evidence regarding the effectiveness of silver diamine fluoride in preventing and arresting caries in elderly adults (p192).<br><br>*Note*. The HRB is only interested in the findings from studies that are focussed on caries prevention and so excluded the caries arrest aspect of the review. |
| **Participants (characteristics and numbers)** | Permanent dentition; topical fluoride, solution; combined intervention.<br><br>The population of interest was adults aged 60 years and over with or without dental caries. The three included trials involved a total of 655 participants. Information in relation to the age and sex of included participants was not provided.<br><br>The total number of participants in the 2 (out of 3) included trials that inform this umbrella review was 572. |
| **Setting/context** | All three trials were conducted in Hong Kong.<br><br>Two trials were conducted in elderly community centres and one trial was conducted in residential and nursing homes. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was silver diamine fluoride (SDF). The comparison group was either other interventions or a placebo.<br><br>The SDF used in all three trials were the same preparation, that is, 38% SDF solution. Disposable microbrushes were used for the painting of SDF on the affected or exposed root surfaces without any excavation of caries.<br><br>In one trial, the treatment group received 38% SDF application every 12 months. The control group received either chlorhexidine or sodium fluoride every three months, or water every 12 months.<br><br>In the second trial, the treatment groups received either (a) 38% SDF + oral health instruction (OHI) or (b) 38% SDF + OHI + OHE (oral health education). SDF application was administered every 12 months and OHE every 6 months. The control group received OHI + water (placebo) every 12 months. The oral health education (OHE) program was directed at controlling the snacking habit, teaching the correct grasp of the toothbrush, and use of additional tooth-cleaning aids. This was administered by a trained dental hygienist and each session lasted for 30 minutes.<br><br>In the third trial (not relevant to this umbrella review), the treatment groups received either (a) 38% SDF or (b) 38% SDF + potassium iodide (KI) every 12 months. The control group received soda water (placebo) every 12 months. This trial is not relevant to HRB purposes. |

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| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• MEDLINE<br>• Embase, and<br>• CENTRAL (Cochrane Central Register of Controlled Trials).<br>Other information sources included all peer-reviewed dental and related journals available online in databases, popular online internet search engines (e.g. Google, Yahoo, etc.), online internet research community websites (https:// www.researchgate.net/), reference crosschecks, personal communications, hand searches and grey literature. The search was conducted from January 2017 to October 2017. No restrictions were placed no language.<br><br>Two review authors independently screened search results (title and abstract screening). Any disputes regarding eligibility of a study were resolved by discussion among the reviewers. It was not reported how data extraction was completed.<br><br>There was no specific mention of a protocol being registered; however, the review authors mentioned that an eligibility protocol was prepared.<br><br>The review received no funding.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The three included trials were published between 2010 and 2016. |
| **Number of primary studies included in the systematic review** | The review authors included three double-blinded randomised controlled trials. Follow-up periods ranged from 6 to 36 months.<br><br>The funding sources of the primary studies were not provided. |
| **Types of studies included** | The review authors included three randomised controlled trials: Tan (2010), Zhang (2013), and Li (2016).<br><br>The results of two trials informed the outcomes of interest to this umbrella review: Tan (2010) and Zhang (2013).<br><br>Reasons for exclusion are provided but not a list of excluded studies. |
| **Country of origin of included studies** | All three trials were conducted in Hong Kong. |

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| **Appraisal instrument(s)** | The Cochrane's Risk of Bias tool was used for assessing the methodological quality in the trial. The following domains were assessed in each included trial:<br>1. Random sequence generation<br>2. Allocation concealment<br>3. Blinding<br>4. Incomplete outcome data<br>5. Selective outcome reporting, and<br>6. Other sources of bias. |
| **Appraisal rating** | The review authors described all three trials as being of high quality and having a low degree of bias.<br><br>However, HRB notes that according to Cochrane's Collaboration trial, at least two trials were categorised as having a high risk of bias in one domain.<br><br>All three trials had a low risk of bias for randomisation and outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | Results were described narratively. The prevented fraction was quantified from the extracted data. |
| **Outcome(s) assessed** | Primary outcome 1: New root caries (measured by mean number of new root carious surfaces and/or prevented fraction; DMFRS)<br><br>Secondary outcome 1: Acute or chronic toxicity associated with SDF during the length of the trial<br><br>Secondary outcome 2: Patient-reported adverse events<br><br>*Note*. All outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: New root caries (DMFS)**<br>In one trial, the prevented fraction for the root caries for 38% SDF was calculated as 71% which was better than chlorhexidine (57%) and sodium fluoride varnish (64%) ($P < 0.001$) at 36 months follow-up. In addition, all three interventions had significantly lower mean number of new root caries surfaces ($P < 0.01$) than the control.<br><br>In the other trial, OHI + 38% SDF had a significantly better effect on prevention ($P < 0.05$) of root caries than OHI alone at 24 months follow-up. Additional improvement was seen with adding OHE to OHI + SDF ($P < 0.05$). |

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| | The mean number of new caries was noted to be 1.33, 1.00, and 0.70 for the control, SDF, and SDF + OHE groups, respectively. The prevention fraction was calculated as 25% and 47% for the SDF + OHI and SDF + OHI + OHE groups, respectively (n = 299 participants commenced the trial, drop out = 39).<br><br>**Secondary outcome 1: Acute or chronic toxicity associated with SDF during the length of the trial**<br>No included trials reported this outcome.<br><br>**Secondary outcome 2: Patient-reported adverse events**<br>No included trials reported this outcome. |
| **Significance/direction** | The available limited evidence on silver diamine fluoride shows that it is effective in preventing root caries in the elderly. More high-quality studies are needed to verify the effectiveness on coronal caries and long-term effects of silver diamine fluoride in the elderly with varying levels of dependency. |
| **Heterogeneity** | The heterogeneity among included studies was not discussed. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as moderate. |
| **References to previously published versions** | N/A |
| Parameter | Sharda *et al.* (2021) |
| **First Author and year of publication** | Sharda *et al.* (2021) |
| **Objectives (exact review question(s) and page number)** | To compare the remineralising potential and caries preventive efficacy of combined therapy using CPP-ACP/bioactive glass/xylitol/ozone and topical fluoride versus topical fluoride monotherapy on high-risk individuals (p403).<br><br>*Note*. The HRB is only interested in the findings from studies that are focussed on caries prevention and so excluded the remineralising aspect of the review. |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (mixed); combined intervention.<br><br>The 26 included trials involved approximately 7,955 participants. All participants were considered at high risk of dental caries. Only data from 16 |

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| | of the trials was pooled. The age of participants ranged from 0 to 70 years. Information pertaining to the sex of included participants was not reported.<br><br>The total number of participants in the 14 (out of 26) included trials that inform this umbrella review was 7,182. |
| **Setting/context** | The trials were conducted in Australia (4 trials), Brazil (2 trials), Costa Rica (2 trials), Denmark (1 trial), Germany (2 trials), Jordan (2 trials), Italy (1 trial), Romania (1 trial), Sweden (1 trial), Switzerland (1 trial), Thailand (3 trials), Turkey (5 trials), and the United States (1 trial).<br><br>The study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was topical fluoride combined with CPP-ACP, xylitol, bioactive glass or ozone. The comparison group was topical fluoride alone.<br><br>In the included trials, topical fluoride was administered as a toothpaste, mouthrinse or varnish. CPP-ACP was administered as a 3% w/v gum, varnish or as a cream/paste. Xylitol was administered in a toothpaste or gum form. Ozone was administered in a gaseous form, and bioactive glass was administered in a cream form. However, in the trials that both reported outcomes that were relevant to this umbrella review and contributed data to the meta-analyses, the only interventions being evaluated were CPP-ACP and xylitol. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Embase<br>• PubMed<br>• Scopus<br>• Web of Science<br>• Cochrane library databases<br>• OpenGrey, and<br>• TRIP.<br><br>Cross-references were screened to obtain additional records. Studies published till May 2020 were considered for inclusion. Language was restricted to English.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved by discussion and consensus.<br><br>The review protocol was registered with PROSPERO (ID: CRD42020150746). |

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| | Any funding source(s) of the review were not reported.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 26 included trials were published between 1995 and 2020. |
| **Number of primary studies included in the systematic review** | The review authors included 26 randomised controlled trials. In at least one trial randomisation occurred at a cluster level. Follow-up periods in the trials that relevant to this umbrella review ranged from 21 days to 36 months.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 26 randomised controlled trials: Al-Batayneh (2020a), Al-Batayneh (2020b), Alexandrino (2017), Almaz (2020), Altenberger (2010), Aykut-Yetkiner (2014), Bailey (2009), Bobu (2019), Brochner (2011), Campus (2009), Chi (2014), Esenlik (2016), Guclu (2016), Huth (2005), Karabekiroglu (2017), Kronenberg (2009), Mendes (2018), Mitrakul (2017), Morgan (2008), Plonka (2013), Pukallus (2013), Sintes (1959), Sintes (2002), Sitthisettapong (2012), Sitthisettapong (2015), and Twetman (1995).<br><br>The results of 14 trials informed the outcomes of this umbrella review: Al-Batayneh (2020a), Almaz (2020), Aykut-Yetkiner (2014), Campus (2009), Chi (2014), Esenlik (2016), Karabekiroglu (2017), Mitrakul (2017), Morgan (2008), Plonka (2013), Pukallus (2013), Sintes (1995), Sintes (2002), and Twetman (1995).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Australia (4 trials), Brazil (2 trials), Costa Rica (2 trials), Denmark (1 trial), Germany (2 trials), Jordan (2 trials), Italy (1 trial), Romania (1 trial), Sweden (1 trial), Switzerland (1 trial), Thailand (3 trials), Turkey (5 trials), and the United States (1 trial). |
| **Appraisal instrument(s)** | Two review authors assessed the risk of bias of included studies using the Cochrane's Collaboration tool for Systematic Reviews. Any disagreements were resolved by discussion with a third review author. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias) |

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| | 6. Selective reporting (reporting bias), and<br>7. Other bias. |
| **Appraisal rating** | Overall, only one trial was categorised as having a low risk of bias. Four trials were categorised as having an unclear risk of bias, and the remaining 21 trials were categorised as having a high risk of bias. Most trials did not report the method of randomisation sequence generation or allocation concealment. In addition, in many trials blinding of the participants/personnel was not done. Of the 14 trials that were relevant to this umbrella review, three were categorised as having an unclear risk of bias, and 11 were categorised as having a high risk of bias.<br><br>Twelve trials were categorised as having a low risk of bias for randomisation, 11 trials were categorised as having an unclear risk of bias for randomisation, and three trials were categorised as having a high risk of bias for randomisation. Of the 14 trials relevant to this umbrella review, six were categorised as having a low risk of bias for randomisation, seven were categorised as having an unclear risk of bias for randomisation, and one was categorised as having a high risk of bias for randomisation.<br><br>Eighteen trials were categorised as having a low risk of bias for outcome ascertainment, six trials were categorised as having an unclear risk of bias outcome ascertainment, and two trials were categorised as having a high risk of bias for outcome ascertainment. Of the 14 trails relevant to this umbrella review, ten were categorised as having a low risk of bias for outcome ascertainment, and four were categorised as having an unclear risk of bias outcome ascertainment.<br><br>The certainty of evidence was assessed with reference to risk of bias, imprecision, inconsistency, indirectness, and publication bias. For the outcomes relevant to this umbrella review, the certainty of evidence was assessed as low.<br><br>Publication bias was not measured. |
| **Method of analysis** | Quantitative analysis was performed using the Review Manager Version 5.4. For the evaluation of post-intervention *S mutans* colony counts, studies with a minimum follow-up of one month were pooled, whereas a minimum follow-up of<br>one year was chosen to assess the mean dental caries increment. A minimum follow-up time was specified for pooling of studies to prevent misleading results and to ensure homogeneity amongst the studies pooled. For the trials that reported the outcome variables as dichotomous data, the estimate of effect expressed as odds ratio along with 95%<br>confidence interval was converted to standard mean difference and standard error. This was pooled with the standardised mean difference |

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| | derived from trials that have reported the same outcome variable as continuous data using the random effect model and generic inverse variance method.<br><br>Due to the variability in the scales used to assess the outcomes, standardised mean differences with 95% Confidence Intervals were used. A p value < 0.05 was considered statistically significant. Due to the high clinical heterogeneity observed, a random effects model was used. Subgroup analysis was carried out for individual agents. Statistical heterogeneity was quantified using the $I^2$ statistic, where an $I^2$ value greater than 50% was considered as moderate to high heterogeneity. |
| **Outcome(s) assessed** | Primary outcome 1: Caries prevention (measured by the mean dental caries increment/proportion of subjects with new carious lesions)<br><br>Secondary outcome 1: *S mutans* counts<br><br>*Note*. Primary outcome 1 is identified as a secondary outcome in the review (the primary outcome identified in the review is related to caries progression). For the HRB's purposes, it is considered a primary outcome. Secondary outcome 1 is identified as a secondary outcome in the review. |
| **Results/findings** | **Primary outcome 1: Caries prevention (mean increment/proportion of participants with new caries)**<br>Of the eight trials that reported this outcome, only five contributed data to the meta-analyses.<br><br>Overall results significantly favoured the combined therapy over topical fluoride use alone (SMD -0.14, 95% CI -0.19 to -0.08, p < 0.00001; 5 trials; 6,448 participants; $I^2$ = 0%; low certainty of evidence).<br><br>Moreover, the subgroup analysis comparing xylitol + topical fluoride combined therapy and topical fluoride alone also showed a significant difference in favour of the combined therapy (SMD -0.14, 95% CI -0.21 to -0.07, p < 0.0001; 2 trials; 1742 participants; $I^2$ = 16%; low certainty of evidence).<br><br>However, the subgroup analysis comparing CPP-ACP + topical fluoride combined therapy and topical fluoride alone showed no significant difference in caries increment (SMD -0.21, 95% CI -0.55 to 0.13, p = 0.23; 3 trials; 2232 participants; $I^2$ = 12%; low certainty of evidence).<br><br>**Primary outcome 2: *S mutans* counts**<br>Of the 11 trials that reported this outcome, only seven contributed data to the meta-analyses. |

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| | Overall results significantly favoured the combined therapy over topical fluoride use alone (SMD -0.28, 95% CI -0.46 to -0.10, p = 0.003; 7 trials; 853 participants; $I^2$ = 18%; low certainty of evidence).<br><br>In addition, the subgroup analysis comparing CPP-ACP + topical fluoride combined therapy and topical fluoride alone also showed a significant difference in favour of the combined therapy (SMD -0.42, 95% CI -0.62 to -0.23, p < 0.0001; 5 trials; 640 participants; $I^2$ = 0%; low certainty of evidence).<br><br>However, the subgroup analysis comparing xylitol + topical fluoride combined therapy and topical fluoride alone showed no significant difference in post intervention *S mutans* counts (SMD -0.02, 95% CI -0.27 to 0.27, p = 0.89; 2 trials; 220 participants; $I^2$ = 0%; low certainty of evidence). |
| **Significance/direction** | Available evidence shows CPP-ACP-fluoride combined therapy is no more effective in preventing new lesions than fluoride use alone. Xylitol, on the other hand, is shown to exert an added benefit over fluoride in preventing caries increment. However, the effect estimate is graded to be of low certainty. Thus, future trials addressing the same research question may have a substantial impact on the results obtained.<br><br>CPP-ACP-fluoride combined therapy exhibits superior remineralization potential and antibacterial effect but not more effective in preventing new lesions over fluoride use alone. Xylitol, on the other hand, is shown to exert an added benefit over fluoride in preventing caries increment. However, the effect estimate is graded to be of low certainty. Thus, future trials addressing the same research question may have a substantial impact on the results obtained. |
| **Heterogeneity** | No significant heterogeneity was observed in any meta-analysis. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence with respect to both outcomes as low.<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Smith *et al.* (2018) |
| **First Author and year of publication** | Smith *et al.* (2018) |

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| **Objectives (exact review question(s) and page number)** | To systematically review the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries (p334). |
| **Participants (characteristics and numbers)** | Primary dentition; topical fluoride, varnishes; topical other chemicals, CHX; combined intervention.<br><br>The population of interest was indigenous children from high-income countries aged five years and under at the time of study completion. As advised by the World Health Organisation, an inclusive definition of the term Indigenous was used (WHO, 2007). Countries categorised as 'high income' were those defined by the World Bank income category (WHO, 2014).<br><br>The four included trials involved a total of 2,311 participants, there was also a secondary analysis of a previous trial included in the study. The age of participants ranged from birth to 5 years at baseline and from 22 months to 5+ years at completion. Information pertaining to the gender of included participants was not provided.<br><br>The total number of participants in the 2 (out of 4) included trials that inform this umbrella review was 1,527. The age of participants in these relevant trials ranged from 4.5 months to 5 years at baseline and 22 months to 5+ years at completion. |
| **Setting/context** | The trials were conducted in Australia (1 trial), Canada (2 trials), and the United States (1 trial).<br><br>The two relevant trials were conducted in Canada (1 trial) and the United States (1 trial).<br><br>All four trials were conducted in Aboriginal communities. Specifically, two trials took place within a dental clinic and one trial took place within a community clinic. It was not specified where the remaining trial took place. |
| **Description of Interventions/ phenomena of interest** | The intervention(s) of interest included any intervention intended to prevent dental caries in Aboriginal children. Studies evaluating interventions to treat dental disease, such as filling of cavities, were excluded.<br><br>The review authors included four studies in the review. Two of these studies evaluated the effect of a 5% w/v sodium fluoride varnish combined with caregiver counselling or health promotion. In one, the fluoride varnish was applied twice yearly and in the second, the fluoride varnish was applied at baseline and at 4 – 6-month intervals.<br><br>The third study evaluated the effect of four weekly applications of a 10% chlorhexidine varnish to mothers and a single application when their offspring were 12, 18, and 24 months old. |

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| | The fourth study evaluated the effect of maternal counselling using motivational interviewing techniques plus access to oral hygiene materials and a dental examination. For the purposes of this umbrella review, the effect of a motivational interviewing technique was not of interest and the findings from the study were therefore excluded (Harrison, 2012).<br><br>Alas, the review authors compared the following three relevant interventions:<br>1. 5% w/v sodium fluoride varnish + caregiver counselling versus caregiver counselling alone<br>2. 5% w/v sodium fluoride varnish versus no intervention<br>3. 10% chlorhexidine varnish versus placebo varnish |
| **Databases and sources searched** | The review authors searched the following sources:<br>• MEDLINE (from January 1946)<br>• Embase (from January 1980)<br>• Cochrane Central Register of Controlled trials (CENTRAL)<br>• Cochrane Library (latest issue)<br>• PubMed (from January 1996)<br>• Cumulative Index to Nursing and Allied Health Literature (CINAHL) (from 1982)<br><br>All databases were searched up to November 2016. The reference lists of all included studies were checked for other potential suitable trials. In addition, the first authors of included trials and known researchers in the field were contacted via e-mail to assist in identifying relevant unpublished and published trials.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening). Disagreements were resolved by discussion. One review author then extracted data from eligible studies using standardised and pilot-tested forms, and these were verified by another review author.<br><br>The review protocol was published and registered with PROSPERO (ID: CRD42016049391).<br><br>The review was supported in funding by a grant from the Australian National Health and Medical Research Council.<br><br>Conflicts of interest were not reported. |

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| **Date range (years) of included studies** | The four included trials were published between 2008 and 2013. |
| **Number of primary studies included in the systematic review** | The review authors included four randomised controlled trials. A fifth study was also included; however, this paper was a secondary analysis of one of the included trials and for ease of interpretation the two papers were referred to as one study. The findings derived from the second analysis were excluded due to both inappropriate study design and irrelevant outcomes (Robertson, 2013).<br><br>Of the four randomised controlled trials, three were randomised on a cluster level and one was randomised on an individual level.<br><br>Funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included four randomised controlled trials and one secondary analysis study: Lawrence (2008), Slade (2011), Robertson (2013), Harrison (2012), Roberts-Thomson (2010).<br><br>The results of two randomised controlled trials were relevant to the objectives of this umbrella review: Lawrence (2008) and Robertson (2013).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Canada (2 trials), and the United States (1 trial).<br><br>The two relevant trials were conducted in Canada (1 trial) and the United States (1 trial). |
| **Appraisal instrument(s)** | Two review authors independently assessed risk of bias of included trials using criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).<br><br>The following domains were assessed in each included trial:<br>1. Sequence generation<br>2. Allocation concealment<br>3. Blinding of participants<br>4. Blinding of personnel<br>5. Blinding of outcome assessors<br>6. Incomplete outcome data, and<br>7. Selective outcome reporting. |
| **Appraisal rating** | Overall, no trials were categorised as having a low risk of bias. |

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| | Three trials were categorised as having a high risk of bias, primarily due to lack of blinding of personnel and outcome assessors.<br><br>One trial was categorised as having an unclear risk of bias, primarily due to its allocation concealment and lack of blinding of participants, personnel and outcome assessors. This trial was referred to as a low-risk of bias, however based on the summary of risk of bias chart it should be labelled unclear.<br><br>The two relevant trials are of high and unclear risk of bias.<br><br>Three trials were categorised as having a low risk of bias for randomisation, and one trial was categorised as having an unclear risk of bias for randomisation. The two relevant trials have a low and unclear risk of bias for randomisation.<br><br>Three trials were categorised as having a low risk of bias for outcome ascertainment, and one trial was categorised as having an unclear risk of bias for outcome ascertainment. The two relevant trials have a low risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | Continuous data were analysed using mean differences and 95% confidence intervals. Dichotomous data were analysed using odds ratios and 95% confidence intervals. All included studies reported sufficient data for analysis. The Cochrane statistical package Review Manager 5 was used for statistical analyses.<br><br>Meta-analyses were not conducted. |
| **Outcome(s) assessed** | Primary outcome 1: Caries increment, measured by the decayed, missing and filled teeth (dmft) index or a variation of this index (e.g. dmfs)<br><br>*Note*. One trial reported caries increment measured using the number of cavitated, arrested, filled or missing tooth surfaces ($d_3$mfs). However, as this index cannot distinguish new caries from progressed caries, the findings from this study were excluded.<br><br>Primary outcome 2: Number of new carious surfaces<br><br>*Note*. Neither of the above primary outcomes are identified in the review as primary or secondary outcomes in the aims or methods section (the primary outcome is identified as “All outcomes related to caries prevalence” p334). However, both outcomes are presented in the results, and for the HRB’s purposes are considered primary outcomes. |

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| **Results/findings** | **Primary outcome 1: Caries increment**<br><u>Comparison 1: 5% w/v sodium fluoride varnish + caregiver counselling versus caregiver counselling alone:</u><br>The mean difference in dmfs index scores at 2 years follow-up was statistically significant in favour of fluoride varnish (MD -2.47, 95% CI -2.57 to -2.37; 1 trial; 1160 participants). Fluoride varnish was applied at baseline and at 4- to 6-month intervals. Caregiver counselling was provided at baseline and at 12- and 24-month visits for both control and intervention groups.<br><br><u>Comparison 2: 5% w/v sodium fluoride varnish versus no intervention:</u><br>No included trials assessing this intervention reported this outcome.<br><br><u>Comparison 3: 10% chlorhexidine varnish versus placebo varnish:</u><br>No included trials assessing this intervention reported this outcome.<br><br>**Primary outcome 2: Number of new carious surfaces**<br><u>Comparison 1: 5% w/v sodium fluoride varnish + caregiver counselling versus caregiver counselling alone:</u><br>No included trials assessing this intervention reported this outcome.<br><br><u>Comparison 2: 5% w/v sodium fluoride varnish versus no intervention:</u><br>No included trials assessing this intervention reported this outcome.<br><br><u>Comparison 3: 10% chlorhexidine varnish versus placebo varnish applied to mother's dentition, assessed in offspring:</u><br>The difference in the mean number of new carious surfaces at the final oral examination between groups was not statistically significant (MD 0.02, 95% CI -1.45 to 1.49; 1 trial; 367 participants). Outcome assessed at 18-20 months follow-up when children were 12, 18 and 24 months old. |
| **Significance/direction** | Fluoride varnish applied at 6-monthly intervals may be beneficial in reducing dental caries in young Indigenous<br>children in high-income countries. The effectiveness of other tested interventions appears to be limited or have no clear benefit. Further research is needed to explore alternative culturally acceptable methods to prevent dental caries.<br><br>There is evidence from two RCTs that the application of fluoride varnish reduces caries prevalence over a 2-year period in young Indigenous children. There is no evidence that chlorhexidine varnish when applied to mothers and infants reduces NNCS.<br><br>This review highlighted the paucity of RCTs relating to the prevention of ECC in Indigenous children from high-income countries. No trials evaluated fluoride in toothpaste, which is convenient and accessible for the prevention of dental caries within communities. |

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| **Heterogeneity** | Heterogeneity among included studies was not discussed. No meta-analyses were conducted. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Hujoel *et al.* (2018) |
| **First Author and year of publication** | Hujoel *et al.* (2018) |
| **Objectives (exact review question(s) and page number)** | To conduct a systematic review of randomised trials assessing the association between personal oral hygiene and dental caries in the absence of the confounding effects of fluoride (p282). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (planned separate, but no outcomes report on primary dentition); Dental hygiene, supervised toothbrushing.<br><br>The three randomised controlled trials involved a total of 743 participants. The age of participants ranged from 10 to 13 years. Two trials involved both females and males, and one trial involved females only. Participant characteristics for the four nonrandomised trials were not provided. |
| **Setting/context** | The three randomised controlled trials were conducted in the United Kingdom (1 trial) and the United States (2 trials). It was not reported where the nonrandomised trials were conducted.<br><br>The study settings were not reported for any included trial. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was personal oral hygiene. Personal oral hygiene was defined as brushing of teeth with or without interproximal cleansing devices. In all three randomised controlled trials, toothbrushing was supervised either daily or biweekly. Trials were excluded in which the effect of personal oral hygiene interventions was combined with fluoride products or dietary interventions and the control group had no such interventions. Trials with a primary aim of assessing chemotherapeutics (e.g., fluoride, chlorhexidine) were also excluded. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Web of Science, and |

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| | • Cochrane Central Register of Controlled Trials.<br><br>Databases were searched for articles published between January 1950 and February 2017. Language was restricted to English. Titles, abstracts, full-text papers and grant reports were screened for additional references.<br><br>Title and abstract screening was conducted, following by full-text screening. It was not reported how many review authors were involved in this process. Though, two review authors independently performed data extraction.<br><br>No protocol was established for this review.<br><br>The funding source of the review and any conflicts of interest were not reported. |
| **Date range (years) of included studies** | The seven included trials were published between 1977 and 1981. |
| **Number of primary studies included in the systematic review** | The review authors included three randomised controlled trials. However, four nonrandomised trials were also included for the purposes of sensitivity analyses. For the randomised controlled trials, two trials randomised participants on an individual level and one trial randomised participants on a cluster level (by classes). Follow-up periods ranged from 29 months to 3 years for these trials.<br><br>In total, only one of the seven included trials reported receiving funding from the commercial industry. |
| **Types of studies included** | The review authors included three randomised controlled trials: Silverstein (1977), Horowitz (1980), and Ashley (1981).<br><br>However, four nonrandomised trials were also included for the purposes of sensitivity analyses: Fosdick (1950), Clark (1974), Spears (1978) and McKee (1977).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The three randomised controlled trials were conducted in the United Kingdom (1 trial) and the United States (2 trials). It was not reported where the nonrandomised trials were conducted. |
| **Appraisal instrument(s)** | The quality of a study was quantified using a modified Jadad scale and the risk of bias was measured using Cochrane's Collaboration tool. The following risk of bias domains were assessed in each included trial:<br>• Random sequence generation<br>• Allocation concealment |

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| | • Blinding of clinical outcome assessment<br>• Incomplete outcome assessment, and<br>• Selective reporting.<br><br>The modified Jadad score is between 0 and 5 where 0 indicates poor quality and 5 indicates highly rigorous quality. “The Jadad modification consisted of changing the word “double- blind” to “single- blind” as it was considered impossible to blind trial participants towards self- performed tasks such as brushing and flossing. Baseline caries comparability was abstracted prior to drop- out to the extent possible. A trial was labelled commercially funded if it reported receiving a grant from an oral hygiene company for the conduct of the study. |
| **Appraisal rating** | Overall, all three randomised controlled trials received a quality rating of “4” using the Jaded score. The nonrandomised trials received one score of “3”, one score of “2” and two scores of “0”.<br><br>The three randomised controlled trials were categorised as having an unclear risk of bias for randomisation, and the four nonrandomised trials were categorised as having a high risk of bias for randomisation.<br><br>The three randomised controlled trials were categorised as having a low risk of bias for outcome ascertainment. For the four nonrandomised trials, two were categorised as having a low risk of bias for outcome ascertainment and two were categorised as having a high risk of bias for outcome ascertainment.<br><br>Meta-regression nor statistical assessment of publication bias was performed due to the limited number of trials and minimal variability in terms of duration or quality of the randomised trials. |
| **Method of analysis** | Summary DMFS estimates were based on random-effects models. The heterogeneity of the trials was evaluated using the heterogeneity chi-squared statistic. Effective sample sizes for the trials were calculated assuming an intracluster coefficient (ρ) of 0.02. This effective sample size was calculated as the total sample size divided by the design effect (1+ρ (m-1)) where m was the average class or school size when the cluster size was unavailable, otherwise m was calculated as the sum of the cluster sizes squared divided by the number of participants in that group when cluster sizes were reported. For trials which assigned classes to treatments, the number of classes in public schools was calculated assuming each class had on average about 20 pupils. Radiographic caries increment scores combined with clinical scores were selected over clinical caries increments alone when both outcomes were available.<br><br>Exploratory analyses were conducted to assess the robustness of the findings. Included in these secondary analyses was an assessment of the |

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| | impact of nonrandomised studies. These nonrandomised studies included different dental outcome scores (such as Decayed, Missing or Filled Teeth or DMFT) for caries and were standardised using the Glass's Δ method. Highly significant heterogeneity was taken as an indication to analyse the data using a random-effects model, not fixed-effects models. All analyses were completed using SAS 9.4, STATA 11.1, and R 3.3.2. |
| **Outcome(s) assessed** | Primary outcome 1: Caries incidence, as measured using DMFS scores<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Caries incidence (DMFS scores)**<br>Results from the three randomised controlled trials found no difference in the incidence of caries between the oral hygiene intervention group and control groups (SMD -0.00, 95% CI -0.15 to 0.15; 3 trials; 681 participants) at 29-36 months follow-up. There was no heterogeneity observed (Chi-squared = 1.88, P = .390)<br><br>Oral hygiene was supervised daily in school in two of the pooled trials and every 2 weeks in the third.<br><br>Results did not change when the four nonrandomised trials were added to the analyses (SMD -0.08, 95% CI -0.27 to 0.10; 7 trials; 1,490 participants), however, significant heterogeneity was observed (Chi-squared = 17.41, P < 0.01). |
| **Significance/direction** | The review did not provide convincing evidence in support of the efficacy of personal oral hygiene in preventing coronal dental caries. |
| **Heterogeneity** | No significant heterogeneity was observed in the main meta-analysis of randomised controlled trials. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of the evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Alirezaei *et al.* (2018) |
| **First Author and year of publication** | Alirezaei *et al.* (2018) |

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| **Objectives (exact review question(s) and page number)** | To evaluate the ability of glass-ionomer cements-based sealants and resin-based sealants to prevent the occurrence of caries and their retention in standard-based clinical studies (p640). |
| **Participants (characteristics and numbers)** | Permanent dentition; sealants, resin.<br><br>The 31 included studies analysed a total of 13,459 permanent first and second molars. Information in relation to the age and gender of included participants was not provided.<br><br>The total number of participants analysed in the 28 (out of 31) included trials that inform this umbrella review was 10,737. |
| **Setting/context** | The trials were conducted in Australia (1 trial), Brazil (6 trials), China (4 trials), Denmark (1 trial), Egypt (1 trial), Finland (3 trials), India (7 trials), Italy (1 trial), Norway (1 trial), Romania (1 trial), Saudi Arabia (1 trial), Turkey (3 trials) and the United States (1 trial).<br><br>The study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was resin-based fissure sealant.<br><br>The comparator was glass-ionomer fissure sealant. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Scopus<br>• Embase<br>• Cochrane Library, and<br>• Institute for Scientific Information Web of Knowledge (all databases, including the Web of Science Core Collection, Biological Abstracts, BIOSIS Citation Index, Current Contents Connect, Data Citation Index, Derwent Innovations Index, Food Science and Technology Abstracts, Inspec, KCI-Korean Journal Database, MEDLINE, SciELO Citation Index, and Zoological Record).<br><br>No restrictions were placed on date of publication or language. A final search was performed on 20 September 2017. The reference lists of included studies and recent systematic reviews were also searched for any additional potentially studies.<br><br>There was no mention of a protocol being prepared or published.<br><br>Two review authors independently screened search results. Disagreements were resolved by discussion and, where necessary, consultation with a third |

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| | reviewer. One review author performed data extraction and a second assessor then cross-checked the data for accuracy and completeness.<br><br>Any funding source(s) of the review were not reported.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 31 included studies were published between 1994 and 2017. |
| **Number of primary studies included in the systematic review** | The review authors included 31 randomised controlled trials. Follow-up periods ranged from 1 to 7 years.<br><br>Funding sources of the primary sources were not reported. |
| **Types of studies included** | The review authors included 31 randomised controlled trials: Forss (1994), Arrow (1995), Raadal (1996), Winkler (1996), Forss (1998), Poulsen (2001), Ganesh (2007), Amin (2008), Kervanto-Seppala (2008), Barja-Fidalgo (2009), Oba (2009), Baseggio (2010), Antonson (2012), Chen (2012a), Chen (2012b), Dhar (2012), Mathur (2012), Ninawe (2012), Ulusu (2012), Bhat (2013), Chen (2013), Kumaran (2013), Cagetti (2014), Zhang (2014), Barlean (2015), Graciano (2015), Hilgert (2015), Haznedaroglu (2016), Pinto Goncalves (2016), Al-Jobair (2017), and Hilgert (2017).<br><br>The results of 28 randomised controlled trials informed the outcomes of interest to this umbrella review: Forss (1994), Arrow (1995), Raadal (1996), Winkler (1996), Forss (1998), Poulsen (2001), Ganesh (2007), Amin (2008), Kervanto-Seppala (2008), Barja-Fidalgo (2009), Oba (2009), Baseggio (2010), Antonson (2012), Chen (2012a), Dhar (2012), Mathur (2012), Ninawe (2012), Ulusu (2012), Bhat (2013), Chen (2013), Kumaran (2013), Cagetti (2014), Barlean (2015), Graciano (2015), Haznedaroglu (2016), Pinto Goncalves (2016), Al-Jobair (2017), and Hilgert (2017).<br><br>A list of excluded studies and the reasons for exclusion were not provided. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Brazil (6 trials), China (4 trials), Denmark (1 trial), Egypt (1 trial), Finland (3 trials), India (7 trials), Italy (1 trial), Norway (1 trial), Romania (1 trial), Saudi Arabia (1 trial), Turkey (3 trials) and the United States (1 trial). |
| **Appraisal instrument(s)** | The quality of included studies was evaluated using the modified Jaded checklist. The following questions were used:<br>• Did the study investigators ask a clearly focused question?<br>• Was a randomised controlled trial used?<br>• Was the method of randomisation appropriate? |

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| | • Was the study described as blinded?<br>• Was there a clear description of the inclusion and exclusion criteria?<br>• Was there a description of any study participants withdrawals and dropouts?<br>• Was the method used to assess success or failure described?<br>• Was the sample size justified (for example, power calculation)?<br>• Was the method used in statistical analysis described?<br><br>Each question was rated as "yes", "no", or "not mentioned". Any trial that earned 7 to 9 yeses was rated as having a low risk of bias, 4 to 6 yeses as having a medium risk of bias, and 1 to 3 yeses as having a high risk of bias. Only trial with a low or medium risk of bias were used in the meta-analysis. |
| **Appraisal rating** | Overall, of the 31 included studies, the review authors described 16 as having a low risk of bias and 15 as having a medium risk of bias. The parameters that most received a "not mentioned" or "no" response were power calculation, blinding, and appropriate randomisation. Of the 28 trials relevant to this umbrella review, 13 had a low risk of bias and 15 had a medium risk of bias.<br><br>Twelve trials were described as having appropriate randomisation and four trials were described as not having appropriate randomisation. In fifteen trials, randomisation was "not mentioned". Of the 28 trials relevant to this umbrella review, 10 had adequate randomisation.<br><br>Eleven trials were described as having adequate blinding and two trials were described as not having adequate blinding. In eighteen trials, blinding was "not mentioned". Of the 28 trials relevant to this umbrella review, eleven had adequate blinding.<br>Publication bias was assessed by drawing funnel plots and testing for asymmetry using the Egger regression method. The results of the funnel plot were not described.<br><br>Publication bias was assessed by drawing funnel plots and testing for asymmetry using the Egger regression method. The results of the funnel plot were presented graphically; however, the implications were not discussed nor described. |
| **Method of analysis** | Due to the considerable heterogeneity among the included studies in relation to patients (age, sex, and oral hygiene), clinician experience, treatment methods, techniques, and materials, the review authors used a random-effects model to pool the data. In addition, the Cochran Q test, the $I^2$ index, and $\tau^2$ were used to assess and quantify the degree of heterogeneity. Odds ratios and 95% confidence intervals were used for the main effect size. |

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| | The significance level was set at P = 0.05. Furthermore, to explore the possible difference between resin-based sealants and glass-ionomer-based sealants, the review authors selected studies in which the investigators compared both types of material systems and conducted a further meta-analysis on these. The software (Comprehensive Meta-Analysis Version 2, Biostat) was used for statistical analyses. |
| **Outcome(s) assessed** | Secondary outcome 1: Retention rate<br><br>*Note*. Secondary outcome 1 is identified as a primary outcome in the review. However, for the HRB's purposes it is considered a secondary outcome. |
| **Outcome(s) excluded from umbrella review** | Primary outcome: Caries development<br><br>As it was not specified whether caries development related to caries initiation or caries progression, the HRB excluded this outcome. |
| **Results/findings** | **Secondary outcome 1: Retention rate**<br>Overall, analyses showed the retention rate of resin-based sealants were significantly greater than that of glass-ionomer-based sealants at at least one year of follow-up (OR 6.01, 95% CI 3.23 to 11.18, p = 0.000; 28 trials; $I^2$ = 96.18%).<br><br>A subgroup analysis specifically comparing high-viscosity glass-ionomer sealants to resin-based sealants also found retention rates to be significantly better in the resin-based sealant group (OR 4.09; 95% CI 1.68 to 9.96, p = 0.002; 5 trials; $I^2$ = 91.23%).<br><br>Another subgroup analysis comparing low-viscosity glass-ionomer with resin fissure sealant also found retention rates to be significantly better in the resin-based sealant group (OR 5.09, 95% CI 2.39 to 10.85, p = 0.000; 18 trials; $I^2$ = 95.88%).<br><br>Similarly, a subgroup analysis comparing resin-modified glass-ionomer sealant to resin fissure sealant also found retention rates to be significantly better in the resin-based sealant group (OR 16.76, 95% CI 2.36 to 119.63, p = 0.000; 5 trials; $I^2$ = 95.75). |
| **Significance/direction** | The retention rate of the conventional resin-based fissure sealants was much higher than that of the glass-ionomer cements. |
| **Heterogeneity** | Considerable heterogeneity was observed among the included studies in relation to patients (age, sex and oral hygiene), clinician experience, treatment methods, techniques, and materials. Alas, review authors used a random effects model to pool the data. Significant statistical heterogeneity was observed in all meta-analyses. |

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| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |

| Parameter | Chong *et al.* (2018) |
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| **First Author and year of publication** | Chong *et al.* (2018) |
| **Objectives (exact review question(s) and page number)** | To evaluate the effectiveness and safety of different types of slow-release fluoride devices on preventing, arresting, or reversing the progression of carious lesions on all surface types of primary (deciduous) and permanent teeth (p5).<br><br>*Note*. The HRB is only interested in the findings from studies that are focussed on caries prevention and so excluded the treatment aspect of this review. |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (planned separate, but only permanent in included trial); topical fluoride, slow-release fluoride devices.<br><br>The one included trial randomised 174 participants and 63 were evaluated in analyses. Participants were children attending schools in the inner city of Leeds, UK presumed to be from disadvantaged backgrounds. Children had a mean age of 8.8 years at baseline and 10.9 years at the end of the study. Number of DMFT (decayed, missing or filled teeth in permanent teeth) or dmft (decayed, missing or filled teeth in primary teeth) were greater than one at the start of the study. In addition, there were greater than one million colony-forming units of *Streptococcus mutans* per millilitre of saliva. Information pertaining to the sex of included participants was not provided. |
| **Setting/context** | The one included trial was conducted in the UK.<br><br>The trial was conducted within school settings. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was slow-release fluoride devices. The desired properties of fluoride-releasing devices include being safe to administer, providing low and continuous intraoral fluoride concentration of at least 1 year, being quick and easy to administer, being robust and being clinically effective. Two types of intraoral fluoride slow-release devices are currently in use, the co-polymer membrane and slow-dissolving fluoride glass beads. |

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| | The comparison group included alternative fluoride treatment, a placebo, no intervention, or 'usual care'.<br><br>In the one included trial, glass beads were attached to buccal surfaces of right maxillary first permanent molar teeth. In the intervention group, glass beads were constituted with fluoride that was designed to be released slowly as the glass dissolved in the mouth.<br><br>In the control group, glass beads were manufactured without fluoride and attached to buccal surfaces of right maxillary first permanent molar teeth. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Oral Health's Trials Register (to 23 January 2018)<br>• Cochrane Central Register of Controlled Trials (CENTRAL; 2017, issue 12) in the Cochrane Library (searched 23 January 2018)<br>• MEDLINE Ovid (1946 to 23 January 2018)<br>• Embase Ovid (1980 to 23 January 2018)<br>• US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) (to 23 January 2018), and<br>• World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) (to 23 January 2018).<br><br>There were no restrictions on language, publication year or publication status. The reference lists of all the included studies were hand searched to identify any additional studies.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening). Disagreements were resolved by discussion with a third review author.<br><br>Two review authors independently extracted data with an itemised form to ensure consistency. Disagreements were resolved through discussion with a third review author.<br><br>The protocol for the review was first published in 2005; no registration number was provided. Differences between the protocol and published review were noted.<br><br>The review was supported in funding by the National Institute for Health Research and the Cochrane Oral Health Global Alliance group.<br><br>None of the review authors declared a conflict of interest. One review author was a Co-ordinating Editor of Cochrane Oral Health. |

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| **Date range (years) of included studies** | The one included trial was published in 2005. |
| **Number of primary studies included in the systematic review** | The review authors included one double-blinded randomised controlled trial. The trial used a parallel group design.<br><br>The one trial was supported in funding by the Wolfston Foundation, a non-profit organisation. |
| **Types of studies included** | The review authors included one double-blind randomised controlled trial: Toumba (2005).<br><br>A list of excluded studies and the reasons for exclusion were provided in an appendix. |
| **Country of origin of included studies** | The one included trial was conducted in the UK. |
| **Appraisal instrument(s)** | At least two review authors undertook the risk of bias assessment of included trials. Any disagreements were resolved by discussion with a third review author.<br><br>Risk of bias assessment was conducted using the standard recommended approach for assessing the risk of bias in studies included in Cochrane Reviews (Higgins 2011). The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias.<br><br>The review authors assigned judgement on the risk of bias for each domain into either one of these categories: high, low, or unclear risk of bias. They also categorised the overall risk of bias of individual trials. Trials were categorised as being at low, high, or unclear risk of bias according to the following criteria:<br>• Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias<br>• High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias, or |

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| | • Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were at unclear risk of bias.<br><br>Publication bias could not be assessed due to the lack of studies required to perform the assessment. |
| **Appraisal rating** | The one included trial had an overall high risk of bias. This was due to having a high risk of bias under the domains of incomplete outcome data and selective reporting.<br><br>The trial had a low risk of bias for randomisation and outcome ascertainment.<br><br>The quality of evidence was assessed with reference to study limitations (risk of bias), directness of evidence, consistency of results, precision of estimates, and risk of publication bias.<br><br>Overall, the quality of evidence in the review was very low. was primarily due to serious study limitations (risk of bias), potential limitations in applicability of the results to the wider population, and an overall small number of participants included. |
| **Method of analysis** | For dichotomous outcomes, the estimate of treatment effect of an intervention was expressed as risk ratios together with 95% confidence intervals or as hazard ratios if these were available as time-to-event data. For continuous outcomes, mean differences and standard deviations were reported.<br><br>Random-effects models would have been used to pool effect estimates; however, as there was only one included trial in the review no meta-analyses were conducted. No subgroup or sensitivity analyses were conducted. |
| **Outcome(s) assessed** | Primary outcome 1: Changes in decayed, missing, and filled teeth, or surfaces, or both (DMFT/DMFS in permanent teeth - dmft/dmfs in primary teeth)<br><br>Secondary outcome 1: Retention of slow-release fluoride devices<br><br>Secondary outcome 2: Harms of slow-release fluoride devices<br><br>Secondary outcome 3: Use of healthcare resources (e.g. time taken to fit, number of visits to the dentist for attention, or re-fitting of slow-release fluoride devices)<br><br>*Note*. All outcomes are identified in the review as presented here. |

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| **Results/findings** | **Primary outcome 1: Changes in decayed, missing, and filled teeth, or surfaces, or both (DMFT/DMFS in permanent teeth, dmft/dmfs in primary teeth).**<br>Caries increment was significantly lower in the intervention group than in the control group at 2 years follow-up (MD -0.72 DMFT, 95% CI -1.23 to -0.21; MD -1.52 DMFS, 95% CI -2.68 to -0.36; 1 trial; 63 participants; very low certainty of evidence).<br><br>No trials reported changes in dmft/dmfs in primary teeth.<br><br>**Secondary outcome 1: Retention of slow-release fluoride devices**<br>Out of 174 children recruited into the trial, only 132 completed the study. Of these, 31 in the intervention group and 32 in the control group still had the devices intact, with an overall 63/132 (47.8%) retention of devices after 2 years.<br><br>**Secondary outcome 2: Harms of slow-release fluoride devices**<br>Harms were not measured or formally reported within the trial report. Despite this loss the devices were well tolerated by the children and there were no reports of irritation etc.<br><br>**Secondary outcome 3: Use of healthcare resources (e.g. time taken to fit, number of visits to the dentist for attention, or re-fitting of slow-release fluoride devices)**<br>The trial reported no data on use of healthcare resources. |
| **Significance/direction** | Evidence from one small randomised controlled trial among primary school children in an area with low fluoride levels in drinking water suggested that slow-release fluoride may reduce the incidence of caries. However, this could be an overestimation, as the results only reported the outcomes among children who retained the devices at 2-year follow-up. The devices were intact in less than half (47.7%) of all participants followed up at 2 years. |
| **Heterogeneity** | The review authors assessed clinical heterogeneity by examining the types of participants (e.g. age), interventions (e.g. method of restoration), and outcomes (e.g. pain relief) in each study. They assessed heterogeneity by inspection of the point estimates and CIs on the forest plots. They assessed the variation in treatment effects by means of Cochran's test for heterogeneity and quantified it using the $I^2$ statistic. However, heterogeneity could not be assessed as only one trial was included in the review. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the quality of the evidence as very low for primary outcome 1, downgraded due to serious attrition bias, relatively small overall sample size and evidence being obtained only from a specific |

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| | group of participants (children with high risk of caries, in an area with low levels of fluoride in tap water.<br><br>The HRB authors graded the certainty of evidence as very low. |
| **References to previously published versions** | Chong LY, Clarkson JE, Dobbyn-Ross L, Bhakta S. Slow-release fluoride devices for the control of dental decay. Cochrane Database of Systematic Reviews 2014, Issue 11. [DOI:10.1002/14651858.CD005101.pub3]<br><br>Bonner BC, Clarkson JE, Dobbyn L, Khanna S. Slow-release fluoride devices for the control of dental decay. Cochrane Database of Systematic Reviews 2006, Issue 4. [DOI: 10.1002/14651858.CD005101.pub2]<br><br>Bonner BC, Clarkson JE. Slow-release fluoride devices for the control of dental decay. Cochrane Database of Systematic Reviews 2005, Issue 1. [DOI: 10.1002/14651858.CD005101] |

| Parameter | Newton *et al.* (2020) extraction |
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| **First Author and year of publication** | Newton *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To determine the difference in level of dental caries in adults and children who chew sugar-free gum (SFG), compared with those who do not chew SFG or use alternatives such as lozenges, candies, rinses, tablets and other non-chewing controls (p4). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (mixed); topical other chemicals, xylitol.<br><br>The 12 included trials involved a total of 6,132 participants. Trial sizes ranged from 34 to 1,402. The age of participants ranged from 3 years to over 60 years. Most trials recruited children as participants, while only trial having adult participants and one recruiting mother-child dyads. Information pertaining to the sex of included participants was not reported.<br><br>*Note*. This review was coded under xylitol due to the subgroup analysis that included xylitol only trials (instead of trials with mixed agents in SFG. Information extracted for GRADE was also extracted from this subgroup analysis, rather than the overall analysis. |
| **Setting/context** | The study countries and study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was sugar-free chewing gum. “Sugar” in this review referred to monosaccharides (i.e. glucose, fructose, galactose) and disaccharides (i.e. sucrose, lactose, maltose). It did not include polyols such |

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| | as xylitol, sorbitol or malitol; therefore, the use of these polyols in gums satisfied “sugar-free” criteria.<br><br>Of the 12 included trials, six exclusively used xylitol as the basis of the intervention, three exclusively used sorbitol, two used both xylitol and sorbitol, and one used tea polyphenol containing gum.<br><br>Treatment frequency ranged from 2 to 3 times daily.<br><br>In terms of the control group, nine used no gum as the control, one used fluoride varnish as the control, one used toothbrushing as the control, and one used gum as the control. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Ovid MEDLINE<br>• Ovid EMBASE<br>• Ovid PsychINFO<br>• Scopus<br>• Web of Science<br>• Allied and Complimentary Medicine Database (AMED)<br>• Cochrane Central Register of Controlled Trials (CENTRAL), and<br>• Open Grey.<br><br>In addition, Prospero and the Cochrane Library of systematic reviews were searched, and the reference lists of included studies and any relevant systematic reviews were checked.<br><br>Articles published between 1 January 1946 and 20 September 2018 were considered for inclusion. Language was restricted to English.<br><br>The review protocol was registered with PROSPERO (ID: CRD42018094676).<br><br>Two review authors independently screened search results (title and abstract, and full-text screening). Disagreements were resolved by input from a third reviewer.<br><br>Two reviewers extracted data based on a pre-determined piloted data extraction list. In the cases of disagreement, a third reviewer was called. Extraction included, but was not limited to the intervention, participant characteristics, relevant study details, and bibliographic details.<br><br>The review was supported in funding by Mars Wrigley.<br><br>None of the review authors declared a conflict of interest. |

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| **Date range (years) of included studies** | The 12 included trials were published between 1983 and 2013. |
| **Number of primary studies included in the systematic review** | The review authors included 11 randomised controlled trials and 1 pre-post trial. Follow-up periods ranged from 6 months to 6 years.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 11 randomised controlled trials and 1 pre-post trial: Glass (1983), Kandelman (1990), Beiswanger (1998), Hujoel (1999), Makinen (1995), Makinen (1995b), Makinen (1996), Mackinen (1996b), Makinen (1998), Alanen (2000), Machiulskiene (2001), Kovari (2003), Szoke (2005), Seki (2011), Al-Haboubi (2012), Hanno (2011), Alamoudi (2012), and Tao (2013).<br><br>A list of excluded studies and the reasons for exclusion were provided. |
| **Country of origin of included studies** | Study countries were not reported. |
| **Appraisal instrument(s)** | Three review authors independently assessed the risk of bias of included trials using the Cochrane tool. The option for disagreements to be resolved through discussion and with the input of a fourth reviewer as required was available. The following domains were assessed in each included trial:<br>• Selection bias<br>• Performance bias<br>• Detection bias<br>• Attrition bias<br>• Reporting bias, and<br>• Other biases. |
| **Appraisal rating** | Overall, according to the Cochrane's Collaboration tool, no trials were assessed as having a low risk of bias. Three trials were assessed as having an unclear risk of bias and nine trials were assessed as having a high risk of bias.<br><br>Nine trials were categorised as having a low risk of bias for randomisation, two trials were categorised as having an unclear risk of bias for randomisation, and one trial was categorised as having a high risk of bias for randomisation.<br><br>Six trials were categorised as having a low risk of bias for outcome ascertainment, four trials were categorised as having an unclear risk of bias |

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| | for outcome ascertainment, and two trials were categorised as having a high risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | To account for the variations in outcomes and the reporting of the caries increment data, the preventive fraction was calculated to produce a more clinically meaningful outcome measure. Three summary measures were calculated: the prevented fraction, standardised mean difference and standardised effect size. The effect size was calculated using the procedure metaeff in Stata v15.1. The metaan command in Stata v15.1 was then used to conduct a random effects maximum likelihood meta-analysis and draw forest plots.<br><br>Meta-analysis was undertaken using data recorded at baseline and at the end of the study, regardless of when this was. Where there were multiple papers reporting outcomes at successive time points, only the final time point published was included. Where more than one sugar-free gum was used, the results were combined, and this was compared to the control group and separate analysis was also undertaken comparing xylitol gum to a control group. Separate analysis of xylitol-only gums was included since this appeared to be the most frequently adopted type of sugar-free gum in trials and the investigators wished to determine whether any recommendations could be made for xylitol gum specifically.<br><br>Where the data for either the control or intervention group was available at both baseline and at the end of the study, the paired data were re-created using the method outlined by Borenstein et al 2011. The correlation between the baseline and the end of study data was assumed to be 0.95 for the control and 0.65 for the intervention group. A sensitivity analysis was conducted with the correlation set at 0.95 for the intervention group.<br><br>Three summary measures were calculated: the prevented fraction (PF), standardised mean difference (SMD) and standardised effect size (ES). The effect size was calculated using the procedure metaeff in Stata v15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). The metaan command in Stata v15.1 was then used to conduct a random effects maximum likelihood meta-analysis and draw forest plots. |
| **Outcome(s) assessed** | Primary outcome 1: caries increment (measured by changes in decayed, missing, and filled teeth, or surfaces, or both (DMFT/DMFS in permanent teeth, dmft/dmfs in primary teeth) and prevented fraction)<br><br>Secondary outcome 1: adverse events |

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| | *Note*. Primary outcome 1 is identified as a primary outcome in the review. The nature of secondary outcome 1 (i.e. primary or secondary) is not made explicit (assumed primary as it is presented alongside primary outcome 1). For the HRB's purposes this outcome is a secondary outcome. |
| **Results/findings** | **Primary outcome 1: Caries increment (Changes in decayed, missing, and filled teeth, or surfaces, or both (DMFT/DMFS in permanent teeth, dmft/dmfs in primary teeth) and prevented fraction).**<br>Analyses showed that the use of sugar-free chewing gum significantly reduced caries increment compared to the control group (PF 28%; 95% CI 7% to 48%; SMD 0.32, 95% CI 0.09 to 0.54; 12 trials; 6,161 participants; $I^2$ = 94.7%). Changing the correlation between the baseline and end of study data to 0.95 produced similar results.<br><br>A separate meta-analysis where the intervention involved xylitol gum only was undertaken and results showed that xylitol gum, too, significantly reduced caries increment compared to a control group (PF 33%, 95% CI 4% to 61%; SMD 0.39, 95% CI -0.01 to 0.79; 8 trials; 3,520 participants; $I^2$ = 91.5%). Follow-up periods were 6 months (1 trial), 9 months (1 trial), 18 months (1 trial), 2 years (1 trial), 3 years (1 trial), 5 years (2 trials), and 6 years (1 trial).<br><br>Xylitol gum was chewed three times per day in 6 trials and once per day in 1 trial. The frequency of chewing was not reported in 1 trial. The concentration of xylitol in gum was only reported in 1 trial (15% and 65% depending on the intervention group).<br><br>*Note*. For the HRBs purposes only the latter meta-analysis was used for grading the certainty of evidence and for data synthesis as this meta-analysis included trial of xylitol gum only, as opposed to a combination of xylitol and sorbitol.<br><br>**Secondary outcome 1: Adverse events**<br>No included trials reported this outcome. |
| **Significance/direction** | Available evidence suggests that the use of sugar-free gum may be effective in reducing the risk of caries development in children. Further research is required to assess the effect of sugar-free gum on caries incidence in adults. |
| **Heterogeneity** | High statistical heterogeneity was observed in all meta-analyses. The review authors stated, "There was a high level of [clinical] heterogeneity in the trials, both in terms of the dosage and frequency of use of the SFGs, as well as in the length of follow-up" p11. They also stated that a sensitivity analysis would have been useful to identify the variables that contributed to the statistical heterogeneity. |

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| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as very low. |
| **References to previously published versions** | N/A |

| Parameter | Zhou *et al.* (2019) extraction |
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| **First Author and year of publication** | Zhou *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To investigate the efficacy of strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities (p507).<br><br>*Note*. The effect of fluoride was not possible to determine because the meta-analysis conducted as part of this review tested the effect of fluoride "as 1mg NaF tablets **or** Fluoride + $NaHCO_3$ + $KH2PO_4$". The review authors also reported the effect of manual **or** powered toothbrushing plus toothpaste containing fluoride **or** calcium sucrose phosphate. The results were therefore excluded from data synthesis. |
| **Participants (characteristics and numbers)** | Primary and permanent (planned separate; permanent for pooled trials, mixed for single trial); systemic fluoride, supplements; combined intervention.<br><br>The population of interest was children and adolescents with intellectual disabilities aged 18 years and under.<br><br>The 14 included studies involved a total of 935 children and adolescents. The number of participants in each study ranged from 20 to 349. One study recruited children with 'mental health issues, regardless of level'. Two studies claimed that their participants had a moderate degree of intellectual impairment ('trainable' category), with the intelligence quotient ranging from 40 to 55. Three studies reported participants with either mild to moderate ID (intellectual disability), moderate to profound ID, or severe ID. Eight studies did not specify the ID levels of their study population, but the authors had mentioned that their target population were intellectually disabled, mentally handicapped, mentally retarded, or diagnosed with mental disorders of different aetiologies. Information pertaining to the age and sex of included participants was not provided.<br><br>The total number of participants in the 3 (out of 14) included trials that inform this umbrella review was 531. |
| **Setting/context** | The study countries and study settings were not reported. |

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| **Description of Interventions/ phenomena of interest** | The intervention(s) of interest was oral health promotion strategies. The comparator was conventional practice or a placebo.<br><br>The effectiveness of both mechanical and chemical strategies had been reported. Tooth brushing was the only mechanical method assessed by the included studies, while chemical strategies included chlorhexidine, plaque-disclosing agent, triclosan-zinc and fluoride.<br><br>Of the three trials relevant to this umbrella review: one evaluated the effect of manual or powered toothbrushing plus toothpaste containing fluoride or calcium sucrose phosphate over one month; one evaluated fluoride tablets (1.0mg NaF) over two years compared to a placebo; and one evaluated the effect of fluoride, NaHCO3, KH2PO4 additives (additives to sugary foods to clean the teeth) over three years compared to no additives. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Cochrane Library<br>• Web of Science, and<br>• Scopus.<br><br>Databases were searched from the commencement date up to the date of 17 April 2017. Studies not in English were excluded. Additional studies were identified through reference linkage.<br><br>The authors stated a protocol was formulated before conducting the review; however, a registration number was not provided.<br><br>Two review authors screened search results (title and abstract, and full-text screening). Disagreements were resolved through consultation with the supervising author. It was not reported how data extraction was completed.<br><br>The review was fully supported in funding by Research Grants Council of the Hong Kong Special Administrative Region, China.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 14 included trials were published between 1975 and 2015. |
| **Number of primary studies included in the systematic review** | The review authors included 14 randomised and nonrandomised controlled trials. Of these, seven were randomised controlled trials and seven were controlled trials. Follow-up periods ranged from ten days to three years. |

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| | The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 14 randomised and nonrandomised controlled trials, these are the 9 trials not relevant to HRB interests: Andrade Meyer (2010), Awasthi (2015), Chibinski (2011), Dever (1979), Francis (1987), Luoma (1979), Montiel-Company (2002), Russell (1978), Shaw (1983), Stabholz (1991), Teitelbaum (2009), Usher (1975), Viana (2014), Liu (2013).<br><br>The results of 3 trials informed the outcomes of interest to this umbrella review: Awasthi (2015), Luoma (1979), and Liu (2013).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The study countries were not reported. |
| **Appraisal instrument(s)** | Risk of bias in the included trials was evaluated by using Risk of Bias Table in Review Manager 5.3 software. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias), and<br>6. Selective reporting (reporting bias).<br><br>Following the criteria defined by the Cochrane Collaboration's tool for assessing risk of bias, each domain was awarded as 'unclear risk', 'low risk' or 'high risk' (Higgins et al. 2011). |
| **Appraisal rating** | The overall risk of bias of the included trials was not reported. However, according to both Cochrane's Collaboration's tool and graphical information provided in the review, it appeared all trials had an unclear or high risk of bias.<br><br>In addition, according to graphical information provided in the review, approximately 10% of studies were at a low risk of bias for randomisation and about 75% of studies were at a low risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | Caries experiences (decayed, missing due to caries, filled teeth or tooth surfaces) were reported in the format of mean difference and standard |

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| | error. GraphPad QuickCalcs (https://www.graphpad.com/quickcalcs) was used to calculate mean difference and standard error. Quantitative analysis was performed by Review Manager 5.3 software. Random-effects model was employed if data had been pooled from three or more trials, and fixed-effect model was used if only two trials were available to conduct meta-analysis. To control the sources of heterogeneity in meta-analysis, the variabilities in interventions and outcome measures had been carefully assessed before data synthesis. Only studies using the same interventions and assessing the same outcomes by the same measurements were synthesised. The significance level was set at 0.05. |
| **Outcome(s) assessed** | Primary outcome 1: Caries experience (measured by decayed, missing and filled due to caries indices at tooth and surface level (DMFT/dmft and DMFS/dmfs)<br><br>*Note*. This outcome is identified in the review as presented here (as a primary outcome). |
| **Results/findings** | **Primary outcome 1: Caries experience (measured by decayed, missing and filled due to caries indices at tooth and surface level in both permanent and primary dentition (DMFT/dmft and DMFS/dmfs)**<br>Three trials in total evaluated the strategies for caries prevention. Of these, two could be pooled in a meta-analysis (Liu et al, 2013; Luoma et al, 1979). Results showed fluoride (as 1mg NaF tablets, or "Fluoride, $NaHCO_3$, $KH2PO_4$") was more effective in caries prevention in permanent teeth than the control at at least two years of follow-up (MD -0.71, 95% CI -1.40 to -0.02, p = 0.04; 2 trials; 509 participants; $I^2$ = 73%).<br><br>The results from the third trial suggested that powered (vs manual) toothbrushes plus calcium sucrose phosphate (vs fluoride) dentifrices would be 'a better alternative' to low fluoride toothpaste in primary and permanent (mixed) dentition (limited information provided). |
| **Significance/direction** | Greater effectiveness of powered toothbrushes had not been confirmed by the included trials, while fluoride was observed to be effective in preventing caries in fluoride-deficient areas. More well-designed long-term randomised controlled trials were warranted to determine the optimal oral health promotion activities for children and adolescents with intellectual disabilities.<br><br>*Note*. The effect of fluoride was not possible to determine because the meta-analysis conducted as part of this review tested the effect of fluoride "as 1mg NaF tablets **or** Fluoride + $NaHCO_3$ + $KH2PO_4$". The review authors also reported the effect of manual **or** powered toothbrushing plus toothpaste containing fluoride **or** calcium sucrose phosphate. The results were therefore excluded from data synthesis. |

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| **Heterogeneity** | The heterogeneity observed in meta-analyses was not explained. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

| Parameter | Alharthy *et al.* (2022) extraction |
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| **First Author and year of publication** | Alharthy *et al.* (2022) |
| **Objectives (exact review question(s) and page number)** | To assess and evaluate the retention and cariostatic effect of hydrophilic and hydrophobic resin-based sealants in primary and/or permanent teeth with at least a follow-up period of 3 months. |
| **Participants (characteristics and numbers)** | Permanent dentition (first and second molars); sealants, resin.<br><br>The population of interest was healthy children aged 5 to 15 years with sound or incipient carious primary or permanent molars.<br><br>The 12 included trials involved a total of 770 participants and 2,276 first and second permanent molars.<br><br>Mean age showed considerable variations with the lowest age being 5–8 years and the highest age was 12–15 years. Sample size also differed significantly between the study groups where the largest sample size was 600 first permanent molars in 150 patients and the smallest sample size was 68 first permanent molars in 17 patients. The type of arch utilized in the trials (maxilla or mandible) showed that all the trials utilised both arches except for three trials that utilised only the mandible.<br><br>Information pertaining to the sex of included participants was not reported. |
| **Setting/context** | The trials were conducted in Germany (1 trial), India (9 trials), Iran (1 trial), and Turkey (1 trial).<br><br>The trials were conducted in the following settings:<br>• A dental practice (1 trial)<br>• A dental centre (1 trial)<br>• A university (2 trials)<br>• A private practice (1 trial) |

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| | • A school (4 trials)<br>• A dental college and hospital (1 trial)<br>• A dental college and research centre (1 trial), and<br>• A dental college (1 trial). |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was the application of hydrophilic or moisture-tolerant resin-based sealants.<br><br>The comparison group was hydrophobic (conventional) resin-based sealants.<br><br>In one trial, the method of isolation was just cotton rolls. In nine trials, the method of isolation was a cotton rolls and saliva ejectors. In one trial, the method of isolation was a rubber dam and saliva ejectors. The last trial used a rubber dam, cotton roll, and suction. The materials were applied as directed by the manufacturer in all trials except for one.<br><br>In three trials, a bonding agent was used before the hydrophobic sealant. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Science Direct<br>• Cochrane Central Register of Controlled Trials<br>• ClinicalTrials.gov<br>• Scopus Wiley, and<br>• Google Scholar.<br>The search was restricted to English language studies. There was no time constraint on publication date (up to September 2021).<br><br>The reference lists of identified published work were hand searched for any additional studies.<br><br>Two review authors independently screened search results (title and abstract, and full-text screening). Disagreements were resolved by discussion or by a third review author.<br><br>Two review authors independently extracted data. Disagreements were resolved with a third author. The extraction took place utilizing a defined process and the data was then documented in a datasheet. “The extracted data included were as follows: publication year, study setting (country), size of the sample, number and type of teeth, the brand and manufacturer of hydrophilic and hydrophobic RBSs, study design, mean age of patients, number of operators, details of intervention, blinding, number of examiners, |

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| | follow-up period, evaluation criteria, and the retention and cariostatic effect outcome" p863.<br><br>The review protocol was registered with PROSPERO (ID: CRD42020221574).<br><br>The review was funded by the Deanship of Scientific Research at King Abdulaziz University, Jeddah.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 12 included trials were published between 2012 and 2021. |
| **Number of primary studies included in the systematic review** | The review authors included 12 randomised and nonrandomised controlled trials. Of these, seven were randomised controlled trials. All used a split-mouth design. The remaining five were nonrandomised controlled trials.<br><br>Follow-up periods ranged from 1 month to 24 months.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 12 randomised and nonrandomised controlled trials: Schlueter (2013), Khatri (2015), Ratnaditya (2015), Askarizadeh (2017), Prabakar (2018), Mohapatra (2020), Priyadharshini (2012), Bhatia (2012), Bhat (2013), Mohanraj (2019), Topal (2019), and Baheti (2020).<br><br>No studies were excluded during full-text screening. |
| **Country of origin of included studies** | The trials were conducted in Germany (1 trial), India (9 trials), Iran (1 trial), and Turkey (1 trial). |
| **Appraisal instrument(s)** | Two review authors assessed the risk of bias in included trials. To assess the risk of bias of randomised controlled trials, Cochrane's risk of bias tool was used. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants/personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias.<br><br>To assess the risk of bias of non-randomised trials, the Newcastle Ottawa scale was used. |

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| | GRADE was used by the authors.<br><br>In the case of any discrepancy between the two authors, a discussion was carried out until an agreement was met. |
| **Appraisal rating** | For the seven randomised controlled trials included in this review, the review authors described five trials as having an overall low risk of bias and two trials as having a high risk of bias.<br><br>However, HRB notes that according to Cochrane's Collaboration tool, the five trials assessed as having a low risk of bias had at least one domain that was assessed as having an unclear risk of bias.<br><br>All seven trials were categorised as having an unclear risk of bias for randomisation. Four trials were categorised as having a low risk of bias for outcome ascertainment, one trial was categorised as having an unclear risk of bias for outcome ascertainment, and two trials were categorised as having a high risk of bias for outcome ascertainment.<br><br>For the nonrandomised controlled trials, four trials were rated as having a good overall score and one was rated fair.<br><br>No trials were reported to have been randomised. In addition, in two trials there was no blinding, in two trials there was single blinding and one trial there was double blinding.<br><br>The quality of evidence was assessed with reference to design restrictions, risk of bias, precision, directness and consistency of the results. The quality of evidence for the different review questions ranged from moderate to very low. Reasons for downgrading were primarily due to indirectness and inconsistency of results.<br><br>The Newcastle Ottawa Scale was used by the same authors to assess the risk of bias in the five non-RCTs that were included. The inter-rater agreement for the evaluation of the risk of bias was very good (Kappa score = 84.3). Four studies were rated as having a good overall score and one was fair. |
| **Method of analysis** | The meta-analysis only included trials with moderate and high methodological quality (higher than five stars). For every review question, articles were organised according to the design by being a randomised or nonrandomised controlled trial to allow for data synthesis by utilisation of the best available evidence.<br><br>Both quantitative and qualitative syntheses were performed. Studies that compared the retention rate of the two types of sealants were presented separately from studies that compared the cariostatic effect. In the case of |

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| | more than one group of hydrophobic arms in the included studies, the higher retention rate was chosen for quantitative synthesis.<br><br>Revman was used to do the meta-analysis. Cochran's Q-test, with a statistically significant P value of 0.1, was used to check for heterogeneity in the studies. Pooled studies were with low to moderate heterogeneity >25% to 75%. A statistically significant P value was set at 0.05. A random-effect model<br>was conducted in case of the presence of two or more studies with the same assessment tool. The formal method of combining individual study data was odds ratios for individual studies. Sensitivity analysis was used after adding all studies and results were then compared.<br><br>Subgrouping in the forest plots was used based on the study design, timeframe for follow-up, and whether or not a bonding agent was used before hydrophobic sealant. |
| **Outcome(s) assessed** | Secondary outcome 1: Sealant retention<br><br>*Note*. Secondary outcome 1 is identified as a primary outcome in the review. However, for the HRB's purposes it is considered a secondary outcome. |
| **Outcome(s) excluded from umbrella review** | Primary outcome: Cariostatic effect<br><br>As this outcome was not adequately defined, it was not possible to determine whether this outcome related to caries prevention, arrest or remineralisation. Therefore, this outcome was excluded. |
| **Results/findings** | **Secondary outcome 1: Sealant retention**<br><u>Group 1: RCTs with 3 months follow-up without bonding agent:</u><br>Sealant retention was significantly greater in the hydrophilic sealants compared to the hydrophobic sealants (OR 3.40, 95% CI 1.77 to 6.55, p = 0.0002; 2 trials; 184 permanent molars; $I^2$ = 0%; moderate quality of evidence).<br><br><u>Group 2: Non-RCTs with 3 months follow-up without bonding agent:</u><br>There was no statistically significant difference in retention rates between the two groups (OR 1.11, 95% CI 0.71 to 1.72, p = 0.65; 2 trials; 468 permanent molars; $I^2$ = 0%; low quality of evidence).<br><br><u>Group 3: RCTs with 6 months follow-up without bonding agent:</u><br>There was no statistically significant difference in sealant retention groups between the hydrophilic and hydrophilic sealants (OR 0.98, 95% CI 0.21 to 4.66, p = 0.98, 2 trials; 152 permanent molars; $I^2$ = 74%; low quality of evidence).<br><br><u>Group 4: Non-RCTs with 6 months follow-up without bonding agent:</u> |

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| | There was no statistically significant difference in retention rates between the hydrophilic and hydrophobic sealants (OR 1.10, 95% CI 0.59 to 2.05, p = 0.77; 2 trials; 628 permanent molars; $I^2$ = 52%; very low quality of evidence).<br><br>Group 5: Non-RCTs with 12 months follow-up without bonding agent:<br>There was no statistically significant difference in retention rates between the hydrophilic and hydrophobic sealants (OR 1.34, 95% CI 0.93 to 1.93, p = 0.12; 2 trials; 887 permanent molars; $I^2$ = 0%; very low quality of evidence).<br><br>Group 6: Non-RCTs with 6 months follow-up with bonding agent:<br>There was no statistically significant difference in retention rates between the hydrophilic and hydrophobic sealants (OR 1.77, 95% CI 0.37 to 8.61, p = 0.48; 2 trials; 220 permanent molars; $I^2$ = 29%; very low quality of evidence).<br><br>Group 7: Non-RCTs with 12 months follow-up with bonding agent:<br>There was no statistically significant difference in retention rates between the hydrophilic and hydrophobic sealant groups (OR 2.42, 95% CI 0.18 to 32.31, p = 0.51; 2 trials, 210 permanent molars; $I^2$ = 68%; very low quality of evidence).<br><br>Sensitivity analysis was used after adding all studies that investigated the retention of both sealants with and without bonding at 3, 6, and 12 months. The results were consistent with results from the main-analyses and found no difference in retention rates between the hydrophobic and hydrophilic sealants. |
| **Significance/direction** | Available evidence suggests that there is no difference in retention rates between hydrophilic and hydrophobic resin-based sealants. The following are the results of this systematic review, which give consistent moderate to extremely low-quality evidence:<br>1. After 3, 6, and 12 months of follow-up, there was no statistical significance in the retention of hydrophilic and hydrophobic RBSs without a bonding agent<br>2. After a 6- and 12-month follow-up, there was no significant statistical difference in the retention of both sealants with a bonding agent, and<br>3. Comparable cariostatic effects of both types of sealants were found after 6- and 12-month follow-ups. |
| **Heterogeneity** | Heterogeneity was mild to moderate among the trials included. Where statistical heterogeneity was observed in analyses, the quality of evidence was downgraded. |
| **Summary for GRADE assessment for HRB report** | The authors graded the certainty of the evidence in relation to retention of hydrophilic and hydrophobic RBs without bonding agent as moderate (for RCTs with 3 months follow-up and RCTs with 12 months follow-up), low (for non-RCTs with 3 months follow-up and RCTs with 6 months follow-up), and |

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| | extremely/very low (for non-RCTs with 6 months follow-up and non-RCTs with 12 months follow-up).<br><br>The authors graded the certainty of the evidence in relation to retention of hydrophilic and hydrophobic RBs with a bonding agent as extremely/very low for RCTs with 6 months follow-up and non-RCTs with 12 months follow-up.<br><br>The HRB authors graded the quality of evidence in this review as very low. |
| **References to previously published versions** | N/A |
| Parameter | Chan *et al.* (2022) extraction |
| **First Author and year of publication** | Chan *et al.* (2022) |
| **Objectives (exact review question(s) and page number)** | To systematically review the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above (p2).<br><br>*Note*. The HRB is only interested in findings from studies focussed on caries prevention and so excluded the caries arrest aspect of the review. |
| **Participants (characteristics and numbers)** | Permanent dentition; topical fluoride, gels, solution and varnishes; combined intervention.<br><br>The population of interest was older adults aged 60 years or above.<br><br>The mean age of participants in the seven included trials ranged from approximately 60 to 84 years. The total number of participants in the included trials was not reported, however the number was calculated to be 1,027. Five trials were conducted in community-dwelling older adults, whereas the other two trials were conducted in older adults under long-term care. Six of the seven clinical trials investigated the effects on root caries, whereas only one trial focused on coronal caries. Information pertaining to the sex of included participants was not reported. |
| **Setting/context** | The trials were conducted in Hong Kong (4 trials), the United Kingdom (2 trials), and the United States (1 trial).<br><br>Two trials were conducted in long-term care facilities and five trials were conducted in a community living setting. |

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| **Description of Interventions/ phenomena of interest** | The intervention of interest was professionally applied fluoride therapy for caries prevention.<br><br>The comparison group was a positive control group administered with either another professionally applied fluoride agent, placebo, or blank (no special intervention).<br><br>Two studies investigated both the preventive and arresting effects of professionally applied fluoride on dental caries, three studies investigated the caries preventive effect only, and two studies investigated the caries arresting effect only.<br><br>The fluoride agents assessed in the five trials that investigated the caries-preventive effect were 5% NaF varnish, 38% SDF solution, and 1.23% APF gel. The other two trials were focussed on caries arrest and thus will not be discussed.<br><br>More specifically, two studies used 5% NaF varnish which were applied on a semi-annual or quarterly basis. Three studies investigated the effectiveness of annual application of 38% SDF solution. One study investigated the semi-application of 1.23% APF gel.<br><br>*Note*. One trial evaluated a combined intervention. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• PubMed<br>• Scopus<br>• Cochrane Library<br>• EMBASE, and<br>• Web of Science.<br><br>The final search was conducted on 31 December 2021. Language was restricted to English. The reference lists of included studies and previous reviews were also searched for any additional studies.<br><br>The review protocol was registered with PROSPERO (ID: CRD42022307025).<br><br>Two review authors screened search results (title and abstract, and full-text screening) and performed data extraction. Disagreements were resolved by consultation with a third review author.<br><br>The review was supported in funding by the General Research Fund 17100820.<br><br>None of the review authors declared a conflict of interest. |

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| **Date range (years) of included studies** | The seven included trials were published between 1993 and 2021. |
| **Number of primary studies included in the systematic review** | The review authors included seven clinical trials. It was not specified whether these were randomised or nonrandomised. Follow-up periods ranged from 12 to 48 months.<br><br>The funding sources of the primary sources were not reported. |
| **Types of studies included** | The review authors included seven clinical trials: Jabir (2021), Tan (2010), Li (2017), Zhang (2013), Wallace (1993), Li (2016), and Sleibi (2021).<br><br>The results of five trials informed the outcomes of interest to this umbrella review: Jabir (2021), Tan (2010), Li (2017), Zhang (2013), and Wallace (1993).<br><br>A list of excluded studies and the reasons for exclusion were provided in an appendix. |
| **Country of origin of included studies** | The trails were conducted in Hong Kong (4 trials), the United Kingdom (2 trials), and the United States (1 trial). |
| **Appraisal instrument(s)** | The risk of bias of the included studies was assessed independently by two review authors according to the Cochrane Handbook for Systematic Review of Interventions (RoB 2.0). The following five domains were assessed in each included study:<br>1. Randomisation process<br>2. Deviations from intended intervention<br>3. Missing outcome data<br>4. Measurement of outcome, and<br>5. Selection of reported results.<br><br>Each domain was rated on three levels (low risk, some concerns, and high risk). The highest level rated among the five domains in the study was marked as the overall risk of bias. Any disagreement between the two reviewers was resolved through discussion with a third researcher. |
| **Appraisal rating** | Overall, five of the included trials were assessed as having a low risk of bias and two were rated as having “some concerns”.<br><br>Five trials were categorised as having a low risk of bias for randomisation and two trials were categorised as having an unclear risk of bias for randomisation. |

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| | Six trials were categorised as having a low risk of bias for measurement of outcome, while one trial was categorised as having an unclear risk of bias for measurement of outcome.<br><br>Publication bias was not reported. |
| **Method of analysis** | For effectiveness in caries prevention, the reported mean difference in the number of new carious lesions between the intervention and control groups, and the caries-prevented fraction were recorded. If no mean difference or caries-prevented fraction was reported, the total/mean number of sound tooth surfaces at baseline that became carious during the follow-up period in both the intervention and control groups were extracted and used to calculate the mean difference and the caries-prevented fraction.<br><br>Meta-analysis (Review Manager 5.4.1, The Cochrane Collaboration, 2020) using the fixed-effects model was used to calculate the mean difference in preventing new caries using professionally applied fluoride therapy compared to the control group. |
| **Outcome(s) assessed** | Primary outcome 1: Root caries prevention (measured by the mean difference in the number of new carious lesions)<br><br>*Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: Mean difference in the number of new carious lesions**<br><u>Comparison 1: 38% SDF versus control/placebo:</u><br>Results from a fixed-effects model showed a statistically significant decrease in the mean number of new root caries in the annual application of 38% SDF solution group when compared with that in the control group at 24-months follow-up (MD -0.55, 95% CI -0.78 to -0.32, $p < 0.00001$; 3 trials; 439 participants; $I^2 = 61\%$).<br><br>The root caries prevented fractions in community-dwelling older adults were 25–47% and 52–62% at 24 and 30 months, respectively. In institutionalised older adults, it was 71% at 36 months. The annual application of 38% SDF solution with or without potassium iodide application showed no statistically significant differences in root caries prevention.<br><br>Combining annual application of 38% SDF with oral health instruction and semi-annual oral health education in community-dwelling older adults showed significant improvement in the root caries preventive effect at 24 months follow-up, resulting in a 47% reduced risk of developing new root carious lesions (n = 84).<br><br>On comparing the effectiveness of a combination of annual application of 5% NaF varnish with 38% SDF in preventing root caries (mean number of new |

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| | root carious lesions), no statistically significant difference between the intervention group and the control group (water) at 36 months follow-up in institutionalised older adults was detected (sample size not reported for this comparison).<br><br><u>Comparison 2: 5% NaF varnish versus water or no treatment:</u> Results from one trial found that institutionalised older adults receiving 5% NaF varnish semi-annually were 15 times more likely to have a reduction in the number of teeth with coronal caries than those without any intervention at 12-months follow-up (n = 190 participants).<br><br>A second trial found that application of 5% NaF varnish every 3 months in institutionalised older adults showed a 64% root caries prevented fraction at 36-months follow-up (n = 80 participants).<br><br><u>Comparison 3: 1.23% APF gel versus placebo:</u><br>Results from one trial showed the root caries prevented fraction in community-dwelling older adults after semi-annual application of APF was 32% at the 48-month follow-up (n = 147 participants). |
| **Significance/direction** | According to the findings of this systematic review, 5% NaF varnish, 38% SDF solution, and 1.23% APF gel are effective in preventing root caries in older adults, and no particular agent is superior. Because only seven clinical trials were found in the literature, more well-designed clinical trials investigating the effectiveness of various methods for caries prevention in older adults should be conducted to provide more evidence for use in clinical practice and public health measures. |
| **Heterogeneity** | Due to the heterogeneity in treatment protocols, such as the type of fluoride agent, intervention method, and follow-up period, not all included trials could be considered for the meta-analysis. The statistical heterogeneity observed in the meta-analysis on the effectiveness of SDF was not explained. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as moderate. |
| **References to previously published versions** | N/A |
| Parameter | Rashed *et al.* (2022) extraction |
| **First Author and year of publication** | Rashed *et al.* (2022) |

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| **Objectives (exact review question(s) and page number)** | To compare pit and fissure sealants with fluoride varnish for the prevention of caries in the first permanent molars of schoolchildren (p2). |
| **Participants (characteristics and numbers)** | Permanent dentition (first molars); sealants, resin.<br><br>The population of interest was schoolchildren aged between six and 12 years who had a sound occlusal surface in the first permanent molars.<br><br>The four included trials involved a total of 1,249 participants. The age of participants in three trials ranged from 6 to 8 years and the age of participants in one trial had a mean of 9.1 years. Information pertaining to the sex of included participants was not reported. |
| **Setting/context** | The study countries and study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was resin-based sealants. The comparison group was fluoride varnish. Trials that compared the glass-ionomer sealant or glass-ionomer cement with fluoride varnish were excluded. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Embase<br>• Google Scholar<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• MEDLINE via Ovid, and<br>• ClinicalTrials.gov.<br><br>Articles published between January 1980 and May 2022 were searched. The reference lists of identified articles were also searched for any additional studies.<br><br>The review protocol was registered with PROSPERO in July 2022 (ID: CRD42022146807).<br><br>Two review authors independently screened the search results to extract the data. Disagreements were resolved by a third review author.<br><br>The review was supported in funding by the deanship of Scientific Research, King Saud University.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The four included trials were published between 1996 and 2014. |

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| **Number of primary studies included in the systematic review** | The review authors included four randomised controlled trials. Two trials used a parallel-group design. All four trials had a follow-up period of 24 months.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included four randomised controlled trials: Bravo (1996), Bravo (1997), Liu (2012), and Salem (2014).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The study countries were not reported. |
| **Appraisal instrument(s)** | The Cochrane Collaboration's tool was used to assess the risk of bias in the included trials. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias),<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other biases.<br><br>Each trial was categorized as low risk, unclear risk, or high risk based on their combined appraisal in the seven domains. |
| **Appraisal rating** | Overall, two trials were described as having a high risk of bias and two trials were described as having an unclear risk of bias.<br><br>Two trials were categorised as having a low risk of bias for randomisation and two trials were categorised as having an unclear risk of bias for randomisation.<br><br>Three trials were categorised as having a low risk of bias for outcome ascertainment and one trial was categorised as having an unclear risk of bias for outcome ascertainment.<br><br>Publication bias was not measured. |
| **Method of analysis** | Meta-analyses were carried out using Review Manager (RevMan) version 5.4. For continuous outcomes, the weighted mean difference was calculated with the corresponding 95% confidence interval (CI). When the outcomes |

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| | were dichotomous, the risk ratio (RR) with its 95% CI was calculated. Heterogeneity was measured using the $I^2$ statistic. When there was heterogeneity ($I^2$ > 50%), a random-effects model was used. |
| **Outcome(s) assessed** | Primary outcome 1: Caries incidence on the surfaces of first permanent molars<br><br>Primary outcome 2: Changes in Decayed, Missing and Filled Surfaces (DMFS) of first permanent molars<br><br>*Note*. Both outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Caries incidence on the surfaces of first permanent molars**<br>Analyses showed no statistically significant difference in caries incidence at 24 months of follow-up between those that received resin-based sealant and those that received fluoride varnish (RR 0.65, 95% CI 0.31 to 1.35, p = 0.26; 3 trials; 2,622 first permanent molars; $I^2$ = 89%).<br><br>**Primary outcome 2: Changes in Decayed, Missing and Filled Surfaces (DMFS) of first permanent molars**<br>Analyses showed no statistically significant difference in DMFS scores at 24 months of follow-up between those that received resin-based sealant and those that received fluoride varnish (SMD -0.13, 95% CI -0.67 to 0.40, p = 0.63; 2 trials; 1,605 first permanent molars; $I^2$ = 92%). |
| **Significance/direction** | Evidence available in this review suggested there is no significant difference between the efficacy of resin-based sealants and that of fluoride varnish in preventing caries in first permanent molars at two years follow-up and emphasized the use of fluoride varnish since it is more affordable and easier to apply. More high-quality studies with longer follow-up periods are required. |
| **Heterogeneity** | There was significant heterogeneity among the studies, which the authors state should be considered when interpreting the findings. They also note that this could be due to the quality of the included studies. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Singal *et al.* (2022) extraction |

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| **First Author and year of publication** | Singal *et al.* (2022) |
| **Objectives (exact review question(s) and page number)** | To extensively review, summarise and to draw best possible evidence for the remineralising and caries preventive efficacy of various CaP (calcium phosphate) derivatives (p2).<br><br>*Note*. The HRB is only interested in findings from studies focussed on caries prevention and so excluded the treatment aspect of the review. |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (coded as mixed for new carious lesions and separate for caries increment); topical other chemicals, calcium phosphate agents; sealants, other combined intervention.<br><br>The population of interest was healthy children aged 1 to 18 years.<br><br>The 26 included trials involved a total of 3,678 participants. The age of participants ranged from 1 to 18 years. Information pertaining to the sex of included participants was not reported.<br><br>The total number of participants in the 11 (out of 26) included trials that inform this umbrella review was 852. |
| **Setting/context** | The trials were conducted in Australia (1 trial), Brazil (1 trial), China (1 trial), Denmark (1 trial), Egypt (2 trials), Finland (1 trial), Greece (1 trial), India (6 trials), Iran (2 trials), Jordan (2 trials), Saudi Arabia (1 trial), Spain (1 trial), Sweden (1 trial), Thailand (2 trials), and Turkey (3 trials).<br><br>The study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was any topical formulation of calcium phosphate agents (TCP, ACP, CPP-ACP, fTCP, calcium sodium phosphosilicate), alone or combined with sodium fluoride or stannous fluoride. There were no restrictions concerning concentration or duration of application. The comparison group was either no treatment, a placebo (which should differ from test products only in that it does not contain calcium phosphate), or topical application of fluoride containing sodium fluoride or stannous fluoride.<br><br>Topical applications (self-applied/professional applied) in the form of toothpaste, cream, varnish, sealant and mouth rinse were used as a delivery method for calcium phosphate agents among all the studies. Among the included studies, fTCP, CPP, ACP varnish and ACP sealant were used in one trial each, whereas three trials used TCP. The remaining 19 trials assessed the efficacy of CPP-ACP. |

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| **Databases and sources searched** | The review authors searched the following sources:<br>• EMBASE<br>• Ovid<br>• PubMed<br>• Scopus<br>• Web of Science, and<br>• Cochrane Central Register of Controlled Trials (CENTRAL).<br>Articles published until April 2021 were considered for inclusion. The reference lists of included studies and other related publications were searched for any additional studies. Language was restricted to English.<br><br>The review protocol was registered with PROSPERO in June 2021 (ID: CRD42021253177).<br><br>Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved by discussion with a third author and consensus was sought by mutual agreement.<br><br>The review was supported by Indian Council of Medical Research, New Delhi, through project titled "Capacity Building for Evidence based child health in the North East Region".<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 24 included trials were published between 2007 and 2021. |
| **Number of primary studies included in the systematic review** | The review authors included 26 randomised controlled trials. Follow-up periods ranged from 48 hours to 24 months.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 26 randomised controlled trials: Al-Batayneh (2020a), Al-Batayneh (2020b), Almaz (2020), Andersson (2007), Aykut-Yetkiner (2014), Bailey (2009), Brochner (2011), Chandak (2016), Chen (2021), Ebrahimi (2017), Esenlik (2016), Fadl (2016), Guclu (2016), Khatri (2021), Llena (2015), Mekky (2021), Memarpour (2014), Mendes (2018), Patel (2017), Radha (2020), Rao (2007), Salamara (2020), Samuel (2021), Sitthisettapong (2012), Sitthisettapong (2015), and Yadav (2021).<br><br>The results of 11 trials informed the outcomes of interest to this umbrella review: Sitthisettapong (2012), Aykut-Yetkiner (2014), Fadl (2016), Chandak |

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| | (2016), Esenlik (2016), Samuel (2017), Patel (2017), Yadav (2019), Khatri (2019), Al-Batayneh (2020b), Almaz (2020).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Australia (1 trial), Brazil (1 trial), China (1 trial), Denmark (1 trial), Egypt (2 trials), Finland (1 trial), Greece (1 trial), India (6 trials), Iran (2 trials), Jordan (2 trials), Saudi Arabia (1 trial), Spain (1 trial), Sweden (1 trial), Thailand (2 trials), and Turkey (3 trials). |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of included trials using the Cochrane's Collaboration tool. Disagreements were resolved by discussion with a third author. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias), and<br>7. Other bias.<br><br>Each trial was classified as having a low, unclear, or high risk of bias in each domain. |
| **Appraisal rating** | Overall, only three of the 26 included trials were assessed to have a low risk of bias. The remaining trials had a high or unclear risk of bias in one or more domains. Of the 11 trials that informed the outcomes of interest to this umbrella review, only one had an overall low risk of bias.<br><br>Eighteen trials were categorised as having a low risk of bias for randomisation. Of the 11 trials that informed the outcomes of interest to this umbrella review, five were categorised as having a low risk of bias for randomisation, one was categorised and high risk, and five as having an unclear risk of bias for randomisation.<br><br>Nineteen trials were categorised as having a low risk of bias for outcome ascertainment. Of the 11 trials that informed the outcomes of interest to this umbrella review, six were categorised as having a low risk of bias for outcome ascertainment and five were categorised has having an unclear risk of bias for outcome ascertainment. |

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| | GRADE was used to assess the certainty of evidence. For all outcomes assessed in this review, the certainty of evidence was assessed as low- or very low- quality. The reasons for downgrading were not specified.<br><br>Publication bias was not assessed due to the limited number of studies available for the meta-analysis. |
| **Method of analysis** | Review Manager version 5.4 software was used for meta-analysis. Trials reporting the outcomes as dichotomous data were analysed using the Mantel Haenszel test and effect measures were reported as Risk Ratio (RR) with 95% Confidence Interval (CI). For the trials that had summarised the results in the form of continuous data, Inverse Variance function was used and effect measures were reported as Standardised Mean Differences (SMD) with 95% CI to avoid errors caused due to different scales of measurements.<br><br>A random-effect model was used throughout the review for analysis to account for high clinical heterogeneity among the studies. Statistical heterogeneity was assessed using the $I^2$ statistic; values < 40% was considered as low, 30%-60% as moderate, 50%-90% as substantial and 75%-100% as considerable heterogeneity. The level of significance was set at P value less than .05. |
| **Outcome(s) assessed** | Primary outcome 1: New carious lesions<br><br>Primary outcome 2: Caries increment (DMFS, DMFT, dmfs, dmft)<br><br>Secondary outcome 1: *S. mutans* count<br><br>*Note*. All the above outcomes are presented as primary outcomes in the review. For the HRB's purposes secondary outcome 1 is a secondary outcome. |
| **Results/findings** | **Primary outcome 1: New carious lesions**<br>The use of ACP-based sealant in a trial with 64 participants showed superior caries preventive effect in one trial with a pediatric population compared to that of fluoride use at 12 months follow-up (experimental group 2/32, comparator group 7/32, P < 0.01; assumed mixed dentition).<br><br>**Primary outcome 2: Caries increment (DMFS, DMFT, dmfs, dmft)**<br>Two trials found no added benefit of using CPP-ACP in preventing dental caries compared to fluoride alone:<br>One examined primary dentition (dmfs; n = 229 participants; CPP-ACP (10% w/v) paste plus fluoride (1000 ppm) toothpaste compared to 1000pm fluoride toothpaste). |

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| | Another examined permanent dentition (DMFT, DMFS; n = 40 participants; CPP-ACP paste plus fluoride toothpaste compared to fluoride toothpaste alone) (both P > 0.05) (both combined interventions, follow-up periods not specified).<br><br>Conversely, one trial (single intervention; 91 participants) found a significant added benefit of using CPP-ACP cream compared to no treatment (experimental group DMFT index = 0.17, control group DMFT index = 2, p < 0.001), and compared to a control group receiving 5% NaF varnish (DMFT index = 0.3, p < 0.001) at 12 months follow-up.<br><br>**Secondary outcome 1: *S. mutans* count**<br>Out of the 8 trials that assessed *S. mutans* count as an outcome, only data from 2 trials could be included in a meta-analysis. The result significantly favoured the use of CPP-ACP as compared to fluoride alone (RR 0.69, 95% CI 0.48 to 0.99, P = 0.04; 2 trials; 150 participants; $I^2$ = 0%; low certainty of evidence). |
| **Significance/direction** | Within the limitation of the systematic review, overall low evidence was generated in favor of the added benefit of using CaP agent with respect to post-intervention *S. mutans* counts. There was insufficient evidence to determine the caries preventive efficacy of CaP derivatives. More well designed and high-quality trials with an adequate sample size and longer follow-up periods are required to help determine the true effect of these agents. |
| **Heterogeneity** | No statistical heterogeneity was observed in the meta-analysis that pertained to outcomes relevant to this umbrella review. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence for the review outcomes. However, the certainty of evidence was graded only in relation to outcomes in which data were pooled. Outcomes relevant to this umbrella review were reported narratively. Therefore, the certainty of evidence for these outcomes is not known. Of the six outcomes for which the certainty of evidence was graded, four were graded as low and two were graded as very low.<br><br>The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Akera *et al.* (2022) extraction |
| **First Author and year of publication** | Akera *et al.* (2022) |

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| **Objectives (exact review question(s) and page number)** | To evaluate the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries (countries with national income per person less than $12,375) (p2). |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (planned separate, but no outcomes report on primary dentition, coded as mixed for plaque outcome); Dental hygiene, supervised toothbrushing; sealants, combined.<br><br>The population of interest was children aged 3 to 16 years who attended primary school.<br><br>The total number of participants among the 34 included studies was not reported. The age of participants ranged from 3 to 16 years. Information pertaining to the sex of included participants was not reported.<br><br>Of the 34 included studies in this review, only three were relevant to the objectives of this umbrella review. The findings from 29 trials were excluded due to the nature of the intervention, and the findings from two trials were excluded due to the nature of the outcomes. |
| **Setting/context** | The studies were conducted in Bulgaria (1 study), Brazil (5 studies), China (3 studies), India (5 studies), Indonesia (1 study), Iran (3 studies), Malaysia (1 study), Myanmar (1 study), Nigeria (1 study), Pakistan (1 study), Philippines (1 study), South Africa (1 study), Taiwan (1 study), Tanzania (3 studies), Thailand (2 studies), Turkey (1 study), and Zimbabwe (1 study).<br><br>All studies were conducted within a school setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was primary school-based interventions. This was defined as comprising any one or more of the following elements: school health policy; provision of oral health education; promoting a healthy school environment; providing access to oral health services; and involving community members. Studies were included if:<br>1. The intervention used schools as the focal site for intervention delivery<br>2. They compared an intervention to no intervention or usual practice<br>3. They were published in English from 1995 to December 2021, and<br>4. The intervention took place in a low- and middle-income country.<br><br>Comparators in all studies were schools that did not receive an intervention or continued to provide usual activities.<br><br>Most interventions were oral health education programmes with various activities. However, five interventions exclusively involved disclosed plaque visualisation, daily tooth brushing at school, application of fissure sealants, |

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| | and zinc supplementation. For the purposes of this umbrella review, as per the inclusion criteria, only the findings from the studies assessing the effectiveness of daily toothbrushing, fissure sealants and zinc supplementation were extracted.<br><br>Most interventions were delivered by either a dentist, teacher, or dentist and teacher combination, while others were delivered by investigators, health counsellors, community members, parents, and school children. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• MEDLINE<br>• Embase<br>• Global Health<br>• CINAHL<br>• Emcare<br>• Scopus<br>• Web of Science<br>• WHO website<br>• Google Advanced, and<br>• Google Scholar.<br><br>The sources were searched between 08/04/2020 and 07/06/2022. Additional search strategies included: hand searching references of included studies, using the UNSW library to access articles unavailable online, and using automatic alerts of new results matching our strategy to update our search.<br><br>One review author performed title and abstract screening. The same review author performed full-text screening and other five reviewers verified the decisions. Disagreements were resolved through discussion. Two review authors independently performed data extraction.<br><br>The review protocol was registered with PROSPERO (ID: CRD42020202599).<br><br>The review received no funding.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 34 included studies were published between 1996 and 2021. |

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| **Number of primary studies included in the systematic review** | The review authors included 34 primary studies. Of these, 24 were cluster randomised controlled trials, two were non-randomised trials, four were quasi-experiments, and four were cohort studies. Of the cohort studies, two were retrospective, and therefore, as per the inclusion criteria for this umbrella review, the findings from these studies were not extracted. Twenty-three studies included in this review had two intervention arms, seven studies had three arms, three had four arms, and one had five arms. Follow-up periods ranged from one month to seven years.<br><br>The funding sources of the primary studies were not reported. |
| **Types of studies included** | The review authors included 34 primary studies: Frencken (2001), Esan (2015), Nyandindi (1996), van Palenstein Helderman (1997), van Wyk (2004), Zacharias (2019), de Farias (2009), de Sousa (2002), Jaime (2015), Simpriano (2017), Tomazoni (2019), Gholami (2015), Saied-Moallemi (2009), Yekaninejad (2012), Chachra (2011), Chauhan (2016), Chounchaisithi (2014), Duijster (2017), Haleem (2012), Hartono (2002), Hebbal (2011), Hebbal (2005), Lai (2016), Monse (2013), Naidu (2017), Nammontri (2013), Peng (2004), Petersen (2004), Swe (2020), Tai (2009), Yusof (2013), Pakhomov (1997), and Uckardes (2009).<br><br>The results of three studies (a non-randomised clustered controlled trial, a randomised controlled trial, and a quasi-experiment) were relevant to the objectives of this umbrella review: Duijster (2017), van Wyk (2004), and Uckardes (2009).<br><br>A list of excluded studies and the reasons for exclusion were provided as supplemental material. |
| **Country of origin of included studies** | The studies were conducted in Bulgaria (1 study), Brazil (5 studies), China (3 studies), India (5 studies), Indonesia (1 study), Iran (3 studies), Malaysia (1 study), Myanmar (1 study), Nigeria (1 study), Pakistan (1 study), Philippines (1 study), South Africa (1 study), Taiwan (1 study), Tanzania (3 studies), Thailand (2 studies), Turkey (1 study), and Zimbabwe (1 study). |
| **Appraisal instrument(s)** | Two review authors independently assessed the methodological quality of included studies using standardised instruments from the JBI for experimental and observational studies. The instrument for experimental studies had 13 domains, while the instrument for observational studies had 11 domains. Judgement was made by classifying domains as “yes”, “no”, “unclear” or “not applicable”. Any disagreements that arose were resolved through discussion. All studies, regardless of the results of their methodological quality, underwent data extraction. |
| **Appraisal rating** | None of the 30 experimental studies scored a “yes” for all 13 domains assessed. Experimental studies showed limitations with respect to randomisation of participants, allocation concealment, blinding of |

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| | participants, persons delivering the intervention and outcome assessors, intention to treat analysis, statistical power analysis and trial design. Of the 30 experimental studies, eight were classified as using true randomisation, four were classified as not using true randomisation, and 18 were classified as unclear. In addition, twelve were classified as having the outcome assessors blinded to treatment assignment, four were classified as not having the outcome assessors blinded to treatment assignment, and 14 were classified as unclear in relation to blinding outcome assessors to treatment assignment.<br><br>Of the three studies relevant of this umbrella review, one was classified as not using true randomisation, one was classified as using true randomisation, and one was classified as unclear in relation to true randomisation. In addition, two were classified as having the outcome assessors blinded to treatment assignment, and one was classified as unclear in relation to blinding outcome assessors to treatment assignment.<br><br>The certainty of evidence was assessed as very low for all oral health outcomes. Studies were downgraded because of limitations in allocation concealment, lack of intention to treat analysis and blinding of participants, those delivering treatment and outcome assessors. In addition, interventions were delivered differently in different settings, and some did not have an adequate sample size.<br><br>Publication bias was not measured due to there being less than 10 studies included in each meta-analysis. |
| **Method of analysis** | Qualitative data were presented in narrative form, including tables to aid data presentation where appropriate.<br>Quantitative data analyses were conducted in RevMan 5.4. Random-effects models were used for all meta-analyses. Standardized mean difference (SMD) scores (rather than raw mean scores) were used in meta-analyses to account for heterogeneity among extracted measures. The review authors used risk ratios (RR) in one meta-analysis.<br><br>Sensitivity and subgroup analyses were conducted; however, the results were not relevant to the objectives of this umbrella review as the studies included in the analyses were assessing an inappropriate intervention or outcome. |
| **Outcome(s) assessed** | Primary outcome 1: Mean difference in dental caries measured by dmft(s)/DMFT(S) scores<br><br>Secondary outcome 1: Difference in plaque<br><br>*Note*. Both outcomes are identified in the review as presented here. |

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| **Results/findings** | **Primary outcome 1: Dental caries measured by DMFT scores or net increment in DMFT scores**<br>Intervention 1: Daily toothbrushing with 0.3ml of toothpaste (containing 1450 ppm free available fluoride) as a supervised group activity versus no intervention:<br>Results from one trial found no difference in DMFT scores in the intervention group compared to the control group (MD -0.00; 95% CI -0.10 to 0.10; p = 0.005; 1,500 participants; very low certainty of evidence). The precise follow-up period was not specified, but it indicated to be at least 2 years.<br><br>Results from the same trial found net increment in DMFT scores to be significantly lower in the intervention group compared to the control group (MD -0.15; 95% CI -0.25 to -0.05; p = 0.06; 1,500 participants; very low certainty of evidence). The precise follow-up period was not specified, but it indicated to be at least 2 years.<br><br>Intervention 2: Fissure sealant programme (unspecified) versus no intervention:<br>Results from one trial found DMFT scores to be significantly lower in the intervention group (assumed after a 7-year follow up, although not explicitly stated) compared to the control group (for 15-year-old children: SMD -1.03, 95% CI -1.28 to -0.78, p < 0.00001; 345 participants; very low certainty of evidence) (for 12 year old children: SMD -0.42, 95% CI -0.60 to -0.24, p < 0.00001; 516 participants; very low certainty of evidence).<br><br>**Secondary outcome 1: Difference in plaque**<br>Intervention 3: Zinc supplementation versus placebo:<br>Results from one trial found no significant difference between the intervention and control groups for plaque outcomes. The certainty of evidence was very low (limited information provided). |
| **Significance/direction** | There was insufficient evidence to determine whether daily supervised toothbrushing, a fissure sealant programme, or zinc supplementation offered within a school setting can reduce the risk of caries development. |
| **Heterogeneity** | The results from the three trials that were relevant to the objectives of this umbrella review were described narratively. |
| **Summary for GRADE assessment for HRB report** | The certainty of evidence was assessed by the review authors as very low for all relevant outcomes. The authors note that they had very little confidence in the effect estimate and acknowledge that the true effect is likely to be substantially different from the estimate of effect. Trials were downgraded because of limitations in allocation concealment, lack of intention to treat analysis and blinding of participants, those delivering treatment and outcome assessors. In addition, interventions were delivered differently in different settings, and some did not have an adequate sample size. |

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| | The HRB authors graded the certainty of evidence as very low. |
| **References to previously published versions** | N/A |
| Parameter | Joury *et al.* (2017) extraction |
| **First Author and year of publication** | Joury *et al.* (2017) |
| **Objectives (exact review question(s) and page number)** | To systematically review the randomised controlled trials (RCTs) that aimed to assess the effectiveness of school-based dental screening versus no screening on improving oral health in children aged 3-18 years (p4).<br><br>*Note*. Only one trial reported on the outcome of interest to this umbrella review. It was not clear whether the findings related to new caries or prevalence of existing caries, and as such the findings were not extracted for use in data synthesis. |
| **Participants (characteristics and numbers)** | Primary and permanent dentition (no trials reported on any outcomes of interest to this umbrella review; coded under both primary and permanent), attendance for dental assessment, scheduled dental appointments.<br><br>The population of interest was children aged 3 to 18 years, of both sexes, from different socio-demographic backgrounds, attending schools.<br><br>The five included trials randomised a total of 28,442 children, of which 19,537 received screening and 8,905 did not receive screening. The age of participants ranged from 5.5 to 15 years. Information pertaining to the sex of included participants was not reported.<br><br>The total number of participants in the only included trial (out of five trials) that inform this umbrella review was 17,098. |
| **Setting/context** | The trials were conducted in India (2 trials) and the United Kingdom (3 trials).<br><br>All trials were conducted within a school setting. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was school-based dental screening. The control group included no screening for oral health.<br><br>The type of dental screening intervention varied across the trials and across different arms of the same trial. The variations in the intervention were in the data collection protocol, the information sent to home, and the personnel who carried out the screening (trained/calibrated dentists versus |

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| | untrained/not calibrated dentists or parents/carers). Also, the trials varied in terms of their approach to the no dental screening group. Most trials screened the control group after the end of the trial's follow-up. However, one trial did not screen the control group at all. |
| **Databases and sources searched** | The review authors searched the following sources:<br>• MEDLINE via Ovid<br>• EMBASE via Ovid<br>• Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register)<br>• Web of Science (Science citation expanded)<br>• ClinicalTrials.gov, and<br>• WHO International Clinical Trials Registry Platform.<br><br>The databases were searched until April 2016. Reference lists of eligible studies and review articles were searched for further relevant studies and contact was sought with experts to obtain grey literature. There were no language restrictions.<br><br>Three sets of two review authors (4 in total) independently screened the title and abstracts of search results. The final decision was made on inclusion of the study based on full text and after discussion between the reviewers. Two review authors independently performed data extraction. Disagreements were resolved through discussion with a third author.<br><br>The review protocol was registered with PROSPERO (ID: CRD42016038828).<br><br>The review received no funding.<br><br>Conflicts of interest were not provided. |
| **Date range (years) of included studies** | The five included trials were published between 2001 and 2014. |
| **Number of primary studies included in the systematic review** | The review authors included five randomised controlled trials. All trials were randomised at a cluster level.<br><br>Sources of the funding for the primary studies were not provided; however, four of the trials were assessed as having a low risk of bias in relation to funding. |
| **Types of studies included** | The review authors included five randomised controlled trials: Cunningham (2009), Donaldson (2001), Hebbal (2005), Milsom (2006), and Praveen (2014). |

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| | The results of one trial informed the outcome of interest to this umbrella review: Milsom (2006).<br><br>The excluded studies at full-text screening were not listed, but the reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in India (2 trials) and the United Kingdom (3 trials). |
| **Appraisal instrument(s)** | Cochrane's criteria of risk of bias assessment was used to assessed the risk of bias of all included trials. The following domains were assessed in each included trial:<br>1. Sequence generation<br>2. Allocation concealment<br>3. Blinding of children and healthcare providers (screeners)<br>4. Blinding of outcome assessors<br>5. Missing outcome data<br>6. Selective reporting, and<br>7. Other sources of bias (including source of funding). |
| **Appraisal rating** | The review authors did not provide an overall risk of bias of the included trials. However, according to Cochrane's Collaboration tool, the HRB notes that all trials had an overall high risk of bias as all trials were categorised as having a high risk of bias for blinding of participants and personnel.<br><br>Four trials were categorised as having a low risk of bias for randomisation and one trial was categorised as having an unclear risk of bias for randomisation. The one trial that was relevant to this umbrella review had a low risk of bias for randomisation.<br><br>One trial was categorised as having a low risk of bias for outcome ascertainment, three trials were categorised as having an unclear risk of bias for outcome ascertainment and one trial was categorised as having a high risk of bias for outcome ascertainment. The one trial that was relevant to this umbrella review had a low risk of bias for outcome ascertainment.<br><br>The certainty of evidence was assessed with reference to risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias. The certainty of evidence for the outcome that pertained to this umbrella review was assessed as low. The reasons for downgrading were due to risk of bias and imprecision. |

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| | A publication bias assessment was planned but not carried out due to the limited number of included trials. |
| **Method of analysis** | Both narrative and quantitative syntheses of included trials' findings were performed. The findings of trials that used the same outcome measure were pooled using random- and fixed-effects meta-analysis. Risk ratios were calculated for dichotomous outcomes, whereas standardised mean differences were planned for continuous outcomes. 95% confidence intervals (95% CI) and two-sided P values were calculated for each outcome.<br><br>In trials where the effects of clustering were present, the standard error of the effect estimates was adjusted using the intra-class correlation coefficient (ICC) to account for the cluster effect. Where adjusted effect estimates or ICC were not available, the ICC from the trial with the lowest risk of bias was used and sensitivity analysis was performed for twice the ICC and half the ICC reported in the study with the lowest risk of bias.<br><br>Heterogeneity between the trials was assessed using both the Chi-square test and the $I^2$ statistic. The $I^2$ values were interpreted in line with Cochrane's Handbook where:<br>• 30% to 60% may represent moderate heterogeneity<br>• 50% to 90% may represent substantial heterogeneity, and<br>• 75% to 100% may represent considerable heterogeneity.<br><br>This was calculated along with whether the heterogeneity was only in magnitude or whether it was in the direction of effects, the chi- squared test of heterogeneity, and the overlap of confidence intervals.<br><br>Sensitivity and subgroup analyses were planned but not carried out due the limited number of included trials. |
| **Outcome(s) assessed** | Primary outcome 1: changes in the prevalence and/or mean number of deciduous and/or permanent teeth with caries (dt > 0; dt; DT > 0; DT; where dt stands for the average number of decayed primary teeth per child and DT stands for the average number of decayed permanent teeth per child)<br><br>Secondary outcome 1: harms of screening<br><br>Secondary outcome 2: oral health-related quality of life<br><br>*Note*. Primary outcome 1 is identified as a primary outcome in the review. Secondary outcome 1 is identified as a primary outcome in the review, but for the HRB's purposes is considered a secondary outcome. Secondary outcome 2 is identified as a secondary outcome in the review. |

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| **Results/findings** | **Primary outcome 1: changes in the prevalence and/or mean number of deciduous and/or permanent teeth with caries**<br>One trial reported this outcome. It was not clear whether the findings related to new caries or prevalence of existing caries, and as such the findings were not extracted.<br><br>**Secondary outcome 1: Harms of screening**<br>No included trials reported this outcome.<br><br>**Secondary outcome 2: Oral health-related quality of life**<br>No included trials reported this outcome. |
| **Significance/direction** | The reviewed evidence suggests no clinical benefit from school-based screening in improving children's oral health. However, there is a lot of uncertainty in this finding because of the quality of evidence. There is a need to conduct well-designed trials with an intensive follow-up arm and cost-effectiveness analysis.<br><br>*Note*. Only one trial reported on the outcome of interest to this umbrella review. It was not clear whether the findings related to new caries or prevalence of existing caries, and as such the findings were not extracted for use in data synthesis. |
| **Heterogeneity** | Of the five trials included in this review, only one measured outcome that were of interest to this umbrella review. As such, heterogeneity could not be assessed as there was only one relevant trial. |
| **Summary for GRADE assessment for HRB report** | The review authors graded the certainty of evidence. However, only one trial reported on the outcome of interest to this umbrella review. It was not clear whether the findings related to new caries or prevalence of existing caries, and as such the findings were not extracted. Therefore, the findings of the review were not extracted or included in the evidence synthesis. |
| **References to previously published versions** | N/A |
| Parameter | Konradsson *et al.* (2020) extraction |
| **First Author and year of publication** | Konradsson *et al.* (2020) |
| **Objectives (exact review question(s) and page number)** | To examine the scientific evidence for the efficacy of stabilised stannous fluoride dentifrice in relation to dental caries, dental erosion, and dentin hypersensitivity when compared with standard fluoride dentifrices in patients with, or at risk of these three dental conditions (p96). |

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| | *Note*. The review authors note in the text and illustrate in Table 2 that two independent examiners examined the outcomes of interest. However, the results varied significantly between the examiners, and the findings of one examiner for one comparison appear to be excluded from the Table. Therefore, the HRB elected not to use the findings in the umbrella review evidence synthesis. |
| **Participants (characteristics and numbers)** | Permanent dentition; combined intervention.<br><br>The population of interest was individuals with, or at risk of, dental caries, dental erosion or dentin hypersensitivity.<br><br>The 21 included trials involved a total of 2,945 participants. Of the trials that reported on age, the age of participants ranged from approximately 10 to 70 years. Of the 13 trials that reported gender, % female ranged from 51% (483/955) to 93% (75/81).<br><br>The total number of participants in the one (out of 22 trials) that inform this umbrella review was 955. The age of participants in this trial was 10+ years old and 51% of participants were female. |
| **Setting/context** | The trials were conducted in China (2 trials), Germany (1 trial), the Netherlands (1 trial), Norway (2 trials), Puerto Rico (1 trial), the United Kingdom (3 trials), the United States (9 trials). Additionally, one trial was conducted in both the United Kingdom and the United States, and one trial was conducted in both Ireland and the United States.<br><br>The one relevant trial to HRB interests took place in Puerto Rico.<br><br>The study settings were not reported. |
| **Description of Interventions/ phenomena of interest** | The intervention of interest was toothbrushing with stabilised $SnF_2$ dentifrice using a manual or electric toothbrush, or treatment with experimental slurries containing stabilised $SnF_2$. The comparison group was toothbrushing with a non-stannous fluoridated dentifrice or non-fluoridated dentifrice/placebo, or no treatment.<br><br>Studies were excluded if the test dentifrices contained stannous chloride or stannous fluoride in combination with potassium nitrate, amino fluorides or chlorhexidine. In addition, studies including $SnF_2$ applied by gels, brushing with ionic or laser toothbrushes, or the use of mouthwashes were excluded.<br><br>In the only included trial relevant to the purposes of this umbrella review, brushing occurred for 1 minute twice per day (during school hours, brushing was supervised). |

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| **Databases and sources searched** | The review authors searched the following sources:<br>• Medline OVID (including Epub Ahead of Print, In-Process and Other Non-Indexed Citations)<br>• Embase, and<br>• Cochrane Library.<br><br>The databases were searched from database inception until January 2018 (for dental caries outcomes). Language was restricted to English and publication year was restricted to 1990 or later. Manual searches were also conducted. The reference lists of included articles were searched to identify any additional relevant studies.<br><br>The review authors formed pairs. Each of the reviewers in a pair independently screened search results (title and abstract, and full-text screening). Disagreements were resolved by discussion. It was not reported how data extraction was completed.<br><br>There was no mention of a protocol being prepared or published for this review.<br><br>Any sources of funding for the review were not reported.<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 21 included trials were published between 2004 and 2017.<br><br>The one relevant trial was published in 2004. |
| **Number of primary studies included in the systematic review** | The review authors included 21 primary studies in the review. Of these, 13 were randomised controlled trials, seven were in situ studies and one trial was a clinical non-randomised trial. Follow-up periods, where reported, ranged from 5 days to 24 months.<br><br>The one relevant trial to HRB interests had a follow-up period of 24 months and was a randomised controlled trial. This trial was sponsored by a toothpaste manufacturer.<br><br>The majority of included studies (n = 19) were sponsored by the manufacturers or had authors employed by a toothpaste manufacturer. |
| **Types of studies included** | The review authors included 21 primary studies: Papas (2007), Stookey (2004), Barlow (2009), Bellamy (2014), Hooper (2007), Hove (2014), Huysmans (2011), West (2017a), West (2017b), Young (2006), Chaknis (2011), He (2011a), He (2011b), He (2011c), He (2014a), He (2014b), Parkinson (2013), Parkinson (2015), Parkinson (2016), Schiff (2005), and Schiff (2006). |

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| | The results of one trial informed the outcomes of interest to this umbrella review: Stookey (2004).<br><br>The excluded studies were not listed, but reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in China (2 trials), Germany (1 trial), Ireland (1 trial), the Netherlands (1 trial), Norway (2 trials), Puerto Rico (1 trial), the United Kingdom (4 trials), the United States (11 trials). One trial was conducted in both the United Kingdom and the United States and one trial was conducted in both Ireland and the United States. |
| **Appraisal instrument(s)** | The two reviewers in each pair independently scored the possible risk of bias for each included study using a tool for risk of bias assessment developed by the Swedish Agency for Health Technology Assessment and Assessment of Social Services. The review authors noted that the SBU tool is similar to the Cochrane tool. The following domains were assessed in each included study:<br>1. Selection bias<br>2. Performance bias<br>3. Detection bias<br>4. Attrition bias, and<br>5. Reporting bias.<br><br>Based on this information, risk of bias was judged as low, medium or high. Any disagreements were resolved by discussion with the other authors. |
| **Appraisal rating** | Overall, six studies were categorised as having a low risk of bias, six studies were categorised as having a medium risk of bias, and nine studies were categorised as having a high risk of bias. The one trial that was relevant to this umbrella review had an overall high risk of bias.<br><br>The risk of bias for the individual domains (selection, performance, detection, attrition, and reporting bias) that were assessed for each included study were not reported.<br><br>Publication bias was not measured. |
| **Method of analysis** | For outcomes that were relevant to this umbrella review, a descriptive analysis was applied since there were few studies available to conduct a quantitative analysis. |
| **Outcome(s) assessed** | Primary outcome 1: caries increment measured in decayed, missing and filled permanent tooth surfaces (DMFS scores) |

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| | *Note*. This outcome is identified in the review as presented here (as the primary outcome). |
| **Results/findings** | **Primary outcome 1: caries increment measured in decayed, missing and filled permanent tooth surfaces (DMFS scores)**<br>One randomised 24-month trial at a high risk of bias evaluated % DMFS reduction after using three different sodium fluoride toothpastes in comparison to a stannous fluoride toothpaste twice per day (at home and supervised in school). The review authors note that all individuals were evaluated independently by two examiners. However, the findings of one examiner for comparison 1 were not reported.<br><br><u>Comparison 1:</u><br>The use of 0.454% $SnF_2$-SHMP (1100 ppm fluoride) resulted in a higher caries reduction compared with the toothpaste containing 1100 ppm F (NaF) toothpaste at 24 months follow-up. However, the result was not statistically significant (Examiner A: 11.9%, P = 0.065; 1 trial; 238 participants).<br><br><u>Comparison 2:</u><br>Results showed that the 500ppm F (NaF) toothpaste did not result in a significantly higher caries reduction compared with the toothpaste containing 1100 ppm F (NaF) toothpaste at 24 months follow-up (Examiner A: 11.9%, P = 0.065; 242 participants).<br><br><u>Comparison 3:</u><br>The 2800 ppm F (NaF) toothpaste resulted in a significantly higher caries reduction compared with the toothpaste containing 1100 ppm F (NaF) toothpaste at 24 months follow-up (Examiner A: 13.0%, P = 0.045; Examiner B: 23.2%, P = 0.003; 1 trial; 235 participants). |
| **Significance/direction** | Only one included trial (with a notably high risk of bias) met the criteria for this umbrella review. The review authors note in the text and illustrate in Table 2 that two independent examiners examined the outcomes of interest. However, the results varied significantly between the examiners, and the findings of one examiner for one comparison appear to be excluded from the Table. Therefore, the HRB chose not to use the findings in the umbrella review evidence synthesis.<br><br>Overall, the review authors concluded that more well-designed randomised controlled trials that are less dependent on commercial interests and performed by independent researchers are needed.<br><br>*Note*. The review authors note in the text and illustrate in Table 2 that two independent examiners examined the outcomes of interest. However, the results varied significantly between the examiners, and the findings of one examiner for one comparison appear to be excluded from the Table. |

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| | Therefore, the HRB elected not to use the findings in the umbrella review evidence synthesis. |
| **Heterogeneity** | Of the 21 studies included in the review, only one reported on an outcome of interest to this umbrella review. As such, heterogeneity could not be assessed. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |
| Parameter | Oliveira *et al.* (2019) |
| **First Author and year of publication** | Oliveira *et al.* (2019) |
| **Objectives (exact review question(s) and page number)** | To investigate primarily whether silver diamine fluoride is superior to placebo or no treatment in preventing the development of new caries lesions in primary teeth.<br><br>To examine the preventive effect of SDF in comparison to other active treatments (p25). |
| **Participants (characteristics and numbers)** | Primary dentition; topical fluoride, solution.<br><br>The population of interest was children between 0 to 12 years of age.<br><br>The four included trials randomised 1,118 children, of whom 915 were evaluated in analyses. Three trials reported the age range of participants, which ranged from 3 to 6 years. One trial reported that the age of participants was 6 years or more (with a mean age of 6.29, and SD of 0.48). At baseline, most participants had high caries experience. Information pertaining to the sex of included participants was not reported.<br><br>The sample size of the only included trial relevant to this umbrella review was not reported. |
| **Setting/context** | The trials were conducted in Brazil (2 trials), China (1 trial), and Cuba (1 trial).<br><br>The study settings were not reported. |

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| **Description of Interventions/ phenomena of interest** | The intervention of interest was topical silver diamine fluoride solution (any concentration or frequency) applied by any health care worker at any setting. The comparison group included no intervention, a placebo, any topical cariostatic agents, resin or glass-ionomer pit and fissure sealants or dental restorative materials.<br><br>Among the included trials, two used 38% SDF applications, one used 30% SDF applications, and one used 12% SDF applications. Application intervals varied from a once-off application to quarterly, biannually, or yearly. Two trials compared SDF to no treatment, one trial compared SDF to both a water placebo and 5% sodium fluoride varnish, and one compared SDF to high-viscosity glass-ionomer cement.<br><br>At baseline, most participants had high caries experience, were not exposed to fluoridated water but were regularly exposed to some sort of topical fluoride product (i.e., fluoride toothpaste or 0.2% sodium fluoride school-based mouth rinse program). |
| **Databases and sources searched** | The review authors searched the following sources:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Embase<br>• Medline via PubMed<br>• Scopus<br>• Web of Science<br>• Lilacs<br>• BBO<br>• Scielo<br>• ClinicalTrials.gov<br>• Brazilian Register of Clinical Trials<br>• EU Clinical Trials Register<br>• ISRCTN registry and Current Controlled Trials<br>• ANZCTR-Australian New Zealand Clinical Trials Register, and<br>• Capes dissertation database.<br><br>The searches were performed in April 2016 and updated in July 2017. Cross-referencing from reviews about silver diamine fluoride for caries prevention or arrest was used to identify further potential articles. There were no language or date of publication restrictions.<br><br>The review protocol was registered with PROSPERO (ID: CRD42016036963). |

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| | Two review authors independently screened search results (title and abstract, and full-text screening), and performed data extraction. Disagreements were resolved by discussion or consultation with a third review author.<br><br>The review was partially funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (PCS – 1609 – 36824).<br><br>None of the review authors declared a conflict of interest. |
| **Date range (years) of included studies** | The 4 included trials (reported in 6 reports) were published between 1991 and 2012. |
| **Number of primary studies included in the systematic review** | The review authors included four randomised controlled trials. It was not specified whether these trials were truly randomised or quasi-randomised. All trials used a parallel group design. Follow-up periods ranged from 12 to 36 months.<br><br>The funding sources of the primary studies were not provided. |
| **Types of studies included** | The review authors included four randomised controlled trials: Bijella (1991), Chu (2002), Dos Santos (2012), and Llodra (2005).<br><br>The excluded studies were not listed, but reasons for exclusion were reported. |
| **Country of origin of included studies** | The trials were conducted in Brazil (2 trials), China (1 trial), and Cuba (1 trial). |
| **Appraisal instrument(s)** | Two review authors independently assessed the risk of bias of all included trials using the Cochrane risk of bias tool. Disagreements between the review authors over the risk of bias in particular studies were resolved by consensus with involvement of a third review author where necessary. The following domains were assessed in each included trial:<br>1. Random sequence generation (selection bias)<br>2. Allocation concealment (selection bias)<br>3. Blinding of participants and personnel (performance bias)<br>4. Blinding of outcome assessment (detection bias)<br>5. Incomplete outcome data (attrition bias)<br>6. Selective reporting (reporting bias)<br>7. Balanced groups at baseline (selection bias), and<br>8. Reliability of measurements (misclassification bias). |

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| **Appraisal rating** | Overall, no trials were categorised as having a low risk of bias. Two trials were categorised as having a high risk of bias and two trials were categorised as having an unclear risk of bias.<br><br>One trial categorised as having a low risk of bias for randomisation, one trial was categorised as having an unclear risk of bias for randomisation, and two trials were categorised as having a high risk of bias for randomisation. The risk of bias for randomisation was unclear in the only included trial relevant to this umbrella review.<br><br>Two trials were categorised as having a low risk of bias for outcome ascertainment, one trial was categorised as having an unclear risk of bias for outcome ascertainment, and one trial was categorised as having a high risk of bias for outcome ascertainment. The risk of bias for outcome ascertainment was unclear in the only included trial relevant to this umbrella review.<br><br>Publication bias was not measured. |
| **Method of analysis** | The primary measure of treatment effect was the difference in mean caries increment at dentin level between silver diamine fluoride and control groups (MD; mean new decayed, filled, and extracted tooth surfaces/teeth in the test group minus mean new decayed, filled, and extracted tooth surfaces/teeth in the control group). The prevented fraction (PF; mean increment in control minus mean increment in intervention groups divided by mean increment in control) was the secondary measure of treatment effect.<br><br>When there were more than one relevant intervention and/or comparison groups they were combined into a single intervention and/or comparison group. Confidence intervals<br>of PF were calculated using Fieller's method. A fixed-effect model and the inverse variance method were used to obtain pooled estimates of caries increment as weighted mean differences and PF when fewer than 4 studies were combined.<br><br>Heterogeneity of studies was assessed by the $\chi 2$ test for heterogeneity and the Higgins index ($I^2$). The studies in the meta-analyses were grouped according to the duration of their follow-up: less than 24 months and 24 months or more. Placebo or no intervention and active treatment (sodium fluoride varnish, FV, and glass-ionomer cement, GIC) comparison groups were analysed separately throughout. Results were only pooled when all necessary data could be obtained. All analyses were carried out in Stata® 14 (StataCorp. LP, College Station, TX, USA). |
| **Outcome(s) assessed** | Primary outcome 1: difference in mean caries increment at dentin level between silver diamine fluoride and control groups (measured by the |

| | |
|---|---|
| | differences in the mean number of new decayed, filled, and extracted tooth surfaces/teeth)<br><br>Secondary outcome 1: adverse events<br><br>*Note*. Both outcomes are identified in the review as presented here. |
| **Results/findings** | **Primary outcome 1: Difference in mean caries increment at dentin level between silver diamine fluoride and control groups**<br><u>Comparison 1: 12% SDF applications versus no treatment:</u><br>Results from one trial (sample size not reported) showed a 10, 38, and 69% decrease in caries incidence in primary tooth surfaces in the test groups (12% SDF applications yearly, biannually and quarterly, respectively) in comparison to the control group (no treatment) at 24 months of follow-up. However, only the differences between quarterly versus yearly 12% SDF applications and quarterly 12% SDF applications versus no treatment were statistically significant.<br><br>**Secondary outcome 1: Adverse events**<br>The only included trial relevant to this umbrella review did not report on adverse events. |
| **Significance/direction** | Available evidence suggests that SDF topical application has the potential to prevent dental caries in primary teeth. However, this evidence is based off a limited number of trials with important limitations regarding study design and implementation. More rigorously designed studies are warranted to ensure unbiased, high-quality evidence on the benefits of SDF applications for caries prevention. |
| **Heterogeneity** | The review authors noted that the included trials differed regarding type of tooth surfaces treated, interval between SDF applications, and other aspects. However, only one trial included in the review was relevant to this umbrella review. |
| **Summary for GRADE assessment for HRB report** | The review authors did not grade the certainty of evidence. The HRB authors graded the certainty of evidence in this review as low. |
| **References to previously published versions** | N/A |

# Appendix I Characteristics table of included reviews

*Table 101 Characteristics table of included reviews*

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary dentition | | | | | | | | | | | | | |
| Attendance for dental assessment (n = 3) | | | | | | | | | | | | | |
| Scheduled dental appointments (n = 2) | | | | | | | | | | | | | |
| Fee *et al.* (2020) | Determine the optimal recall interval of dental check-up for oral health in a primary care setting. | Primary and permanent dentition; non-invasive | Norway (1) and UK (1) | 1736 | 3 to 18+ years | 53-59% female (1); not reported (1) | Recall interval (time between recall visits/routine dental check-up) | Each other | incremental number of decayed, missing, filled, and sound tooth surfaces (dmfs); number of tooth surfaces with any caries | 24 to 48 months | RCT (2) | 1992 to 2020 | Yes, one trial |
| Joury *et al.* (2017) | Systematically review the randomised controlled trials that aimed to assess the effectiveness of school-based dental screening versus no screening on improving oral health in children aged 3-18 years. | Primary and permanent dentition; non-invasive | Total: India (2) and UK (3); Included: UK (1) | Total: 28442; Included: 17098 | Total: 5.5 to 15 years; Included: 6 to 8 years | Not reported | School-based dental screening | No oral health screening | Changes in prevalence and/or mean number of primary and permanent teeth with active caries | Total: 2 to 4 months; Included: 4 months | Total: RCT (5); Included: RCT (1) | Total: 2001 to 2014; Included: 2006 | Not reported |
| Scheduled primary care appointments (n = 1) | | | | | | | | | | | | | |
| Chou *et al.* (2021) | Determine how effective oral screening (including risk assessment) performed by a primary care clinician is in preventing dental caries in children younger than age 5 years. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (2), Sweden (3), UK (1), and USA (10); Included: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (1), Sweden (3), UK (1), and USA (1) | Total: 106694; Included: 11979 | 0 to 4 years | Total: 36-56% female (21), not reported (12); Included: 36-56% female (15), not reported (8) | Referral to a dentist by primary care clinician; treatments (dietary fluoride supplementation, topical fluoride application, xylitol, silver diamine fluoride) | No intervention; placebo | increment measured by the number of decayed, missing, and filled surfaces and teeth (dmft/dmfs); caries incidence | 12 to 36 months | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (1), observational studies (3) | 1967 to 2020 | Total: Yes, twenty-one trials; Included: Yes, fifteen trials |
| Dental hygiene (n = 3) | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Supervised toothbrushing (n = 3) | | | | | | | | | | | | | |
| Hujoel *et al.* (2018) | Conduct a systematic review of randomised trials assessing the association between personal oral hygiene and dental caries in the absence of the confounding effects of fluoride. | Primary and permanent dentition; non-invasive | UK (1) and USA (2) | 743 | 10 to 13 years | Both males and females (2); only females (1) | Personal oral hygiene (brushing teeth supervised with or without interproximal cleansing devices) | No intervention | Incidence rates of caries (DMFS/DMFT) | 29 to 36 months | RCT (3) | 1977 to 1981 | Yes, one trial |
| Akera *et al.* (2022) | Evaluate the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | Primary and permanent dentition; non-invasive | Total: Bulgaria (1), Brazil (5), Cambodia (1), China (3), India (5), Indonesia (1), Iran (3), Malaysia (1), Myanmar (1), Nigeria (1), Pakistan (1), Philippines (1), South Africa (1), Taiwan (1), Tanzania (3), Thailand (2), Turkey (1), and Zimbabwe (1); Included: Cambodia (1), South Africa (1), and Turkey (1) | Not reported | Total: 3 to 16 years; Included: 6 to 15 years | Not reported | School health policy; provision of oral health education; promoting a healthy school environment; providing access to oral health services; involving community members; daily toothbrushing; fissure sealants; zinc supplementation | No intervention | incidence of dental caries (DMFT); plaque | 24 to 84 months | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Total: 1996 to 2021; Included: 2004 to 2017 | Not reported |
| Dos Santos *et al.* (2018) | Assess the effects of supervised toothbrushing on caries incidence in children and adolescents. | Primary and permanent dentition; non-invasive | Brazil (1), Germany (1), Jordan (1), and USA (1) | Not reported | 2 to 14 years | Not reported | Supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | No supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | Caries incidence (proportion of caries-free children); caries increment (dmft/dmfs or DMFT/DMFS); cumulative survival rates | 21 to 36 months | RCT/quasi-RCT (4) | 1978 to 2016 | Yes, one trial |
| Flossing (n = 0) | | | | | | | | | | | | | |
| **Interdental cleaning devices (n = 0)** | | | | | | | | | | | | | |
| **Professional scaling or cleaning (n = 0)** | | | | | | | | | | | | | |
| **Systemic fluoride (n = 5)** | | | | | | | | | | | | | |
| **Milk (n = 2)** | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yeung *et al.* (2015) | Assess the effects of milk fluoridation for preventing dental caries at a community level. | Primary and permanent dentition; non-invasive | Russia (1) | 180 | 3 years | Not reported | Fluoridated milk (2.5mg per litre) | Standard milk | caries increment (DMFT/DMFS); caries increment (dmft/dmfs); adverse effects; dental pain due to decay; antibiotics due to dental infections; requirement for general anaesthesia due to dental procedures for caries | 36 months | RCT (1) | 2004 | Yes, one trial |
| Cagetti *et al.* (2012) | Evaluate the presence of scientific evidence relating to the effects of fluoride intake via food on the occurrence of carious lesions. | Primary and permanent dentition; non-invasive | Indonesia (1), not reported (2) | 978 | 3.5 to 19 years (mean) | 53% female (1), 54% female (1), not reported (1) | Milk and sugar fluoridation | Standard milk; not reported | caries increment (dmfs/dmft); caries increment (DMFS/DMFT) | 18 to 21 months | Clinical trials (3) | 2002 to 2009 | Not reported |
| Salt (n = 1) | | | | | | | | | | | | | |
| Cagetti *et al.* (2012) | Evaluate the presence of scientific evidence relating to the effects of fluoride intake via food on the occurrence of carious lesions. | Primary and permanent dentition; non-invasive | Indonesia (1), not reported (2) | 978 | 3.5 to 19 years (mean) | 53% female (1), 54% female (1), not reported (1) | Milk and sugar fluoridation | Standard milk; not reported | caries increment (dmfs/dmft); caries increment (DMFS/DMFT) | 18 to 21 months | Clinical trials (3) | 2002 to 2009 | Not reported |
| Sugar (n = 1) | | | | | | | | | | | | | |
| Cagetti *et al.* (2012) | Evaluate the presence of scientific evidence relating to the effects of fluoride intake via food on the occurrence of carious lesions. | Primary and permanent dentition; non-invasive | Indonesia (1), not reported (2) | 978 | 3.5 to 19 years (mean) | 53% female (1), 54% female (1), not reported (1) | Milk and sugar fluoridation | Standard milk; not reported | caries increment (dmfs/dmft); caries increment (DMFS/DMFT) | 18 to 21 months | Clinical trials (3) | 2002 to 2009 | Not reported |
| Supplements (n = 3) | | | | | | | | | | | | | |
| Tubert-Jeannin *et al.* (2011) | Evaluate the effects of fluoride supplements in the form of tablets (chewable or not), drops, lozenges, and chewing gums for preventing dental caries in children. | Primary and permanent dentition; non-invasive | Denmark (1), Sweden (4), Taiwan (1), UK (1), and USA (4) | 7196 | 2 to 12 years | Both males and females (3), not reported (8) | Fluoride supplements (tablets, drops, lozenges, or chewing gum); with or without vitamins; with or without topical fluorides (rinse, application, varnish, toothpaste); with | No fluoride supplements; no treatment; placebo | caries experience measured by dmft/dmfs (within and between groups); caries experience measured by DMFT/DMFT (within and between groups); new carious tooth surfaces; plaque; adverse events | 24 to 72 months | RCT (11) | 1968 to 2008 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | or without non-fluoride-based measures (chlorhexidine, xylitol, sealants, oral hygiene interventions) | | | | | | |
| Zhou *et al.* (2019) | Investigate the efficacy of strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. | Primary and permanent dentition; non-invasive | Not reported | Total: 935; Included: 531 | Under 18 | Not reported | Mechanical (toothbrushing) and chemical (chlorhexidine, plaque-disclosing agent, triclosan-zinc, fluoride) oral health promotion strategies | Placebo; no treatment | caries prevention (dmfs/DMFS; dmft/DMFT) | Total: 10 days to 36 months; Included: 1 to 36 months | Total: RCT (7); non-RCT (7); Included: RCT (2); non-RCT (1) | Total: 1975 to 2015; Included: 1979 to 2013 | Not reported |
| Chou *et al.* (2021) | Determine how effective oral screening (including risk assessment) performed by a primary care clinician is in preventing dental caries in children younger than age 5 years. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (2), Sweden (3), UK (1), and USA (10); Included: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (1), Sweden (3), UK (1), and USA (1) | Total: 106694; Included: 11979 | 0 to 4 years | Total: 36-56% female (21), not reported (12); Included: 36-56% female (15), not reported (8) | Referral to a dentist by primary care clinician; treatments (dietary fluoride supplementation, topical fluoride application, xylitol, silver diamine fluoride) | No intervention; placebo | increment measured by the number of decayed, missing, and filled surfaces and teeth (dmft/dmfs); caries incidence | 12 to 36 months | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (1), observational studies (3) | 1967 to 2020 | Total: Yes, twenty-one trials; Included: Yes, fifteen trials |
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | |
| Vitamin D (n = 0) | | | | | | | | | | | | | |
| Calcium (n = 0) | | | | | | | | | | | | | |
| Sialagogues (n = 1) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing | No intervention; fluoride toothpaste/varnish/gel; conventional care; each | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | other; placebo | | | controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | |
| Zinc (n = 0) | | | | | | | | | | | | | |
| Topical fluoride (n = 9) | | | | | | | | | | | | | |
| Toothpaste (n = 2) | | | | | | | | | | | | | |
| Walsh *et al.* (2019) | Determine and compare the effects of toothpastes of different fluoride concentrations (parts per million) in preventing dental caries in children, adolescents, and adults. | Primary and permanent dentition; non-invasive | Total: Australia (2), Brazil (3), Canada (2), China (1), Denmark (1), France (5), Germany (2), Guatemala (2), Iceland (1), India (1), Italy (2), Japan (1), Lithuania (1), Puerto Rico (1), Sweden (6), Switzerland (6), UK (22), and USA (37); Included: Australia (1), | Total: 67835; Included: 41807 | 1 to 93 years | Total: Both males and females (66), only males (3), only females (2), not reported (25); Included: | Fluoride toothpaste (0ppm, 250ppm, 440 to 550ppm, 1000 to 1250 ppm, 1450 to 1500 ppm, 1700 to 2200 ppm, 2400 to 2800 ppm) and toothbrushing | Each other; non-fluoride toothpaste; no toothpaste | incidence of caries (change in proportion of participants developing new caries); adverse effects | Total: 12+ months; Included: 22 months to 60 months | Total: RCT (96); Included: RCT (27) | Total: 1955 to 2014; Included: 1962 to 2014 | Yes, fifty-three trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Brazil (1), China (1), France (1), Germany (1), Iceland (1), India (1), Sweden (3), Switzerland (1), UK (9), and USA (7) | | | Both males and females (15), only females (2), not reported (8) | | | | | | | |
| Santos *et al.* (2013) | Evaluate the effects of low and standard fluoride toothpastes on the prevention of caries in the primary dentition of pre-schoolers and moderate to severe forms of fluorosis in the permanent dentition. | Primary and permanent dentition; non-invasive | Brazil (1), Germany (1), Sweden (1), and UK (2) | 5376 | 1 to 6 years | Not reported | Low (<600ppm) and standard (1000-1500ppm) fluoride toothpastes | Each other | Caries increment (dmfs/dmft); proportion of children developing caries; proportion of children developing fluorosis | 12+ months | RCT/non-RCT (5) | 1974 to 2010 | Not reported |
| Mouthrinses (n = 0) | | | | | | | | | | | | | |
| Foams (n = 0) | | | | | | | | | | | | | |
| Gels (n = 1) | | | | | | | | | | | | | |
| Marinho *et al.* (2015) | Determine the effectiveness and safety of fluoride gels in preventing dental caries in the child and adolescent population. | Primary and permanent dentition; non-invasive | Brazil (4), Canada (1), China (1), Europe (7), Israel (1), USA (13), and Venezuela (1) | 9140 | 2 to 15 years | Both males and females (27); only males (1) | Topical fluoride in the form of gels | Placebo; no treatment | Caries increment in permanent tooth surfaces, reported as change from baseline; caries increment in primary tooth surfaces, reported as change from baseline; development of new caries; change in proportion of children not remaining caries-free; tooth staining; signs of acute toxicity during application; mucosal irritation/oral soft-tissue allergic reaction | 12 to 36 months | RCT (27), cluster RCT (1) | 1964 to 2005 | Yes, thirteen trials |
| Solution (n = 2) | | | | | | | | | | | | | |
| Oliveira *et al.* (2019) | Investigate primarily whether silver diamine fluoride is superior to placebo or no treatment in preventing the development of | Primary dentition; non-invasive | Brazil (2), China (1), and Cuba (1) | 1118 | 3 to 6+ years | Not reported | Topical silver diamine fluoride solution professionally applied (38%, 30%, 12%, 5%) | No intervention; placebo; topical cariostatic agents; resin or glass- | Caries incidence (difference in mean caries increment); adverse events | 24 months | RCT (4); Included: RCT (1) | 1991 to 2012 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | new caries lesions in primary teeth. | | | | | | | ionomer pit and fissure sealants; dental restorative materials | | | | | |
| Chou *et al.* (2021) | Determine how effective oral screening (including risk assessment) performed by a primary care clinician is in preventing dental caries in children younger than age 5 years. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (2), Sweden (3), UK (1), and USA (10); Included: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (1), Sweden (3), UK (1), and USA (1) | Total: 106694; Included: 11979 | 0 to 4 years | Total: 36-56% female (21), not reported (12); Included: 36-56% female (15), not reported (8) | Referral to a dentist by primary care clinician; treatments (dietary fluoride supplementation, topical fluoride application, xylitol, silver diamine fluoride) | No intervention; placebo | increment measured by the number of decayed, missing, and filled surfaces and teeth (dmft/dmfs); caries incidence | 12 to 36 months | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (1), observational studies (3) | 1967 to 2020 | Total: Yes, twenty-one trials; Included: Yes, fifteen trials |
| Slow-release fluoride devices (n = 1) | | | | | | | | | | | | | |
| Chong *et al.* (2018) | Evaluate the effectiveness and safety of different types of slow-release fluoride devices on preventing, arresting, or reversing the progression of carious lesions on all surface types of primary (deciduous) and permanent teeth. | Primary and permanent dentition; non-invasive | UK (1) | 174 | 10.9 years (mean) | Not reported | Slow-release fluoride devices (co-polymer membrane or slow-dissolving fluoride glass beads) | Alternative fluoride treatment; placebo; no intervention; no treatment | Caries increment (dmfs/dmft or DMFS/DMFT); retention of slow-release fluoride devices; harms of slow-release fluoride devices; use of healthcare resources | 24 months | RCT (1) | 2005 | Yes, one trial |
| Varnishes (n = 3) | | | | | | | | | | | | | |
| Marinho *et al.* (2013) | Evaluate the effectiveness and safety of fluoride varnishes in preventing dental caries in the child/adolescent population. | Primary and permanent dentition; non-invasive | Brazil (3), Canada (2), China (3), Germany (2), India (2), Spain (1), Sweden (6), UK (2), and USA (1) | 12455 | 1 to 15 years | Not reported | Topical fluoride in the form of varnishes | Placebo; no treatment | caries increment (d(e/m)fs/d(e/m)ft and DMFS/DMFT) proportion of children developing one or more new caries; adverse events; use of health service resources | 36 months | RCT/quasi-RCT (17), cluster RCT (5) | 1979 to 2012 | Yes, one trial |
| Carvalho *et al.* (2010) | Assess whether there is evidence that professional application of fluoride varnish | Primary dentition; non-invasive | Total: China (1), Poland (1), Sweden (4), and USA (2); Included: Not clear | Total: 2501; Included: 2378 | 6 months to 5 years | Not reported | Topical fluoride varnish (5% NaF; 1% Difluorsilano) | Each other | Caries increment (dmfs); adverse effects | 24 to 30 months | Total: Cluster RCT (2), RCT (6); Included: | 1979 to 2006 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | reduces the incidence of dental caries in primary dentition in children of up to six years of age. | | | | | | | | | | Cluster RCT (2), RCT (5) | | |
| Smith *et al.* (2018) | Systematically review the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | Primary dentition; non-invasive | Total: Australia (1), Canada (2), and USA (1); Included: Canada (1) and USA (1) | Total: 2311; Included: 1527 | Total: 0 to 5+ years; Included: 4.5 months to 5+ years | Not reported | 5% sodium fluoride varnish and caregiver counselling; 5% sodium fluoride varnish; 10% chlorhexidine varnish | Caregiver counselling alone; no treatment; placebo | Caries increment (dmfs); caries incidence (number of new carious surfaces) | 18 to 24 months | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | 2008 to 2013 | Not reported |
| Mixed (n = 0) | | | | | | | | | | | | | |
| Topical other chemicals (n = 11) | | | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 2) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | | | |
| Wang *et al.* (2017) | Assess the anti-caries effect of a variety of non-fluoride agents in primary teeth, with an updated and expanded literature database search. | Primary dentition; non-invasive | Not reported | Total: 4269; Included: 4075 | 0 to 11 years | Not reported | Non-fluoride agents (topical arginine mint confection; CPP-ACP; 1 - 40 % chlorhexidine; 0.12-1% chlorhexidine; triclosan; xylitol tablet) | Placebos; fluoride | Caries increment (dmft/dmfs and deft/defs); change in the proportion of participants developing new caries on primary teeth; adverse events | 12 to 36 months | Total: RCT (14); Included: RCT (12) | 1994 to 2015 | Not reported |
| Arginine and its derivatives (n = 0)<br>CHX (n = 5) | | | | | | | | | | | | | |
| Walsh *et al.* (2015) | Assess the effects of chlorhexidine-containing oral products (toothpastes, mouthrinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. | Primary and permanent dentition; non-invasive | Australia (2), Brazil (1), China (1), Scotland (1), Spain (1), Suriname (1), and Sweden (1) | 2876 | 0 to 15 years | 48-52% female (5); only females (1), not reported (2) | Chlorhexidine varnish and gel (0.12%, 1%, 10%, 40%) | No treatment; placebo | Caries increment (DMFS/DMFT or dmfs/dmft); caries incidence (presence or absence of new caries); % sound surfaces; S. mutans counts; pain; adverse events | 24 to 36 months | RCT (6), cluster RCT (2) | 1997 to 2013 | Yes, one trial |
| James *et al.* (2010) | Summarize the evidence of the effectiveness of chlorhexidine varnish at preventing caries in the permanent and primary teeth of children and adolescents compared to placebo or no treatment, using data | Primary and permanent dentition; non-invasive | Not reported | 2934 | 4 to 18 years | Not reported | Chlorhexidine varnish | Placebo; no treatment; fluoride varnish | Caries increment (dmfs/DMFS); adverse events | 24 to 36 months | RCT/quasi-RCT (12) | 1995 to 2008 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | from randomised controlled trials only. | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |
| Wang *et al.* (2017) | Assess the anti-caries effect of a variety of non-fluoride agents in primary teeth, with an updated and expanded | Primary dentition; non-invasive | Not reported | Total: 4269; Included: 4075 | 0 to 11 years | Not reported | Non-fluoride agents (topical arginine mint confection; CPP-ACP; 1 - 40 % chlorhexidine; | Placebos; fluoride | Caries increment (dmft/dmfs and deft/defs); change in the proportion of participants developing | 12 to 36 months | Total: RCT (14); Included: RCT (12) | 1994 to 2015 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | literature database search. | | | | | | 0.12-1% chlorhexidine; triclosan; xylitol tablet) | | new caries on primary teeth; adverse events | | | | |
| Smith *et al.* (2018) | Systematically review the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | Primary dentition; non-invasive | Total: Australia (1), Canada (2), and USA (1); Included: Canada (1) and USA (1) | Total: 2311; Included: 1527 | Total: 0 to 5+ years; Included: 4.5 months to 5+ years | Not reported | 5% sodium fluoride varnish and caregiver counselling; 5% sodium fluoride varnish; 10% chlorhexidine varnish | Caregiver counselling alone; no treatment; placebo | Caries increment (dmfs); caries incidence (number of new carious surfaces) | 18 to 24 months | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | 2008 to 2013 | Not reported |
| Calcium phosphate agents (n = 3) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | | | | | | | |
| Wang *et al.* (2017) | Assess the anti-caries effect of a variety of non-fluoride agents in primary teeth, with an updated and expanded literature database search. | Primary dentition; non-invasive | Not reported | Total: 4269; Included: 4075 | 0 to 11 years | Not reported | Non-fluoride agents (topical arginine mint confection; CPP-ACP; 1 - 40 % chlorhexidine; 0.12-1% chlorhexidine; triclosan; xylitol tablet) | Placebos; fluoride | Caries increment (dmft/dmfs and deft/defs); change in the proportion of participants developing new caries on primary teeth; adverse events | 12 to 36 months | Total: RCT (14); Included: RCT (12) | 1994 to 2015 | Not reported |
| Singal *et al.* (2022) | Extensively review, summarise, and to draw best possible evidence for the remineralising and caries preventive efficacy of various calcium phosphate derivatives. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), China (1), Denmark (1), Egypt (2), Finland (1), Greece (1), India (6), Iran (2), Jordan (2), Saudi Arabia (1), Spain (1), Sweden (1), Thailand (2), and Turkey (3); Included: Egypt (1), Finland (1), India (4), Jordan (1), Saudi Arabia (1), Thailand (1), and Turkey (2) | Total: 3678; Included: 852 | Total: 0 to 18 months; Included: 2 days to 12 months | Not reported | Topical formulation of calcium phosphate agents (alone or combined with sodium fluoride/stannous fluoride) | No intervention; placebo; topical application of fluoride (containing sodium fluoride or stannous fluoride) | Caries preventive benefit (dmfs/dmft or DMFS/DMFT); S. mutans count | 12 to 24 months | Total: RCT (26); Included: RCT (11) | Total: 2007 to 2021; Included: 2012 to 2020 | Not reported |
| Ozone (n = 0) | | | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | | | |
| Probiotics (n = 3) | | | | | | | | | | | | | |
| Hao *et al.* (2021) | Explore and verify the effectiveness and safety of Bifidobacterium in preventing caries, explore its potential value in clinical application, and guide further clinical research. | Primary and permanent dentition; non-invasive | Not reported | 479 | 0 to 25 years | Not reported | Bifidobacterium (yogurt, ice cream, curd, and slow-release pacifier tablets) | Placebo | Caries incidence (occurrence of deciduous tooth caries); S. mutans count in saliva; S. mutans count in plaque; Lactobacillus counts in saliva; Lactobacillus counts in plaque; adverse events | 24 to 48 months | RCT (10) | 2005 to 2020 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jørgensen *et al.* (2016) | Review and summarise the available literature on the prevention of caries in early childhood through biofilm engineering with probiotic bacteria. | Primary dentition; non-invasive | Chile, Finland, Sweden | Total: 1715; Included: 647 | Total: 0 to 6 years; Included: 1 to 5 years | Not reported | Live probiotic bacteria (milk with Lactobacillus rhamnosus LB21; milk with Lactobacillus rhamnosus SP1; probiotic lozenges with streptococcus-derived strains) | Placebo | Caries increment (defs/deft); caries incidence (proportion of children remaining caries-free following intervention) | 12 to 21 months | Total: Cluster RCT (2), RCT (5); Included: Cluster RCT (2), RCT (1) | Total: 2001 to 2016; Included: 2009 to 2016 | Not reported |
| Twetman *et al.* (2021) | Explore the preventive effect of probiotic supplements on the development of early childhood caries. | Primary dentition; non-invasive | Total: Chile (2), Colombia (1), Finland (2), Sweden (2), and Thailand (2); Included: Chile (2), Colombia (1), Sweden (2), and Thailand (2) | Total: 2363; Included: 1663 | Total: 0 to 6 years; Included: 1 to 5 years | Not reported | Live probiotic bacteria (milk or tablets/lozenges) | Placebo (milk or tablets/lozenges); no treatment | Increment of caries on tooth or surface level (new decayed teeth/surfaces); adverse events | 6 to 24 months | Total: RCT (9); Included: RCT (7) | Total: 2001 to 2021; Included: 2009 to 2021 | Not reported |
| Propolis (n = 0) | | | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | | | |
| Riley *et al.* (2015) | Assess the effects of different xylitol-containing products on preventing dental caries in children and adults. | Primary and permanent dentition; non-invasive | Costa Rica (2), Estonia (1), Finland (2), Republic of the Marshall Islands (1), Sweden (2), and USA (2) | 7969 | 0 to 18+ years | 66% female (1); both males and females (9) | Xylitol-containing products (lozenges, candy, syrup, tablets, toothpaste, wipes) | Placebo; no treatment | Caries preventive benefit (ds/dmfs or DMFS/DFS); adverse events | 12 to 48 months | Cluster RCT (2); RCT (8) | 1991 to 2014 | Yes, four trials |
| Chou *et al.* (2021) | Determine how effective oral screening (including risk assessment) performed by a primary care clinician is in preventing dental caries in children younger than age 5 years. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (2), Sweden (3), UK (1), and USA (10); Included: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (1), Sweden (3), UK (1), and USA (1) | Total: 106694; Included: 11979 | 0 to 4 years | Total: 36-56% female (21), not reported (12); Included: 36-56% female (15), not reported (8) | Referral to a dentist by primary care clinician; treatments (dietary fluoride supplementation, topical fluoride application, xylitol, silver diamine fluoride) | No intervention; placebo | increment measured by the number of decayed, missing, and filled surfaces and teeth (dmft/dmfs); caries incidence | 12 to 36 months | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (1), observational studies (3) | 1967 to 2020 | Total: Yes, twenty-one trials; Included: Yes, fifteen trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |
| Wang *et al.* (2017) | Assess the anti-caries effect of a variety of non-fluoride agents in primary teeth, with an updated and expanded literature database search. | Primary dentition; non-invasive | Not reported | Total: 4269; Included: 4075 | 0 to 11 years | Not reported | Non-fluoride agents (topical arginine mint confection; CPP-ACP; 1 - 40 % chlorhexidine; 0.12-1% chlorhexidine; | Placebos; fluoride | Caries increment (dmft/dmfs and deft/defs); change in the proportion of participants developing new caries on primary teeth; adverse events | 12 to 36 months | Total: RCT (14); Included: RCT (12) | 1994 to 2015 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | triclosan; xylitol tablet) | | | | | | |
| Sorbitol (n = 0) | | | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 1) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |
| Sealants (n = 3) | | | | | | | | | | | | | |
| Resin (n = 2) | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ramamurthy *et al.* (2022) | Evaluate the effects of sealants compared to no sealant or a different sealant in preventing pit and fissure caries on the occlusal surfaces of primary molars in children and to report the adverse effects and the retention of different types of sealants. | Primary dentition; non-invasive | Brazil (1), China (1), Denmark (1), France (1), India (2), Spain (1), Turkey (1), and UK (1) | 1120 | 18 months to 8 years | 42.3-60% female (7); not reported (2) | Sealant; resin-based sealants; newer types of sealant materials | Each other | Incidence of new dental caries (risk of developing at least one new carious lesion); mean caries increment (dmfs/dmft or DMFT/DMFS); retention of sealant; adverse events and safety of sealant | 12 to 36 months | RCT (9) | 1998 to 2021 | Yes, one trial |
| Lam *et al.* (2020) | Systematically assess randomized controlled trials and summarize the evidence on the effectiveness of different sealants in prevention and arrest of the pit and fissure occlusal caries in primary molars of children. | Primary dentition; non-invasive | China (1), Denmark (1), Greenland (1), India (1), Kuwait (1), Turkey (1), and UK (1) | 980 | 18 months to 8 years | Not reported | Pit and fissure sealant (resin-based, glass-ionomer/resin-modified, auto-polymerized resin-based, fissure sealants) | No treatment; each other; topical fluoride | Caries incidence (diagnosis of new carious lesions on sound occlusal surfaces); sealant retention | 12 to 24 months | RCT (7) | 1998 to 2015 | Not reported |
| Glass-ionomer (n = 2) | | | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | Evaluate the effects of sealants compared to no sealant or a different sealant in preventing pit and fissure caries on the occlusal surfaces of primary molars in children and to report the adverse effects and the retention of different types of sealants. | Primary dentition; non-invasive | Brazil (1), China (1), Denmark (1), France (1), India (2), Spain (1), Turkey (1), and UK (1) | 1120 | 18 months to 8 years | 42.3-60% female (7); not reported (2) | Sealant; resin-based sealants; newer types of sealant materials | Each other | Incidence of new dental caries (risk of developing at least one new carious lesion); mean caries increment (dmfs/dmft or DMFT/DMFS); retention of sealant; adverse events and safety of sealant | 12 to 36 months | RCT (9) | 1998 to 2021 | Yes, one trial |
| Lam *et al.* (2020) | Systematically assess randomized controlled trials and summarize the evidence on the effectiveness of different sealants in | Primary dentition; non-invasive | China (1), Denmark (1), Greenland (1), India (1), Kuwait (1), Turkey (1), and UK (1) | 980 | 18 months to 8 years | Not reported | Pit and fissure sealant (resin-based, glass-ionomer/resin-modified, auto-polymerized | No treatment; each other; topical fluoride | Caries incidence (diagnosis of new carious lesions on sound occlusal surfaces); sealant retention | 12 to 24 months | RCT (7) | 1998 to 2015 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | prevention and arrest of the pit and fissure occlusal caries in primary molars of children. | | | | | | resin-based, fissure sealants) | | | | | | |
| Ormocer (n = 0) | | | | | | | | | | | | | |
| Hybrid (n = 0) | | | | | | | | | | | | | |
| Combined (n = 1) | | | | | | | | | | | | | |
| Akera *et al.* (2022) | Evaluate the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | Primary and permanent dentition; non-invasive | Total: Bulgaria (1), Brazil (5), Cambodia (1), China (3), India (5), Indonesia (1), Iran (3), Malaysia (1), Myanmar (1), Nigeria (1), Pakistan (1), Philippines (1), South Africa (1), Taiwan (1), Tanzania (3), Thailand (2), Turkey (1), and Zimbabwe (1); Included: Cambodia (1), South Africa (1), and Turkey (1) | Not reported | Total: 3 to 16 years; Included: 6 to 15 years | Not reported | School health policy; provision of oral health education; promoting a healthy school environment; providing access to oral health services; involving community members; daily toothbrushing; fissure sealants; zinc supplementation | No intervention | incidence of dental caries (DMFT); plaque | 24 to 84 months | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Total: 1996 to 2021; Included: 2004 to 2017 | Not reported |
| Other (n = 0) | | | | | | | | | | | | | |
| Laser (n = 1) | | | | | | | | | | | | | |
| Pagano *et al.* (2020) | Verify whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures. | Primary and permanent dentition; non-invasive | Australia (1), Belgium (1), Brazil (3), India (1), Turkey (2), and USA (1) | 269 (participants) and 1628 (teeth) | 6 to 38 years | 35-94% females (4); not reported (5) | Laser application (carbon dioxide; nodymium-doped yttrium alinium garnet; argon; erbium-doped yttrium aluminium garnet; erbium chromium yttrium scandium gallium garnet) alone or with any traditional prophylactic | No treatment; placebo; placebo with traditional prophylactic intervention; traditional prophylactic intervention alone | Caries incidence (number of cases with new caries); sealant retention; adverse events | 12 to 48 months | RCT (7); controlled clinical trials (2) | 1996 to 2005 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | intervention (acidulated phosphate fluoride gel/foam; enamel pit and fissure resin sealant; fluoride varnish) | | | | | | |
| Subgroup: Mother of unborn/toddlers (treatment given to mothers, outcomes tested on children) | | | | | | | | | | | | | |
| Systemic fluoride (n = 2) | | | | | | | | | | | | | |
| Supplements (n = 2) | | | | | | | | | | | | | |
| Takahashi *et al.* (2017) | Evaluate the effects of women taking fluoride supplements (tablets, drops, lozenges, or chewing gum) compared with no fluoride supplementation during pregnancy to prevent caries in the primary teeth of children. | Primary dentition; non-invasive | USA (1) | 1400 | Not reported | Only females | Fluoride supplements (tablets, drops, lozenges, or chewing gum) | Placebo; no treatment | Caries preventive benefit (number of children with caries in the primary teeth and dmft/dmfs); fluorosis; adverse effects | 36 months to 60 months | RCT (1) | 1997 | Yes, one trial |
| Xiao *et al.* (2019) | Systematically review the scientific evidence relating to the association between prenatal oral health care, reduced carriage of S. mutans, and early childhood caries prevention. | Primary dentition; non-invasive | Total: Australia (1), Germany (1), Japan (2), and USA (1); Included: Germany (1), Japan (1), and USA (1) | Total: 2017 pregnant women/1699 children: Included: 1368 pregnant women/1094 children | 15 months to 5 years (children) | Not reported | Prenatal oral health care (fluoride supplement; prevention of transmission of cariogenic bacteria; oral health education; xylitol gum) | No intervention | caries incidence (DMFS/dmfs); salivary S. mutans counts | 36 to 60 months | Total: RCT (3), prospective cohort study (1), nested case-control cohort study (1); Included: RCT (2), prospective cohort study (1) | Total: 1997 to 2016; Included: 1997 to 2010 | Not reported |
| Topical other chemicals (n = 2) | | | | | | | | | | | | | |
| Xylitol (n = 2) | | | | | | | | | | | | | |
| Riggs *et al.* (2019) | Assess the effects of interventions targeted | Primary and permanent | Total: Australia (1), Brazil (3), Belarus (1), | Total: 23732; | 17 to 44 years | Not reported | Antimicrobial treatments | Placebo; no treatment | Caries incidence (deft/defs; dmft/dmfs; | 12 to 36 months | Total: RCT (12), cluster | Total: 1993 to 2017; | Yes, two trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | dentition; non-invasive | Canada (2), Finland (2), Sweden (1), Uganda (2), UK (1), USA (3), not reported (1); Included: Brazil (1), Finland (1), Sweden (1), USA (2), not reported (1) | Included: 907 | (mothers) /0 to 13 months (children) | | (chlorhexidine and iodine-sodium-fluoride solution and prophylaxis); xylitol | | DMFT/DMFS); microbiological presence (mothers and children); plaque; adverse events | | RCT (5); Included: RCT (6) | Included: 1993 to 2013 | |
| Xiao *et al.* (2019) | Systematically review the scientific evidence relating to the association between prenatal oral health care, reduced carriage of S. mutans, and early childhood caries prevention. | Primary dentition; non-invasive | Total: Australia (1), Germany (1), Japan (2), and USA (1); Included: Germany (1), Japan (1), and USA (1) | Total: 2017 pregnant women/1699 children: Included: 1368 pregnant women/1094 children | 15 months to 5 years (children) | Not reported | Prenatal oral health care (fluoride supplement; prevention of transmission of cariogenic bacteria; oral health education; xylitol gum) | No intervention | caries incidence (DMFS/dmfs); salivary S. mutans counts | 36 to 60 months | Total: RCT (3), prospective cohort study (1), nested case-control cohort study (1); Included: RCT (2), prospective cohort study (1) | Total: 1997 to 2016; Included: 1997 to 2010 | Not reported |
| Topical other chemicals (n = 3) | | | | | | | | | | | | | |
| CHX (n = 3) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | | | |
| Smith *et al.* (2018) | Systematically review the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | Primary dentition; non-invasive | Total: Australia (1), Canada (2), and USA (1); Included: Canada (1) and USA (1) | Total: 2311; Included: 1527 | Total: 0 to 5+ years; Included: 4.5 months to 5+ years | Not reported | 5% sodium fluoride varnish and caregiver counselling; 5% sodium fluoride varnish; 10% chlorhexidine varnish | Caregiver counselling alone; no treatment; placebo | Caries increment (dmfs); caries incidence (number of new carious surfaces) | 18 to 24 months | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | 2008 to 2013 | Not reported |
| Riggs *et al.* (2019) | Assess the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (3), Belarus (1), Canada (2), Finland (2), Sweden (1), Uganda (2), UK (1), USA (3), not reported (1); Included: Brazil (1), Finland (1), Sweden (1), USA (2), not reported (1) | Total: 23732; Included: 907 | 17 to 44 years (mothers) /0 to 13 months (children) | Not reported | Antimicrobial treatments (chlorhexidine and iodine-sodium-fluoride solution and prophylaxis); xylitol | Placebo; no treatment | Caries incidence (deft/defs; dmft/dmfs; DMFT/DMFS); microbiological presence (mothers and children); plaque; adverse events | 12 to 36 months | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Total: 1993 to 2017; Included: 1993 to 2013 | Yes, two trials |
| Subgroup: Combined interventions delivered to mothers of unborn/toddlers | | | | | | | | | | | | | |
| Topical other chemicals + topical other chemicals (n = 1) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free | No intervention; fluoride toothpaste/varnish/gel; conventional care; each | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | other; placebo | | | clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | |
| Topical other chemicals + other (n = 1) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | |
| CHX + other (n = 1) | | | | | | | | | | | | | |
| Riggs *et al.* (2019) | Assess the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (3), Belarus (1), Canada (2), Finland (2), Sweden (1), Uganda (2), UK (1), USA (3), not reported (1); Included: Brazil (1), Finland (1), Sweden (1), USA (2), not reported (1) | Total: 23732; Included: 907 | 17 to 44 years (mothers) /0 to 13 months (children) | Not reported | Antimicrobial treatments (chlorhexidine and iodine-sodium-fluoride solution and prophylaxis); xylitol | Placebo; no treatment | Caries incidence (deft/defs; dmft/dmfs; DMFT/DMFS); microbiological presence (mothers and children); plaque; adverse events | 12 to 36 months | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Total: 1993 to 2017; Included: 1993 to 2013 | Yes, two trials |
| Complex combined interventions (n = 1) | | | | | | | | | | | | | |
| Xiao *et al.* (2019) | Systematically review the scientific evidence relating to the association between prenatal oral health care, reduced carriage of S. mutans, and early | Primary dentition; non-invasive | Total: Australia (1), Germany (1), Japan (2), and USA (1); Included: Germany (1), Japan (1), and USA (1) | Total: 2017 pregnant women/1699 children: Included: 1368 | 15 months to 5 years (children) | Not reported | Prenatal oral health care (fluoride supplement; prevention of transmission of cariogenic bacteria; oral | No intervention | caries incidence (DMFS/dmfs); salivary S. mutans counts | 36 to 60 months | Total: RCT (3), prospective cohort study (1), nested case-control cohort | Total: 1997 to 2016; Included: 1997 to 2010 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | childhood caries prevention. | | | pregnant women/1094 children | | | health education; xylitol gum) | | | | study (1); Included: RCT (2), prospective cohort study (1) | | |
| Subgroup: Combined interventions in primary dentition | | | | | | | | | | | | | |
| Topical fluoride + topical fluoride (n = 1) | | | | | | | | | | | | | |
| Carvalho *et al.* (2010) | Assess whether there is evidence that professional application of fluoride varnish reduces the incidence of dental caries in primary dentition in children of up to six years of age. | Primary dentition; non-invasive | Total: China (1), Poland (1), Sweden (4), and USA (2); Included: Not clear | Total: 2501 ; Included: 2378 | 6 months to 5 years | Not reported | Topical fluoride varnish (5% NaF; 1% Difluorsilano) | Each other | Caries increment (dmfs); adverse effects | 24 to 30 months | Total: Cluster RCT (2), RCT (6); Included: Cluster RCT (2), RCT (5) | 1979 to 2006 | Not reported |
| Topical fluoride + topical other chemicals (n = 4) | | | | | | | | | | | | | |
| Wang *et al.* (2017) | Assess the anti-caries effect of a variety of non-fluoride agents in primary teeth, with an updated and expanded literature database search. | Primary dentition; non-invasive | Not reported | Total: 4269; Included: 4075 | 0 to 11 years | Not reported | Non-fluoride agents (topical arginine mint confection; CPP-ACP; 1 - 40 % chlorhexidine; 0.12-1% chlorhexidine; triclosan; xylitol tablet) | Placebos; fluoride | Caries increment (dmft/dmfs and deft/defs); change in the proportion of participants developing new caries on primary teeth; adverse events | 12 to 36 months | Total: RCT (14); Included: RCT (12) | 1994 to 2015 | Not reported |
| Walsh *et al.* (2015) | Assess the effects of chlorhexidine-containing oral products (toothpastes, mouthrinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. | Primary and permanent dentition; non-invasive | Australia (2), Brazil (1), China (1), Scotland (1), Spain (1), Suriname (1), and Sweden (1) | 2876 | 0 to 15 years | 48-52% female (5); only females (1), not reported (2) | Chlorhexidine varnish and gel (0.12%, 1%, 10%, 40%) | No treatment; placebo | Caries increment (DMFS/DMFT or dmfs/dmft); caries incidence (presence or absence of new caries); % sound surfaces; S. mutans counts; pain; adverse events | 24 to 36 months | RCT (6), cluster RCT (2) | 1997 to 2013 | Yes, one trial |
| Singal *et al.* (2022) | Extensively review, summarise, and to draw best possible evidence for the remineralising and caries preventive | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), China (1), Denmark (1), Egypt (2), Finland (1), Greece (1), India (6), Iran (2), Jordan (2), Saudi Arabia (1), | Total: 3678; Included: 852 | Total: 0 to 18 months; Included: 2 days to | Not reported | Topical formulation of calcium phosphate agents (alone or combined with | No intervention; placebo; topical application of fluoride | Caries preventive benefit (dmfs/dmft or DMFS/DMFT); S. mutans count | 12 to 24 months | Total: RCT (26); Included: RCT (11) | Total: 2007 to 2021; Included: 2012 to 2020 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | efficacy of various calcium phosphate derivatives. | | Spain (1), Sweden (1), Thailand (2), and Turkey (3); Included: Egypt (1), Finland (1), India (4), Jordan (1), Saudi Arabia (1), Thailand (1), and Turkey (2) | | 12 months | | sodium fluoride/stannous fluoride) | (containing sodium fluoride or stannous fluoride) | | | | | |
| Gupta *et al.* (2020a) | Compare the effectiveness of topical fluoride and povidone iodine with topical fluoride alone for the prevention of dental caries among 1- to 12-year-old children. | Primary and permanent dentition; non-invasive | Total: China (1), Iran (1), Saudi Arabia (1), and USA (4); Included: China (1), Iran (1), Saudi Arabia (1), and USA (3) | Total: 1020; Included: 406 | Total: 1 to 12 years; Included: 2 to 12 years | Not reported | Topical fluoride and povidone iodine (acidulated phosphate fluoride gel and povidone iodine; fluoride form and povidone iodine; 5% sodium fluoride varnish and povidone iodine; 0.2% sodium fluoride varnish and povidone iodine) | Topical fluoride alone | Caries incidence (presence or absence of new carious lesions); S. mutans count/plaque biofilm accumulation; Lactobacillus count | 12 months | Total: RCT (5), non-RCT (1), retrospective cohort study (1); Included: RCT (5), non-RCT (1) | 2005 to 2016 | Not reported |
| Topical fluoride + other (n = 7) | | | | | | | | | | | | | |
| Smith *et al.* (2018) | Systematically review the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | Primary dentition; non-invasive | Total: Australia (1), Canada (2), and USA (1); Included: Canada (1) and USA (1) | Total: 2311; Included: 1527 | Total: 0 to 5+ years; Included: 4.5 months to 5+ years | Not reported | 5% sodium fluoride varnish and caregiver counselling; 5% sodium fluoride varnish; 10% chlorhexidine varnish | Caregiver counselling alone; no treatment; placebo | Caries increment (dmfs); caries incidence (number of new carious surfaces) | 18 to 24 months | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | 2008 to 2013 | Not reported |
| Lam *et al.* (2020) | Systematically assess randomized controlled trials and summarize the evidence on the effectiveness of different sealants in prevention and arrest of the pit and fissure occlusal caries in primary molars of children. | Primary dentition; non-invasive | China (1), Denmark (1), Greenland (1), India (1), Kuwait (1), Turkey (1), and UK (1) | 980 | 18 months to 8 years | Not reported | Pit and fissure sealant (resin-based, glass-ionomer/resin-modified, auto-polymerized resin-based, fissure sealants) | No treatment; each other; topical fluoride | Caries incidence (diagnosis of new carious lesions on sound occlusal surfaces); sealant retention | 12 to 24 months | RCT (7) | 1998 to 2015 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dos Santos *et al.* (2018) | Assess the effects of supervised toothbrushing on caries incidence in children and adolescents. | Primary and permanent dentition; non-invasive | Brazil (1), Germany (1), Jordan (1), and USA (1) | Not reported | 2 to 14 years | Not reported | Supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | No supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | Caries incidence (proportion of caries-free children); caries increment (dmft/dmfs or DMFT/DMFS); cumulative survival rates | 21 to 36 months | RCT/quasi-RCT (4) | 1978 to 2016 | Yes, one trial |
| Walsh *et al.* (2019) | Determine and compare the effects of toothpastes of different fluoride concentrations (parts per million) in preventing dental caries in children, adolescents, and adults. | Primary and permanent dentition; non-invasive | Total: Australia (2), Brazil (3), Canada (2), China (1), Denmark (1), France (5), Germany (2), Guatemala (2), Iceland (1), India (1), Italy (2), Japan (1), Lithuania (1), Puerto Rico (1), Sweden (6), Switzerland (6), UK (22), and USA (37); Included: Australia (1), Brazil (1), China (1), France (1), Germany (1), Iceland (1), India (1), Sweden (3), Switzerland (1), UK (9), and USA (7) | Total: 67835; Included: 41807 | 1 to 93 years | Total: Both males and females (66), only males (3), only females (2), not reported (25); Included: Both males and females (15), only females (2), not reported (8) | Fluoride toothpaste (0ppm, 250ppm, 440 to 550ppm, 1000 to 1250 ppm, 1450 to 1500 ppm, 1700 to 2200 ppm, 2400 to 2800 ppm) and toothbrushing | Each other; non-fluoride toothpaste; no toothpaste | incidence of caries (change in proportion of participants developing new caries); adverse effects | Total: 12+ months; Included: 22 months to 60 months | Total: RCT (96); Included: RCT (27) | Total: 1955 to 2014; Included: 1962 to 2014 | Yes, fifty-three trials |
| Dos Santos *et al.* (2013) | Assess the effects of fluoride toothpastes on the prevention of caries in the primary dentition of preschool children. | Primary dentition; non-invasive | China (4), Lithuania (1), and UK (3) | 13097 | 8 months to 7 years | Both males and females (1); not reported (7) | Fluoride toothpastes | Placebo; no treatment | Caries-preventive effect (proportion of children developing dental caries or dmfs/dmft) | 12+ months | RCT (8) | 1998 to 2008 | Not reported |
| Marinho *et al.* (2016) | Determine the effectiveness and safety of fluoride mouthrinses in preventing dental caries in the child/adolescent population. | Permanent dentition; non-invasive | Brazil (3), Canada (2), Chile (1), Denmark (2), Finland (1), Netherlands (1), New Zealand (2), Puerto Rico (1), South Africa (1), Sweden (6), UK (4), and USA (13) | 15813 | 5 to 14 years | Not reported | Topical fluoride in the form of a mouthrinse (sodium fluoride; acidulated phosphate fluoride; stannous fluoride; sodium monofluorophosphate; amine fluoride; ammonium fluoride) in concentrations | Placebo; no treatment | Caries preventive benefit (DMFS/DMFT; defs/deft; proportion of children developing new caries); adverse event (tooth staining); adverse event (signs of acute toxicity); adverse event (mucosal irritation/oral allergic reaction) | 24 to 36 months | Cluster RCT (1); RCT/quasi-RCT (36) | 1965 to 2005 | Yes, eleven trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | from 100ppm to 3000ppm fluoride | | | | | | |
| de Sousa *et al.* (2019) | Assess the effectiveness of fluoride varnish in reducing the risk of developing new dentine caries lesions and caries-related hospitalisations in pre-schoolers and to assess whether its effectiveness is influenced by baseline caries levels. | Primary dentition; non-invasive | Australia (1), Brazil (1), Canada (1), Chile (1), China (3), Germany (1), Greece (1), Iran (2), Ireland (1), Poland (1), Scotland (1), Sweden (4), and USA (2) | 16877 | 6 months to 5 years | Not reported | Fluoride varnish with or without an oral health programme | Placebo; no treatment; no intervention | Caries incidence (proportion of children developing new dentine caries lesions or dmfs/dmft); adverse events | 12 to 36 months | Cluster RCT (6), RCT (14) | 1979 to 2018 | Not reported |
| Systemic fluoride + topical other chemical (n = 1) | | | | | | | | | | | | | |
| Jørgensen *et al.* (2016) | Review and summarise the available literature on the prevention of caries in early childhood through biofilm engineering with probiotic bacteria. | Primary dentition; non-invasive | Chile, Finland, Sweden | Total: 1715; Included: 647 | Total: 0 to 6 years; Included: 1 to 5 years | Not reported | Live probiotic bacteria (milk with Lactobacillus rhamnosus LB21; milk with Lactobacillus rhamnosus SP1; probiotic lozenges with streptococcus-derived strains) | Placebo | Caries increment (defs/deft); caries incidence (proportion of children remaining caries-free following intervention) | 12 to 21 months | Total: Cluster RCT (2), RCT (5); Included: Cluster RCT (2), RCT (1) | Total: 2001 to 2016; Included: 2009 to 2016 | Not reported |
| Sealants + other (n = 1) | | | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | Evaluate the effects of sealants compared to no sealant or a different sealant in preventing pit and fissure caries on the occlusal surfaces of primary molars in children and to report the adverse effects and the retention of different types of sealants. | Primary dentition; non-invasive | Brazil (1), China (1), Denmark (1), France (1), India (2), Spain (1), Turkey (1), and UK (1) | 1120 | 18 months to 8 years | 42.3-60% female (7); not reported (2) | Sealant; resin-based sealants; newer types of sealant materials | Each other | Incidence of new dental caries (risk of developing at least one new carious lesion); mean caries increment (dmfs/dmft or DMFT/DMFS); retention of sealant; adverse events and safety of sealant | 12 to 36 months | RCT (9) | 1998 to 2021 | Yes, one trial |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Complex combined interventions (n = 4) | | | | | | | | | | | | | |
| Yu *et al.* (2021) | Assess whether the combined use of professional fluoride application and regular fluoride toothpaste has additional benefit than using regular fluoride toothpaste alone for children under 16. | Primary and mixed dentition; non-invasive | Brazil (1), Greece (1), Sweden (1), UK (2), and USA (1) | 5034 | 1 to 8 years | Not reported | Combined use of professional fluoride application and regular fluoride toothpaste (>1000pm) | Self-applied regular fluoride toothpaste alone | Caries increment (D(M/E)FS/D(M/E)FT or d(m/e)fs/d(m/e)ft; patient-reported outcomes; adverse events | 24 to 36 months | Cluster RCT (3); RCT (3) | 2007 to 2017 | Not reported |
| de Sousa *et al.* (2019) | Assess the effectiveness of fluoride varnish in reducing the risk of developing new dentine caries lesions and caries-related hospitalisations in pre-schoolers and to assess whether its effectiveness is influenced by baseline caries levels. | Primary dentition; non-invasive | Australia (1), Brazil (1), Canada (1), Chile (1), China (3), Germany (1), Greece (1), Iran (2), Ireland (1), Poland (1), Scotland (1), Sweden (4), and USA (2) | 16877 | 6 months to 5 years | Not reported | Fluoride varnish with or without an oral health programme | Placebo; no treatment; no intervention | Caries incidence (proportion of children developing new dentine caries lesions or dmfs/dmft); adverse events | 12 to 36 months | Cluster RCT (6), RCT (14) | 1979 to 2018 | Not reported |
| Chou *et al.* (2021) | Determine how effective oral screening (including risk assessment) performed by a primary care clinician is in preventing dental caries in children younger than age 5 years. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (2), Sweden (3), UK (1), and USA (10); Included: Australia (1), Brazil (1), Canada (1), Chile (1), Greece (1), Iran (3), Kosovo (1), Scotland (1), Sweden (3), UK (1), and USA (1) | Total: 106694; Included: 11979 | 0 to 4 years | Total: 36-56% female (21), not reported (12); Included: 36-56% female (15), not reported (8) | Referral to a dentist by primary care clinician; treatments (dietary fluoride supplementation, topical fluoride application, xylitol, silver diamine fluoride) | No intervention; placebo | increment of decayed, missing, and filled surfaces or teeth (dmft/dmfs); caries incidence | 12 to 36 months | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (1), observational studies (3) | 1967 to 2020 | Total: Yes, twenty-one trials; Included: Yes, fifteen trials |
| Dos Santos *et al.* (2018) | Assess the effects of supervised toothbrushing on caries incidence in children and adolescents. | Primary and permanent dentition; non-invasive | Brazil (1), Germany (1), Jordan (1), and USA (1) | Not reported | 2 to 14 years | Not reported | Supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | No supervised toothbrushing (with no fluoride; 500ppm fluoride; | Caries incidence (proportion of caries-free children); caries increment (dmft/dmfs or DMFT/DMFS); cumulative survival rates | 21 to 36 months | RCT/quasi-RCT (4) | 1978 to 2016 | Yes, one trial |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 1000ppm fluoride) | | | | | |
| Permanent dentition | | | | | | | | | | | | | |
| Attendance for dental assessment (n = 2) | | | | | | | | | | | | | |
| Scheduled dental appointments (n = 2) | | | | | | | | | | | | | |
| Fee *et al.* (2020) | Determine the optimal recall interval of dental check-up for oral health in a primary care setting. | Primary and permanent dentition; non-invasive | Norway (1) and UK (1) | 1736 | 3 to 18+ years | 53-59% female (1); not reported (1) | Recall interval (time between recall visits/routine dental check-up) | Each other | incremental number of decayed, missing, filled, and sound tooth surfaces (dmfs); number of tooth surfaces with any caries | 24 to 48 months | RCT (2) | 1992 to 2020 | Yes, one trial |
| Joury *et al.* (2017) | Systematically review the randomised controlled trials that aimed to assess the effectiveness of school-based dental screening versus no screening on improving oral health in children aged 3-18 years. | Primary and permanent dentition; non-invasive | Total: India (2) and UK (3); Included: UK (1) | Total: 28442; Included: 17098 | Total: 5.5 to 15 years; Included: 6 to 8 years | Not reported | School-based dental screening | No oral health screening | Changes in prevalence and/or mean number of primary and permanent teeth with active caries | Total: 2 to 4 months; Included: 4 months | Total: RCT (5); Included: RCT (1) | Total: 2001 to 2014; Included: 2006 | Not reported |
| Scheduled primary care appointments (n = 0) | | | | | | | | | | | | | |
| Dental hygiene (n = 3) | | | | | | | | | | | | | |
| Supervised toothbrushing (n = 2) | | | | | | | | | | | | | |
| Hujoel *et al.* (2018) | Conduct a systematic review of randomised trials assessing the association between personal oral hygiene and dental caries in the absence of the confounding effects of fluoride. | Primary and permanent dentition; non-invasive | UK (1) and USA (2) | 743 | 10 to 13 years | Both males and females (2); only females (1) | Personal oral hygiene (brushing teeth supervised with or without interproximal cleansing devices) | No intervention | Incidence rates of caries (DMFS/DMFT) | 29 to 36 months | RCT (3) | 1977 to 1981 | Yes, one trial |
| Dos Santos *et al.* (2018) | Assess the effects of supervised toothbrushing on caries incidence in children and adolescents. | Primary and permanent dentition; non-invasive | Brazil (1), Germany (1), Jordan (1), and USA (1) | Not reported | 2 to 14 years | Not reported | Supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | No supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | Caries incidence (proportion of caries-free children); caries increment (dmft/dmfs or DMFT/DMFS); cumulative survival rates | 21 to 36 months | RCT/quasi-RCT (4) | 1978 to 2016 | Yes, one trial |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Flossing (n = 0) | | | | | | | | | | | | | |
| Interdental cleaning devices (n = 1) | | | | | | | | | | | | | |
| Worthington *et al.* (2019) | Evaluate the effectiveness of interdental cleaning devices used at home, in addition to toothbrushing, compared with toothbrushing alone, for preventing and controlling periodontal diseases, caries, and plaque. | Permanent dentition; non-invasive | Canada (2), Germany (1), Guatemala (1), Italy (1), Netherlands (3), UK (2), and USA (23) | 3929 | 18 to 78 years | 40-89% female (23); not reported (12) | Floss (automated or manual); interdental brush; tooth cleaning stick (wooden or rubber/manual or electric); oral irrigation | Each other | DMFS; plaque; adverse effect | 1 to 9 months | RCT (35) | 1972 to 2017 | Not reported |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | | | |
| Systemic fluoride (n = 4) | | | | | | | | | | | | | |
| Milk (n = 2) | | | | | | | | | | | | | |
| Yeung *et al.* (2015) | Assess the effects of milk fluoridation for preventing dental caries at a community level. | Primary and permanent dentition; non-invasive | Russia (1) | 180 | 3 years | Not reported | Fluoridated milk (2.5mg per litre) | Standard milk | caries increment (DMFT/DMFS); caries increment (dmft/dmfs); adverse effects; dental pain due to decay; antibiotics due to dental infections; requirement for general anaesthesia due to dental procedures for caries | 36 months | RCT (1) | 2004 | Yes, one trial |
| Cagetti *et al.* (2012) | Evaluate the presence of scientific evidence relating to the effects of fluoride intake via food on the occurrence of carious lesions. | Primary and permanent dentition; non-invasive | Indonesia (1), not reported (2) | 978 | 3.5 to 19 years (mean) | 53% female (1), 54% female (1), not reported (1) | Milk and sugar fluoridation | Standard milk; not reported | caries increment (dmfs/dmft); caries increment (DMFS/DMFT) | 18 to 21 months | Clinical trials (3) | 2002 to 2009 | Not reported |
| Salt (n = 1) | | | | | | | | | | | | | |
| Cagetti *et al.* (2012) | Evaluate the presence of scientific evidence relating to the effects of fluoride intake via food on the occurrence of carious lesions. | Primary and permanent dentition; non-invasive | Indonesia (1), not reported (2) | 978 | 3.5 to 19 years (mean) | 53% female (1), 54% female (1), not reported (1) | Milk and sugar fluoridation | Standard milk; not reported | caries increment (dmfs/dmft); caries increment (DMFS/DMFT) | 18 to 21 months | Clinical trials (3) | 2002 to 2009 | Not reported |
| Sugar (n = 1) | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cagetti *et al.* (2012) | Evaluate the presence of scientific evidence relating to the effects of fluoride intake via food on the occurrence of carious lesions. | Primary and permanent dentition; non-invasive | Indonesia (1), not reported (2) | 978 | 3.5 to 19 years (mean) | 53% female (1), 54% female (1), not reported (1) | Milk and sugar fluoridation | Standard milk; not reported | caries increment (dmfs/dmft); caries increment (DMFS/DMFT) | 18 to 21 months | Clinical trials (3) | 2002 to 2009 | Not reported |
| Supplements (n = 2) | | | | | | | | | | | | | |
| Tubert-Jeannin *et al.* (2011) | Evaluate the effects of fluoride supplements in the form of tablets (chewable or not), drops, lozenges, and chewing gums for preventing dental caries in children. | Primary and permanent dentition; non-invasive | Denmark (1), Sweden (4), Taiwan (1), UK (1), and USA (4) | 7196 | 2 to 12 years | Both males and females (3), not reported (8) | Fluoride supplements (tablets, drops, lozenges, or chewing gum); with or without vitamins; with or without topical fluorides (rinse, application, varnish, toothpaste); with or without non-fluoride-based measures (chlorhexidine, xylitol, sealants, oral hygiene interventions) | No fluoride supplements; no treatment; placebo | caries experience measured by dmft/dmfs (within and between groups); caries experience measured by DMFT/DMFT (within and between groups); new carious tooth surfaces; plaque; adverse events | 24 to 72 months | RCT (11) | 1968 to 2008 | Not reported |
| Zhou *et al.* (2019) | Investigate the efficacy of strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. | Primary and permanent dentition; non-invasive | Not reported | Total: 935; Included: 531 | Under 18 | Not reported | Mechanical (toothbrushing) and chemical (chlorhexidine, plaque-disclosing agent, triclosan-zinc, fluoride) oral health promotion strategies | Placebo; no treatment | caries prevention (dmfs/DMFS; dmft/DMFT) | Total: 10 days to 36 months; Included: 1 to 36 months | Total: RCT (7); non-RCT (7); Included: RCT (2); non-RCT (1) | Total: 1975 to 2015; Included: 1979 to 2013 | Not reported |
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | |
| Vitamin D (n = 0) | | | | | | | | | | | | | |
| Calcium (n = 0) | | | | | | | | | | | | | |
| Sialagogues (n = 1) | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |
| Zinc (n = 0) | | | | | | | | | | | | | |
| Topical fluoride (n = 9) | | | | | | | | | | | | | |
| Toothpaste (n = 2) | | | | | | | | | | | | | |
| Walsh *et al.* (2019) | Determine and compare the effects of toothpastes of different | Primary and permanent | Total: Australia (2), Brazil (3), Canada (2), China (1), Denmark (1), | Total: 67835; | 1 to 93 years | Total: Both males and females | Fluoride toothpaste (0ppm, 250ppm, | Each other; non-fluoride | incidence of caries (change in proportion of participants developing | Total: 12+ months; Included: | Total: RCT (96); | Total: 1955 to 2014; | Yes, fifty-three trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | fluoride concentrations (parts per million) in preventing dental caries in children, adolescents, and adults. | dentition; non-invasive | France (5), Germany (2), Guatemala (2), Iceland (1), India (1), Italy (2), Japan (1), Lithuania (1), Puerto Rico (1), Sweden (6), Switzerland (6), UK (22), and USA (37); Included: Australia (1), Brazil (1), China (1), France (1), Germany (1), Iceland (1), India (1), Sweden (3), Switzerland (1), UK (9), and USA (7) | Included: 41807 | | (66), only males (3), only females (2), not reported (25); Included: Both males and females (15), only females (2), not reported (8) | 440 to 550ppm, 1000 to 1250 ppm, 1450 to 1500 ppm, 1700 to 2200 ppm, 2400 to 2800 ppm) and toothbrushing | toothpaste; no toothpaste | new caries); adverse effects | 22 months to 60 months | Included: RCT (27) | Included: 1962 to 2014 | |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), Sweden (1), UK (1), and USA (2) | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |
| Mouthrinses (n = 2) | | | | | | | | | | | | | |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), Sweden (1), UK (1), and USA (2) | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |
| Wierichs *et al.* (2015) | Critically summarize and evaluate results of clinical studies | Permanent dentition; non-invasive | Total: Brazil (1), Canada (1), China (3), Denmark (1), Hungary (1), Israel | Total: 10136; | Total: 20 to 101 years; | Not reported | Preventive dental regimes (oral health | Placebo; each other; no intervention | New root caries lesions (DMFRS) | Total: 5 to 60 months; | Total: RCT (29), non-RCT (1); | 1987 to 2013 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | investigating chemical agents to reduce initiation of RCLs or inactive existing ones. | | (1), Netherlands (2), Spain (1), Switzerland (1), Sweden (5), UK (3), USA (9), and Germany/Switzerland (1); Included: Not reported | Included: 7573 | Included: Not reported | | instruction) and chemical agents (chlorhexidine; fluoride; ozone) | | | Included: 12 to 38 months | Included: Not reported | | |
| Foams (n = 0) | | | | | | | | | | | | | |
| Gels (n = 3) | | | | | | | | | | | | | |
| Marinho *et al.* (2015) | Determine the effectiveness and safety of fluoride gels in preventing dental caries in the child and adolescent population. | Primary and permanent dentition; non-invasive | Brazil (4), Canada (1), China (1), Europe (7), Israel (1), USA (13), and Venezuela (1) | 9140 | 2 to 15 years | Both males and females (27); only males (1) | Topical fluoride in the form of gels | Placebo; no treatment | Caries increment in permanent tooth surfaces, reported as change from baseline; caries increment in primary tooth surfaces, reported as change from baseline; development of new caries; change in proportion of children not remaining caries-free; tooth staining; signs of acute toxicity during application; mucosal irritation/oral soft-tissue allergic reaction | 12 to 36 months | RCT (27), cluster RCT (1) | 1964 to 2005 | Yes, thirteen trials |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), Sweden (1), UK (1), and USA (2) | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |
| Chan *et al.* (2022) | Systematically review the effectiveness of professionally applied fluoride therapy in preventing and | Permanent dentition; non-invasive | Hong Kong (4), UK (2), and USA (1) | 1027 | 60 to 84 years (mean) | Not reported | Fluoride therapy (5% sodium fluoride varnish; 38% silver diamine fluoride | Fluoride agent; placebo; no intervention | Root caries preventive effect (mean difference in the number of new carious lesions and root | 12 to 48 months | Clinical trials (7) | 1993 to 2021 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | arresting dental caries in older adults aged 60 years or above. | | | | | | solution; 1.23 APF gel) | | caries prevented fraction) | | | | |
| Solution (n = 4) | | | | | | | | | | | | | |
| Grandjean *et al.* (2021) | Determine the effectiveness of silver diamine fluoride in preventing and arresting root caries lesions in elders. | Permanent dentition; non-invasive | Not reported | 552 | 65+ years | Not reported | Professional application of silver diamine fluoride | Not reported | Root caries incidence (mean new carious root surfaces) | 24 to 36 months | RCT (3) | 2010 to 2017 | Not reported |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), Sweden (1), UK (1), and USA (2) | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |
| Subbiah *et al.* (2018) | Evaluate the scientific evidence regarding the effectiveness of silver diamine fluoride in preventing and arresting caries in elderly adults. | Permanent dentition; non-invasive | Total: Hong Kong (3); Included: Hong Kong (2) | Total: 655; Included: 572 | Not reported | Not reported | 38% Silver diamine fluoride | Placebo; no treatment | Caries preventive effect (mean number of new root caries surfaces or root caries prevented fraction); adverse effects | 24 to 36 months | Total: RCT (3); Included: RCT (2) | Total: 2010 to 2016; Included: 2010 to 2013 | Not reported |
| Chan *et al.* (2022) | Systematically review the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | Permanent dentition; non-invasive | Hong Kong (4), UK (2), and USA (1) | 1027 | 60 to 84 years (mean) | Not reported | Fluoride therapy (5% sodium fluoride varnish; 38% silver diamine fluoride solution; 1.23 APF gel) | Fluoride agent; placebo; no intervention | Root caries preventive effect (mean difference in the number of new carious lesions and root caries prevented fraction) | 12 to 48 months | Clinical trials (7) | 1993 to 2021 | Not reported |
| Slow-release fluoride devices (n = 1) | | | | | | | | | | | | | |
| Chong *et al.* (2018) | Evaluate the effectiveness and safety of different types of slow-release fluoride devices on preventing, | Primary and permanent dentition; non-invasive | UK (1) | 174 | 10.9 years (mean) | Not reported | Slow-release fluoride devices (co-polymer membrane or slow-dissolving | Alternative fluoride treatment; placebo; no | Caries increment (dmfs/dmft or DMFS/DMFT); retention of slow-release fluoride devices; harms of slow- | 24 months | RCT (1) | 2005 | Yes, one trial |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | arresting, or reversing the progression of carious lesions on all surface types of primary (deciduous) and permanent teeth. | | | | | | fluoride glass beads) | intervention; no treatment | release fluoride devices; use of healthcare resources | | | | |
| Varnishes (n = 4) | | | | | | | | | | | | | |
| Marinho *et al.* (2013) | Evaluate the effectiveness and safety of fluoride varnishes in preventing dental caries in the child/adolescent population. | Primary and permanent dentition; non-invasive | Brazil (3), Canada (2), China (3), Germany (2), India (2), Spain (1), Sweden (6), UK (2), and USA (1) | 12455 | 1 to 15 years | Not reported | Topical fluoride in the form of varnishes | Placebo; no treatment | caries increment (d(e/m)fs/d(e/m)ft and DMFS/DMFT) proportion of children developing one or more new caries; adverse events; use of health service resources | 36 months | RCT/quasi-RCT (17), cluster RCT (5) | 1979 to 2012 | Yes, one trial |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), Sweden (1), UK (1), and USA (2) | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |
| Wierichs *et al.* (2015) | Critically summarize and evaluate results of clinical studies investigating chemical agents to reduce initiation of RCLs or inactive existing ones. | Permanent dentition; non-invasive | Total: Brazil (1), Canada (1), China (3), Denmark (1), Hungary (1), Israel (1), Netherlands (2), Spain (1), Switzerland (1), Sweden (5), UK (3), USA (9), and Germany/Switzerland (1); Included: Not reported | Total: 10136; Included: 7573 | Total: 20 to 101 years; Included: Not reported | Not reported | Preventive dental regimes (oral health instruction) and chemical agents (chlorhexidine; fluoride; ozone) | Placebo; each other; no intervention | New root caries lesions (DMFRS) | Total: 5 to 60 months; Included: 12 to 38 months | Total: RCT (29), non-RCT (1); Included: Not reported | 1987 to 2013 | Not reported |
| Chan *et al.* (2022) | Systematically review the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries | Permanent dentition; non-invasive | Hong Kong (4), UK (2), and USA (1) | 1027 | 60 to 84 years (mean) | Not reported | Fluoride therapy (5% sodium fluoride varnish; 38% silver diamine fluoride solution; 1.23 APF gel) | Fluoride agent; placebo; no intervention | Root caries preventive effect (mean difference in the number of new carious lesions and root caries prevented fraction) | 12 to 48 months | Clinical trials (7) | 1993 to 2021 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | in older adults aged 60 years or above. | | | | | | | | | | | | |
| Mixed (n = 0) | | | | | | | | | | | | | |
| Topical other chemicals (n = 8) | | | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 1) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | and both USA and Canada (1) | | | | | | | | | | |
| Arginine and its derivatives (n = 0)<br>CHX (n = 4) | | | | | | | | | | | | | |
| Walsh *et al.* (2015) | Assess the effects of chlorhexidine-containing oral products (toothpastes, mouthrinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. | Primary and permanent dentition; non-invasive | Australia (2), Brazil (1), China (1), Scotland (1), Spain (1), Suriname (1), and Sweden (1) | 2876 | 0 to 15 years | 48-52% female (5); only females (1), not reported (2) | Chlorhexidine varnish and gel (0.12%, 1%, 10%, 40%) | No treatment; placebo | Caries increment (DMFS/DMFT or dmfs/dmft); caries incidence (presence or absence of new caries); % sound surfaces; S. mutans counts; pain; adverse events | 24 to 36 months | RCT (6), cluster RCT (2) | 1997 to 2013 | Yes, one trial |
| Wierichs *et al.* (2015) | Critically summarize and evaluate results of clinical studies investigating chemical agents to reduce initiation of RCLs or inactive existing ones. | Permanent dentition; non-invasive | Total: Brazil (1), Canada (1), China (3), Denmark (1), Hungary (1), Israel (1), Netherlands (2), Spain (1), Switzerland (1), Sweden (5), UK (3), USA (9), and Germany/Switzerland (1); Included: Not reported | Total: 10136; Included: 7573 | Total: 20 to 101 years; Included: Not reported | Not reported | Preventive dental regimes (oral health instruction) and chemical agents (chlorhexidine; fluoride; ozone) | Placebo; each other; no intervention | New root caries lesions (DMFRS) | Total: 5 to 60 months; Included: 12 to 38 months | Total: RCT (29), non-RCT (1); Included: Not reported | 1987 to 2013 | Not reported |
| James *et al.* (2010) | Summarize the evidence of the effectiveness of chlorhexidine varnish at preventing caries in the permanent and primary teeth of children and adolescents compared to placebo or no treatment, using data from randomised controlled trials only. | Primary and permanent dentition; non-invasive | Not reported | 2934 | 4 to 18 years | Not reported | Chlorhexidine varnish | Placebo; no treatment; fluoride varnish | Caries increment (dmfs/DMFS); adverse events | 24 to 36 months | RCT/quasi-RCT (12) | 1995 to 2008 | Not reported |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | |
| Calcium phosphate agents (n = 2) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/th | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | ymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | controlled trials (7), clinical controlled trials (8) | | |
| Singal *et al.* (2022) | Extensively review, summarise, and to draw best possible evidence for the remineralising and caries preventive efficacy of various calcium phosphate derivatives. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), China (1), Denmark (1), Egypt (2), Finland (1), Greece (1), India (6), Iran (2), Jordan (2), Saudi Arabia (1), Spain (1), Sweden (1), Thailand (2), and Turkey (3); Included: Egypt (1), Finland (1), India (4), Jordan (1), Saudi Arabia (1), Thailand (1), and Turkey (2) | Total: 3678; Included: 852 | Total: 0 to 18 months; Included: 2 days to 12 months | Not reported | Topical formulation of calcium phosphate agents (alone or combined with sodium fluoride/stannous fluoride) | No intervention; placebo; topical application of fluoride (containing sodium fluoride or stannous fluoride) | Caries preventive benefit (dmfs/dmft or DMFS/DMFT); S. mutans count | 12 to 24 months | Total: RCT (26); Included: RCT (11) | Total: 2007 to 2021; Included: 2012 to 2020 | Not reported |
| Ozone (n = 0) | | | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | | | |
| Probiotics (n = 0) | | | | | | | | | | | | | |
| Propolis (n = 0) | | | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Riley *et al.* (2015) | Assess the effects of different xylitol-containing products on preventing dental caries in children and adults. | Primary and permanent dentition; non-invasive | Costa Rica (2), Estonia (1), Finland (2), Republic of the Marshall Islands (1), Sweden (2), and USA (2) | 7969 | 0 to 18+ years | 66% female (1); both males and females (9) | Xylitol-containing products (lozenges, candy, syrup, tablets, toothpaste, wipes) | Placebo; no treatment | Caries preventive benefit (ds/dmfs or DMFS/DFS); adverse events | 12 to 48 months | Cluster RCT (2); RCT (8) | 1991 to 2014 | Yes, four trials |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |
| Riggs *et al.* (2019) | Assess the effects of interventions targeted | Primary and permanent | Total: Australia (1), Brazil (3), Belarus (1), | Total: 23732; | 17 to 44 years | Not reported | Antimicrobial treatments | Placebo; no treatment | Caries incidence (deft/defs; dmft/dmfs; | 12 to 36 months | Total: RCT (12), cluster | Total: 1993 to 2017; | Yes, two trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | dentition; non-invasive | Canada (2), Finland (2), Sweden (1), Uganda (2), UK (1), USA (3), not reported (1); Included: Brazil (1), Finland (1), Sweden (1), USA (2), not reported (1) | Included: 907 | (mothers) /0 to 13 months (children) | | (chlorhexidine and iodine-sodium-fluoride solution and prophylaxis); xylitol | | DMFT/DMFS); microbiological presence (mothers and children); plaque; adverse events | | RCT (5); Included: RCT (6) | Included: 1993 to 2013 | |
| Antonio *et al.* (2011) | Assess the overall caries preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. | Permanent dentition; non-invasive | Estonia (1), Kuwait (1), Sweden (1) | 947 | 10 to 27 years | Not reported | Xylitol products (candies or lozenges) | No intervention; placebo; preventive procedures | Caries increment (DMFS/DMFT) | 18 to 36 months | Clinical controlled trial (1), RCT (2) | 2000 to 2008 | Not reported |
| Sorbitol (n = 0) | | | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 2) | | | | | | | | | | | | | |
| Antonio *et al.* (2011) | Assess the overall caries preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. | Permanent dentition; non-invasive | Estonia (1), Kuwait (1), Sweden (1) | 947 | 10 to 27 years | Not reported | Xylitol products (candies or lozenges) | No intervention; placebo; preventive procedures | Caries increment (DMFS/DMFT) | 18 to 36 months | Clinical controlled trial (1), RCT (2) | 2000 to 2008 | Not reported |
| Sealants (n = 10) | | | | | | | | | | | | | |
| Resin (n = 8) | | | | | | | | | | | | | |
| Alsabek *et al.* (2021) | Determine the effectiveness of hydrophilic resin-based sealant in preventing pits and fissures caries in permanent teeth. | Permanent dentition; non-invasive | Not reported | 2561 (teeth) | 5 to 15 years | Not reported | Hydrophilic resin-based sealants | No treatment; topical fluoride; conventional resin-based sealant; other treatment options | Retention rate; caries incidence | 6 to 12 months | RCT (13) | 2012 to 2019 | Not reported |
| Alirezaei *et al.* (2018) | Evaluate the ability of glass-ionomer cements and resin-based sealants to prevent the occurrence of caries and their retention in standard-based clinical studies. | Permanent dentition; non-invasive | Total: Australia (1), Brazil (6), China (4), Denmark (1), Egypt (1), Finland (3), India (7), Italy (1), Norway (1), Romania (1), Saudi Arabia (1), Turkey (3), and USA (1); Included: Australia (1), Brazil (5), China (2), Denmark (1), Egypt (1), Finland (3), | Total: 13459; Included: 10737 | Not reported | Not reported | Resin-based fissure sealant | Glass-ionomer fissure sealant | Retention rate; caries development | 12 to 84 months | Total: RCT (31); Included: RCT (28) | 1994 to 2017 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | India (7), Italy (1), Norway (1), Romania (1), Saudi Arabia (1), Turkey (3), and USA (1) | | | | | | | | | | |
| Alharthy *et al.* (2022) | Assess and evaluate the retention and cariostatic effect of hydrophilic and hydrophobic resin-based sealants in primary and/or permanent teeth with at least a follow-up period of 3 months. | Primary and permanent dentition; non-invasive | Germany (1), India (9), Iran (1), Turkey (1) | 770 | 5 to 15 years | Not reported | Hydrophilic resin-based sealants | Hydrophobic resin-based sealants | Sealant retention | 1 to 24 months | RCT (7), non-RCT (5) | 2012 to 2020 | Not reported |
| Rashed *et al.* (2022) | Compare pit and fissure sealants with fluoride varnish for the prevention of caries in the first permanent molars of schoolchildren. | Permanent dentition; non-invasive | Not reported | 1249 | 6 to 9 years | Not reported | Resin-based sealants | Fluoride varnish | Caries incidence; caries increment (DMFS) | 24 months | RCT (4) | 1996 to 2014 | Not reported |
| Kashbour *et al.* (2020) | Evaluate the relative effectiveness of dental sealants (fissure sealant) compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | Permanent dentition; non-invasive | Total: Brazil (2), China (3), Germany (1), Iran (1), Latvia (1), Norway (1), Spain (1), and UK (1) Included: Brazil (2), China (3), Germany (1), Latvia (1), Norway (1), Spain (1), and UK (1) | Total: 3374; Included: 2010 | 5 to 10 years | Both males and females | Pit and fissure sealants of all materials (except first generation resin-based sealants) | Fluoride varnish | Occurrence of a new dental carious lesion on treated occlusal surfaces of molars or premolars; Caries increment (changes in decayed, missing, and filled figures at surface, tooth, and whole-mouth levels); time taken to apply pit and fissure sealant or fluoride varnish over a 2-year study period; number of visits to the dentist for repair of sealant or fluoride varnish application; safety of using sealants and fluoride varnishes assessed by presence or absence of adverse events | 12 to 36 months | Total: RCT (11) ; Included: RCT (10) | 2001 to 2017 | Yes, six trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ahovuo-Saloranta *et al.* (2017) | Compare the effects of different types of fissure sealants in preventing caries un occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. | Permanent dentition; non-invasive | Australia (1), Brazil (5), Canada (1), China (6), Colombia (1), Egypt (1), Finland (2), France (1), India (2), New Zealand (1), Norway (1), Spain (1), Sweden (1), Syrian Arab Republic (1), Thailand (1), Turkey (3), UK (4), and USA (5) | 7924 | 5 to 16 years | Not reported | Resin-based sealant; glass-ionomer-based sealant | No sealant; each other | Caries preventive benefit (incidence of carious lesions); caries increment (DMFS); adverse events; sealant retention | 12 to 84 months | RCT (38) | 1976 to 2014 | Yes, seven trials |
| CADTH (2016) | Review the evidence with respect to clinical effectiveness, specifically caries prevention, and cost effectiveness of dental sealants and preventative resins when applied to permanent teeth of children and adolescents. | Permanent dentition; non-invasive | Total: Brazil (1), China (1), Finland (1), France (1), Italy (1), Latvia (1), Philippines (1), Portugal (1), and USA (1); Included: Brazil (1), France (1), Latvia (1), and Philippines (1). | Total: 2025; Included: 1656 | Total: 0 to 14 years; Included: 6.4 to 10 years | Not reported | Dental sealants and preventive resins (resin-based sealant; composite resin; high viscosity glass-ionomer sealant) | No dental sealant; supervised toothbrushing alone; preventive resin use | Caries incidence (development of cavitated dentine lesions) | 12 to 36 months | Total: Systematic review (4), randomised controlled trials (4), retrospective cohort study (1), evidence-based clinical practice guideline (1); Included: RCT (4) | Total: 2011 to 2016; Included: 2012 to 2016 | Not reported |
| Li *et al.* (2020) | Accurately evaluate the efficacy of first permanent molars caries management between fluoride sealant and fluoride varnish. | Permanent dentition; non-invasive | Not reported | 3289 | 6 to 9 years | 48-53% female (6); not reported (2) | Fluoride sealant (resin-based or glass-ionomer); fluoride varnish | Each other; water; blanks; oral health education | Caries incidence (DMFS) | 24 to 36 months | RCT (8) | 1984 to 2017 | Not reported |
| Glass-ionomer (n = 4) | | | | | | | | | | | | | |
| Kashbour *et al.* (2020) | Evaluate the relative effectiveness of dental sealants (fissure sealant) compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for | Permanent dentition; non-invasive | Total: Brazil (2), China (3), Germany (1), Iran (1), Latvia (1), Norway (1), Spain (1), and UK (1) Included: Brazil (2), China (3), Germany (1), Latvia (1), Norway (1), Spain (1), and UK (1) | Total: 3374; Included: 2010 | 5 to 10 years | Both males and females | Pit and fissure sealants of all materials (except first generation resin-based sealants) | Fluoride varnish | Occurrence of a new dental carious lesion on treated occlusal surfaces of molars or premolars; Caries increment (changes in decayed, missing, and filled figures at surface, tooth, and whole-mouth | 12 to 36 months | Total: RCT (11) ; Included: RCT (10) | 2001 to 2017 | Yes, six trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | | | | | | | | levels); time taken to apply pit and fissure sealant or fluoride varnish over a 2-year study period; number of visits to the dentist for repair of sealant or fluoride varnish application; safety of using sealants and fluoride varnishes assessed by presence or absence of adverse events | | | | |
| Ahovuo-Saloranta *et al.* (2017) | Compare the effects of different types of fissure sealants in preventing caries un occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. | Permanent dentition; non-invasive | Australia (1), Brazil (5), Canada (1), China (6), Colombia (1), Egypt (1), Finland (2), France (1), India (2), New Zealand (1), Norway (1), Spain (1), Sweden (1), Syrian Arab Republic (1), Thailand (1), Turkey (3), UK (4), and USA (5) | 7924 | 5 to 16 years | Not reported | Resin-based sealant; glass-ionomer-based sealant | No sealant; each other | Caries preventive benefit (incidence of carious lesions); caries increment (DMFS); adverse events; sealant retention | 12 to 84 months | RCT (38) | 1976 to 2014 | Yes, seven trials |
| Wright *et al.* (2016) | Summarise the available evidence regarding the effect of dental sealants for the prevention of pit-and-fissure occlusal caries in primary and permanent molars on children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with another head-to-head comparison to inform the development of a joint evidence-based clinical practice guideline by the American Dental Association and the | Primary and permanent dentition; non-invasive | Australia (1), Brazil (5), Canada (1), China (3), Colombia (1), Egypt (1), Germany (1), India (2), Spain (1), Turkey (4), and USA (3) | 9349 | 3 to 16 years | Not reported | Sealants (resin-based; glass-ionomer; resin-modified glass-ionomer; polyacid-modified) | Each other; fluoride varnishes; no intervention | Caries incidence (identification of new carious lesions); lack of retention; adverse effects | 24 to 84 months | RCT (23) | 1976 to 2016 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | American Academy of Paediatric Dentistry. | | | | | | | | | | | | |
| CADTH (2016) | Review the evidence with respect to clinical effectiveness, specifically caries prevention, and cost effectiveness of dental sealants and preventative resins when applied to permanent teeth of children and adolescents. | Permanent dentition; non-invasive | Total: Brazil (1), China (1), Finland (1), France (1), Italy (1), Latvia (1), Philippines (1), Portugal (1), and USA (1); Included: Brazil (1), France (1), Latvia (1), and Philippines (1). | Total: 2025; Included: 1656 | Total: 0 to 14 years; Included: 6.4 to 10 years | Not reported | Dental sealants and preventive resins (resin-based sealant; composite resin; high viscosity glass-ionomer sealant) | No dental sealant; supervised toothbrushing alone; preventive resin use | Caries incidence (development of cavitated dentine lesions) | 12 to 36 months | Total: Systematic review (4), randomised controlled trials (4), retrospective cohort study (1), evidence-based clinical practice guideline (1); Included: RCT (4) | Total: 2011 to 2016; Included: 2012 to 2016 | Not reported |
| Ormocer (n = 1) | | | | | | | | | | | | | |
| Ahovuo-Saloranta *et al.* (2017) | Compare the effects of different types of fissure sealants in preventing caries un occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. | Permanent dentition; non-invasive | Australia (1), Brazil (5), Canada (1), China (6), Colombia (1), Egypt (1), Finland (2), France (1), India (2), New Zealand (1), Norway (1), Spain (1), Sweden (1), Syrian Arab Republic (1), Thailand (1), Turkey (3), UK (4), and USA (5) | 7924 | 5 to 16 years | Not reported | Resin-based sealant; glass-ionomer-based sealant | No sealant; each other | Caries preventive benefit (incidence of carious lesions); caries increment (DMFS); adverse events; sealant retention | 12 to 84 months | RCT (38) | 1976 to 2014 | Yes, seven trials |
| Hybrid (n = 1) | | | | | | | | | | | | | |
| Wright *et al.* (2016) | Summarise the available evidence regarding the effect of dental sealants for the prevention of pit-and-fissure occlusal caries in primary and permanent molars on children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with | Primary and permanent dentition; non-invasive | Australia (1), Brazil (5), Canada (1), China (3), Colombia (1), Egypt (1), Germany (1), India (2), Spain (1), Turkey (4), and USA (3) | 9349 | 3 to 16 years | Not reported | Sealants (resin-based; glass-ionomer; resin-modified glass-ionomer; polyacid-modified) | Each other; fluoride varnishes; no intervention | Caries incidence (identification of new carious lesions); lack of retention; adverse effects | 24 to 84 months | RCT (23) | 1976 to 2016 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | another head-to-head comparison to inform the development of a joint evidence-based clinical practice guideline by the American Dental Association and the American Academy of Paediatric Dentistry. | | | | | | | | | | | | |
| Combined (n = 4) | | | | | | | | | | | | | |
| Wright *et al.* (2016) | Summarise the available evidence regarding the effect of dental sealants for the prevention of pit-and-fissure occlusal caries in primary and permanent molars on children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with another head-to-head comparison to inform the development of a joint evidence-based clinical practice guideline by the American Dental Association and the American Academy of Paediatric Dentistry. | Primary and permanent dentition; non-invasive | Australia (1), Brazil (5), Canada (1), China (3), Colombia (1), Egypt (1), Germany (1), India (2), Spain (1), Turkey (4), and USA (3) | 9349 | 3 to 16 years | Not reported | Sealants (resin-based; glass-ionomer; resin-modified glass-ionomer; polyacid-modified) | Each other; fluoride varnishes; no intervention | Caries incidence (identification of new carious lesions); lack of retention; adverse effects | 24 to 84 months | RCT (23) | 1976 to 2016 | Not reported |
| CADTH (2016) | Review the evidence with respect to clinical effectiveness, specifically caries prevention, and cost effectiveness of dental sealants and preventative resins when applied to permanent teeth of | Permanent dentition; non-invasive | Total: Brazil (1), China (1), Finland (1), France (1), Italy (1), Latvia (1), Philippines (1), Portugal (1), and USA (1); Included: Brazil (1), France (1), Latvia (1), and Philippines (1). | Total: 2025; Included: 1656 | Total: 0 to 14 years; Included: 6.4 to 10 years | Not reported | Dental sealants and preventive resins (resin-based sealant; composite resin; high viscosity glass-ionomer sealant) | No dental sealant; supervised toothbrushing alone; preventive resin use | Caries incidence (development of cavitated dentine lesions) | 12 to 36 months | Total: Systematic review (4), randomised controlled trials (4), retrospective cohort study (1), evidence- | Total: 2011 to 2016; Included: 2012 to 2016 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | children and adolescents. | | | | | | | | | | based clinical practice guideline (1); Included: RCT (4) | | |
| Akera *et al.* (2022) | Evaluate the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | Primary and permanent dentition; non-invasive | Total: Bulgaria (1), Brazil (5), Cambodia (1), China (3), India (5), Indonesia (1), Iran (3), Malaysia (1), Myanmar (1), Nigeria (1), Pakistan (1), Philippines (1), South Africa (1), Taiwan (1), Tanzania (3), Thailand (2), Turkey (1), and Zimbabwe (1); Included: Cambodia (1), South Africa (1), and Turkey (1) | Not reported | Total: 3 to 16 years; Included: 6 to 15 years | Not reported | School health policy; provision of oral health education; promoting a healthy school environment; providing access to oral health services; involving community members; daily toothbrushing; fissure sealants; zinc supplementation | No intervention | incidence of dental caries (DMFT); plaque | 24 to 84 months | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Total: 1996 to 2021; Included: 2004 to 2017 | Not reported |
| Li *et al.* (2020) | Accurately evaluate the efficacy of first permanent molars caries management between fluoride sealant and fluoride varnish. | Permanent dentition; non-invasive | Not reported | 3289 | 6 to 9 years | 48-53% female (6); not reported (2) | Fluoride sealant (resin-based or glass-ionomer); fluoride varnish | Each other; water; blanks; oral health education | Caries incidence (DMFS) | 24 to 36 months | RCT (8) | 1984 to 2017 | Not reported |
| Other (n = 0) | | | | | | | | | | | | | |
| Laser (n = 1) | | | | | | | | | | | | | |
| Pagano *et al.* (2020) | Verify whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by | Primary and permanent dentition; non-invasive | Australia (1), Belgium (1), Brazil (3), India (1), Turkey (2), and USA (1) | 269 (participants) and 1628 (teeth) | 6 to 38 years | 35-94% females (4); not reported (5) | Laser application (carbon dioxide; nodymium-doped yttrium alinium garnet; argon; erbium-doped yttrium aluminium garnet; erbium chromium yttrium scandium | No treatment; placebo; placebo with traditional prophylactic intervention; traditional prophylactic intervention alone | Caries incidence (number of cases with new caries); sealant retention; adverse events | 12 to 48 months | RCT (7); controlled clinical trials (2) | 1996 to 2005 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | improving traditional etching procedures. | | | | | | gallium garnet) alone or with any traditional prophylactic intervention (acidulated phosphate fluoride gel/foam; enamel pit and fissure resin sealant; fluoride varnish) | | | | | | |
| Subgroup: Combined interventions in permanent dentition | | | | | | | | | | | | | |
| Topical fluoride + topical fluoride (n = 4) | | | | | | | | | | | | | |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), Sweden (1), UK (1), and USA (2) | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |
| Yu *et al.* (2021) | Assess whether the combined use of professional fluoride application and regular fluoride toothpaste has additional benefit than using regular fluoride toothpaste alone for children under 16. | Primary and mixed dentition; non-invasive | Brazil (1), Greece (1), Sweden (1), UK (2), and USA (1) | 5034 | 1 to 8 years | Not reported | Combined use of professional fluoride application and regular fluoride toothpaste (>1000pm) | Self-applied regular fluoride toothpaste alone | Caries increment (D(M/E)FS/D(M/E)FT or d(m/e)fs/d(m/e)ft; patient-reported outcomes; adverse events | 24 to 36 months | Cluster RCT (3); RCT (3) | 2007 to 2017 | Not reported |
| Wierichs *et al.* (2015) | Critically summarize and evaluate results of clinical studies investigating chemical agents to reduce initiation of RCLs or inactive existing ones. | Permanent dentition; non-invasive | Total: Brazil (1), Canada (1), China (3), Denmark (1), Hungary (1), Israel (1), Netherlands (2), Spain (1), Switzerland (1), Sweden (5), UK (3), USA (9), and | Total: 10136; Included: 7573 | Total: 20 to 101 years; Included: Not reported | Not reported | Preventive dental regimes (oral health instruction) and chemical agents (chlorhexidine; fluoride; ozone) | Placebo; each other; no intervention | DMFRS | Total: 5 to 60 months; Included: Not reported | Total: RCT (29), non-RCT (1); Included: RCT (18), non-RCT (1) | 1987 to 2013 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Germany/Switzerland (1); Included: Not reported | | | | | | | | | | |
| Chan *et al.* (2022) | Systematically review the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | Permanent dentition; non-invasive | Hong Kong (4), UK (2), and USA (1) | 1027 | 60 to 84 years (mean) | Not reported | Fluoride therapy (5% sodium fluoride varnish; 38% silver diamine fluoride solution; 1.23 APF gel) | Fluoride agent; placebo; no intervention | Root caries preventive effect (mean difference in the number of new carious lesions and root caries prevented fraction) | 12 to 48 months | Clinical trials (7) | 1993 to 2021 | Not reported |
| Topical fluoride + topical other chemicals (n = 4) | | | | | | | | | | | | | |
| Gupta *et al.* (2020a) | Compare the effectiveness of topical fluoride and povidone iodine with topical fluoride alone for the prevention of dental caries among 1- to 12-year-old children. | Primary and permanent dentition; non-invasive | Total: China (1), Iran (1), Saudi Arabia (1), and USA (4); Included: China (1), Iran (1), Saudi Arabia (1), and USA (3) | Total: 1020; Included: 406 | Total: 1 to 12 years; Included: 2 to 12 years | Not reported | Topical fluoride and povidone iodine (acidulated phosphate fluoride gel and povidone iodine; fluoride form and povidone iodine; 5% sodium fluoride varnish and povidone iodine; 0.2% sodium fluoride varnish and povidone iodine) | Topical fluoride alone | Caries incidence (presence or absence of new carious lesions); S. mutans count/plaque biofilm accumulation; Lactobacillus count | 12 months | Total: RCT (5), non-RCT (1), retrospective cohort study (1); Included: RCT (5), non-RCT (1) | 2005 to 2016 | Not reported |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | trials (7), clinical controlled trials (8) | | |
| Singal *et al.* (2022) | Extensively review, summarise, and to draw best possible evidence for the remineralising and caries preventive efficacy of various calcium phosphate derivatives. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), China (1), Denmark (1), Egypt (2), Finland (1), Greece (1), India (6), Iran (2), Jordan (2), Saudi Arabia (1), Spain (1), Sweden (1), Thailand (2), and Turkey (3); Included: Egypt (1), Finland (1), India (4), Jordan (1), Saudi Arabia (1), Thailand (1), and Turkey (2) | Total: 3678; Included: 852 | Total: 0 to 18 months; Included: 2 days to 12 months | Not reported | Topical formulation of calcium phosphate agents (alone or combined with sodium fluoride/stannous fluoride) | No intervention; placebo; topical application of fluoride (containing sodium fluoride or stannous fluoride) | Caries preventive benefit (dmfs/dmft or DMFS/DMFT); S. mutans count | 12 to 24 months | Total: RCT (26); Included: RCT (11) | Total: 2007 to 2021; Included: 2012 to 2020 | Not reported |
| Riley *et al.* (2015) | Assess the effects of different xylitol-containing products on preventing dental caries in children and adults. | Primary and permanent dentition; non-invasive | Costa Rica (2), Estonia (1), Finland (2), Republic of the Marshall Islands (1), Sweden (2), and USA (2) | 7969 | 0 to 18+ years | 66% female (1); both males and females (9) | Xylitol-containing products (lozenges, candy, syrup, tablets, toothpaste, wipes) | Placebo; no treatment | Caries preventive benefit (ds/dmfs or DMFS/DFS); adverse events | 12 to 48 months | Cluster RCT (2); RCT (8) | 1991 to 2014 | Yes, four trials |
| Topical fluoride + other (n = 8) | | | | | | | | | | | | | |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | | Sweden (1), UK (1), and USA (2) | | | | (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | | | | | | |
| Dos Santos *et al.* (2018) | Assess the effects of supervised toothbrushing on caries incidence in children and adolescents. | Primary and permanent dentition; non-invasive | Brazil (1), Germany (1), Jordan (1), and USA (1) | Not reported | 2 to 14 years | Not reported | Supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | No supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | Caries incidence (proportion of caries-free children); caries increment (dmft/dmfs or DMFT/DMFS); cumulative survival rates | 21 to 36 months | RCT/quasi-RCT (4) | 1978 to 2016 | Yes, one trial |
| Walsh *et al.* (2019) | Determine and compare the effects of toothpastes of different fluoride concentrations (parts per million) in preventing dental caries in children, adolescents, and adults. | Primary and permanent dentition; non-invasive | Total: Australia (2), Brazil (3), Canada (2), China (1), Denmark (1), France (5), Germany (2), Guatemala (2), Iceland (1), India (1), Italy (2), Japan (1), Lithuania (1), Puerto Rico (1), Sweden (6), Switzerland (6), UK (22), and USA (37); Included: Australia (1), Brazil (1), China (1), France (1), Germany (1), Iceland (1), India (1), Sweden (3), Switzerland (1), UK (9), and USA (7) | Total: 67835; Included: 41807 | 1 to 93 years | Total: Both males and females (66), only males (3), only females (2), not reported (25); Included: Both males and females (15), only females (2), not reported (8) | Fluoride toothpaste (0ppm, 250ppm, 440 to 550ppm, 1000 to 1250 ppm, 1450 to 1500 ppm, 1700 to 2200 ppm, 2400 to 2800 ppm) and toothbrushing | Each other; non-fluoride toothpaste; no toothpaste | incidence of caries (change in proportion of participants developing new caries); adverse effects | Total: 12+ months; Included: 22 to 60 months | Total: RCT (96); Included: RCT (27) | Total: 1955 to 2014; Included: 1962 to 2014 | Yes, fifty-three trials |
| Konradsson *et al.* (2020) | Review the scientific evidence for the efficacy of stabilised stannous fluoride dentifrice in relation to dental caries, dental erosion, and dentin hypersensitivity. | Permanent dentition; non-invasive | Total: China (2), Germany (1), Netherlands (1), Norway (2), Puerto Rico (1), UK (3), USA (9), UK/USA (1), and Ireland/USA (1); Included: Puerto Rico (1) | Total: 2945; Included: 955 | Total: 10 to 70 years; Included: 10+ years | Total: 51-93% female (13); not reported (8); Included: 51% female (1) | Toothbrushing with stabilised stannous fluoride dentifrice (manual or electric) or experimental slurries containing stannous fluoride | Toothbrushing with a non-stannous fluoridated dentifrice or non-fluoridated dentifrice/placebo; no treatment | DMFS | Total: 5 days to 24 months; Included: 24 months | Total: RCT (13), in-situ (7), non-RCT (1); Included: RCT (1) | Total: 2004 to 2017; Included: 2004 | Total: Yes, nineteen trials; Included: Yes, one trial |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marinho *et al.* (2016) | Determine the effectiveness and safety of fluoride mouthrinses in preventing dental caries in the child/adolescent population. | Permanent dentition; non-invasive | Brazil (3), Canada (2), Chile (1), Denmark (2), Finland (1), Netherlands (1), New Zealand (2), Puerto Rico (1), South Africa (1), Sweden (6), UK (4), and USA (13) | 15813 | 5 to 14 years | Not reported | Topical fluoride in the form of a mouthrinse (sodium fluoride; acidulated phosphate fluoride; stannous fluoride; sodium monofluorophosphate; amine fluoride; ammonium fluoride) in concentrations from 100ppm to 3000ppm fluoride | Placebo; no treatment | Caries preventive benefit (DMFS/DMFT; defs/deft; proportion of children developing new caries); adverse event (tooth staining); adverse event (signs of acute toxicity); adverse event (mucosal irritation/oral allergic reaction) | 24 to 36 months | Cluster RCT (1); RCT/quasi-RCT (36) | 1965 to 2005 | Yes, eleven trials |
| Pagano *et al.* (2020) | Verify whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures. | Primary and permanent dentition; non-invasive | Australia (1), Belgium (1), Brazil (3), India (1), Turkey (2), and USA (1) | 269 (participants) and 1628 (teeth) | 6 to 38 years | 35-94% females (4); not reported (5) | Laser application (carbon dioxide; nodymium-doped yttrium alinium garnet; argon; erbium-doped yttrium aluminium garnet; erbium chromium yttrium scandium gallium garnet) alone or with any traditional prophylactic intervention (acidulated phosphate fluoride gel/foam; enamel pit and fissure resin sealant; fluoride varnish) | No treatment; placebo; placebo with traditional prophylactic intervention; traditional prophylactic intervention alone | Caries incidence (number of cases with new caries); sealant retention; adverse events | 12 to 48 months | RCT (7); controlled clinical trials (2) | 1996 to 2005 | Not reported |
| Riggs *et al.* (2019) | Assess the effects of interventions targeted at pregnant women, | Primary and permanent | Total: Australia (1), Brazil (3), Belarus (1), Canada (2), Finland (2), | Total: 23732; | 17 to 44 years (mothers) | Not reported | Antimicrobial treatments (chlorhexidine | Placebo; no treatment | Caries incidence (deft/defs; dmft/dmfs; DMFT/DMFS); | 12 to 36 months | Total: RCT (12), cluster RCT (5); | Total: 1993 to 2017; | Yes, two trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | dentition; non-invasive | Sweden (1), Uganda (2), UK (1), USA (3), not reported (1); Included: Brazil (1), Finland (1), Sweden (1), USA (2), not reported (1) | Included: 907 | /0 to 13 months (children) | | and iodine-sodium-fluoride solution and prophylaxis); xylitol | | microbiological presence (mothers and children); plaque; adverse events | | Included: RCT (6) | Included: 1993 to 2013 | |
| Akera *et al.* (2022) | Evaluate the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | Primary and permanent dentition; non-invasive | Total: Bulgaria (1), Brazil (5), Cambodia (1), China (3), India (5), Indonesia (1), Iran (3), Malaysia (1), Myanmar (1), Nigeria (1), Pakistan (1), Philippines (1), South Africa (1), Taiwan (1), Tanzania (3), Thailand (2), Turkey (1), and Zimbabwe (1); Included: Cambodia (1), South Africa (1), and Turkey (1) | Not reported | Total: 3 to 16 years; Included: 6 to 15 years | Not reported | School health policy; provision of oral health education; promoting a healthy school environment; providing access to oral health services; involving community members; daily toothbrushing; fissure sealants; zinc supplementation | No intervention | incidence of dental caries (DMFT); plaque | 24 to 84 months | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Total: 1996 to 2021; Included: 2004 to 2017 | Not reported |
| Topical fluoride + oral health instruction/education (n = 5) | | | | | | | | | | | | | |
| Hendre *et al.* (2017) | Provide a systematic review of the evidence regarding the effectiveness of silver diamine fluoride in arresting or preventing root caries in older adults. | Permanent dentition; non-invasive | Hong Kong (3) | Total: 541; Included: 474 | Total: 60 to 89 years; Included: 72.2 to 78.8 years | Not reported | 38% Silver diamine fluoride | 5% sodium fluoride varnish; 1% chlorhexidine varnish; placebo | Prevented fraction; mean increments of new root caries surfaces | 24 to 36 months | RCT (3) | Total: 2010 to 2016; Included: 2010 to 2013 | Not reported |
| Oliveira *et al.* (2018) | Perform a qualitative and quantitative synthesis of the scientific evidence on the effect of SDF for preventing and arresting dental caries on exposed root surfaces of adults. | Permanent dentition; non-invasive | Hong Kong (3) | 895 | 72.1 to 78.8 years (mean) | Not reported | 38% topical silver diamine fluoride applied by a healthcare worker | Placebo | Difference in mean caries increment; adverse events | 12 to 36 months | RCT (3) | 2010 to 2017 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subbiah *et al.* (2018) | Evaluate the scientific evidence regarding the effectiveness of silver diamine fluoride in preventing and arresting caries in elderly adults. | Permanent dentition; non-invasive | Total: Hong Kong (3); Included: Hong Kong (2) | Total: 655; Included: 572 | Not reported | Not reported | 38% Silver diamine fluoride | Placebo; no treatment | Caries preventive effect (mean number of new root caries surfaces or root caries prevented fraction); adverse effects | 24 to 36 months | Total: RCT (3); Included: RCT (2) | Total: 2010 to 2016; Included: 2010 to 2013 | Not reported |
| Zhang *et al.* (2020) | Summarise and synthesise the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | Permanent dentition; non-invasive | Canada (1), Hong Kong (3), Netherlands (1), Sweden (1), UK (1), and USA (2) | 4030 | 49 to 83 years (mean) | Not reported | Professionally or self-applied topical fluorides (sodium fluoride varnish, silver diamine fluoride solution, acidulated phosphate fluoride gel, fluoride toothpastes, mouth rinse) | Each other; placebo; no intervention | Root caries increment | 24 to 36 months | Clinical controlled trial (9) | 1987 to 2017 | Not reported |
| Chan *et al.* (2022) | Systematically review the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | Permanent dentition; non-invasive | Hong Kong (4), UK (2), and USA (1) | 1027 | 60 to 84 years (mean) | Not reported | Fluoride therapy (5% sodium fluoride varnish; 38% silver diamine fluoride solution; 1.23 APF gel) | Fluoride agent; placebo; no intervention | Root caries preventive effect (mean difference in the number of new carious lesions and root caries prevented fraction) | 12 to 48 months | Clinical trials (7) | 1993 to 2021 | Not reported |
| Topical other chemicals + other (n = 5) | | | | | | | | | | | | | |
| Hendre *et al.* (2017) | Provide a systematic review of the evidence regarding the effectiveness of silver diamine fluoride in arresting or preventing root caries in older adults. | Permanent dentition; non-invasive | Hong Kong (3) | Total: 541; Included: 474 | Total: 60 to 89 years; Included: 72.2 to 78.8 years | Not reported | 38% Silver diamine fluoride | 5% sodium fluoride varnish; 1% chlorhexidine varnish; placebo | Prevented fraction; mean increments of new root caries surfaces | 24 to 36 months | RCT (3) | Total: 2010 to 2016; Included: 2010 to 2013 | Not reported |
| Slot *et al.* (2011) | Systematically evaluate the current literature to determine the effect of the use of chlorhexidine varnish on root caries incidence and activity. | Permanent dentition; non-invasive | Not reported | 451 | 44.44 to 78.8 years (mean) | 63-65% female (2); not reported (4) | Chlorhexidine varnish (1%; 10%; 40%) | Placebo; control treatment; fluoride varnish | Root caries incidence (DMF-RS) | 12 to 36 months | RCT (6) | 1991 to 2010 | Yes, two trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |
| Tubert-Jeannin *et al.* (2011) | Evaluate the effects of fluoride supplements in the form of tablets (chewable or not), drops, lozenges, and chewing gums for preventing dental caries in children. | Primary and permanent dentition; non-invasive | Denmark (1), Sweden (4), Taiwan (1), UK (1), and USA (4) | 7196 | 2 to 12 years | Both males and females (3), not reported (8) | Fluoride supplements (tablets, drops, lozenges, or chewing gum); with or without vitamins; with or without topical | No fluoride supplements; no treatment; placebo | caries experience measured by dmft/dmfs (within and between groups); caries experience measured by DMFT/DMFT (within and between groups); new | 24 to 72 months | RCT (11) | 1968 to 2008 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | fluorides (rinse, application, varnish, toothpaste); with or without non-fluoride-based measures (chlorhexidine, xylitol, sealants, oral hygiene interventions) | | carious tooth surfaces; plaque; adverse events | | | | |
| Riggs *et al.* (2019) | Assess the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (3), Belarus (1), Canada (2), Finland (2), Sweden (1), Uganda (2), UK (1), USA (3), not reported (1); Included: Brazil (1), Finland (1), Sweden (1), USA (2), not reported (1) | Total: 23732; Included: 907 | 17 to 44 years (mothers) /0 to 13 months (children) | Not reported | Antimicrobial treatments (chlorhexidine and iodine-sodium-fluoride solution and prophylaxis); xylitol | Placebo; no treatment | Caries incidence (deft/defs; dmft/dmfs; DMFT/DMFS); microbiological presence (mothers and children); plaque; adverse events | 12 to 36 months | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Total: 1993 to 2017; Included: 1993 to 2013 | Yes, two trials |
| Sealants + other (n = 4) | | | | | | | | | | | | | |
| Kashbour *et al.* (2020) | Evaluate the relative effectiveness of dental sealants (fissure sealant) compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | Permanent dentition; non-invasive | Total: Brazil (2), China (3), Germany (1), Iran (1), Latvia (1), Norway (1), Spain (1), and UK (1) Included: Brazil (2), China (3), Germany (1), Latvia (1), Norway (1), Spain (1), and UK (1) | Total: 3374; Included: 2010 | 5 to 10 years | Both males and females | Pit and fissure sealants of all materials (except first generation resin-based sealants) | Fluoride varnish | Occurrence of a new dental carious lesion on treated occlusal surfaces of molars or premolars; Caries increment (changes in decayed, missing, and filled figures at surface, tooth, and whole-mouth levels); time taken to apply pit and fissure sealant or fluoride varnish over a 2-year study period; number of visits to the dentist for repair of sealant or fluoride varnish application; safety of using sealants and fluoride varnishes assessed by presence or | 12-36 months | Total: RCT (11) ; Included: RCT (10) | 2001 to 2017 | Yes, six trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | absence of adverse events | | | | |
| Ahovuo-Saloranta *et al.* (2017) | Compare the effects of different types of fissure sealants in preventing caries un occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. | Permanent dentition; non-invasive | Australia (1), Brazil (5), Canada (1), China (6), Colombia (1), Egypt (1), Finland (2), France (1), India (2), New Zealand (1), Norway (1), Spain (1), Sweden (1), Syrian Arab Republic (1), Thailand (1), Turkey (3), UK (4), and USA (5) | 7924 | 5 to 16 years | Not reported | Resin-based sealant; glass-ionomer-based sealant | No sealant; each other | Caries preventive benefit (incidence of carious lesions); caries increment (DMFS); adverse events; sealant retention | 12 to 84 months | RCT (38) | 1976 to 2014 | Yes, seven trials |
| Pagano *et al.* (2020) | Verify whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures. | Primary and permanent dentition; non-invasive | Australia (1), Belgium (1), Brazil (3), India (1), Turkey (2), and USA (1) | 269 (participants) and 1628 (teeth) | 6 to 38 years | 35-94% females (4); not reported (5) | Laser application (carbon dioxide; nodymium-doped yttrium alinium garnet; argon; erbium-doped yttrium aluminium garnet; erbium chromium yttrium scandium gallium garnet) alone or with any traditional prophylactic intervention (acidulated phosphate fluoride gel/foam; enamel pit and fissure resin sealant; fluoride varnish) | No treatment; placebo; placebo with traditional prophylactic intervention; traditional prophylactic intervention alone | Caries incidence (number of cases with new caries); sealant retention; adverse events | 12 to 48 months | RCT (7); controlled clinical trials (2) | 1996 to 2005 | Not reported |
| Zhang *et al.* (2019) | Assess the clinical effects of laser preparation compared to other types of chemical or mechanical preparation of the tooth surfaces used in fissure sealant placement. | Permanent dentition; non-invasive | Australia (1), Bulgaria (1), India (1), Turkey (2) | 201 | 6 to 38 years | Not reported | Lasers as a pre-treatment for pit-and-fissure sealing (Er, Cr: YSGG; carbon dioxide; Er: YAG with acid etching) | Acid etching | Retention rate; incidence of caries; adverse events; dental anxiety | 18 to 24 months | RCT (5) | 1996 to 2018 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Complex combined interventions (n = 3) | | | | | | | | | | | | | |
| Kashbour *et al.* (2020) | Evaluate the relative effectiveness of dental sealants (fissure sealant) compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | Permanent dentition; non-invasive | Total: Brazil (2), China (3), Germany (1), Iran (1), Latvia (1), Norway (1), Spain (1), and UK (1) Included: Brazil (2), China (3), Germany (1), Latvia (1), Norway (1), Spain (1), and UK (1) | Total: 3374; Included: 2010 | 5 to 10 years | Both males and females | Pit and fissure sealants of all materials (except first generation resin-based sealants) | Fluoride varnish | Occurrence of a new dental carious lesion on treated occlusal surfaces of molars or premolars; Caries increment (changes in decayed, missing, and filled figures at surface, tooth, and whole-mouth levels); time taken to apply pit and fissure sealant or fluoride varnish over a 2-year study period; number of visits to the dentist for repair of sealant or fluoride varnish application; safety of using sealants and fluoride varnishes assessed by presence or absence of adverse events | 12-36 months | Total: RCT (11) ; Included: RCT (10) | 2001 to 2017 | Yes, six trials |
| Antonio *et al.* (2011) | Assess the overall caries preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. | Permanent dentition; non-invasive | Estonia (1), Kuwait (1), Sweden (1) | 947 | 10 to 27 years | Not reported | Xylitol products (candies or lozenges) | No intervention; placebo; preventive procedures | Caries increment (DMFS/DMFT) | 18 to 36 months | Clinical controlled trial (1), RCT (2) | 2000 to 2008 | Not reported |
| Dos Santos *et al.* (2018) | Assess the effects of supervised toothbrushing on caries incidence in children and adolescents. | Primary and permanent dentition; non-invasive | Brazil (1), Germany (1), Jordan (1), and USA (1) | Not reported | 2 to 14 years | Not reported | Supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | No supervised toothbrushing (with no fluoride; 500ppm fluoride; 1000ppm fluoride) | Caries incidence (proportion of caries-free children); caries increment (dmft/dmfs or DMFT/DMFS); cumulative survival rates | 21 to 36 months | RCT/quasi-RCT (4) | 1978 to 2016 | Yes, one trial |
| Mixed dentition | | | | | | | | | | | | | |
| Attendance for dental assessment (n = 0) | | | | | | | | | | | | | |
| Scheduled dental appointments (n = 0) | | | | | | | | | | | | | |
| Scheduled primary care appointments (n = 0) | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dental hygiene (n = 0) | | | | | | | | | | | | | |
| Supervised toothbrushing (n = 0) | | | | | | | | | | | | | |
| Flossing (n = 0) | | | | | | | | | | | | | |
| Interdental cleaning devices (n = 0) | | | | | | | | | | | | | |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | | | |
| Systemic fluoride (n = 0) | | | | | | | | | | | | | |
| Milk (n = 0) | | | | | | | | | | | | | |
| Salt (n = 0) | | | | | | | | | | | | | |
| Sugar (n = 0) | | | | | | | | | | | | | |
| Supplements (n = 0) | | | | | | | | | | | | | |
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | |
| Vitamin D (n = 1) | | | | | | | | | | | | | |
| Hujoel (2013) | Provide a systematic review of the available controlled clinical trial data on supplementation with vitamin D for dental caries prevention when compared to no such supplementation, in any population. | Primary and permanent dentition; non-invasive | Austria (1), Canada (4), New Zealand (1), Sweden (1), UK (6), and USA (11) | 2827 | 2 to 16 years | Both males and females (15); only males or females (4); not reported (5) | Vitamin D3 (800IU; 3750IU; erythemal doses; full-spectrum fluorescent lighting) | Placebo | Caries preventive effect (multiple measures of caries incidence including: DMFS/DMFT) | 12 months (median) | Cluster RCT (11), RCT (13) | 1924 to 1989 | Yes, thirteen trials |
| Calcium (n = 0) | | | | | | | | | | | | | |
| Sialagogues (n = 0) | | | | | | | | | | | | | |
| Zinc (n = 0) | | | | | | | | | | | | | |
| Topical fluoride (n = 1) | | | | | | | | | | | | | |
| Toothpaste (n = 1) | | | | | | | | | | | | | |
| Figuero *et al.* (2017) | Evaluate the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systematically healthy patients. | Primary and permanent dentition; non-invasive | Total: Brazil (2), Denmark (2), Germany (2), Greece (1), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2); Included: Brazil (1), Denmark (1), | Total: 4880; Included: 4418 | 3 to 61 years | Both males and females (11); only females (1); not reported (15) | Professional tooth-cleaning; motivational programmes and oral health instructions; self-performed tooth-cleaning; | Any mechanical or chemical plaque control regime; placebo; no treatment | Plaque levels; caries increment | 3 to 240 months | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: | Total: 1973 to 2015; Included: 1973 to 2013 | Yes, four trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Germany (2), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2) | | | | chlorhexidine products) | | | | RCT (15), clinical controlled trials (9) | | |
| Mouthrinses (n = 1) | | | | | | | | | | | | | |
| Figuero *et al.* (2017) | Evaluate the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systematically healthy patients. | Primary and permanent dentition; non-invasive | Total: Brazil (2), Denmark (2), Germany (2), Greece (1), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2); Included: Brazil (1), Denmark (1), Germany (2), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2) | Total: 4880; Included: 4418 | 3 to 61 years | Both males and females (11); only females (1); not reported (15) | Professional tooth-cleaning; motivational programmes and oral health instructions; self-performed tooth-cleaning; chlorhexidine products) | Any mechanical or chemical plaque control regime; placebo; no treatment | Plaque levels; caries increment | 3 to 240 months | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: RCT (15), clinical controlled trials (9) | Total: 1973 to 2015; Included: 1973 to 2013 | Yes, four trials |
| Foams (n = 0) | | | | | | | | | | | | | |
| Gels (n = 0) | | | | | | | | | | | | | |
| Solution (n = 0) | | | | | | | | | | | | | |
| Slow-release fluoride devices (n = 0) | | | | | | | | | | | | | |
| Varnishes (n = 0) | | | | | | | | | | | | | |
| Mixed (n = 0) | | | | | | | | | | | | | |
| Topical other chemicals (n = 6) | | | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 0) | | | | | | | | | | | | | |
| Arginine and its derivatives (n = 0) | | | | | | | | | | | | | |
| CHX (n = 2) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong | Not reported | Total: 9 months to 101 years; Included: | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription | No intervention; fluoride toothpaste/varnish/gel; conventional | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | the market in the United States. | | (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | 1 to 87 years | | (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | care; each other; placebo | | | trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | |
| Figuero *et al.* (2017) | Evaluate the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systematically healthy patients. | Primary and permanent dentition; non-invasive | Total: Brazil (2), Denmark (2), Germany (2), Greece (1), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2); Included: Brazil (1), Denmark (1), Germany (2), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2) | Total: 4880; Included: 4418 | 3 to 61 years | Both males and females (11); only females (1); not reported (15) | Professional tooth-cleaning; motivational programmes and oral health instructions; self-performed tooth-cleaning; chlorhexidine products) | Any mechanical or chemical plaque control regime; placebo; no treatment | Plaque levels; caries increment | 3 to 240 months | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: RCT (15), clinical controlled trials (9) | Total: 1973 to 2015; Included: 1973 to 2013 | Yes, four trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Calcium phosphate agents (n = 0) | | | | | | | | | | | | | |
| Ozone (n = 0) | | | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | | | |
| Probiotics (n = 1) | | | | | | | | | | | | | |
| Poorni *et al.* (2019) | Review the published literature with the purpose of knowing the importance of using various probiotic Streptococcus strains as a preventive and therapeutic method for dental caries management. | Unspecified dentition; non-invasive | Not reported | 159 | Not reported | Not reported | Probiotic Streptococcus strains (lozenges or oral tablets) | Placebo; no treatment | Development of new dental caries; S. Mutans counts | 3 months | Total: non-randomised clinical trials (2), in-vitro trials (3); Included: non-randomised controlled trials (2) | Total: 2013 to 2017 Included: 2013 to 2015 | Not reported |
| Propolis (n = 0) | | | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | | | |
| Marghalani *et al.* (2017) | Evaluate the effectiveness of xylitol in reducing dental caries in children compared to no treatment, a placebo, or preventive strategies. | Primary and permanent dentition; non-invasive | Belize (2), Costa Rica (2), Estonia (1), Finland (2), Lithuania (1), Sweden (1), and USA (1) | 5965 | 6 months to 14 years | Not reported | Xylitol products (gum, dentifrice, lozenges, wipes) | No treatment; placebo; routine preventive care | Caries increment (dmfs/dmft; DMFS/DMFT) | 12 to 36 months | Cluster RCT (3); RCT (2); non-RCT (5) | 1995 to 2012 | Not reported |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | trials (7), clinical controlled trials (8) | | |
| Newton *et al.* (2020) | Determine the difference in level of dental caries in adults and children who chew sugar-free gum, compared with those who do not chew sugar-free gum or use alternatives such as lozenges, candies, rinses, tablets, and other non-chewing controls. | Primary and permanent dentition; non-invasive | Not reported | 6132 | 3 to 60+ years | Not reported | Sugar-free chewing gum (xylitol; sorbitol; or both) | No gum; fluoride varnish; toothbrushing ; normal gum | Caries preventive benefit (dmfs/dmft; DMFS/DMFT); adverse events | 6 to 72 months | RCT (11), pre-post (1) | 1983 to 2013 | Not reported |
| Riley *et al.* (2015) | Assess the effects of different xylitol-containing products on preventing dental caries in children and adults. | Primary and permanent dentition; non-invasive | Costa Rica (2), Estonia (1), Finland (2), Republic of the Marshall Islands (1), Sweden (2), and USA (2) | 7969 | 0 to 18+ years | 66% female (1); both males and females (9) | Xylitol-containing products (lozenges, candy, syrup, tablets, toothpaste, wipes) | Placebo; no treatment | Caries preventive benefit (ds/dmfs or DMFS/DFS); adverse events | 12 to 48 months | Cluster RCT (2); RCT (8) | 1991 to 2014 | Yes, four trials |
| Sorbitol (n = 0) | | | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 0) | | | | | | | | | | | | | |
| Sealants (n = 1) | | | | | | | | | | | | | |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Resin (n = 0) | | | | | | | | | | | | | |
| Glass-ionomer (n = 0) | | | | | | | | | | | | | |
| Ormocer (n = 0) | | | | | | | | | | | | | |
| Hybrid (n = 0) | | | | | | | | | | | | | |
| Combined (n = 0) | | | | | | | | | | | | | |
| Other (n = 1) | | | | | | | | | | | | | |
| Singal *et al.* (2022) | Extensively review, summarise, and to draw best possible evidence for the remineralising and caries preventive efficacy of various calcium phosphate derivatives. | Primary and permanent dentition; non-invasive | Total: Australia (1), Brazil (1), China (1), Denmark (1), Egypt (2), Finland (1), Greece (1), India (6), Iran (2), Jordan (2), Saudi Arabia (1), Spain (1), Sweden (1), Thailand (2), and Turkey (3); Included: Egypt (1), Finland (1), India (4), Jordan (1), Saudi Arabia (1), Thailand (1), and Turkey (2) | Total: 3678; Included: 852 | Total: 0 to 18 months; Included: 2 days to 12 months | Not reported | Topical formulation of calcium phosphate agents (alone or combined with sodium fluoride/stannous fluoride) | No intervention; placebo; topical application of fluoride (containing sodium fluoride or stannous fluoride) | Caries preventive benefit (dmfs/dmft or DMFS/DMFT); S. mutans count | 12 to 24 months | Total: RCT (26); Included: RCT (11) | Total: 2007 to 2021; Included: 2012 to 2020 | Not reported |
| Laser (n = 0) | | | | | | | | | | | | | |
| Subgroup: Mother of unborn/toddlers (treatment given to mothers, outcomes tested on mixed dentition of offspring) | | | | | | | | | | | | | |
| Other systemic chemicals (n = 1) | | | | | | | | | | | | | |
| Calcium (n = 1) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | | | | chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | | | | trials (7), clinical controlled trials (8) | | |
| Subgroup: Combined interventions in mixed dentition | | | | | | | | | | | | | |
| Topical fluoride + topical other chemicals (n = 2) | | | | | | | | | | | | | |
| Gupta *et al.* (2020b) | Compare the effectiveness of combined therapy using topical fluoride along with an antibacterial agent (Povidone Iodine/Chlorhexidine/Xylitol/Triclosan/Cetylpyridinium Chloride) versus topical fluoride monotherapy in preventing dental caries among 1- to 16-year-old children. | Primary and permanent dentition; non-invasive | Not reported | Total: 6003; Included: 5793 | 2 to 16 years | Not reported | Topical fluoride combined with an antibacterial agent (povidone iodine, chlorhexidine, xylitol, triclosan, or cetylpyridinium chloride) | Topical fluoride alone | Caries increment (method of measurement not specified); mean salivary S. mutans counts | 12 to 36 months | Total: Cluster RCT (2), RCT (14); Included: Cluster RCT (2), RCT (12) | 1995 to 2016 | Not reported |
| Sharda *et al.* (2021) | Compare the remineralising potential and caries preventive efficacy of combined therapy using CPP-ACP/bioactive | Primary and permanent dentition; non-invasive | Total: Australia (4), Brazil (2), Costa Rica (2), Denmark (1), Germany (2), Jordan (2), Italy (1), Romania (1), Sweden (1), Switzerland (1), | Total: 7955; Included: 7182 | Total: 0 to 70 years; Included: 0 to 23 years | Not reported | Topical fluoride combined with CPP-ACP, xylitol, bioactive glass or ozone | Topical fluoride alone | Caries preventive benefit (dmfs/dmft; DMFT/DMFS; proportion of participants with new carious lesions); S mutans counts | 24 to 36 months | Total: RCT (26); Included: RCT (14) | 1995 to 2020 | Not reported |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | glass/xylitol/ozone and topical fluoride versus topical fluoride monotherapy on high-risk individuals. | | Thailand (3), Turkey (5), and USA (1); Included: Australia (3), Costa Rica (2), Jordan (1), Italy (1), Sweden (1), Thailand (1), Turkey (4), and USA (1) | | | | | | | | | | |
| Topical other chemicals + topical other chemicals (n = 1) | | | | | | | | | | | | | |
| Rethman *et al.* (2011) | Present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | Primary and permanent dentition; non-invasive | Total: Argentina (1), Australia (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (6), Germany (3), Hong Kong (1), Hungary (1), India (2), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (2), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (13), UK (2), USA (5), Venezuela (2), and both USA and Canada (1); Included: Argentina (1), Belize (2), Brazil (1), Canada (2), China (3), Costa Rica (2), Estonia (2), Finland (5), Germany (2), Hong Kong (1), Hungary (1), India (1), Italy (1), Lithuania (1), Kuwait (1), Madagascar (1), Marshall Islands (1), Netherlands (3), New Zealand (1), Puerto Rica (1), Scotland (1), Serbia (1), Spain (2), Suriname (1), Sweden (9), UK (1), USA (5), Venezuela (2), and both USA and Canada (1) | Not reported | Total: 9 months to 101 years; Included: 1 to 87 years | Not reported | Non-fluoride caries preventive agents requiring professional application or prescription (Sucrose-free polyol chewing gums; xylitol candy; xylitol dentifrice; triclosan; iodine; chlorhexidine varnish; chlorhexidine/thymol varnish; chlorhexidine mouth rinses; chlorhexidine gels; calcium and/or phosphate agents with and without casein derivatives; sialagogues; use of non-fluoride agents in mother to prevent caries in children) | No intervention; fluoride toothpaste/varnish/gel; conventional care; each other; placebo | caries increment (measured by dmfs/dmft, DMFS/DMFT, and defs/deft) | 10 to 84 months | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | 1972 to 2010 | Yes, five trials |

| Author (year) | Research question | Study population(s) (dentition and tooth type) | Countries | Sample size | Ages | Gender | Study interventions | Study comparator(s) | Study outcome(s) | Time frame for follow-up (actual) | Primary study design included | Primary study years | Industry funding for primary studies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Topical other chemicals + other (n = 1) | | | | | | | | | | | | | |
| Zhou *et al.* (2019) | Investigate the efficacy of strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. | Primary and permanent dentition; non-invasive | Not reported | Total: 935; Included: 531 | Under 18 | Not reported | Mechanical (toothbrushing) and chemical (chlorhexidine, plaque-disclosing agent, triclosan-zinc, fluoride) oral health promotion strategies | Placebo; no treatment | caries prevention (dmfs/DMFS; dmft/DMFT) | Total: 10 days to 36 months; Included: 1 to 36 months | Total: RCT (7); non-RCT (7); Included: RCT (2); non-RCT (1) | Total: 1975 to 2015; Included: 1979 to 2013 | Not reported |
| Complex combined interventions (n = 2) | | | | | | | | | | | | | |
| Yu *et al.* (2021) | Assess whether the combined use of professional fluoride application and regular fluoride toothpaste has additional benefit than using regular fluoride toothpaste alone for children under 16. | Primary and mixed dentition; non-invasive | Brazil (1), Greece (1), Sweden (1), UK (2), and USA (1) | 5034 | 1 to 8 years | Not reported | Combined use of professional fluoride application and regular fluoride toothpaste (>1000pm) | Self-applied regular fluoride toothpaste alone | Caries increment (D(M/E)FS/D(M/E)FT or d(m/e)fs/d(m/e)ft; patient-reported outcomes; adverse events | 24 to 36 months | Cluster RCT (3); RCT (3) | 2007 to 2017 | Not reported |
| Figuero *et al.* (2017) | Evaluate the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systematically healthy patients. | Primary and permanent dentition; non-invasive | Total: Brazil (2), Denmark (2), Germany (2), Greece (1), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2); Included: Brazil (1), Denmark (1), Germany (2), Norway (2), Russia (1), Sweden (9), Switzerland (1), Tanzania (2), UK (3), and USA (2) | Total: 4880; Included: 4418 | 3 to 61 years | Both males and females (11); only females (1); not reported (15) | Professional tooth-cleaning; motivational programmes and oral health instructions; self-performed tooth-cleaning; chlorhexidine products) | Any mechanical or chemical plaque control regime; placebo; no treatment | Plaque levels; caries increment | 3 to 240 months | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: RCT (15), clinical controlled trials (9) | Total: 1973 to 2015; Included: 1973 to 2013 | Yes, four trials |

# Appendix J High-level summaries of included systematic reviews

*Table 102 High-level summaries of included systematic reviews*

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| Primary dentition | | | | |
| Attendance for dental assessment (n = 3) | | | | |
| Scheduled dental appointments (n = 2) | | | | |
| Fee *et al.* (2020) | Investigated the optimal recall interval of dental check-up (fixed-length, risk-based (decided by the clinician), or no recall/patient-driven attendance) for oral health in a primary care setting. | It was not clear if there was a meaningful difference in increment of decayed, missing, filled and sound tooth surfaces (dmfs) between a 24- and a 12-month recall period in primary teeth at 2 years follow-up (1 trial).<br><br>Neither of the included trials reported on differences between the remaining recall interval comparisons involving 24-month, 6-month and risk-based recall intervals in primary teeth.<br><br>The overall evidence on recall intervals between dental check-ups for children and adolescents was uncertain. There is a paucity of evidence pertaining to the effects of different recall intervals on the prevention of caries in primary dentition. | Moderate | High |
| Joury *et al.* (2017) | Assessed the effectiveness of school-based dental screening versus no screening on improving oral health in children. | Only one trial reported on the outcome of interest to this umbrella review. It was not clear whether the findings related to new caries or prevalence of existing caries, and as such the findings were not extracted. | Moderate | Critically low |
| Scheduled primary care appointments (n = 1) | | | | |
| Chou *et al.* (2021) | Investigated the effect of primary care oral screening and preventive interventions (fluoride supplements, topical fluoride | None of the included trials reported on the effect of oral screening performed by a primary care clinician or the effect of referral by a primary care clinician to a dental health care | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | application, silver diamine fluoride, or xylitol) on preventing and arresting dental caries in children younger than 5 years. | professional on the prevention of caries (measured by the increment of decayed, missing and filled surfaces/teeth (dmfs/t) and/or incidence of caries) in primary teeth. | | |
| Dental hygiene (n = 3) | | | | |
| Supervised toothbrushing (n = 3) | | | | |
| Hujoel *et al.* (2018) | Assessed the association between personal oral hygiene (including supervised toothbrushing) and dental caries in the absence of the confounding effects of fluoride. | None of the included trials reported on the effect of supervised toothbrushing on the incidence of caries in primary teeth. | Low | Critically low |
| Akera *et al*. (2022) | Evaluated the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | None of the included trials reported on the effect of supervised toothbrushing on the incidence of dental caries in primary teeth. | Very low | Critically low |
| Dos Santos *et al.* (2018) | Assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. | None of the included trials reported on the effect of supervised toothbrushing as a standalone intervention on the incidence of caries in primary teeth. | Very low | Low |
| Flossing (n = 0) | | | | |
| Interdental cleaning devices (n = 0) | | | | |
| Professional scaling or cleaning (n = 0) | | | | |
| Systemic fluoride (n = 5) | | | | |
| Milk (n = 2) | | | | |
| Yeung *et al.* (2015) | Assessed the effects of milk fluoridation on caries prevention at a community level. | There was very low-certainty evidence of significant lower caries increment in the primary teeth of children (measured by changes in decayed, missing and filled teeth (dmft)), in the fluoridated milk group in which children consumed 180-200ml milk per day (2.5mg fluoride per litre) using a 200g cup compared to the non-fluoridated milk group at 3 years | Very low | High |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | follow-up (1 trial).<br><br>*Note*. This was a single trial review. | | |
| Cagetti *et al.* (2012) | Examined the effectiveness of fluoridated food in caries prevention. | There was very low-certainty evidence of lower caries increment in the primary teeth (measured by decayed, missing and filled teeth (dmft) increment) of children who consumed 200ml of fluoridated milk per day (2.5mg fluoride per litre) compared to children in the control group at 21 months follow-up (1 trial), resulting in a prevented fraction of 69%.<br><br>There was also very low-certainty evidence of lower caries increment in the primary teeth (measured by decayed, missing and filled surfaces (dmfs) increment) of children who consumed 150ml of fluoridated milk per day (2.5mg fluoride per litre) compared to children in the control group at 21 months follow-up (1 trial), resulting in a prevented fraction of 75%. | Very low | Critically low |
| Salt (n = 1) | | | | |
| Cagetti *et al.* (2012) | Examined the effectiveness of fluoridated food in caries prevention. | None of the included trials reported on the effect of fluoridated salt on the caries increment (measured by changes in decayed, missing and filled surfaces/teeth (dmfs/t)) in primary teeth. | Very low | Critically low |
| Sugar (n = 1) | | | | |
| Cagetti *et al.* (2012) | Examined the effectiveness of fluoridated food in caries prevention. | None of the included trials reported on the effect of fluoridated sugar on the caries increment (measured by changes in decayed, missing and filled surfaces/teeth (dmfs/t)) in primary teeth. | Very low | Critically low |
| Supplements (n = 3) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| Tubert-Jeannin *et al.* (2011) | Evaluated the effects of fluoride supplements in the form of tablets (chewable or not), drops, lozenges and chewing gums for preventing dental caries in children. | There was low-certainty evidence of no significant effect of the administration of fluoride tablets (1mg NaF, 1 per day) compared with no tablets in final caries experience (indicated by the decayed, missing and filled teeth (dmft)) prevented fraction) at 24-36 months follow-up (1 trial).<br><br>However, there was very low-certainty evidence from another trial (which included 115 children with cleft lip and/or palate) of a beneficial effect of the administration of fluoride tablets (0.5mg NaF, 1 per day) or fluoride drops (0.25mg NaF, 2 per day) compared with no tablets or drops in final caries experience (indicated by both the decayed, missing and filled surfaces (dmfs) and the decayed, missing and filled teeth (dmft) prevented fraction) at 24 months follow-up (1 trial), resulting in a 73% and 65% reduction in dmfs and dmft, respectively, when compared with no fluoride supplementation. The certainty of evidence was downgraded to very low because this trial was not pooled and so this evidence was reported from a single trial with a sample size of 98 (for dmft) and 115 (for dmfs).<br><br>There was low-certainty evidence of no benefit from the use of fluoride supplements (tablets) when compared with the use of topical fluoride (mouthrinse, varnish, toothpaste) in final caries experience (indicated by the decayed, missing and filled surfaces (dmfs) prevented fraction) at 24-36 months follow-up (2 trials). One of the pooled trials administered 0.25mg NaF sucking tablets twice per day, and the other administered 1mg NaF chewing tablets once per | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | day.<br><br>Overall, there was weak evidence of the use of fluoride supplements in preventing dental caries in primary teeth. When fluoride supplements were compared with the use of topical fluorides or other preventive measures, there was no clear evidence of a differential effect on primary teeth. | | |
| Chou *et al.* (2021) | Investigated the effect of primary care oral screening and preventive interventions (fluoride supplements, topical fluoride application, silver diamine fluoride, or xylitol) on preventing and arresting dental caries in children younger than 5 years. | There was very low-certainty evidence of a reduction in caries incidence (measured by the number of decayed, missing and filled surfaces (dmfs) and whole teeth (dmft)) with the use of 0.25mg fluoride drops or chews, among Taiwanese children with cleft lips compared to no fluoride supplementation (1 trial; randomised). The mean percent reduction ranged from 52%-72% for dmft and 51%-81% for dmfs.<br><br>There was very low-certainty evidence of a reduction in caries incidence (measured by the number of decayed, missing and filled teeth (dmft)) with the use of dietary fluoride supplementation compared to no fluoride supplementation (4 non-randomised trials; narrative synthesis). The mean percent reduction ranged from 32%-69%.<br><br>*Note*. The precise nature of the interventions in the 4 trials reported on above were not described in the text. As such, the possibility of combined interventions is not known.<br><br>Specific follow-up periods for these outcomes were not | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | reported; however, the review authors noted that the follow-up periods of included trials ranged from 1-3 years. Overall the authors noted that dietary fluoride supplementation appeared to be effective at preventing caries in higher risk children younger than 5 years. | | |
| Zhou *et al.* (2019) | Investigated the efficacy of strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. | The results of this review were presented in a way that makes the determination of the effect of specific interventions not possible. Therefore, the findings were excluded from data synthesis. | Low | Critically low |
| Other systemic chemicals (n = 1) | | | | |
| Vitamin D (n = 0) | | | | |
| Calcium (n = 0) | | | | |
| Sialagogues (n = 1) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | None of the included trials reported on the effect of sialagogues on caries increment (measured by the number of new decayed, missing and filled surfaces/teeth (dmfs/t)) in primary teeth. | Very low | Critically low |
| Zinc (n = 0) | | | | |
| Topical fluoride (n = 9) | | | | |
| Toothpaste (n = 2) | | | | |
| Walsh *et al.* (2019) | Assessed and compared the effects of toothpastes of different fluoride concentrations (parts per million (ppm)) in preventing dental caries in children, adolescents, and adults. | There was low-certainty evidence of lower caries incidence (lower proportion of children developing new caries) in the higher fluoride (1450 ppm) toothpaste group compared to children in the lower fluoride (440 ppm) toothpaste group at 60 months follow-up (1 trial).<br><br>Overall, there was some evidence of a dose-response relationship in the caries-preventive effect of fluoride toothpaste. However, the review authors note that evidence | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | on the primary dentition of young children is particularly scarce. The review authors also reported on caries increment (d(e/m)fs or d(e/m)ft) as an outcome in trials of fluoride toothpaste interventions. However, these data related to cavitated carious lesions at the $d_3$ level only (i.e. caries involving dentine). As it was not possible to distinguish caries initiation from caries progression in Walsh *et al*.'s reported findings, these outcomes were not extracted for the purposes of this overview of reviews.<br><br>*Note*. Although the majority of trials (70% of all included trials) were judged to be free from the possibility of contamination or co-intervention (or both), trials where both the intervention and control group received any additional potentially active agent in the toothpaste were included, and 30% of all included trials did not provide sufficient information to assess the risk of bias in this domain. The review authors noted that contamination was possible in the trial. | | |
| Santos *et al.* (2013) | Evaluated the effects of low and standard fluoride toothpastes on the prevention of caries in the primary dentition of pre-schoolers and moderate to severe forms of fluorosis in the permanent dentition. | There was low-certainty evidence indicating the proportion of children developing caries in primary teeth was higher in the low fluoride (<600 ppm) toothpaste group compared to the standard fluoride (1000-1500 ppm) toothpaste group (3 trials). The follow-up period was not specified. However, the review authors only included trials with a follow-up period of at least 1 year and noted that the shortest trial period in the review was 2 years. Overall, the authors noted that no evidence was found to support the use of low fluoride toothpastes by pre-schoolers as they increased the risk of | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | caries in primary dentition.<br><br>*Note*. Due to inadequate descriptions of the nature of the interventions and outcome measures, these findings were not included in the evidence synthesis. The findings on caries increment in this review can be found in the extraction file in Appendix H. | | |
| Mouthrinses (n = 0) | | | | |
| Foams (n = 0) | | | | |
| Gels (n = 1) | | | | |
| Marinho *et al.* (2015) | Examined the effectiveness and safety of fluoride gels in preventing dental caries in the child and adolescent population. | There was low-certainty evidence of a benefit of fluoride gel on the reduction of caries increment (measured by change from baseline in decayed (extracted/missing) and filled surfaces (d(e/m)fs)) compared to a placebo/no treatment control group at approximately 3 years follow-up (3 trials), equating to a 20% reduction on average in d(e/m)fs. However, the review authors were less certain of this effect compared to that in the permanent dentition.<br><br>Two of these trials involved self-application and one involved professional application. Two of these trials involved self-application and one involved professional application. The concentration of fluoride was 5000 ppm (applied approximately 76 times per year) and 12,500 ppm (applied approximately 130 times per year) in the self-application trials, and 4500 ppm (applied twice per year) in the professional-application trial. In addition, two out of the three pooled trials reported exposure to additional forms of fluoride (water, tablets and/or toothpaste). However, this | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | was considered background fluoride exposure, rather than part of the intervention of interest.<br><br>There was very low-certainty evidence indicating the proportion of children not remaining caries free on primary tooth surfaces was lower in the fluoride gel group (APF 5000 ppm applied approximately 76 times per year) compared to the placebo group at 1.5 years follow-up (1 trial). This outcome was identified as a secondary outcome in the review. The certainty of evidence was downgraded to very low because the outcome was informed by a single trial with a sample size of 145. Participants in this trial had exposure to fluoridated water. However, this was considered background fluoride exposure, rather than part of the intervention of interest.<br><br>*Note*. Sixteen out of all 28 included trials, including one of the 3 trials above, reported the performance of some form of prior (professional or self-performed) tooth prophylaxis before administering the gel. The review authors considered prior tooth cleaning as a possible part of the technique of gel application and not as a separate intervention on its own. Post-hoc meta regression analyses showed no significant association between effect estimates and prior prophylaxis. | | |
| Solution (n = 2) | | | | |
| Oliveira *et al.* (2019) | Investigated primarily whether silver diamine fluoride is superior to placebo or no treatment in preventing caries in primary teeth. | There was very low-certainty evidence of a 10%, 38%, and 69% decrease in caries incidence in primary tooth surfaces in the test groups (12% SDF applications yearly, biannually and quarterly, respectively) in comparison to the control group | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | (no treatment) at 24 months follow-up (1 trial). However, only the differences between quarterly versus yearly 12% SDF applications and quarterly 12% SDF applications versus no treatment were statistically significant. The certainty of evidence was downgraded to very low because this outcome was informed by a single trial and no sample size was reported for that trial.<br><br>*Note*. The review authors noted that at baseline, participants were regularly exposed to some sort of topical fluoride product (i.e. fluoride toothpaste or 0.2% NaF mouth rinse). However, this was existing/background fluoride exposure, rather than part of the intervention of interest. | | |
| Chou *et al.* (2021) | Investigated the effect of primary care oral screening and preventive interventions (fluoride supplements, topical fluoride application, silver diamine fluoride, or xylitol) on preventing and arresting dental caries in children younger than 5 years. | None of the included trials reported on the effect of silver diamine fluoride on the prevention of caries (measured by the increment of decayed, missing and filled surfaces/teeth (dmfs/t) and/or incidence of caries) in primary teeth. | Very low | Critically low |
| Slow-release fluoride devices (n = 1) | | | | |
| Chong *et al.* (2018) | Evaluated the effectiveness and safety of different types of slow-release fluoride devices on preventing, arresting, or reversing the progression of carious lesions on all surface types of primary (deciduous) and permanent teeth. | None of the included trials reported on the effect of a slow-releasing fluoride device on the prevention of caries (measured by decayed, missing and filled surfaces/teeth (dmfs/t) increment) in the primary teeth of children from disadvantaged backgrounds.<br><br>*Note*. This was a single trial review. | Very Low | Moderate |
| Varnishes (n = 3) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| Marinho *et al.* (2013) | Evaluated the effectiveness and safety of fluoride varnishes in preventing dental caries in the child/adolescent population. | There was low-certainty evidence of a decrease in caries increment (measured by decayed, extracted/missing and filled primary tooth surfaces (d(e/m)fs; 10 trials) and whole teeth (d(e/m)ft; 2 trials)) in children with the use of fluoride varnish (applied at least once per year) compared to either no treatment or a placebo control group at nearest to 3 years follow-up. The pooled results showed a 37% reduction in d(e/m)fs and a 65% reduction in d(e/m)ft increment.<br><br>There was low-certainty evidence of a reduction, albeit no significant difference, in the proportion of children developing one or more new caries between the fluoride varnish group (applied at least once per year) and the no treatment/placebo group (5 trials). Follow-up periods for this outcome were not specified. This outcome appeared to be identified as a secondary outcome in the review.<br><br>Overall, review authors found no significant evidence for the effectiveness of fluoride varnish in preventing the development of one or more new caries in primary dentition. However, the application of fluoride varnishes two to four times a year in the primary dentition was associated with a reduction in caries increment.<br><br>*Note*. 7/22 trials reported some form of non-fluoride tooth prophylaxis prior to administering the varnish and 14/22 trials reported some other exposure to fluoride (water, rinses, tablets, toothpaste, or milk). However, this was noted existing/background fluoride exposure, rather than part of | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | the intervention of interest.<br><br>*Note*. 4/10 pooled trials on d(e/m)fs increment were combined interventions involving oral health education/counselling/instruction, 1/2 pooled trials on d(e/m)ft increment was a combined intervention involving oral health instruction, and 2/5 pooled trials on proportion developing new caries were combined interventions involving oral health counselling. | | |
| Carvalho *et al.* (2010) | Evaluated whether conclusive evidence exists that the professional application of fluoride varnish decreases dental caries incidence in preschool children. | There was low-certainty evidence from 5 trials of significantly lower caries incidence (measured by the presence of a cavitated lesion (mean increment of decayed, missing and filled surfaces (dmfs) and prevented fraction)) with the application of 5% NaF varnish (4 trials) or 1% Difluorsilano varnish (1 trial) compared to no treatment or oral health education at 2 years follow-up (one trial had a 9-month follow-up) (5 trials; narrative synthesis). Varnish was applied every 6 months in 4 trials and every 4 months in 1 trial. The dmfs prevented fraction ranged from 30%-63%.<br><br>Conversely, there was low-certainty evidence of no significant reduction in caries incidence (measured by the presence of a cavitated lesion (mean increment of decayed, missing and filled surfaces (dmfs) and prevented fraction)) with the use of 5% NaF varnish compared to no treatment at 2 years follow-up (1 trial).<br><br>Overall, review authors concluded that fluoride varnish can reduce the incidence of caries in the primary teeth of children | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | six years of age or younger. However, the results provided no conclusive scientific evidence.<br><br>*Note*. 6/8 included trials reported some exposure to fluoride (either water, toothpaste, or tablets). However, this was existing/background fluoride exposure, rather than part of the intervention of interest. One trial involved a combined intervention, and this is described below in the combined interventions in primary teeth subsection. | | |
| Smith *et al.* (2018) | Systematically reviewed the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | None of the included trials reported on the effect of sodium fluoride varnish on caries increment or number of new carious surfaces in primary teeth. | Moderate | Low |
| Mixed (n = 0) | | | | |
| Topical other chemicals (n = 11) | | | | |
| Antioxidants (n = 0) | | | | |
| Toothpaste (n = 0) | | | | |
| Antimicrobial agents (minus CHX) (n = 2) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | None of the included trials reported on the effect of triclosan on caries increment (measured by the number of new decayed, missing and filled surfaces/teeth (dmfs/t)) in primary teeth.<br><br>Four of the included trials reported on the effect of 10% povidone-iodine compared to fluoride foam or saline on coronal caries after one application. However, these trials appear to focus on caries arrest or reduction in caries progression. | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Wang *et al.* (2017) | Assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. | There was moderate-certainty evidence of a lower caries increment (measured by decayed, missing and filled surfaces (dmfs) and whole teeth (dmft)) when using 0.3% triclosan varnish applied twice per year compared to no treatment at 1 year follow-up (1 trial).<br><br>None of the included trials reported on the effect of triclosan on the proportion of participants developing new caries in primary teeth. | Moderate | Low |
| Arginine and its derivatives (n = 0) | | | | |
| CHX (n = 5) | | | | |
| Walsh *et al.* (2015) | Assessed the effects of chlorhexidine-containing oral products (toothpastes, mouthrinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. | There was low-certainty evidence of no significant difference in caries increment (measured by change from baseline in decayed, missing and filled surfaces/teeth (dmfs/t-molar)) between the CHX varnish group (1% applied every 3 months over 2 years in one trial, and 40% applied every 6 months over approx. 3 years, pooled) and the no treatment/placebo group at 24 months follow-up (2 trials). None of the included trials examined the difference in caries incidence (measured by the number of children developing new caries over the course of the trial) between a CHX varnish group and a no control group. neither of the pooled trials reported the provision of other preventive treatment (e.g. oral health instruction) before or during the study period.<br><br>None of the included trials examined the effect of CHX gel as a standalone intervention on caries increment or incidence in primary dentition. | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | Overall, review authors conclude that there is little-to-no evidence to support or refute the use of chlorhexidine varnish in preventing caries in primary dentition. | | |
| James *et al.* (2010) | Summarised the evidence of the effectiveness of chlorhexidine varnish at preventing caries in the permanent and primary teeth of children and adolescents compared to placebo or no treatment, using data from randomised controlled trials only. | There was very low-certainty evidence of a lower caries increment (measured by the decayed, missing and filled surfaces (dmfs-molar) index) with the use of 40% chlorhexidine varnish applied every 6 months compared to a placebo at 2 years follow-up (1 trial; children from low SES background), resulting in a 37.3% reduction in the caries increment in dentine for the CHX varnish group.<br><br>*Note*. All trials reported some exposure to fluoride (either water, toothpaste or mouthrinse). However, this was existing/background fluoride exposure, rather than part of the intervention of interest. | Very low | Critically low |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of a no significant difference in caries increment (measured by the number of new decayed and filled teeth (dft)) following the application of 1% chlorhexidine gel (professionally applied using trays 3 consecutive days every 3 months) compared to no gel at 18 months follow-up (1 trial). Participants in both groups also had exposure to fluoride toothpaste. However, this was noted to be existing/background fluoride exposure, rather than part of the intervention of interest.<br><br>None of the included trials reported on the effect of chlorhexidine varnish or mouthrinses on caries increment (measured by the number of new decayed, missing and filled surfaces/teeth (dmfs/t)) in primary teeth. | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Wang *et al.* (2017) | Assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. | There was moderate-certainty evidence of a significant reduction in caries increment (measured by decayed, extracted/missing and filled surfaces (d(e/m)fs) and whole teeth (d(e/m)ft)) with the use of chlorhexidine compared to placebo/no treatment in primary teeth at 2-3 years follow-up (4 trials; narrative synthesis). One trial used 1% CHX gel applied 4 times per year, 2 trials used 40% CHX varnish applied every 6 months, and 1 trial used 1% CHX-thymol varnish applied every 2 months. Two trials reported on defs scores, two trials reported on dmfs-molar scores specifically, one trial reported on dmfs scores, and one trial reported on dmft scores.<br><br>None of the included trials reported on the effect of chlorhexidine as a standalone intervention on the proportion of participants developing new caries in primary teeth.<br><br>Overall, review authors concluded that chlorhexidine may be more effective than placebo in preventing caries in primary dentition. | Moderate | Low |
| Smith *et al.* (2018) | Systematically reviewed the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | None of the included trials reported on the effect of 10% chlorhexidine varnish on caries increment or number of new carious surfaces in primary teeth. | Moderate | Low |
| Calcium phosphate agents (n = 3) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | None of the included trials reported on the effect of calcium phosphate agents on caries increment (measured by the number of new decayed, missing and filled surfaces/teeth (dmfs/t)) in primary teeth. | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Wang *et al.* (2017) | Assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. | There was very low-certainty evidence of a smaller increase in caries increment (measured by decayed, missing and filled teeth (dmft)) with the use of CPP-ACP mousse twice per day compared to no treatment or fluoride varnish at 12 months follow-up (1 trial). The certainty of evidence was downgraded by 2 to very low because this outcome was informed by a single trial with a total sample size of 122 participants, but the combined sample size of the three groups analysed in these comparisons was 91 (30 in the CPP-ACP group, 29 in the fluoride varnish group, and 32 in the no treatment group).<br><br>None of the included trials reported on the effect of CPP-ACP as a standalone intervention on the proportion of participants that developed new caries in primary teeth. | Moderate | Low |
| Singal *et al.* (2022) | Reviewed the evidence for the remineralising and caries preventive efficacy of various CaP (calcium phosphate) derivatives. | None of the included trials examined the preventive efficacy (measured by increment of decayed, missing and filled surfaces/teeth (dmfs/t)) of calcium phosphate agents as a standalone intervention in primary dentition. | Low | Critically low |
| Ozone (n = 0) | | | | |
| Nanomaterials (n = 0) | | | | |
| Probiotics (n = 3) | | | | |
| Hao *et al.* (2021) | Explored the effectiveness and safety of Bifidobacterium in preventing caries. | There was very low-certainty evidence of no significant difference in caries incidence (measured by the occurrence of deciduous tooth caries) with the use of 100g or 300g Bifidobacterium delivered using slow-release tablets/pacifiers compared to placebo tablets/pacifiers in primary teeth at 2 years and 4 years follow-up (2 trials; narrative synthesis). | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Jørgensen *et al.* (2016) | Reviewed the available literature on the prevention of caries in early childhood through biofilm engineering with probiotic bacteria. | There was very low-certainty evidence of a significant lower caries increment (measured by the decayed surfaces (ds) prevented fraction) with the use of streptococcus-based probiotic lozenges compared to placebo lozenges at 12 months follow-up (1 trial). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 138 (effective sample size of approx. 110 as the dropout was 20%). The presence of caries was 24% in the test group following intervention compared with 47% in the placebo group.<br><br>*Note*. The review authors noted that the results were obtained in spite of the fact that approximately 80% of the families reported supervised toothbrushing twice daily and a far from optimal compliance with the probiotic lozenges. | Low | Low |
| Twetman *et al.* (2021) | Explored the preventive effect of probiotic supplements on the development of early childhood caries. | There was low-certainty evidence of a significant decrease in caries increment (measured via several variations of the dmfs and dmft indices)) with the consumption of probiotic tablets/milk (Streptococcus/Lactobacillus/Bifidobacterium) compared to placebo tablets/milk at 6-24 months follow-up (7 trials). The seven trials varied in relation to the type of bacteria, the amount consumed, the frequency of consumption, and mode of delivery (tablets and milk). 6/7 trials used probiotic milk (2 used 50 powder milk once per day, 3 used 150ml powder or fresh milks on weekdays, and 1 used 200ml powder milk on weekdays), and 1/7 trials used probiotic tablets (1 per day).<br><br>*Note*. At least one of the pooled trials involved a combined | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | intervention in which in which the milk consumed by participants contained both probiotics and 2.5 mg/kg fluoride. | | |
| Propolis (n = 0) | | | | |
| Silicates (n = 0) | | | | |
| Xylitol (n = 4) | | | | |
| Riley *et al.* (2015) | Assessed the effects of different xylitol-containing products on preventing dental caries in children and adults. | There was very low-certainty evidence of a preventive benefit (measured by mean number of decayed primary teeth) of the consumption of xylitol (8g per day) syrup compared to control (low-dose xylitol; 2.67g per day) syrup in the primary dentition of infants at 1 year follow-up (1 trial), resulting in a 58% reduction in caries.<br><br>There was low-certainty evidence of no preventive benefit (measured by the increment of decayed, missing and filled surfaces (dmfs) and prevented fraction) of the consumption of xylitol (0.48-1g per day) sucking tablets compared to no treatment over 18 months at 2 years follow-up (1 trial), albeit the prevented fraction was marginally significant and equated to a 53% reduction in caries in favour of xylitol sucking tablets. The same trial also reported on the dichotomous presence or absence of a dmfs increment and similarly, found no significant difference in this outcome at 2 years follow-up.<br><br>There was very low-certainty evidence of no preventive benefit (measured dichotomously by the presence or absence of an increment in decayed, missing and filled surfaces (dmfs)) following the consumption of xylitol tablets | Moderate | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | (200-600mg per day administered via a slow-release pacifier or crushed up on a spoon) compared to control tablets, consumed over 24 months at 2 years follow-up (1 trial).<br><br>There was very low-certainty evidence of no preventive benefit (measured dichotomously by the presence or absence of an increment in decayed, missing and filled surfaces (dmfs)) of xylitol wipes (two wipes to clean the teeth and gums three times per day, 4.2g xylitol per day) compared to a control wipe at 1 year follow-up (1 trial).<br><br>The certainty of evidence was downgraded (by one for a sample size between 100 and 199, and by two for a sample size of 99 or less) because the trials could not be pooled and therefore results from different interventions including different outcome measures were presented individually as single trials, all with small sample sizes (94 participants, 118 participants, 62 participants, and 44 participants).<br><br>None of the included trials reported on the preventive effect (measured by the increment of decayed, missing and filled surfaces (dmfs) and/or the dichotomous presence or absence of a dmfs increment) of xylitol-containing lozenges, candy or (non-fluoride) toothpaste.<br><br>Overall, the evidence was insufficient to determine whether any xylitol-containing product can prevent caries in infants, older children, or adults. | | |

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| Chou *et al.* (2021) | Investigated the effect of primary care oral screening and preventive interventions (fluoride supplements, topical fluoride application, silver diamine fluoride, or xylitol) on preventing and arresting dental caries in children younger than 5 years. | There was very low-certainty evidence of a reduction in caries (measured by the increment of decayed, missing and filled surfaces (dmfs)) with the consumption of xylitol tablets (one 0.5 mg tablet at bedtime for 6 months, followed by two tablets daily) compared to no xylitol at 2 years follow-up (1 trial). However, the difference was not statistically significant.<br><br>There was very low-certainty evidence of a no significant difference in the risk of caries incidence (measured by both the increment decayed, missing and filled surfaces (dmfs) and caries incidence) with the use of xylitol wipes (two at a time, three times per day (estimated daily dosage 4.2 g) every 3 months for 1 year) compared to placebo wipes (1 trial). The precise follow-up period was not specified. | Very low | Critically low |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of a significant difference in favour of xylitol syrup (8g per day) compared to 2.67g of xylitol syrup per day on caries increment (measured by the number of new decayed, missing and filled surfaces (dmfs)) in the primary dentition of children in the Marshall Islands at 10 months follow-up (1 trial). Limited information was reported. The findings of the second trial that evaluated the effect of xylitol on caries increment in primary dentition were analysed in a meta-analysis along with trials evaluating permanent dentition. Therefore, the results were not extracted. | Very low | Critically low |
| Wang *et al.* (2017) | Assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. | One trial showed a reduction in caries incidence (measured by decayed, missing and filled surfaces (dmfs) and the number of children with new caries) with the consumption of | Moderate | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | 0.5-1.0 g xylitol tablets taken once per day for 6 months and twice per day for 1.5 years, compared to no treatment at 24-months follow-up (1 trial). However, the differences were not statistically significant. The certainty of evidence for the percentage of children with new caries outcome was downgraded by 1 to low because this outcome was informed by a single trial with a sample size of 118 participants.<br><br>One trial showed a reduction in caries incidence (measured by number of decayed, missing and filled surfaces (dmfs)) with the consumption of 7.8g xylitol gummy bears (3 per day) compared to placebo gummy bears at 30 months follow-up (1 trial). However, the difference was not statistically significant. This trial, together with the previous trial, provide moderate-certainty evidence of no significant reduction in caries incidence (measured by number of decayed, missing and filled surfaces (dmfs)) with the consumption of xylitol (tablets or gummies) compared to no treatment/placebo.<br><br>There was very low-certainty evidence of lower caries incidence (measured by the number of children developing new caries) with the use of xylitol wipes (6 wipes per day; 4.2g/d) compared to placebo wipes at 12 months follow-up (1 trial). The certainty of evidence was downgraded by 2 to very low because this outcome was informed by a single trial with a very small sample size (37 participants). | | |
| Sorbitol (n = 0) | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 1) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | None of the included trials reported on the effect of polyols on caries increment (measured by the number of new decayed, missing and filled surfaces/teeth (dmfs/t)) in primary teeth. | Very low | Critically low |
| Sealants (n = 3) | | | | |
| Resin (n = 2) | | | | |
| Ramamurthy *et al.* (2022) | Evaluated the effectiveness of sealants compared to no sealant or a different sealant in preventing pit and fissure caries on the occlusal surfaces of primary molars in children and to report the adverse effects and the retention of different types of sealants. | Two trials compared the effectiveness of fluoride-releasing resin-based sealant with resin-based sealant on incidence of new dental caries in second primary molars. However, the review authors were unable to include the data in pooled analyses due to inadequate information. The findings were therefore not reported.<br><br>There was very low-certainty evidence of no difference in incidence of dental caries (measured by the risk of developing ≥ 1 new carious lesions) following application of auto-polymerised resin-based sealant compared with light polymerised resin-based sealant at 24-36 months follow-up (1 trial). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 52 participants.<br><br>None of the included trials compared the effectiveness of fluoride-releasing resin-based sealant as a standalone intervention with no sealant on incidence of new dental caries or mean caries increment (measured by change in decayed, missing and filled surfaces/teeth (dmfs/t)).<br><br>None of the included trials compared the effectiveness of | Moderate | High |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | flowable resin composite with resin-based sealant on incidence of new dental caries or mean caries increment (measured by change in decayed, missing and filled surfaces/teeth (dmfs/t)).<br><br>None of the included trials compared the effectiveness of auto-polymerised resin-based sealant compared with polymerised resin-based sealant on mean caries increment (measured by change in decayed, missing and filled surfaces/teeth (dmfs/t)). | | |
| Lam *et al.* (2020) | Assessed the evidence on the effectiveness of different sealants in prevention and arrest of the pit and fissure occlusal caries in primary molars of children. | None of the included trials reported on the effectiveness of resin-based sealant versus no sealant on caries incidence (measured by the diagnosis of new carious lesions established from sound occlusal surfaces leading to localized enamel breakdown on the occlusal surface) in primary teeth.<br><br>There was very low-certainty evidence of a significantly lower caries incidence rate with the application of resin-based sealant compared to glass-ionomer (or resin-modified glass-ionomer) sealant at 6 months follow-up. However, the results were no longer statistically significant at 18 months follow-up (1 trial). The results from a second trial that evaluated this comparison were not extracted by the review authors due to the manner in which the results were presented in the trial.<br><br>None of the included trials reported on the effectiveness of amorphous calcium phosphate (ACP)-containing resin-based sealant (ACP-RBS) or fluoride-containing resin-based sealant | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | (F-RBS) versus no sealant in primary teeth.<br><br>There was very low-certainty evidence of no significant difference in caries incidence with the use of resin-based sealant compared to the use of F-RBS or the use of amorphous calcium phosphate-resin-based sealant (ACP-RBS) at 24 months follow-up (1 trial). There was also very low-certainty evidence of no significant difference in caries incidence with the use of auto polymerised resin-based sealant compared to the use of light-curing resin-based sealant at 24 months follow-up (1 trial).<br><br>The certainty of evidence was downgraded to very low because these comparisons were informed by single trials with very small sample sizes (89 participants, 75 participants, and 52 participants). | | |
| Glass-ionomer (n = 2) | | | | |
| Ramamurthy *et al.* (2022) | Evaluated the effects of sealants compared to no sealant or a different sealant in preventing pit and fissure caries on the occlusal surfaces of primary molars in children and to report the adverse effects and the retention of different types of sealants. | None of the included trials compared the effectiveness of glass-ionomer based sealant as a standalone intervention with no sealant on incidence of new dental caries or mean caries increment (measured by change in decayed, missing and filled surfaces/teeth (dmfs/t)).<br><br>One trial compared the effectiveness of glass-ionomer based sealant with resin-based sealant on incidence of new dental caries in second primary molars. However, the review authors were unable to determine the outcome due to inadequate availability of information. The findings were therefore not reported. | Moderate | High |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | None of the included trials compared the effectiveness of glass-ionomer based sealant with resin-based sealant on mean caries increment (measured by change in decayed, missing and filled surfaces/teeth (dmfs/t)). | | |
| Lam *et al.* (2020) | Assessed assess randomized controlled trials and summarize the evidence on the effectiveness of different sealants in prevention and arrest of the pit and fissure occlusal caries in primary molars of children. | There was low-certainty evidence of no significant difference in caries incidence (measured by the diagnosis of new carious lesions established from sound occlusal surfaces leading to localized enamel breakdown on the occlusal surface) with the use of glass-ionomer based sealant compared to no sealant at 12 months follow-up (1 trial). | Low | Critically low |
| Ormocer (n = 0) | | | | |
| Hybrid (n = 0) | | | | |
| Combined (n = 1) | | | | |
| Akera *et al*. (2022) | Evaluated the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | None of the included trials reported on the effect of fissure sealants on the incidence of dental caries in primary teeth. | Very low | Critically low |
| Other (n = 0) | | | | |
| Laser (n = 1) | | | | |
| Pagano *et al.* (2020) | Evaluated whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures. | There was very low-certainty evidence of a significant decrease in caries incidence (measured by the number of cases with new caries) in first and second primary molars when using a Nd:YAG laser alone compared to no treatment at 1 year follow-up (1 trial). | Very low | Critically low |
| Subgroup: Interventions delivered to mothers of unborn/toddlers | | | | |
| Systemic fluoride (n = 2) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Supplements (n = 2) | | | | |
| Takahashi *et al.* (2017) | Evaluated the effects of women taking fluoride supplements (tablets, drops, lozenges or chewing gum) compared with no fluoride supplementation during pregnancy to prevent caries in the primary teeth of children. | There was very low-certainty evidence of no significant caries preventive benefit (measured by both the number of children with caries, and mean difference in decayed and filled tooth surfaces (dfs)) of fluoride supplements (1 dose of 2.2mg NaF tablet once daily from the 4th months of pregnancy) taken by women during pregnancy compared to a placebo in preventing dental caries in the primary teeth of offspring at 3 years and 5 years follow-up (1 trial).<br><br>*Note*. This outcome was part of a larger intervention in which the offspring received fluoride drops from birth to 2 years of age and a single 0.5mg tablet daily for children aged 2 to 3 years.<br><br>*Note*. This was a single trial review. | Very low | High |
| Xiao *et al.* (2019) | Systematically reviewed the scientific evidence relating to the association between prenatal oral health care, reduced carriage of S. Mutans, and early childhood caries prevention. | There is very low-certainty evidence of no significant reduction in caries incidence (measured by the number of decayed, missing and filled surfaces (dmfs)) with fluoride supplementation (daily 1 mg fluoride tablet, taken by pregnant women, beginning with the 4th month of pregnancy until the end of pregnancy) compared to no fluoride intake at 5 years follow-up (1 trial).<br><br>*Note*. This outcome was part of a larger intervention in which the offspring in both the intervention and the control group received a daily drop of fluoride water from birth to 2 years of age, followed by a daily 0.5-mg tablet from 2 to 3 years of age. | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Topical other chemicals (n = 2) | | | | |
| Xylitol (n = 2) | | | | |
| Riggs *et al.* (2019) | Assessed the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | There was very low-certainty evidence of no significant difference in risk of caries incidence (measured by the decayed, missing and filled teeth (dmft) index) following maternal consumption of xylitol chewing gum (beginning three months after the birth of the baby, continuing until the child was three years of age; average daily dose of xylitol 6-7g, average consumption frequency four times per day) versus 3 applications of chlorhexidine varnish at 6, 12 and 18 months after the birth of the child, with follow-up when the child was 2 years of age (1 trial).<br><br>There was very low-certainty evidence of no significant difference in the risk of caries incidence (measured by caries presence in the primary teeth, as well as the decayed, extracted and filled surfaces (defs) index and defs categories (1-3; 3-4; ≥ 5)) following maternal consumption of xylitol chewing gum (650 mg xylitol; 1 piece chewed for 5 minutes 3 times per day, commencing 6 months postpartum until 18 months postpartum) compared with consumption of CHX + xylitol gum (containing 532.5 mg xylitol, 5.0 mg chlorhexidine, and 141.9 mg sodium fluoride) (1 trial). The follow-up period was not specified for this trial.<br><br>The certainty of evidence was downgraded to very low because these trial were not pooled and so the evidence was reported from single trials (159 randomised in the first trial and 96 analysed in the second trial). | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Xiao *et al.* (2019) | Systematically reviewed the scientific evidence relating to the association between prenatal oral health care, reduced carriage of S. Mutans, and early childhood caries prevention. | None of the included trials reported on the effect of xylitol chewing gum on caries incidence (measured by the number of decayed, missing and filled surfaces (dmfs)) in the offspring of mothers who received the intervention. | Very low | Critically low |
| Topical other chemicals (n = 3) | | | | |
| CHX (n = 3) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of no significant difference in caries increment (measured by the number of new decayed and filled surfaces (dfs) with the use of 10% chlorhexidine varnish (4 weekly applications 6 months after delivery, following by a single application every once every 6 months) compared to a placebo at 4 years follow-up (1 trial). | Very low | Critically low |
| Smith *et al.* (2018) | Systematically reviewed the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | There was moderate-certainty evidence of no significant difference in caries incidence (measured by the number of new carious surfaces) in the primary dentition of children whose mother's received four weekly applications of 10% chlorhexidine varnish and a single application when their child was 12, 18 and 24 months old, compared to placebo varnish at 18-20 months follow-up (1 trial). | Moderate | Low |
| Riggs *et al.* (2019) | Assessed the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | None of the included trials reported on the effect of maternal use of chlorhexidine as a standalone intervention on caries incidence (measured by presence of new caries and/or the decayed, missing and filled surfaces/teeth (dmfs/t) indices) in the primary dentition of offspring. | Low | Low |
| Subgroup: Combined interventions delivered to mothers of unborn/toddlers | | | | |
| Topical other chemicals + topical other chemicals (n = 1) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of a significant benefit of xylitol gum (6-7g/day, gum chewed 4 times per day from 3 months postpartum to 24 months postpartum) + 40% chlorhexidine varnish at 6, 12 and 18 months postpartum on the incidence of caries (measured by the increment of decayed, missing and filled (dmf) teeth) at 5 years follow-up (1 trial). | Very low | Critically low |
| Topical other chemicals + other (n = 1) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of a significant reduction in caries experience (measured by the increment of decayed, extracted and filled (defs) teeth) with the use of 1% chlorhexidine gel (applied up to 3 years post-partum) plus a preventive programme compared to a control group that received a preventive programme only at 7 years follow-up (1 trial). The nature of the preventive programme was unspecified, but the authors noted that a regular caries preventive program includes routine and periodic examination by a dentist, patient education, dietary advice and appropriate use of professional and home fluoride products and dental sealants. | Very low | Critically low |
| CHX + other (n = 1) | | | | |
| Riggs *et al.* (2019) | Assessed the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | The review authors conducted a meta-analysis of 3 trials to examine the effect of maternal consumption of chlorhexidine or iodine-NaF + prophylaxis versus placebo on caries presence in the primary dentition of offspring. However, the precise nature of the intervention is unclear given the fact that the data were pooled. Therefore, the findings were excluded from data synthesis. | Low | Low |
| Complex combined interventions (n = 1) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Xiao *et al.* (2019) | Systematically reviewed the scientific evidence relating to the association between prenatal oral health care, reduced carriage of S. Mutans, and early childhood caries prevention. | There was very low-certainty evidence of lower caries incidence (measured by proportion of children with new caries and by the decayed, missing and filled surfaces (dmfs) index) in the offspring of pregnant women who received the "primary-primary prevention" intervention compared to the offspring of pregnant women who did not receive the intervention at both 3- and 5-years follow-up (1 trial). This intervention consisted of dental examination findings, individual preventive self-care oral health instruction, instruction on avoiding microbe transmission, caries aetiology education, and referral for dental treatment if needed (at first pregnancy visit), education about infection related to maternal-child caries transmission (at second pregnancy visit (>8 months gestational age), maternal oral exam and oral health instruction (after birth visit, 0-3 years), and offspring oral health instruction, teeth cleaning and topical fluoride and chlorhexidine varnish application (after birth, 3-4 years of age). | Very low | Critically low |
| Subgroup: Combined interventions in primary dentition | | | | |
| Topical fluoride + topical fluoride (n = 1) | | | | |
| Carvalho *et al.* (2010) | Evaluated whether conclusive evidence exists that the professional application of fluoride varnish decreases dental caries incidence in preschool children. | There was very low-certainty evidence of lower caries increment (measured by increment of decayed, missing and filled surfaces (dmfs)) with the combined use of 5% NaF varnish applied every 6 months + 0.025% sodium fluoride toothpaste compared to a control group that received oral health counselling at 24 months follow-up (1 trial). The statistical significance was not reported. However, the reduced risk was 15%. The certainty of evidence was downgraded to very low because this outcome was informed | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | by a single trial with a sample size of 173.<br><br>*Note*. 27% of the participants in this trial regularly used fluoride tablets. However, this was existing/background fluoride exposure, rather than part of the intervention of interest. | | |
| Topical fluoride + topical other chemicals (n = 4) | | | | |
| Wang et al. (2017) | Assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. | There was low-certainty evidence of a significant reduction in caries increment (measured by increment of decayed, extracted and filled surfaces (defs)) with the combined use of fluoride toothpaste (unknown fluoride concentration) + confections containing arginine (unknown concentration), 4 times per day compared to control confection + fluoride toothpaste at both 6- and 12-months follow-up (1 trial). The certainty of evidence was downgraded by 1 to low because this outcome was informed by a single trial with a sample size of 195.<br><br>There was low-certainty evidence (for consistency with Walsh et al. (2015) as using the same trial evidence) of no significant caries reducing potential (measured by difference in the proportion of participants developing new caries on primary teeth) with the combined use of 0.12% chlorhexidine gel applied one daily + twice daily toothbrushing with fluoride toothpaste compared to no gel + twice daily toothbrushing with fluoride toothpaste at 24 months follow-up (2 trials; narrative synthesis). The caries rate in the intervention and control groups in both trials was very low. | Moderate | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | There was moderate-certainty evidence of no significant caries reducing potential (measured by difference in the proportion of participants developing new caries on primary teeth) with the combined use of 10% CPP-ACP paste applied once daily and twice daily toothbrushing with fluoride toothpaste compared to twice daily toothbrushing with fluoride toothpaste at 24 months follow-up (1 trial). | | |
| Walsh et al. (2015) | Assessed the effects of chlorhexidine-containing oral products (toothpastes, mouthrinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. | There was low-certainty evidence of no significant difference in the incidence of caries (measured by decayed, missing and filled teeth (dmft) scores) when using 0.12% chlorhexidine gel applied by caregivers every 6 months after evening toothbrushing with 0.304% fluoride toothpaste, compared to no treatment at 24 months follow-up (2 trials). However, there was low-certainty evidence of no difference in the presence of new caries in primary teeth following the same intervention compared to no treatment at 24 months follow-up.<br><br>*Note*. The review authors noted that oral health instruction and dietary advice was provided to caregivers in both trials.<br><br>Overall, the review authors concluded that there was little evidence to support or refute the use of chlorhexidine gel plus fluoride toothpaste in preventing caries in primary dentition. | Low | Low |
| Singal et al. (2022) | Reviewed the evidence for the remineralising and caries preventive efficacy of various CaP (calcium phosphate) derivatives. | There was low-certainty evidence of no added caries preventive benefit (measured by the decayed, missing and filled surfaces (dmfs) index) with the combined use of 10% CPP-ACP paste + 1000 ppm fluoride toothpaste (frequency | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | not reported) compared to the use of 1000 ppm fluoride toothpaste (1 trial). The follow-up period was not specified. | | |
| Gupta *et al.* (2020a) | Compared the effectiveness of topical fluoride and povidone iodine with topical fluoride alone for the prevention of dental caries among 1–12-year-old children. | There was very low-certainty evidence of no difference in the risk of caries incidence (measured by the presence of absence of new carious lesions) between the combined intervention group receiving topical fluoride (mixed) + povidone iodine compared to the use of topical fluoride alone (3 trials). The follow-up period was not specified. However, it was likely 1 year. The combined interventions applied in the 3 trials were: 1.23% APF gel + 10% PI solution every week for one month (then the gel and PI were applied alternately every 3 months for one year); 1.23% APF gel + 2mL PI application + oral prophylaxis + complete restorative therapy (one treatment); 1% PI + 5% NaF varnish 3 times a year. | Very low | Critically low |
| Topical fluoride + other (n = 7) | | | | |
| Smith *et al.* (2018) | Systematically reviewed the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. | There was moderate-certainty evidence of a significant reduction in caries increment (measured by increment of decayed, missing and filled surfaces (dmfs)) with the combined use of 5% NaF varnish applied at baseline and at 4- to 6-month intervals + caregiver counselling compared to caregiver counselling alone at 24 months follow-up (1 trial). Caregiver counselling was provided at baseline and at 12- and 24-month visits for both control and intervention groups.<br><br>*Note*. The precise nature of the caregiver counselling intervention component was not described. | Moderate | Low |
| Lam *et al.* (2020) | Assessed assess randomized controlled trials and summarize the evidence on the | There was very low-certainty evidence of significantly lower caries incidence rate with the combined use of 5% NaF | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | effectiveness of different sealants in prevention and arrest of the pit and fissure occlusal caries in primary molars of children. | varnish + light-cured fissure sealants compared to the use of fluoride varnish alone at 1 year follow-up; however, the difference was not significant at 2 years follow-up (1 trial).<br><br>There was very low-certainty evidence of no significant difference in caries incidence rate between the resin infiltration + fluoride varnish group and the resin-based sealant + fluoride varnish (concentration/dose not specified) group at 24 months follow-up. Subgroup analyses also showed no significant difference in caries incidence between participants in the resin-based sealant + fluoride varnish group compared to participants the fluoride varnish group alone at 24-months follow-up (1 trial).<br><br>The certainty of evidence was downgraded to very low because the findings from these interventions were informed by single trials; the sample size in the first trial was 147 at the 1-year follow-up and 47 at the 2-year follow-up and the sample size in the second trial was 47. | | |
| Dos Santos *et al.* (2018) | Assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. | There was very low-certainty evidence of significantly lower caries incidence (measured by the proportion of children remaining caries-free) and caries increment (measured by both the number of decayed, missing and filled surfaces and teeth (dmfs and dmft)) following the combined use of fluoride toothpaste (500 ppm) + supervised toothbrushing (intensive daily dental hygiene in kindergartens) compared to occasional (3-4 times per year) instruction for teeth cleaning at 27-29 months follow-up (families in both groups were provided with fluoride toothpaste) (1 trial). | Very low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Walsh *et al.* (2019) | Assessed and compared the effects of toothpastes of different fluoride concentrations (parts per million (ppm)) in preventing dental caries in children, adolescents, and adults. | There was very low-certainty evidence of lower incidence of caries (measured by the proportion of children developing new caries) in the high fluoride group (1450 ppm) combined with supervised toothbrushing compared to the lower fluoride group (250 ppm) combined with supervised toothbrushing at 22 months follow-up (1 trial). However, the difference was not statistically significant. The certainty of evidence was downgraded to very low because the findings from this intervention were informed by a single trial with a sample size of 69.<br><br>There was low-certainty evidence of significantly lower incidence of caries (measured by the proportion of children developing new caries) in the high fluoride group (1055 ppm) combined with supervised toothbrushing compared to the lower fluoride group (550 ppm) combined with supervised toothbrushing at 36 months follow-up (1 trial). | Low | Low |
| Dos Santos *et al*. (2013) | Assessed the effects of fluoride toothpastes on the prevention of caries in the primary dentition of preschool children. | There was low-certainty evidence of a caries-preventive effect (as measured by the increment of decayed, missing and filled surface (dmfs) and dmfs prevented fraction) of low fluoride (<600 ppm) toothpaste compared to no intervention/control (2 trials), indicating a 40% reduction in dmfs increment. However, the effect was not evident when caries prevention was measured by decayed, missing and filled teeth (dmft; 24% reduction in dmft increment) (2 trials) or as the proportion of children developing dental caries (2 trials). Follow-up periods were not specified. However, the review authors only included trials with a follow-up period of at least 1 year. | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | There was low-certainty evidence of a significant caries-preventive effect (as measured by decayed, missing and filled surface (dmfs) prevented fraction (5 trials); decayed, missing and filled teeth (dmft) prevented fraction (1 trial) or as the proportion of children developing dental caries (2 trials)) of standard fluoride (1000-1500 ppm) toothpaste compared to no intervention/control (2 trials). Results showed a reduction of 31% and 16% in dmfs and dmft increment, respectively. Follow-up periods were not specified; however, the review authors only included trials with a follow-up period of at least 1 year.<br><br>Overall, preschool children who brushed their teeth with standard fluoride toothpastes experienced were less likely to develop caries. The evidence of the effectiveness of low fluoride toothpastes on the prevention of dental caries is ambiguous.<br><br>*Note*. 7/8 trials assessed the combined effects of fluoride toothpaste and oral health education, making this a review of a combined intervention. | | |
| Marinho *et al.* (2016) | Assessed the effectiveness and safety of fluoride mouthrinses in preventing dental caries in the child/adolescent population. | None of the included trials reported on the effect of fluoride mouthrinse on either caries increment in primary teeth (measured by decayed, extracted and filled surfaces (defs) and whole teeth (deft)) or children not remaining caries free in primary teeth).<br><br>*Note*. All trials tested supervised use of fluoride mouthrinse | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | as part of school-based supervised mouthrinsing programmes, making this a review of a combined intervention. | | |
| de Sousa *et al.* (2019) | Assessed the effectiveness of fluoride varnish in reducing the risk of developing new dentine caries lesions in pre-schoolers and to assess whether its effectiveness is influenced by baseline caries levels. | There was very low-certainty evidence of a lower proportion of children developing new dentine carious lesions with the use of fluoride varnish (5% NaF in 13 trials, 0.1% Difluorsilano in 2 trials, and 0.9% Difluorsilano in 1 trial) applied at 6-month intervals in 15 trials (a 3-month interval in 1 trial) compared to no varnish at 12-36 months follow-up (16 trials; 10 included combined interventions), equating to a 12% reduced risk. However, the findings were not statistically significant when the review authors considered the prediction intervals.<br><br>There was very low-certainty evidence of lower caries incidence (measured by the decayed, missing and filled surfaces (dmfs) index) in the fluoride varnish group (5% NaF in 8 trials, 0.1% Difluorsilano in 2 trials, and 0.9% Difluorsilano in 1 trial) applied at 6-month intervals in 9 trials (3-month intervals in 2 trials) compared to the control groups at 24-36 months follow-up (11 trials; 7 included combined interventions), equating to a 24% reduction in dmfs with the use of fluoride varnish.<br><br>There was very low-certainty evidence of no difference in caries incidence (measured by the decayed, missing and filled teeth (dmft) index) in the fluoride varnish group (5% NaF in 4 trials and 0.1% Difluorsilano in 1 trial) applied at 6-month intervals compared to the control groups at months 24-36 | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | months follow-up (5 trials; 2 included combined interventions), equating to a 31% reduction in dmft with the use of fluoride varnish.<br><br>Overall, at the surface level, the results showed a statistically significant difference favouring fluoride varnish; however, the difference may be clinically irrelevant. At the individual level, the review authors concluded that fluoride varnish showed a modest and uncertain anticaries effect in pre-schoolers.<br><br>*Note*. 13/20 included trials involved combined interventions with oral health education (5 trials), OHE plus supervised toothbrushing (2 trials), dietary counselling (4 trials), and/or fluoridated toothpaste (2 trials). The findings from subgroup analyses were not synthesised given the number of combined interventions.<br><br>*Note*. At least 17/20 included trials reported some exposure to fluoride (either water, toothpaste or tablets). However, this was existing/background fluoride exposure, rather than part of the intervention of interest. | | |
| Systemic fluoride + topical other chemicals (n = 1) | | | | |
| Jørgensen *et al.* (2016) | Reviewed the available literature on the prevention of caries in early childhood through biofilm engineering with probiotic bacteria. | There was low-certainty evidence of a significant reduction in caries increment (measured by the increment of decayed, missing and filled surfaces (dmfs)) and caries incidence (measured by the proportion of children remaining caries-free following intervention) with the use of probiotic-containing fluoridated milk (Lactobacillus rhamnosus; | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | consumed 5 days per week for 21 months) compared the use of non-fluoridated milk without probiotics at 21 months follow-up (1 trial). | | |
| Sealants + other (n = 1) | | | | |
| Ramamurthy *et al.* (2022) | Evaluated the effects of sealants compared to no sealant or a different sealant in preventing pit and fissure caries on the occlusal surfaces of primary molars in children and to report the adverse effects and the retention of different types of sealants. | There was very low-certainty evidence of a lower risk of caries incidence (measured by the risk of developing ≥ 1 new carious lesions) among children allocated to receive fluoride-releasing resin-based sealants combined with oral hygiene + dietary recommendations compared to no sealant + oral hygiene + dietary recommendations at 12 and 24 months follow-up (1 trial). This trial also reported a significantly lower caries incidence (measured by mean number of new cavitated occlusal lesions) in the sealed molars compared to the control molars at 24 months follow-up. The certainty of evidence was downgraded by 2 to very low because this outcome was informed by a single trial with a sample size of 88.<br><br>Data from the two trials evaluating the effectiveness of glass-ionomer based sealant versus no sealant could not be pooled due to differences in study design. There was moderate-certainty evidence from the first trial of similar caries incidence (measured by the risk of developing ≥ 1 new carious lesion) among children allocated to receive glass-ionomer-based sealants combined with motivation and oral health instruction compared to those in the no intervention group at 12-30 months follow-up (1 trial). This trial did, however, report a significantly lower caries increment (measured by increment of decayed, missing and filled teeth | Moderate | High |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | (dmft)) in the sealant group compared to the no intervention group at 12 months follow-up.<br><br>There was low-certainty of evidence from the second trial of a lower risk of caries incidence among children allocated to receive glass-ionomer-based sealants combined with instruction to use a low fluoride toothpaste + a demonstration on proper tooth brushing technique, compared to those in the no sealant group who received the same instruction and demonstration, at 6 and 12 months follow-up (1 trial). This trial also, however, reported no significant difference in caries increment (measured by caries increment at the occlusal surfaces of first primary molars) in the sealant group compared to the no sealant group at 12 months follow-up. The certainty of evidence was downgraded by 1 to low because this outcome was informed by a single trial with a sample size of 107. | | |
| Complex combined interventions (n = 4) | | | | |
| Yu *et al.* (2021) | Assessed whether the combined use of professional fluoride application and regular fluoride toothpaste has additional benefit than using regular fluoride toothpaste alone for children under 16. | There was moderate-certainty evidence of no significant reduction in caries increment (measured by increment of decayed, missing/extracted and filled surfaces (d(m/e)fs), no trials reported on whole teeth (d(m/e)ft)) with the combined use of fluoride varnish (5% NaF in 5 trials, and 0.9% difluorosilane in 1 trial, applied every 6 months) + fluoride toothpaste (1000-1450 ppm) + additional active intervention components in 5 out of the 6 pooled trials (oral health education and/or counselling in 5 trials, dietary counselling in 2 trials, supervised toothbrushing in 2 trials, and "usual care" in 1 trial) compared to control groups that received all active | Moderate | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | intervention components with the exception of the fluoride varnish in 4 out of 5 trials with combined interventions (the control was "usual care" in 1 trial), at 24-36 months follow-up (6 trials).<br><br>*Note*. At least 2/6 included trials reported some exposure to fluoride (either water or milk). However, this was existing/background fluoride exposure, rather than part of the interventions of interest. | | |
| de Sousa *et al.* (2019) | Assessed the effectiveness of fluoride varnish in reducing the risk o developing new dentine caries lesions in pre-schoolers and to assess whether its effectiveness is influenced by baseline caries levels. | There was very low-certainty evidence of no significant difference in caries incidence (measured by the proportion of children developing caries) between the combined intervention group (consisting of 5% NaF varnish applied every 6 months + oral health education + dietary counselling + 500 ppm fluoride toothpaste) compared to the no-intervention group at 24 months follow-up (1 trial). In the same trial, there was very low-certainty evidence of significantly lower caries increment (measured by increment of decayed, missing and filled surfaces (dmfs)) in the group that received the combined intervention compared to the no-intervention group, at 24 months follow-up.<br><br>There was very low-certainty evidence of no difference in caries incidence (measured by the proportion of children developing caries) between the combined intervention group (consisting of 5% NaF varnish applied every 6 months oral health education + dietary counselling + 1450 ppm fluoride toothpaste) compared to a control group that received oral health education + dietary counselling, at 36 months follow- | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | up (1 trial).<br><br>There was very low-certainty evidence of no significant difference in caries increment (measured by increment of decayed, missing and filled teeth (dmft)) in the group that received a combined intervention consisting of 5% NaF varnish + oral health education + dietary counselling compared to a control group that received placebo water-based coloured solution + oral health education + dietary counselling, at 12 months follow-up (1 trial). | | |
| Chou *et al.* (2021) | Investigated the effect of primary care oral screening and preventive interventions (fluoride supplements, topical fluoride application, silver diamine fluoride, or xylitol) on preventing and arresting dental caries in children younger than 5 years. | There was very low-certainty evidence of a significant decrease in caries increment (measured by increment of decayed, missing and filled surfaces/teeth (dmfs/t)) with the use of topical fluoride compared to a placebo or no topical fluoride at 1-3 years follow-up (13 trials). The type of fluoride and concentration of fluoride varied greatly. Six trials used 5% NaF varnish, one trial used 1.23% APF foam, one trial used 0.9% Difluorsilane varnish, one trial used 1.5% ammonium fluoride varnish, two trials used 50mg/mL Durphat toothpaste, one trial used 0.5mL Profluorid varnish, and one trial used a varnish consisting of 22,600 ppl fluoride. The frequency of application was 6 months in 11 trials, 4 months in one trial, and 3 months in one trial.<br><br>*Note*. 12/13 of these trials involved complex combined interventions, approximately have involved three or more active components. The most common additional intervention components were parental oral health education (8 trials, OHE provided at different intervals), | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | parental toothbrushing training/instruction (3 trials; frequency of training/instruction varied), the provision of toothbrushes and fluoride toothpaste (4 trials; fluoride concentration and frequency of provision varied), and supervised toothbrushing (3 trials, supervision frequency varied). | | |
| Dos Santos *et al.* (2018) | Assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. | There was very low-certainty evidence of significantly higher proportion of children remaining caries-free and significantly lower caries increment (measured by increment of decayed, extracted and filled teeth (deft)) following an intervention consisting of 30-min oral hygiene instruction sessions + practical demonstration and application of toothbrushing technique on five consecutive school days, which was repeated twice a year by a dental hygienist and a research assistant + daily school-supervised toothbrushing by a research assistant with the use of 500 ppm fluoride toothpaste (1 trial). The comparison group received 30-min oral hygiene instruction sessions on five consecutive school days, which was repeated twice a year by a dental hygienist and a research assistant. At 4 years follow-up, the proportion of children the remained caries-free in primary teeth in the intervention group was 14%, compared to 9.4% in the control group. | Very low | Low |
| Permanent dentition | | | | |
| Attendance for dental assessment (n = 2) | | | | |
| Scheduled dental appointments (n = 2) | | | | |
| Fee *et al.* (2020) | Investigated the optimal recall interval of dental check-up for oral health in a primary care setting. | It was not clear if there was a meaningful difference in increment of Decayed, Missing and Filled Tooth Surfaces (DMFS) between a 24- and a 12-month recall period in | Moderate | High |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | permanent teeth at 2 years follow-up (1 trial).<br><br>There was moderate-certainty evidence of little to no difference between the 6-month and risk-based recall intervals in the number of permanent tooth surfaces with any caries at 4 years follow-up (1 trial).<br><br>There was moderate-certainty evidence from the same trial of little to no difference in the number of permanent tooth surfaces with any caries in adults when comparing 24-month recall with either 6-month or risk-based recall at 4 years follow-up. | | |
| Joury *et al.* (2017) | Assessed the effectiveness of school-based dental screening versus no screening on improving oral health in children. | Only one trial reported on the outcome of interest to this umbrella review. It was not clear whether the findings related to new caries or prevalence of existing caries, and as such the findings were not extracted. | Moderate | Critically low |
| Scheduled primary care appointments (n = 0) | | | | |
| Dental hygiene (n = 3) | | | | |
| Supervised toothbrushing (n = 2) | | | | |
| Hujoel *et al.* (2018) | Assessed the association between personal oral hygiene (supervised toothbrushing) and dental caries in the absence of the confounding effects of fluoride. | There was low-certainty evidence of no significant difference in the incidence of dental caries (measured by Decayed, Missing and Filled Surfaces (DMFS) scores) between the oral hygiene intervention group (supervised toothbrushing, daily or biweekly) and no intervention control groups at 29 months - 3 years follow-up (3 trials). | Low | Critically low |
| Dos Santos *et al.* (2018) | Assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. | There was very low-certainty evidence of no difference in caries increment (measured by both Decayed, Missing and Filled Surfaces (DMFS) and Teeth (DMFT)) following daily school-based supervised toothbrushing with non-fluoride | Very low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | toothpaste compared to no intervention at 21 months follow-up (1 trial). | | |
| Flossing (n = 0) | | | | |
| Interdental cleaning devices (n = 1) | | | | |
| Worthington *et al.* (2019) | Evaluated the effectiveness of interdental cleaning devices used at home, in addition to toothbrushing, compared with toothbrushing alone, for preventing and controlling periodontal diseases, caries, and plaque. | Only approximately half of the included trials involved supervised use of interdental cleaning devices. The HRB were unable to determine which trials of these were relevant to the purposes of the umbrella review. Therefore, the findings were excluded from data synthesis. | Low | Low |
| Professional scaling or cleaning (n = 0) | | | | |
| Systemic fluoride (n = 4) | | | | |
| Milk (n = 2) | | | | |
| Yeung *et al.* (2015) | Assessed assess the effect of milk fluoridation for preventing dental caries at a community level. | There was very low-certainty evidence of significantly lower caries increment in the permanent teeth of children (measured by changes in Decayed, Missing and Filled Teeth (DMFT)) in the fluoridated milk group in which children consumed 180-200ml milk per day using a 200g cup compared to the non-fluoridated milk group at 3 years follow-up (1 trial).<br><br>*Note*. This was a single trial review. | Very low | High |
| Cagetti *et al.* (2012) | Examined the effectiveness of fluoridated food in caries prevention. | None of the included trials reported on the effect of fluoridated milk on the caries increment, measured by changes in Decayed, Missing and Filled Surfaces/Teeth (DMFS/T) in permanent teeth. | Very low | Critically low |
| Salt (n = 1) | | | | |
| Cagetti *et al.* (2012) | Examined the effectiveness of fluoridated food in caries prevention. | None of the included trials reported on the effect of fluoridated salt on the caries increment, measured by | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | changes in Decayed, Missing and Filled Surfaces/Teeth (DMFS/T) in permanent teeth. | | |
| Sugar (n = 1) | | | | |
| Cagetti *et al.* (2012) | Examined the effectiveness of fluoridated food in caries prevention. | There was very low-certainty evidence of lower caries increment in the permanent teeth (measured by Decayed, Missing and Filled Surfaces (DMFS)) of participants who consumed fluoridated sugar (10 ppm F) compared to children in the control group at 18 months follow-up (1 trial). In this trial, fluoridated sugar was used as an ingredient in tea and porridge. | Very low | Critically low |
| Supplements (n = 2) | | | | |
| Tubert-Jeannin *et al.* (2011) | Evaluated the effects of fluoride supplements in the form of tablets (chewable or not), drops, lozenges and chewing gums for preventing dental caries in children. | There was low-certainty evidence of a benefit from the use of fluoride supplements (tablet, drops, lozenges, and gums) compared to no supplement in final caries experience (measured by the Decayed, Missing and Filled Surfaces (DMFS; 3 trials) and the Decayed, Missing and Filled Teeth (DMFT; 3 trials) prevented fraction) at 24-36 months follow-up, resulting in an average reduction of 24% and 29% in DMFS and DMFT, respectively. The review authors noted that participants in two of the pooled trials had some other exposure to fluoride (via fluoridated water in one trial and an unspecified source of fluoride in the other trial).<br><br>There was low-certainty evidence of a benefit from the use of APF tablets specifically (1 mg F) administered once or twice a day compared to no supplement in final caries experience (measured by the Decayed, Missing and Filled Surfaces (DMFS) prevented fraction) at 55 months and 72 months follow-up (1 of the above trials), resulting in an | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | average reduction of 25% and 28% reduction on average in DMFS after 55 months and 72 months, respectively.<br><br>There was low-certainty evidence of no benefit from the use of fluoride supplements (tablets or lozenges) when compared with the used of topical fluoride (mouthrinse, varnish, fluoridated toothpaste) in final caries experience (measured by the Decayed, Missing and Filled Surfaces (DMFS) prevented fraction) at 24-36 months follow-up (4 trials).<br><br>There was low-certainty evidence (respectively) of no benefit from the use of fluoride supplements when compared with the used of topical fluoride (mouth rinse, varnish, fluoridated toothpaste) in final caries experience (measured by the Decayed, Missing and Filled Surfaces (DMFS) prevented fraction) at 48 months follow-up (1 trial) and 60 months follow-up (2 trials). A significant positive effect was observed in one trial at 96 months follow-up; however, the level of dropout was very high.<br><br>Overall, there was evidence of the use of fluoride supplements in preventing dental caries in permanent teeth. When fluoride supplements were compared with the use of topical fluorides or other preventive measures, there was no clear evidence of a differential effect on permanent dentition. | | |
| Zhou *et al.* (2019) | Investigated the efficacy of strategies in caries and gingivitis prevention among | The results of this review were presented in a way that makes the determination of the effect of specific | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | children and adolescents with intellectual disabilities. | interventions not possible. Therefore, the findings were excluded from data synthesis. | | |
| Other systemic chemicals (n = 1) | | | | |
| Vitamin D (n = 0) | | | | |
| Calcium (n = 0) | | | | |
| Sialagogues (n = 1) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | None of the included trials reported on the effect of sialagogues on caries increment (measured by the number of new Decayed, Missing and Filled Surfaces/Teeth (DMFS/T)) in permanent teeth. | Very low | Critically low |
| Zinc (n = 0) | | | | |
| Topical fluoride (n = 9) | | | | |
| Toothpaste (n = 2) | | | | |
| Walsh *et al.* (2019) | Assessed and compared the effects of toothpastes of different fluoride concentrations (parts per million (ppm)) in preventing dental caries in children, adolescents, and adults. | There was low-certainty evidence of no difference in the proportion of children developing new caries in immature permanent dentition in the 250 ppm fluoride toothpaste group compared to children in the 0 ppm fluoride toothpaste group at 2 years follow-up (2 trials). There was low-certainty evidence of a lower (but not statistically significant) proportion of children developing new caries in immature permanent dentition in the 1000-1250 ppm fluoride toothpaste group compared to children in the 0 ppm fluoride toothpaste group at 12-60 months follow-up (7 trials; one trial consisted of a combined intervention involving supervised toothbrushing). There was low-certainty evidence of a significantly lower proportion of children developing new caries in immature permanent dentition in the 1450-1500 ppm fluoride toothpaste group compared to children in the 0 | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | ppm fluoride toothpaste group at 36 months follow-up (1 trial).<br><br>None of the included trials reported on the effect of fluoride concentration on the proportion of children developing new caries in mature permanent dentition.<br><br>Overall, there is some evidence of a dose-response relationship in the caries-preventive effect of fluoride toothpaste, with the magnitude of the caries-preventive effect estimate increasing as the distance between the lower and higher fluoride concentration increases.<br><br>*Note*. Although the majority of trials (70% of all included trials) were judged to be free from the possibility of contamination or co-intervention (or both), trials where both the intervention and control group received any additional potentially active agent in the toothpaste were included, and 30% of all included trials did not provide sufficient information to assess the risk of bias in this domain. | | |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | There was low-certainty evidence from network meta-analysis that daily use of 1100-1500 ppm fluoride toothpaste was more effective than a control in preventing root caries in permanent teeth (measured by both decayed root (D-root), and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). | Low | Low |
| Mouthrinses (n = 2) | | | | |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self- | There was low-certainty evidence from network meta-analysis of a non-significant effect of daily use of 0.05% | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | applied topical fluoride treatments for the prevention of root caries. | sodium fluoride mouthrinse compared to a control in preventing root caries in permanent teeth (measured by both decayed root (D-root), and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). However, there was low-certainty evidence from the same analysis of a significant effect of daily use of 0.2% sodium fluoride mouthrinse compared to a control in preventing root caries. | | |
| Wierichs *et al.* (2015) | Evaluated results of clinical studies investigating chemical agents to reduce initiation of root caries lesions (RCLs) or inactivate existing ones. | There was very low-certainty evidence that the initiation of new root caries lesions (measured by the number of Decayed, Missing and Filled Root Surfaces (DMFRS)) was significantly lower between patients who rinsed with 225-900 ppm NaF mouthrinse compared with those that rinsed with a placebo mouthrinse at 24-38 months follow-up (4 trials). | Very low | Critically low |
| Foams (n = 0) | | | | |
| Gels (n = 3) | | | | |
| Marinho *et al.* (2015) | Examined the effectiveness and safety of fluoride gels in preventing dental caries in the child and adolescent population. | There was low-certainty evidence of a large preventive effect of fluoride gel on the reduction of caries increment (measured by change from baseline in Decayed Missing and Filled Surfaces (DMFS)) compared to a placebo/no treatment control group at approximately 3 years follow-up (25 trials). The use of this intervention was associated with a 28% reduction on average in DMFS.<br><br>There was low-certainty evidence of a large preventive effect of fluoride gel on the reduction of caries increment (measured by change from baseline in Decayed Missing and Filled Teeth (DMFT)) compared to a placebo/no treatment control group at approximately 3 years follow-up (10 trials). | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | The use of this intervention was associated with a 32% reduction on average in DMFT.<br><br>There was low-certainty evidence of a significantly lower proportion of children developing 1 ≥ or more new caries in permanent tooth surfaces between the fluoride gel groups (NaF 4500 ppm and SnF2 2425 ppm) and the placebo group at 3 years follow-up (1 trial). In the same trial there was very low-certainty evidence that the change in the proportion of participants not remaining caries free on permanent tooth surfaces in the fluoride gel groups (NaF 4500 ppm and SnF2 2425 ppm) at a 3-year and a 1.5-year follow-up was lower than the change in the proportion of participants not remaining caries free in the control group. These two outcomes were identified as secondary outcomes in the review.<br><br>The fluoride concentrations across all included trials ranged from 2425 ppm F (SnF2) to 12,500 ppm F (AmF and NaF), with the majority of trials using 12,300 ppm F APF gel concentration. The frequency of application was required to be at least once a year but varied greatly across the included trials.<br><br>*Note*. Sixteen out of all included 28 trials reported information about the performance of some form of prior (professional or self-performed) tooth prophylaxis before administering the gel. The review authors considered the prior tooth cleaning as a possible part of the technique of gel | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | application and not as a separate intervention on its own. Post-hoc meta regression analyses showed no significant association between effect estimates and prior prophylaxis. | | |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | There was low-certainty evidence from network meta-analysis that semi-annual professional application of 1.2% APF gel was more effective than a control in preventing root caries in permanent teeth (measured by both decayed root (D-root), and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). | Low | Low |
| Chan *et al.* (2022) | Reviewed the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | There was very low-certainty evidence of a benefit of semi-annual application of 1.23% APF gel in the prevention of root caries (measured by the root caries prevented fraction) in community-dwelling older adults compared to a placebo at 48-month follow-up, resulting in a 32% reduction in the initiation of root caries (1 trial). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 147. | Low | Critically low |
| Solution (n = 4) | | | | |
| Grandjean *et al.* (2021) | Evaluated the effectiveness of silver diamine fluoride in preventing and arresting root caries lesions in elders. | There was low-certainty evidence of significantly lower root caries incidence (measured by mean new root carious surfaces) in older adults following application of silver diamine fluoride compared to controls at 24 months follow-up (3 trials) and at 30-36 months follow up (2 trials), demonstrating a significant protective impact of SDF on initiation of root caries lesions. | Low | Critically low |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | There was low-certainty evidence from network meta-analysis that both annual professional application of 38% SDF solution and annual application of 38% SDF solution followed by potassium iodide (to prevent discolouration) were more | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | effective than a control in preventing root caries in permanent teeth (measured by both decayed root (D-root), and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). | | |
| Subbiah *et al.* (2018) | Evaluated the scientific evidence regarding the effectiveness of silver diamine fluoride in preventing and arresting caries in elderly adults. | There was moderate-certainty evidence of a significant benefit of 38% SDF every 12 months in preventing the initiation of root caries (measured by the Decayed, Missing and Filled Root Surfaces index) compared to a control (resulting in a 71% reduced risk), as well as compared to chlorhexidine (resulting in a 57% reduced risk) and sodium fluoride varnish (resulting in a 64% reduced risk), in institutionalised elderly adults at 36 months follow-up (1 trial).<br><br>There was moderate-certainty evidence of a significant benefit of 38% SDF every 12 months in preventing the initiation of root caries (measured by the Decayed, Missing and Filled Root Surfaces index) compared to a control in community-dwelling elderly adults at 36 and 24 months follow-up (1 trial; limited information was available on the standalone intervention arm compared to the combined intervention arms in this trial, including on the precise sample sizes of the individual groups). | Moderate | Critically low |
| Chan *et al.* (2022) | Reviewed the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | There was low-certainty evidence of a benefit of annual application of 38% SDF in the prevention of root caries (measured by the mean number of new root carious lesions and root caries prevented fraction) in pooled samples of community-dwelling and institutionalised older adults compared to a control at 24 months follow-up (3 trials). | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | Across these trials, the risk of root caries in community-dwelling older adults was reduced by 25-47% and 52-62% at 24 and 30 months, respectively. In institutionalised older adults, it was reduced by 71% at 36 months. Application with or without potassium iodide application showed no statistically significant differences in root caries prevention. | | |
| Slow-release fluoride devices (n = 1) | | | | |
| Chong *et al.* (2018) | Evaluated the effectiveness and safety of different types of slow-release fluoride devices on preventing, arresting, or reversing the progression of carious lesions on all surface types of primary (deciduous) and permanent teeth. | There was very low-certainty evidence of significantly lower caries increment (measured by both Decayed, Missing and Filled Surfaces (DMFS) and Decayed, Missing and Filled Teeth (DMFT)) with the use of a slow-releasing fluoride device (glass beads with fluoride) compared to a control (glass bead without fluoride) in children from disadvantaged backgrounds (1 trial), suggesting that slow-release fluoride may reduce the incidence of caries.<br><br>*Note*. This was a single trial review. | Very low | Moderate |
| Varnishes (n = 4) | | | | |
| Marinho *et al.* (2013) | Evaluated the effectiveness and safety of fluoride varnishes in preventing dental caries in the child/adolescent population. | There was low-certainty evidence of a substantial caries-preventive benefit (measured by change in Decayed, Missing and Filled Surfaces (DMFS; 13 trials) and whole teeth (DMFT; 5 trials)) with the use of fluoride varnish (applied at least once per year) compared to no treatment/placebo at nearest to 3 years follow-up, resulting in a 43% and a 44% reduction in caries increment for DMFS and DMFT, respectively.<br><br>There was low-certainty evidence of no difference in the proportion of children developing one or more new caries between the fluoride varnish (applied at least once per year) | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | group and the no treatment/placebo group (5 trials). Follow-up periods for this outcome were not specified. This outcome was identified as a secondary outcome in the review.<br><br>The fluoride concentration in 18/22 trials was 22,600 ppm (range: 7000-56300). Overall, review authors found evidence for a significant benefit of fluoride varnish in preventing new caries in permanent dentition.<br><br>*Note*. 5/13 pooled trials on DMFS reported some form of non-fluoride tooth prophylaxis prior to administering the varnish and all 13 trials involved some other exposure to fluoride (water, mouthrinse, toothpaste or unspecified). 2/5 pooled trials on DMFT reported some form of non-fluoride tooth prophylaxis prior to administering the varnish and all 5 trials involved some other exposure to fluoride (water, mouthrinse, toothpaste or unspecified). 1/5 pooled trials on proportion of children developing caries involved some form of non-fluoride tooth prophylaxis prior to administering the varnish and 4/5 trials involved some other exposure to fluoride (water, mouthrinse, toothpaste or milk).<br><br>*Note*. 6/13 pooled trials on DMFS increment were combined interventions involving supervised mouthrinsing or toothbrushing, oral health education/instruction/motivation, and dietary advice. 2/5 pooled trials on DMFT increment were combined interventions involving supervised toothbrushing, oral health instruction/motivation, and dietary advice. See data extraction document for additional | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | information. 2/5 pooled trials on proportion of children developing caries were combined interventions involving oral health education. | | |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | There was low-certainty evidence from network meta-analysis that quarterly professional application of 5% NaF varnish was more effective than the control in preventing root caries in permanent teeth (measured by both decayed root (D-root) and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). | Low | Low |
| Wierichs *et al.* (2015) | Evaluated results of clinical studies investigating chemical agents to reduce initiation of root caries lesions (RCLs) or inactivate existing ones. | There was very low-certainty evidence that significantly lower initiation of new root caries lesions (measured by the number of Decayed, Missing and Filled Root Surfaces (DMFRS)) with use of professionally applied 38% SDF varnish compared to placebo varnish at 24-36 months follow-up (2 trials), indicating that professionally-applied SDF varnish may reduce the initiation of RCLs. | Very low | Critically low |
| Chan *et al.* (2022) | Reviewed the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | There was very low-certainty evidence of a benefit of semi-annual application of 5% NaF varnish in the prevention of coronal caries (measured by the mean difference in the number of teeth with coronal caries) in institutionalised older adults compared to treatment at 12 months follow-up, resulting in participants in the intervention group being 15 times less likely to have coronal caries (1 trial).<br><br>There was very low-certainty evidence of a benefit of 3-monthly application of 5% NaF varnish in the prevention of root caries (measured by root caries prevented fraction) in institutionalised older adults compared to water at 36 months follow-up, resulting in a 64% root caries prevented | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | fraction (1 trial).<br><br>The certainty of evidence was downgraded to very low because these outcomes were informed by single trials (the first trial had a sample size of 190, and the second trial had a sample size of 80). | | |
| Mixed (n = 0) | | | | |
| Topical other chemicals (n = 8) | | | | |
| Antioxidants (n = 0) | | | | |
| Toothpaste (n = 0) | | | | |
| Antimicrobial agents (minus CHX) (n = 1) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | None of the included trials reported on the effect of triclosan on caries increment (measured by the number of new Decayed, Missing and Filled Surfaces/Teeth (DMFS/T)) in permanent teeth.<br><br>Four of the included trials reported on the effect of 10% povidone-iodine compared to fluoride foam or saline on coronal caries after one application. However, these trials appear to focus on caries arrest or reduction in caries progression. | Very low | Critically low |
| Arginine and its derivatives (n = 0) | | | | |
| CHX (n = 4) | | | | |
| Walsh *et al.* (2015) | Assessed the effects of chlorhexidine-containing oral products (toothpastes, mouthrinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. | There was low-certainty evidence of no appreciable difference in caries increment (measured by change from baseline in Decayed, missing and filled Surfaces (DMFS)) when using chlorhexidine varnish (10% and 40%) compared to no treatment/placebo in the permanent teeth of children at 30- and 36-months follow-up (2 trials). None of the | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | included trials reported on the effect of chlorhexidine gel on caries increment in permanent dentition.<br><br>Overall, review authors concluded that there is little evidence to support or refute the use of chlorhexidine varnish in preventing caries in permanent dentition.<br><br>*Note*. In one of the pooled trials, participants received comprehensive caries advice and demonstrations in oral hygiene techniques. | | |
| Wierichs *et al.* (2015) | Evaluated results of clinical studies investigating chemical agents to reduce initiation of root caries lesions (RCLs) or inactivate existing ones. | There was very low-certainty evidence that significantly lower initiation of new root caries lesions (measured by the number of Decayed, Missing and Filled Root Surfaces (DMFRS)) with use of professionally applied 1% or 10% CHX varnish compared to placebo varnish at 12-36 months follow-up (3 trials), indicating that professionally applied CHX varnish may reduce the initiation of RCLs. | Very low | Critically low |
| James *et al.* (2010) | Summarised the evidence of the effectiveness of chlorhexidine varnish at preventing caries in the permanent and primary teeth of children and adolescents compared to placebo or no treatment, using data from randomised controlled trials only. | There was very low-certainty evidence from 6 parallel-group trials of no significant difference in caries increment (measured by the Decayed, Missing and Filled Surfaces (DMFS) index) in the chlorhexidine varnish groups compared to the placebo/control groups (6 trials; narrative synthesis). Follow-up periods ranged from 2-3 years. CHX % was 1% (3 trials), 10% (1 trial) and 40% (2 trials), applied every 1-2 months (1 trial), 3 months (3 trials), or 6 months (2 trials).<br><br>There was very low-certainty and inconsistent evidence from 4 split-mouth trials. Two trials reported a significant effect of 1% CHX varnish applied every 4 months (1 trial) and 40% CHX | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | varnish applied every 3-4 months (1 trial) for preventing caries (measured by the DMFS index) on the occlusal surfaces of first permanent molars (1 trial) and first and second permanent molars (1 trial) compared to a placebo varnish or a control at 2 years follow-up (2 trials; narrative synthesis). The other two trials reported no significant effect of 1% CHX varnish applied every 3 months (1 trial) or every 2 weeks for 2.5 months (1 trial) placebo varnish at 1- and 2-years follow-up (2 trials; narrative synthesis).<br><br>There was very low-certainty evidence was a slightly higher caries increment (measured by increment of Decayed, Missing and Filled Surfaces (DMFS) approximal) with the use of 1% CHX-thymol varnish compared to the use of 0.1% fluoride varnish (both applied every 3 months) at 3 years follow-up (1 trial). However, the difference was not statistically significant.<br><br>*Note*. All trials reported some exposure to fluoride (either water, toothpaste or mouth rinse). However, this was existing/background fluoride exposure, rather than part of the intervention of interest. | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of no statistically significant difference in caries incidence (measured by the Decayed, Missing and Filled Surfaces (DMFS) index in 3 trials and "caries rate" in 1 trial) between those received a 0.05-0.12% chlorhexidine mouthrinse and those that received a control/placebo at 2 years (3 trials) and 5 years (1 trial) follow-up. Frequency of application was every day in 2 trials, | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | every day for 5 days and then every 3rd week in 1 trial, and daily for 1 month followed by weekly for 5 months in 1 trial. The concentration of chlorhexidine was 0.12% in two trials and 0.05% in one trial. Chlorhexidine concentration was not reported in one trial.<br><br>*Note*. One of the pooled trials delivered a combined intervention involving mouthrinse consisting of CHX + fluoride followed by brushing twice a day with toothpaste having the same composition as rinse. In addition, in three out of the four pooled trials, participants were reported to have some exposure to fluoride (toothpaste or varnish). However, this was considered background fluoride exposure, rather than part of the intervention of interest.<br><br>There was very low-certainty evidence of a benefit of 1% CHX gel for caries increment (measured by Decayed (Extracted) and Filled Surfaces (D(E)FS) approximal lesions) compared to placebo gel at 3 years follow-up (2 trials; narrative synthesis). Conversely, there was very low-certainty evidence from two other trials of no benefit of CHX gel (1% in 1 trial and 0.5% in the other) on caries increment (measured by Decayed and Filled Surfaces (DFS; 1 trial) and Decayed Surfaces (DS; 1 trial)) compared to a placebo gel at 1 year and 18 months follow-up (2 trials; narrative synthesis).<br><br>*Note*. In the first two trials, participants received professional flossing immediately prior to application of the gel, presumably as a preparation measure for the gel. In addition, | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | participants in three out of the four trials narratively synthesised were reported to have some exposure to fluoride (water, toothpaste, tablets and/or mouthrinse). However, this was considered background fluoride exposure, rather than part of the intervention of interest<br><br>There was very low-certainty evidence of a significant reduction in root caries index (RCI) following the application of 1:1 chlorhexidine/thymol varnish at 1, 3, 6, 9, and 12 months compared to a placebo at 1 year follow-up (1 trial).<br><br>*Note*. Participants were reported to have exposure to fluoridated water. However, again, this was considered background fluoride exposure, rather than part of the intervention of interest. | | |
| Calcium phosphate agents (n = 2) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of no benefit of casein derivatives coupled with calcium phosphate in a mouthrinse (3 times per day) on caries increment (measured Decayed and Filled Surfaces (DFS)) compared to a 0.5% NaF mouthrinse among patients with salivary gland dysfunction at 1 year follow-up (1 trial).<br><br>There was very low-certainty evidence of no significant difference between the use of toothpaste containing casein phosphopeptide (brush 2 times per day for 5 minutes over 12 months) compared to a fluoride-containing dentifrice on caries increment (measured Decayed Surfaces (DS)) at 2 years follow-up (1 year after completing intervention) (1 | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | trial). However, both toothpastes were significantly better than a placebo. | | |
| Singal *et al.* (2022) | Reviewed the evidence for the remineralising and caries preventive efficacy of various CaP (calcium phosphate) derivatives. | There was very low-certainty evidence of an added benefit of using CPP-ACP cream (concentration/frequency not reported) to prevent caries (measured by Decayed, Missing and Filled Teeth (DMFT) index) compared to no treatment, and compared to 5% fluoride varnish at 12 months follow-up (1 trial). Limited information was provided. The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 91 participants. | Low | Critically low |
| Ozone (n = 0) | | | | |
| Nanomaterials (n = 0) | | | | |
| Probiotics (n = 0) | | | | |
| Propolis (n = 0) | | | | |
| Silicates (n = 0) | | | | |
| Xylitol (n = 4) | | | | |
| Riley *et al.* (2015) | Assessed the effects of different xylitol-containing products on preventing dental caries in children and adults. | There was moderate-certainty evidence of no preventive benefit (measured by increment of Decayed, Missing and Filled Surfaces (DMFS)) with the consumption of xylitol (5g and 4.7g per day) lozenges compared to control lozenges or not treatment in the permanent dentition of adults and children at 33-48 months follow-up (2 trials; narrative synthesis).<br><br>*Note*. The review authors reported that participants in both trials also had exposure to fluoride (water, toothpaste and/or a history of professionally applied fluoride). However, this was considered existing/background fluoride exposure, | Moderate | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | rather than part of the interventions of interest.<br><br>None of the included trials reported on the preventive effect (measured by increment of Decayed, Missing and Filled Surfaces (DMFS)) of xylitol-containing candy, syrup, sucking tablets, (non-fluoride) toothpaste, tablets, or wipes in permanent dentition. Overall, the evidence was insufficient to determine whether xylitol-containing product can prevent caries in the permanent dentition of children or adults. | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of no significant benefit of 422mg xylitol candies (2 x 3 times per day) on caries increment (measured by increment of Decayed, Missing and Filled Surfaces (DMFS)) compared to conventional care (including preventive varnish) on high-risk patients at 2 years follow-up (1 trial). | Very low | Critically low |
| Riggs *et al.* (2019) | Assessed the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age). | None of the included trials reported on the effect of xylitol on caries increment (measured by the number of new Decayed, Missing and Filled Surfaces/Teeth (DMFS/T)) in permanent teeth. This outcome was identified as a secondary outcome in the review. | Low | Low |
| Antonio *et al.* (2011) | Assessed the overall caries preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. | There was very low-certainty evidence from a single trial of no significant difference in the prevention of caries (measured by total proximal Decayed, Missing and Filled Surfaces (DMFS) scores, and 2-year incidence of proximal enamel carious lesions) between the 42.2% xylitol lozenge group (2 tablets, 3 times a day) compared to the control group who received oral health education and application of fluoride varnish 2 or 3 times per year at 2 years follow-up (1 | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | trial). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 179 participants (2 test groups and a control group who commenced the trial; dropout percentages were 28% (test group 1; the 42.2% xylitol lozenge group), 26% (test group 2), and 8% (control group)). | | |
| Sorbitol (n = 0) | | | | |
| Polyols (e.g. gum or candies with sorbitol, xylitol, and other polyols combined) (n = 1) | | | | |
| Antonio *et al.* (2011) | Assessed the overall caries preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. | The only included trial of a standalone intervention did not carry out any statistical tests between the 49% xylitol candy groups (xylitol/maltitol and xylitol/polydextrose) and the control group, who received no additional preventive care outside routine local measures. However, there was low-certainty evidence of the lowest 3-year increment in caries (measured by Decayed, Missing and Filled Surfaces (DMFS)) in the xylitol groups compared to the control group (1 trial). The trial sample size was 412 participants (2 test groups and a control group who commenced the trial; dropout percentages were 23.2% (test group 1a; the first xylitol/maltitol group who stopped candy consumption after 2 years), 17.9% (test group 1b; the second xylitol/maltitol group who stopped candy consumption after 3 years), 13.3% (test group 2a; the first xylitol/polydextrose group who stopped candy consumption after 2 years), 29% (test group 2b; the second xylitol/polydextrose group who stopped candy consumption after 3 years), and 18.8% (control group)). | Low | Low |
| Sealants (n = 10) | | | | |
| Resin (n = 8) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Alsabek *et al.* (2021) | Evaluated the effectiveness of hydrophilic resin-based sealant (RBS) in preventing pits and fissures caries in permanent teeth. | There was low-certainty evidence no difference in caries incidence between teeth that received hydrophilic resin-based sealants and control teeth (resin-based sealant) in permanent teeth at 6 months follow-up (4 trials) or at 12 months follow-up (5 trials; 4 of trials in the previous analysis and 1 additional trial). This outcome was identified as a secondary outcome in the review.<br><br>Overall, the review authors recommended hydrophilic resin-based sealants where absolute isolation is not accomplished (uncooperative paediatric patient, semi-erupted teeth, outreach centres, etc.,). | Low | Critically low |
| Alirezaei *et al.* (2018) | Evaluated the ability of glass-ionomer cement-based sealants and resin-based sealants to prevent the occurrence of caries and their retention in standard-based clinical studies. | It was not specified in the review whether the outcome that appeared relevant to the purposes of this umbrella review (caries development) related to caries initiation or caries progression. Therefore, the findings were not extracted. The findings related to retention rate can be found in the extraction file in Appendix H. | Very low | Critically low |
| Alharthy *et al.* (2022) | Evaluated evaluate the retention and cariostatic effect<br>of hydrophilic and hydrophobic resin-based sealants in primary and/or permanent teeth with at least a follow-up period of 3 months. | It was not specified in the review whether the outcome that appeared relevant to the purposes of this umbrella review (cariostatic effect) related to caries prevention, arrest or remineralisation. Therefore, the findings were not extracted. The findings related to retention rate can be found in the extraction file in Appendix H. | Very low | Critically low |
| Rashed *et al.* (2022) | Compared pit and fissure sealants with fluoride varnish for the prevention of caries in the first permanent molars of schoolchildren. | There was low-certainty evidence of no significant difference in caries incidence on the surfaces of first permanent molars between participants who received resin-based sealant compared to those who received fluoride varnish at 24 months follow-up (3 trials). | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | There was low-certainty evidence of no significant difference in caries increment (measured by change in Decayed, Missing and Filled Surfaces (DMFS) of first permanent molars) between participants who received resin-based sealant compared to those who received fluoride varnish at 24 months follow-up (2 trials).<br><br>Overall, there was no significant difference between the efficacy of resin-based sealants and that of fluoride varnish in preventing caries in first permanent molars at two years follow-up. The review authors emphasised the use of fluoride varnish since it is more affordable and easier to apply. | | |
| Kashbour *et al.* (2020) | Evaluated the effectiveness of dental sealants compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | There was low-certainty evidence of no superiority of resin-based dental sealants in preventing the occurrence of new dentinal carious lesions on the first permanent molars of children and adolescents compared to fluoride varnish at 2-3 years follow-up (4 trials). The trials assessed odds of caries at different levels (person/child (2 trials), tooth (1 trial), and surfaces (1 trial)), which could have affected precision of different estimates.<br><br>Overall, the review found no evidence suggesting the superiority of resin-based fissure sealants over fluoride varnish in preventing the occurrence of new dentinal carious lesions on the first permanent molars of children and adolescents. Data were insufficient to reach conclusions from standalone resin-based sealant interventions about changes from baseline in decayed, missing and filled (DMF) figures at | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | surface, tooth and whole-mouth levels, observed within 12 months from the initial treatment.<br><br>*Note*. One of the above pooled trials delivered a combined intervention whereby all participants were encouraged to use fluoride tablets (fluoride concentration not specified), received annual information and motivation about dental care, and participated in fluoride rinsing with 0.5% sodium fluoride solution at school. In addition, in one of the trials, 90% of toothpastes on sale in the area contained fluoride. However, this can be considered background fluoride exposure, rather than part of the intervention of interest. | | |
| Ahovuo-Saloranta *et al.* (2017) | Compared the effects of different types of fissure sealants in preventing caries in occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. | There was moderate-certainty evidence of a caries preventive effect (measured by incidence of carious lesions on treated occlusal surfaces of molars or premolars) of second-, third-, and fourth-generation resin-based sealants compared to no sealant at 24 months follow-up (7 trials). The caries preventive effect was also evidence at 12 months follow-up, and maintained at 36-, 48-, and 54-months follow-up (4 trials).<br><br>There was moderate-certainty of evidence of a significant caries preventive effect (measured by increment of Decayed and Filled Surfaces (DFS)) associated with the application of auto-polymerised resin-based sealant compared a control at 24 months follow-up (1 trial).<br><br>*Note*. In four out of the seven pooled trials, participants had exposure to some form of fluoride (water or toothpaste). | Moderate | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | However, this was considered background fluoride exposure, rather than part of the intervention of interest.<br><br>*Note*. Participants in the trial single trial were exposed to fluoridated water and toothpaste. However, this was considered background exposure rather than part of the intervention of interest. | | |
| CADTH (2016) | Reviewed the evidence with respect to clinical effectiveness, specifically caries prevention, and cost effectiveness of dental sealants and preventative resins when applied to permanent teeth of children and adolescents. | There was low-certainty evidence of a significant reduction in caries incidence (defined as new carious lesions) in permanent first molars that received resin-based sealant compared to those that received no sealant at 1 year follow-up (1 trial). Participants were children from low socio-economic backgrounds. The findings were consistent at 3 years follow-up.<br><br>Conversely, there was low-certainty evidence no difference in caries incidence (measured by the initiation of cavitated dentine lesions) between high-risk occlusal surfaces of permanent first molars that received composite resin sealant compared to participants who received supervised tooth brushing at 3 years follow-up (1 trial). Participants were children from low socio-economic backgrounds (the trial involved 3 groups and had a total sample size of 242 children; although it is not clear if the sample sizes of the two groups that informed this comparison was >200, the certainty of evidence was not downgraded).<br><br>*Note*. Participants in the second trial had exposure to fluoridated water. However, this was considered background | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | fluoride exposure, rather than part of the intervention of interest. | | |
| Li *et al.* (2020) | Evaluated the efficacy of first permanent molars caries management between fluoride sealant and fluoride varnish. | There was very low-certainty evidence of no significant difference in caries incidence of enrolled children between the resin-based sealant group and the fluoride varnish (22,600 ppm; biannual application) group at 2-3 years follow-up (2 trials). | Very low | Critically low |
| Glass-ionomer (n = 4) | | | | |
| Kashbour *et al.* (2020) | Evaluated the effectiveness of dental sealants compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | There was low-certainty evidence of no superiority of glass-ionomer dental sealants in preventing the occurrence of new dentinal carious lesions on the first permanent molars of children and adolescents compared to fluoride varnish at 1-, 2- and 3-years follow-up (3 trials). Limited information was reported.<br><br>Data were insufficient to reach conclusions from standalone glass-ionomer based sealant interventions about caried increment (measured by changes from baseline in Decayed, Missing and Filled (DMF) figures at surface, tooth and whole-mouth levels).<br><br>*Note*. In one of the three trials, participants in both groups received oral health education, and in this trial, there was a benefit for glass-ionomer sealant over fluoride varnish among children at high risk of caries, but no statistical information was provided. | Low | Low |
| Ahovuo-Saloranta *et al.* (2017) | Compared compare the effects of different types of fissure sealants in preventing caries in occlusal surfaces of permanent teeth in | There was moderate-certainty evidence of no significant difference in the incidence of caries (measured by increment of Decayed and Filled Surfaces (DFS)) following application of | Moderate | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | children and adolescents at different levels of caries incidence. | glass-ionomer-based sealants compared with no sealant at 24 months follow-up (1 trial). *Note*. Participants in this trial had exposure to fluoridated water. However this was considered background fluoride exposure, rather than part of the intervention of interest.<br><br>There was moderate-certainty evidence of no significant difference in caries incidence (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars) associated with the application of glass-ionomer based sealant compared to resin-based sealant at 12 months follow-up (6 trials; four compared low-viscosity glass-ionomers to resin sealants and two compared resin-modified glass-ionomers to resin sealants). *Note*. One of these trials involved the delivery of a combined intervention wherein participants received OHI at baseline, which was reinforced at every visit. In addition, it was reported in two of the pooled trials that participants had exposure to fluoride (water or toothpaste). However this was considered background exposure rather than part of the intervention of interest.<br><br>There was moderate-certainty evidence of no significant difference in caries incidence (measured by the incidence of carious lesions on treated occlusal surfaces of molars or premolars) associated with the application of low-viscosity glass-ionomers compared to resin-based sealants at 24 months follow-up (10 trials), or the application of high-viscosity glass-ionomers compared to resin-based sealants at | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | 24 months follow-up (2 trials). However, when comparing resin-modified glass-ionomers with resin-based sealants, there was moderate-certainty evidence of a significant difference in caries incidence (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars) associated with resin-based sealants over resin-modified glass-ionomers at 24 months follow-up (2 trials). *Note*. Three out of the 10 trials in the first pooled analysis involved combined interventions in which participants received OHI at leach clinic visit (1 trial), oral prophylaxis (1 trial), and a complex intervention (OHE, dietary counselling, fluoride toothpaste (600 ppm), and fluoride foam (6000 ppm) at each clinic visit (at 6 and 12 months). In addition, two of the 10 trials reported participant exposure to other forms of fluoride (water or toothpaste). In the second pooled analysis, one of the two trials in the second pooled analysis involved a combined intervention whereby participants received oral health education at baseline. In addition, both trials reported participant exposure to fluoridated water. However, fluoride this was considered background exposure rather than part of the intervention of interest. In the third pooled analysis, one of the two pooled trials involved a combined intervention in which participants in both groups received oral health instruction at baseline and used fluoridated toothpaste for the duration of the trial intervention.<br><br>When comparing glass-ionomers with resin-based sealants at 36-48 months follow-up, results were inconsistent. There was moderate-certainty evidence of a significantly lower | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | caries incidence (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars) associated with resin-based sealants compared to glass-ionomers at 36-48 months follow-up (5 trials; narrative synthesis). Three of those trials compared low-viscosity glass-ionomers with resins and two compared resin-modified glass-ionomer with resins. *Note*. In one of these trial participants were exposed to fluoridated water. However, there was moderate-certainty evidence of no significant difference in caries incidence (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars) from two other trials comparing low-viscosity glass-ionomers with resins 36-48 months follow-up (2 trials; narrative synthesis). Alternatively, two trials found a superior effect of glass-ionomer sealants compared to resin-based sealants. There was moderate-certainty evidence from the first trial of a significant difference in favour of low-viscosity glass-ionomer sealant compared to second-generation resin sealant at 44 months follow-up, and there was moderate-certainty evidence from the second trials of a significant difference in favour of atraumatic restorative treatment (ART) high-viscosity glass-ionomer with light-curing sealants compared to resin-composite sealants at 48 months follow-up.<br><br>There was very low-certainty of evidence of no caries preventive benefit (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars) associated with high-viscosity glass-ionomer sealant compared to resin-based sealant at 60 months follow-up (1 | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | trial). Likewise. there was very low-certainty of evidence of no caries preventive benefit (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars) associated with low-viscosity glass-ionomer sealant compared to resin-based sealant at 84 months follow-up (1 trial). The certainty of evidence was downgraded to very low because these trials were not pooled, had different follow-up periods, and very small samples sizes (20 in the first trial and 97 in the second).<br><br>Data were insufficient to reach conclusions about glass-ionomer based sealant versus no sealant on caries incidence (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars). | | |
| Wright *et al.* (2016) | Summarised the available evidence regarding the effect of dental sealants for the prevention of pit-and-fissure occlusal caries in primary and permanent molars on children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with another head-to-head comparison to inform the development of a joint evidence-based clinical practice guideline by the American Dental Association and the American Academy of Paediatric Dentistry. | There was very low-certainty evidence of no significant difference in caries incidence (defined as the identification of a new carious lesion on the occlusal surface of permanent molars) between participants who received glass-ionomer based sealants and participants who received resin-based sealants at 2-3 years (9 trials) or 4-7 years (1 trial) follow-up.<br><br>There was very low-certainty evidence of no significant difference in caries incidence between participants who received glass-ionomer based sealants and participants who received resin-modified glass-ionomer sealants at 2-3 years follow-up (1 trial).<br><br>There was very low-certainty evidence of no significant difference in caries incidence between participants who | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | received resin-modified glass-ionomer sealants and participants who received polyacid-modified resin sealants at 2-3 years follow-up (1 trial). | | |
| CADTH (2016) | Reviewed the evidence with respect to clinical effectiveness, specifically caries prevention, and cost effectiveness of dental sealants and preventative resins when applied to permanent teeth of children and adolescents. | There was low-certainty evidence no difference in caries incidence (measured by the incidence of cavitated dentine lesions) between high-risk occlusal surfaces of permanent first molars that received composite atraumatic restorative treatment-high-viscosity glass-ionomer cement (ART-GIC) compared to participants who received supervised tooth brushing at 3 years follow-up (1 trial). | Low | Critically low |
| Ormocer (n = 1) | | | | |
| Ahovuo-Saloranta *et al.* (2017) | Compared compare the effects of different types of fissure sealants in preventing caries in occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. | There was very low-certainty evidence of a caries preventive benefit (measured by incidence of carious lesions on treated occlusal surfaces or molars or premolars) associated with the comparator (low-viscosity glass-ionomer sealant) compared to ormocer sealant at 24 months follow-up (1 trial); the presence of caries was 32% for ormocer sealant and 16% for glass-ionomer sealant. The certainty of evidence was downgraded by 2 to very low because this outcome was informed by a single trial with a sample size of 50 (effective sample size of 37).<br><br>Data were insufficient to reach conclusions about ormocer based sealant interventions on caries increment (measured by increment in Decayed, Missing and Filled Surfaces (DMFS)). | Moderate | Low |
| Hybrid (n = 1) | | | | |
| Wright *et al.* (2016) | Summarised summarise the available evidence regarding the effect of dental | There was very low-certainty evidence of no significant difference in caries incidence (defined as the identification of | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | sealants for the prevention of pit-and-fissure occlusal caries in primary and permanent molars on children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with another head-to-head comparison to inform the development of a joint evidence-based clinical practice guideline by the American Dental Association and the American Academy of Paediatric Dentistry. | a new carious lesion on the occlusal surface of permanent molars) between participants who received polyacid-modified resin sealants and participants who received resin-based sealants at 2-3 years follow-up (1 trial). | | |
| Combined (n = 4) | | | | |
| Wright *et al.* (2016) | Summarised summarise the available evidence regarding the effect of dental sealants for the prevention of pit-and-fissure occlusal caries in primary and permanent molars on children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with another head-to-head comparison to inform the development of a joint evidence-based clinical practice guideline by the American Dental Association and the American Academy of Paediatric Dentistry. | There was very low-certainty evidence of significantly lower caries incidence (defined as the identification of a new carious lesion on the occlusal surface of permanent molars) among participants who received sealants compared to participants who did not receive sealants at 2-3 years (6 trials; risk reduced by 76%), 4-7 years (3 trials; risk reduced by 79%) and 7 years or longer follow-up (2 trials; risk reduced by 85%). Results were similar when sealants were compared to fluoride varnish at 2-3 years (2 trials; risk reduced by approximately 73%), 4-7 years (2 trials; reduced risk by 81%) and 7 years or longer (1 trial; reduced risk by 71%) follow-up.<br><br>Overall, the results suggested that the use of sealants compared with control groups that did not use sealants or fluoride varnish groups reduces the incidence of carious lesions in the occlusal surfaces of permanent molars by approximately 80% in children and adolescents. | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| CADTH (2016) | Reviewed the evidence with respect to clinical effectiveness, specifically caries prevention, and cost effectiveness of dental sealants and preventative resins when applied to permanent teeth of children and adolescents. | There was very low-certainty evidence of no significant caries preventive effect (caries incidence) of dental sealant applied to pre-molars (combination not specified but assumed resin-based and glass-ionomer) compared to no sealant application at 12 months follow-up (1 trial). Limited information was provided. The certainty of evidence was downgraded to very low because this intervention was informed by a single trial with a sample size of 122 children. | Low | Critically low |
| Akera *et al.* (2022) | Evaluated the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | There was very low-certainty evidence of significantly lower dental caries (measured by Decayed, Missing and Filled Teeth (DMFT) scores) in the group that took part in a fissure sealant intervention programme compared to a control group after (assumed) 7 years follow-up (1 trial). Limited information was provided. | Very low | Critically low |
| Li *et al.* (2020) | Evaluated the efficacy of first permanent molars caries management between fluoride sealant and fluoride varnish. | There was very low-certainty evidence of no significant difference in caries incidence (measured as incidence of new caries in 4 trials and Decayed, Missing and Filled Surfaces (DMFS) in 1 trial, and both incidence of new caries and DMFS in 1 trial)) of first permanent molars' occlusal surfaces between the fluoride resin-based sealant group and the fluoride varnish (22,600 ppm in 5 trials and 7,700 in 1 trial; biannual application) group at 2-3 years follow-up (6 trials). Five out of six trials used resin-based sealants in the intervention group and 1 used glass-ionomer based sealants in the intervention group.<br><br>There was very low-certainty evidence of no significant difference in caries incidence (measured as number of new Decayed, Missing and Filled Surfaces (DMFS)) of first | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | permanent molars between the fluoride sealant group and the fluoride varnish (22,600 ppm; biannual application) group and 2 years follow-up (3 trials). Two out of three trials used resin-based sealants in the intervention group and one used resin-modified glass-ionomer cement in the intervention group. | | |
| Other (n = 0) | | | | |
| Laser (n = 1) | | | | |
| Pagano *et al.* (2020) | Evaluated whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures. | There was very low-certainty evidence of no significant difference in caries incidence (measured by the number of cases with new caries) in first permanent molars when using a $CO_2$ laser alone compared to no treatment at 4 years follow-up (1 trial). | Very low | Critically low |
| Subgroup: Combined interventions in permanent dentition | | | | |
| Topical fluoride + topical fluoride (n = 4) | | | | |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | There was low-certainty evidence from network meta-analysis that combined daily use of 1100-1500 ppm fluoride toothpaste and amine/stannous fluoride (AmF/SnF2; 250 ppm fluoride) mouthrinse was not more effective than a control in preventing root caries in permanent teeth (measured by both decayed root (D-root) and decayed and filled root (DF-root)) at 2 years follow-up (9 trials).<br><br>There was low-certainty evidence from network meta-analysis that combined daily use of 1100-1500 ppm fluoride toothpaste and 0.05% NaF mouthrinse (250 ppm fluoride) was more effective than a control in preventing root caries in permanent teeth (measured by both decayed root (D-root) | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). | | |
| Yu *et al.* (2021) | Assessed whether the combined use of professional fluoride application and regular fluoride toothpaste has additional benefit than using regular fluoride toothpaste alone for children under 16. | None of the included trials reported on the effect combined use of professional fluoride application and regular fluoride toothpaste on caries increment (measured by Decayed, Missing/Extracted and Filled Surfaces/Teeth (D(M/E)FS/T)) in permanent dentition. | Moderate | Critically low |
| Wierichs *et al.* (2015) | Evaluated results of clinical studies investigating chemical agents to reduce initiation of root caries lesions (RCLs) or inactivate existing ones. | There was very low-certainty evidence of no significant difference in the initiation of new root carious lesions (measured by the change in Decayed, Missing and Filled Root Surfaces (DMFRS) in one trial and the change in Root Caries Index (RCI) in the other) between the intervention group that used a combination of AmF/SnF2 containing dentifrice (1400ppm fluoride) and AmF/SnF2 mouthrinse (250ppm fluoride) and the control group that used a combination of NaF-containing dentifrice (1400ppm fluoride) and NaF mouthrinse (250 ppm fluoride) at 5 and 24 months follow-up (2 trials). | Very low | Critically low |
| Chan *et al.* (2022) | Reviewed the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | There was very low-certainty evidence of no significant difference in the prevention of root caries (measured by the mean difference in the number of new root carious lesions) between the annual combined application of 5% NaF varnish and 38% silver diamine fluoride compared to a control in institutionalised older adults at 36 months follow-up (1 trial). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial and the sample size for this comparison was not reported by the systematic review authors. | Low | Critically low |
| Topical fluoride + topical other chemicals (n = 4) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Gupta *et al.* (2020a) | Compared compare the effectiveness of topical fluoride and povidone iodine with topical fluoride alone for the prevention of dental caries among 1–12-year-old children. | For the purposes of this umbrella review, the results from the meta-analysis of new carious lesions on permanent teeth between the intervention (combined use of topical fluoride + povidone iodine) and control groups could not be used as data from the retrospective cohort study was included in the pooled analysis. | Very low | Critically low |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of a significant reduction in caries increment (measured by increment of Decayed, Missing and Filled Surfaces (DMFS)) with the combined use of Dicalcium phosphate dihydrate + 0.243% NaF dentifrice (twice daily) with 0.243% NaF dentifrice at 2 years follow-up, concluding that the addition of dicalcium phosphate dihydrate improved anticaries efficacy (1 trial).<br><br>There was very low-certainty evidence of no significant difference in root caries index (RCI) with the initial application of 5% chlorhexidine gel followed by daily 1% Chlorhexidine gel + 0.1% NaF compared to 0.1% NaF gel alone at 18 months follow-up (1 trial). | Very low | Critically low |
| Singal *et al.* (2022) | Reviewed the evidence for the remineralising and caries preventive efficacy of various CaP (calcium phosphate) derivatives. | There was very low-certainty evidence of no added caries preventive benefit (measured by both Decayed, Missing and Filled Surfaces (DMFS) and Teeth (DMFT)) with the combined use of CPP-ACP paste plus fluoride toothpaste (concentration/frequency not specified) compared to fluoride toothpaste alone (1 trial). The follow-up period was not specified. Limited information was provided. The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 40 participants. | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Riley *et al.* (2015) | Assessed the effects of different xylitol-containing products on preventing dental caries in children and adults. | There was moderate-certainty evidence of a significantly lower caries increment (measured by the increment of Decayed and Filled Surfaces (DFS) with the use of fluoride toothpaste containing 10% xylitol (daily dosage not reported) compared to a control at 30-36 months follow-up, resulting in a 13% reduced risk of developing caries (2 trials). In one trial, participants used 0.243% NaF toothpaste (1100ppm fluoride) and in the other, participants under 0.836% sodium monofluorophosphate toothpaste (1100 ppm fluoride).<br><br>*Note*. The review authors reported that in both trials, participants had exposure to fluoride (water and/or salt). However, this was considered existing background exposure rather than part of the intervention of interest. | Moderate | Low |
| Topical fluoride + other (n = 8) | | | | |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | There was low-certainty evidence from network meta-analysis that daily combined use of 1100-1500 ppm fluoride toothpaste and 1.66mg NaF tablets was not more effective than a control in preventing root caries in permanent teeth (measured by both decayed root (D-root) and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). | Low | Low |
| Dos Santos *et al.* (2018) | Assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. | There was very low-certainty of evidence of no caries preventive benefit (measured by cumulative survival rate of occlusal first molar surfaces with no caries) following daily school-based supervised toothbrushing with 1000 ppm fluoride toothpaste compared to no intervention at 3 years follow-up (1 trial). No information regarding the increment of caries or the proportion of children who developed new caries lesions in both groups was available in this trial. | Very low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | *Note*. While participants in the control group did not receive the intervention, they did receive an oral hygiene kit containing a toothbrush, a 1000 ppm fluoride toothpaste, plaque-disclosing toothpaste and dental floss. They were instructed on how to use these devices and were encouraged to brush their teeth twice daily. | | |
| Walsh *et al.* (2019) | Assessed and compared the effects of toothpastes of different fluoride concentrations (parts per million (ppm)) in preventing dental caries in children, adolescents, and adults. | There was low-certainty evidence of no significant difference in caries incidence (measured by the proportion of children developing new caries) following the combined use of higher fluoride toothpaste (1450-1500 ppm) + supervised toothbrushing compared with the combined use of lower fluoride toothpaste (1000-1200 ppm) + supervised toothbrushing at 36 months follow-up (2 trials).<br><br>*Note*. The review authors reported that participants in both trials had exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. | Low | Low |
| Konradsson *et al.* (2020) | Examined the scientific evidence for the efficacy of stabilised stannous fluoride dentifrice in relation to dental caries, dental erosion, and dentin hypersensitivity when compared with standard fluoride dentifrices in patients with, or at risk of these three dental conditions. | The review authors noted in the text and illustrated in Table 2 that two independent examiners examined the outcomes of interest. However, the results varied significantly between the examiners, and the findings of one examiner appear to be excluded from the Table. Therefore, the findings were excluded from data synthesis. | Low | Critically low |
| Marinho *et al.* (2016) | Assessed the effectiveness and safety of fluoride mouthrinses in preventing dental caries in the child/adolescent population. | There was low-certainty evidence of a large caries-preventive benefit (measured by Decayed, Missing and Filled Surfaces (DMFS) prevented fraction) from the supervised use of | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | fluoride mouthrinse versus placebo/no treatment at nearest to 3 years follow-up (35 trials), resulting in an approximately 27% reduction in DMFS from the daily-fortnightly supervised use of fluoride mouthrinse at 2 main strengths (230 ppm and 900 ppm fluoride).<br><br>*Note*. In 15 out of the 35 pooled trials, participants were reported to have exposure to fluoride (water, toothpaste, varnish, tablets, or unspecified systemic fluoride). However, this was considered background fluoride exposure rather than part of the intervention of interest. In addition, one out of the 35 pooled trials involved the delivery of a complex intervention, in which participants in both groups received oral health instruction and professional prophylaxis in addition to the supervised used of fluoride mouthrinse.<br><br>There was low-certainty evidence of a moderate-to-large caries-preventive benefit (measured by Decayed, Missing and Filled Teeth (DMFT) prevented fraction) from the supervised use of fluoride mouthrinse versus placebo/no treatment at nearest to 3 years follow-up (13 trials), resulting in an approximately 23% reduction in DMFT from the daily-fortnightly supervised use of fluoride mouthrinse at 2 main strengths (230ppm F and 900 ppm F).<br><br>*Note*. In one out of the 13 pooled trials, participants were reported to have exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. None of the pooled | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | trials involved the delivery of a complex intervention.<br><br>There was low-certainty evidence of no significant difference in the proportion of children who developed 1 ≥ or more new caries in permanent teeth between the supervised fluoride mouthrinse groups and the placebo/no treatment groups at 2-3 years follow-up (3 trials). There was insufficient information available to draw any reliable conclusions on the effect of supervised fluoride mouthrinse use at reducing the development of new caries. This outcome was identified as a secondary outcome in the review.<br><br>Note. In one out of the three pooled trials, participants were reported to have exposure to fluoride toothpaste. However, this was considered background fluoride exposure rather than part of the intervention of interest. None of the pooled trials involved the delivery of a complex intervention.<br><br>*Note*. All trials tested supervised use of fluoride mouthrinse, making this a review of a combined intervention. | | |
| Pagano *et al.* (2020) | Evaluated whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures. | There was very low-certainty evidence of a significantly lower number of cases with new caries following the combined use of 1.23% acidulated phosphate fluoride gel (frequency not reported) and Nd:YAG laser compared to the use of fluoride gel alone at 1 year follow-up (1 trial). | Very low | Critically low |
| Riggs *et al.* (2019) | Assessed the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the | There was low-certainty evidence of no significant difference in caries increment (measured by the increment of Decayed, Missing and Filled Surfaces (DMFS)) following the combined | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | first year of life, for preventing early childhood caries (from birth to six years of age). | use of iodine-NaF solution + prophylaxis (professional dental scaling or cleaning; 6 applications in 1 trial and 3 applications in the other) compared to a placebo at 12-36 months follow-up (2 trials). This outcome was identified as a secondary outcome in the review.<br><br>*Note*. One of these trials involved the delivery of a complex interventions in which participants received oral health education at baseline at a follow-up (at 6 months and at 12 months). | | |
| Akera *et al.* (2022) | Evaluated the effectiveness of school-based interventions in improving oral health compared to no intervention or usual practice among primary school children in low- and middle-income countries. | There was very low-certainty evidence of significantly lower dental caries (measured by net increment in DMFT scores) in the intervention group that received daily supervised toothbrushing with 0.3ml of fluoride toothpaste (1450 ppm fluoride) compared to a control group (1 trial). The precise follow-up period was not specified but appeared to be at least 2 years. However, the same trial reported no significant difference in DMFT scores between the intervention and control groups.<br><br>Overall, there was insufficient evidence available to determine whether supervised toothbrushing offered within a school-setting can reduce the risk of caries. | Very low | Critically low |
| Topical fluoride + oral health instruction/education (n = 5) | | | | |
| Hendre *et al.* (2017) | Reviewed the evidence regarding the effectiveness of silver diamine fluoride in arresting or preventing root caries in older adults. | There was low-certainty evidence of a significantly lower root caries incidence (measured by the mean number of new root caries surfaces and root caries prevented fraction) following the annual application of 38% silver diamine fluoride + oral health instruction compared to a control (water) + oral | Moderate | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | health instruction at 3 years follow-up, resulting in a 71% reduced risk (1 trial). In the same trial, there was low-certainty evidence of significantly lower root caries incidence (measured by the mean number of new root caries surfaces and root caries prevented fraction) following the quarterly application of 5% NaF varnish + oral health instruction compared to a control (water) + oral health instruction at 3 years follow-up, resulting in a 64% reduced risk (1 trial). The certainty of evidence was downgraded by 1 to low because, while the total sample size at 3 years follow-up was 203 participants, the trial involved a total of 3 test groups, only two of which involved topical fluoride. As such, the sample size for these two comparisons must have been <200.<br><br>There was very low-certainty evidence of a significantly lower caries incidence (measured by the mean number of new root caries surfaces and root caries prevented fraction) following the annual application of 38% silver diamine fluoride solution on sound exposed root surfaces + oral health instruction compared with water + oral health instruction (25% reduced risk) at 2 years follow-up (1 trial). The effect was amplified when tailored biannual oral health education was added to SDF + oral health instruction, resulting in a 47% reduced risk at 2 years follow-up. The certainty of evidence was downgraded by 2 to very low because the sample size of this comparison was 84 participants (as reported in Chan *et al*.) | | |
| Oliveira *et al.* (2018) | Examined the scientific evidence on the effect of SDF for preventing and arresting | There was low-certainty evidence of a significant caries preventive benefit (measured by the mean number of new root carious lesions) following the annual application of 38% | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | dental caries on exposed root surfaces of adults. | silver diamine fluoride solution + oral health instruction compared to a placebo + oral health instruction at 24 months follow-up (3 trials). The same effect was found at 12 months (2 trials) and 30+ months (2 trials) follow-up, with a 50.30%-68.35% reduced risk of developing root caries among elderly adults depending on the length of follow-up.<br><br>In one of these trials, there was low-certainty evidence or a significant caries preventive benefit (measured by the mean number of new root carious lesions) following the annual application of 38% silver diamine fluoride solution + oral health instruction + biannual oral health education compared to placebo + oral health instruction at 24 months follow-up (1 trial).<br><br>In another one of these trials, there was low-certainty evidence of no significant difference in caries prevention (measured by the mean number of new root carious lesions) following the combined use of annual application of 38% silver diamine fluoride solution + oral health instruction compared to 3-monthly application of fluoride varnish + oral health instruction at any of the follow-up periods analysed (12, 24 or 36 months) (1 trial).<br><br>In the same trial, there was low-certainty evidence of no significant difference in caries prevention (measured by the mean number of new root carious lesions) following the combined use of annual application of 38% silver diamine fluoride + oral health instruction compared to 3-monthly | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | application of chlorhexidine varnish + oral health instruction at 24 months follow-up (1 trial).<br><br>*Note*. The review authors reported that participants in all trials had exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. | | |
| Subbiah *et al.* (2018) | Evaluated the scientific evidence regarding the effectiveness of silver diamine fluoride in preventing and arresting caries in elderly adults. | There was moderate-certainty evidence of a significant caries preventive effect (measured by the Decayed, Missing and Filled Root Surfaces index) following the combined use of 38% silver diamine fluoride solution + oral health instruction compared to oral health instruction alone at 24 months follow-up (1 trial), results in a 25% reduced risk of developing root caries.<br><br>There was moderate-certainty evidence from the same trial of a significant caries preventive effect (measured by the Decayed, Missing and Filled Root Surfaces index) following the annual application of 38% silver diamine fluoride solution + oral health instruction + biannual oral health education compared to oral health instruction at 24 months follow-up, resulting in a 47% reduced risk of developing root caries. | Moderate | Critically low |
| Zhang *et al.* (2020) | Synthesised the best clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. | There was low-certainty evidence from network meta-analysis that annual professional application of 38% silver diamine fluoride solution + oral health education was more effective than the control in preventing root caries in permanent teeth (measured by both decayed root (D-root) and decayed and filled root (DF-root)) at 2 years follow-up (9 trials). | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Chan *et al.* (2022) | Reviewed the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years or above. | There was very low-certainty evidence of a significant root caries preventive effect (measured by the mean difference in the number of new carious lesions) following the annual application 38% silver diamine fluoride solution with oral health instruction and biannual oral health education compared to a control in community-dwelling older adults 24 months follow-up, resulting in a 47% reduced risk of developing new root carious lesions (1 trial). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 84. | Low | Critically low |
| Topical other chemicals + other (n = 5) | | | | |
| Hendre *et al.* (2017) | Reviewed the evidence regarding the effectiveness of silver diamine fluoride in arresting or preventing root caries in older adults. | There was low-certainty evidence of significantly lower root caries incidence (measured by the mean number of new root caries surfaces) following the application of 1% CHX varnish + oral health instruction compared to a control (water) + oral health instruction at 3 years follow-up, resulting in a 57% reduced risk (1 trial). The certainty of evidence was downgraded by 1 to low because, while the total sample size at 3 years follow-up was 203 participants, the trial involved a total of 3 test groups, only one of which involved a topical chemical other than fluoride (i.e. CHX). As such, the sample size for this comparison must have been <200. | Moderate | Critically low |
| Slot *et al.* (2011) | Evaluated the current literature to determine the effect of the use of chlorhexidine varnish on root caries incidence and activity. | There was moderate-certainty evidence of significantly lower root caries incidence (measured by Decayed, Missing and Filled Root Surfaces (DMFRS)) in the chlorhexidine varnish group compared to the control/placebo group (3 trials; 2 evaluated 1% chlorhexidine varnish in an elderly population and 1 trial evaluated 10% chlorhexidine varnish in xerostomia patients). The frequency of application was every 3 months | Moderate | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | in two trials, and twice in the first week followed by application at 1, 3, 6, 9, and 12 months in one trial. The follow-up periods for the three trials were 3 years, 1 year and 13 months.<br><br>*Note*. In one out of the three pooled trials, participants received oral health instruction at baseline, and in two out of the three pooled trials, participants received professional prophylaxis, either at baseline or every 3 months alongside the application of chlorhexidine varnish. One of the pooled trials involved the delivery of a complex intervention in which participants received oral health instruction + professional oral prophylaxis (both at baseline) + the application of chlorhexidine varnish. | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low- certainty evidence of a significant reduction in caries increment (measured by increment of Decayed, Missing and Filled Surfaces (DMFS)) following the use of an arginine bicarbonate/calcium phosphate combination toothpaste (3 times daily) compared to fluoride toothpaste at 1 year follow-up. However, the difference between the groups was smaller in magnitude at 2 years follow-up (1 trial).<br><br>There was very low-certainty evidence of a significant reduction in root caries index (RCI) following the application of 1:1 chlorhexidine/thymol varnish + oral health instruction every 3 months compared to oral health instruction alone at 3 years follow-up (1 trial). | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | The certainty of evidence was downgraded to very low because these outcomes were informed by single trials.<br><br>*Note*. The review authors noted that participants in the first trials had exposure to fluoridated salt. However, this was considered background fluoride exposure rather than part of the intervention of interest.<br><br>There was very low-certainty evidence of a significant reduction in caries incidence (measured by increment of Decayed, Missing and Filled Surfaces (DMFS)) in the sucrose-free polyol gum group compared to the no gum group (9 trials). Follow-up periods were 2 years (4 trials), 2.5 years (1 trial), 3 years (3 trials), and 40 months (1 trial). Subgroup analyses showed that xylitol gum has the highest caries reduction effect, followed by gums with a combination of polyols, followed by sorbitol gum. However, when the non-randomised studies were excluded and adjustments were made within the subset of studies with unit of analysis errors, the result in favour of sucrose-free polyol gum became statistically nonsignificant.<br><br>In most of the trials, gum chewing was conducted under supervised conditions, making this analysis of a combined intervention. Frequency of gum chewing was between 2 and 6 times per day with a duration of chewing ranging from 10 to 20 minutes. In the relevant trials, the concentration of sorbitol ranged from 50-70%, the concentration of xylitol ranged from 4.3-65%, the concentration of mannitol ranged | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | from 4-70%, and the concentration of carbamide was 2.3%.<br><br>*Note*. In 7/9 trials, participants had exposure to fluoride (water, toothpaste, mouthrinse, and/or varnish). However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest. | | |
| Tubert-Jeannin *et al.* (2011) | Evaluated the effects of fluoride supplements in the form of tablets (chewable or not), drops, lozenges and chewing gums for preventing dental caries in children. | There was very low-certainty evidence of no significant difference in caries increment (measured by change in Decayed, Missing and filled Surfaces (DMFS) following the combined use of 422mg xylitol + 0.5mg NaF lozenges compared to xylitol-only lozenges at 24 months follow-up (1 trial). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 115 participants.<br><br>*Note*. In this trial, all the participants were encouraged to brush their teeth with fluoride toothpastes two times a day during the entire study period. In addition, participants had exposure to fluoridated water. However, this was considered background fluoride exposure, rather than part of the intervention of interest. | Low | Low |
| Riggs *et al.* (2019) | Assessed the effects of interventions targeted at pregnant women, new mothers, or other primary caregivers of infants in the first year of life, for preventing early childhood caries (from birth to six years of age) . | There was very low-certainty evidence of no significant difference in caries increment (measured by the increment of Decayed, Missing and Filled Teeth (DMFT)) following the combined application of 10% chlorhexidine varnish (four treatments, one per week over four weeks, commencing when offspring were about 6 months old, i.e. around the time of first tooth emergence) + professional prophylaxis prior to the commencement of the trial compared to placebo | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | varnish at 36 months follow-up (1 trial). This outcome was identified as a secondary outcome in the review. The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 66 participants. | | |
| Sealants + other (n = 4) | | | | |
| Kashbour *et al.* (2020) | Evaluated the effectiveness of dental sealants compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | There was very low-certainty evidence of significantly lower likelihood of new caries (measured by mean DMF increment on occlusal surfaces of first permanent molars) following the application of resin-modified glass-ionomer cement + oral health education (1 hour, every 3 months) compared to the application of fluoride varnish (applied biannually) + oral health education among children classified at high-risk for caries at 2 years follow-up (1 trial). There was no statistically significant difference found among children classified as low-risk. The certainty of evidence was downgraded to very low because the findings from this intervention were informed by a single trial with a sample size of 95 participants for this particular comparison.<br><br>There was low-certainty evidence of a slight benefit of resin-based sealant combined with oral health education on caries increment (measured by change from baseline in both Decayed, Missing and Filled Surfaces (DMFS) and Teeth (DMFT)) compared to 0.1% fluoride varnish applied every 6 months (4 applications in total) + oral health education (the frequency of education was not made explicit but appears to be every 3 months) at 2 years follow-up (1 trial). The review authors concluded that the slight benefit that was observed | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | appeared not to be clinically important.<br><br>*Note*. The review authors reported that participants in the first trial also had exposure to fluoride toothpaste (93% of participants) and fluoridated water. However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest. | | |
| Ahovuo-Saloranta *et al*. (2017) | Compared compare the effects of different types of fissure sealants in preventing caries in occlusal surfaces of permanent teeth in children and adolescents at different levels of caries incidence. | There was very low-certainty evidence of significantly smaller likelihood of new caries (measured by mean DMF increment on occlusal surfaces of first permanent molars (DMFS)) with the application of resin-modified glass-ionomer cement + oral health education (1 hour, every 3 months) compared to the application of fluoride varnish (applied biannually) + oral health education among children classified as high-risk for caries at 2 years follow-up (1 trial). There was no statistically significant difference found among children classified as low-risk. The certainty of evidence was downgraded by 2 to very low because this intervention was informed by a single trial with a sample size of 95 for this particular comparison.<br><br>There was low-certainty of evidence (for consistency with Kashbour *et al*. (2020) as using the same trial evidence) of a significant caries preventive effect (measured by increment of Decayed, Missing and Filled Surfaces (DMFS) on permanent molars) following the application of light-cured, fluoride-releasing resin-based sealant + oral health education (the frequency of education delivery was not reported) compared to a control group that received oral health education only at 2 years follow-up (1 trial). | Moderate | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Pagano *et al.* (2020) | Evaluated whether the use of laser at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries and fluoride uptake, and retention of sealant materials by improving traditional etching procedures. | There was very low-certainty evidence of a significant reduction in caries incidence (measured by the number of cases with new caries) following the combined use of CO2 laser with sealants (limited information reported) compared to a control group of untreated teeth at 4 years follow-up, resulting in a 78% reduced risk of developing new caries (1 trial).<br><br>There was very low-certainty evidence of a significant reduction in caries incidence (measured by the number of cases with new caries) following the combined use of Er: YAG laser with sealants (limited information reported) compared to sealant application alone at 18 months follow-up, resulting in a 56% reduced risk of developing new caries (1 trial). | Very low | Critically low |
| Zhang *et al.* (2019) | Assessed the clinical effects of laser preparation compared to other types of chemical or mechanical preparation of the tooth surfaces used in fissure sealant placement. | There was very low-certainty evidence of no significant difference in the incidence of caries on permanent premolars and molars between the Er, Cr: YSGG laser group and the acid etching (control) group prior to application of a light-cure, low-viscosity, fluoride-releasing sealant at 2 years follow-up (1 trial).<br><br>There was very low-certainty evidence of no significant difference in the incidence of caries on first permanent molars between the Er: YAG laser plus acid etching group and the acid etching only (control) group prior to application of a light-cured, nano-filled sealant at 18 months follow-up (1 trial). | Very low | Critically low |
| Complex combined interventions (n = 3) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Antonio *et al.* (2011) | Assessed the overall caries preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. | There was very low-certainty evidence of significant lower caries increment (measured by increment of Decayed, Missing and Filled Surfaces (DMFS) and Teeth (DMFT)) in the 49% xylitol candy group (1 xylitol candy, 3 times every school day) compared to the control group at 1.5 years follow-up (1 trial). Participants in both the intervention and control groups received oral health education, supervised toothbrushing, sealant application, and restorative care. The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 126 (effective sample size was approximately 106 (16.6% dropout)). | Low | Low |
| Kashbour *et al.* (2020) | Evaluated the effectiveness of dental sealants compared with fluoride varnishes, or fissure sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents. | There was very low-certainty evidence of lower caries increment (measured by change from baseline in Decayed, Missing and Filled Surfaces (DMFS) at whole mouth level) between the application of resin-based fissure sealant + fluoride varnish (applied semi-annually, concentration not reported) + oral hygiene instruction + supervised toothbrushing compared to fluoride varnish + oral hygiene instruction + supervised toothbrushing at 2 years follow-up (1 trial). They also found evidence of a significantly lower likelihood of caries incidence (measured by the occurrence of new caries on sound occlusal surfaces). The certainty of evidence was downgraded to very low because this outcome was informed by a single trial with a sample size of 92 participants.<br><br>*Note*. The review authors reported that a small proportion (5%) of participants in this trial also had exposure to fluoride | Low | Low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| | | tablets and the water was fluoridated in the community. However, this was considered existing/background fluoride exposure, rather than part of the interventions of interest. | | |
| Dos Santos *et al.* (2018) | Assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. | There was very low-certainty evidence of significantly higher proportion of children remaining caries-free and significantly lower caries increment (measured by increment of Decayed, Missing and Filled Teeth (DMFT)) following an intervention consisting of 30-min oral hygiene instruction sessions + practical demonstration and application of toothbrushing technique on five consecutive school days, which was repeated twice a year by a dental hygienist and a research assistant + daily school-supervised toothbrushing by a research assistant with the use of 1000 ppm fluoride toothpaste. The comparison group received 30-min oral hygiene instruction sessions on five consecutive school days, which was repeated twice a year by a dental hygienist and a research assistant. At 4 years follow-up, the proportion of children the remained caries-free in primary teeth in the intervention group was 43.6%, compared to 33% in the control group. | Very low | Low |
| Mixed dentition | | | | |
| Attendance for dental assessment (n = 0) | | | | |
| Scheduled dental appointments (n = 0) | | | | |
| Scheduled primary care appointments (n = 0) | | | | |
| Dental hygiene (n = 0) | | | | |
| Supervised toothbrushing (n = 0) | | | | |
| Flossing (n = 0) | | | | |
| Interdental cleaning devices (n = 0) | | | | |
| Professional scaling or cleaning (n = 0) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Systemic fluoride (n = 0) | | | | |
| Milk (n = 0) | | | | |
| Salt (n = 0) | | | | |
| Sugar (n = 0) | | | | |
| Supplements (n = 0) | | | | |
| Other systemic chemicals (n = 1) | | | | |
| Vitamin D (n = 1) | | | | |
| Hujoel (2013) | Assessed the impact of vitamin D on dental caries prevention. | There was low-certainty evidence of a significant caries preventive effect (measured by multiple measures of caries incidence) of vitamin D supplementation (D2, D3, or UV radiation, pooled) compared to a control (24 trials). The specific follow-up period was not specified. However, the review authors note that the median follow-up period across the trials was 12 months. The median dose of vitamin D2 supplementation in the included trials was 3,750 IU and the median dose of vitamin D3 was 800 IU. Either erythemal (4 trials) or full-spectrum fluorescent lighting (2 trials) was used in the trials that examined UV radiation. Subgroup analyses indicated a significant caries preventive effect of all three forms of vitamin D (D2 in 15 trials, D3 in 12 trials, and UV radiation in 6 trials).<br><br>Overall, the review authors concluded that supplemental vitamin D was associated with a 47% reduced risk of caries and may reduce the incidence of dental caries. | Low | Critically low |
| Calcium (n = 0) | | | | |
| Sialagogues (n = 0) | | | | |
| Zinc (n = 0) | | | | |
| Topical fluoride (n = 1) | | | | |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
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| Toothpaste (n = 1) | | | | |
| Figuero *et al.* (2017) | Evaluated the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systemically health patients. | Some results presented in the text of this review are not consistent with results presented in the review tables. As a result of this, and the limited information provided in the review regarding the nature of the interventions and the findings, the findings were excluded from data synthesis. | Very low | Critically low |
| Mouthrinses (n = 1) | | | | |
| Figuero *et al.* (2017) | Evaluated the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systemically health patients. | Some results presented in the text of this review are not consistent with results presented in the review tables. As a result of this, and the limited information provided in the review regarding the nature of the interventions and the findings, the findings were excluded from data synthesis. | Very low | Critically low |
| Foams (n = 0) | | | | |
| Gels (n = 0) | | | | |
| Solution (n = 0) | | | | |
| Slow-release fluoride devices (n = 0) | | | | |
| Varnishes (n = 0) | | | | |
| Mixed (n = 0) | | | | |
| Topical other chemicals (n = 6) | | | | |
| Antioxidants (n = 0) | | | | |
| Toothpaste (n = 0) | | | | |
| Antimicrobial agents (minus CHX) (n = 0) | | | | |
| Arginine and its derivatives (n = 0) | | | | |
| CHX (n = 2) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of no significant difference in caries incidence between those that received a 1:1 chlorhexidine/thymol varnish applied every 3 months (for 1 year in 1 trial and 2 years in the other) and those that received no varnish at 1- and 2-years follow-up (2 trials | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | pooled; 1 on primary dentition and the other on mixed dentition). | | |
| Figuero *et al.* (2017) | Evaluated the effect of mechanical and/or chemical plaque control methods on plaque reduction and on caries increment in systemically health patients. | Some results presented in the text of this review are not consistent with results presented in the review tables. As a result of this, and the limited information provided in the review regarding the nature of the interventions and the findings, the findings were excluded from data synthesis. | Very low | Critically low |
| Calcium phosphate agents (n = 0) | | | | |
| Ozone (n = 0) | | | | |
| Nanomaterials (n = 0) | | | | |
| Probiotics (n = 1) | | | | |
| Poorni *et al.* (2019) | Reviewed the published literature with the purpose of knowing the importance of using various probiotic Streptococcus strains as a preventive and therapeutic method for dental caries management. | There was very low-certainty evidence of a significantly reduced likelihood of developing new dental caries with the use of *salivarius* M18 in lozenges (2 lozenges per day for 3 months) compared to a placebo (1 trial). No follow-up period was reported. Limited information was provided, including information pertaining to the type of dentition examined. | Very low | Critically low |
| Propolis (n = 0) | | | | |
| Silicates (n = 0) | | | | |
| Xylitol (n = 4) | | | | |
| Marghalani *et al.* (2017) | Evaluated the effectiveness of xylitol in reducing dental caries in children compared to no treatment, a placebo, or preventive strategies. | There was very low-certainty evidence of significantly lower caries increment (measured by mean Decayed, Missing and Filled Surfaces/Teeth (DMFS/T) and decayed, missing and filled surfaces/teeth (dmfs/t)) with the use of xylitol (gum in 6 trials, toothpaste in 2 trials, lozenges in 1 trial, and wipes in 1 trial) compared to no xylitol control groups at at least 1 year follow-up (10 trials). The dose of xylitol in gum was 2.5g/day (1 trial), 2.9g/day (1 trial), 4.3-8.5g/day (1 trial), 5g/day (2 trials) and 10.67g/day (1 trial). The dose of xylitol in | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | toothpaste 10% (2 trials). The dose of xylitol provided in lozenges was 2.5g/day (1 trial). The dose of xylitol provided in wipes was 4.2g/day (1 trial). Overall, the review authors reported a small potential benefit of xylitol at reducing caries incidence the permanent dentition of in children. The results also showed the effect of xylitol may be greater with higher xylitol doses (greater than 4g per day). This potential effect of dosage was observational, as dose was not randomized in the included trials.<br><br>*Note*. 2/10 included trials involved a combined intervention (the first involved supervised toothbrushing at home and at school twice per day with toothpaste containing 10% xylitol + 0.243% NaF/silica, and the second involved supervised toothbrushing at home and at school twice per day with toothpaste containing10% xylitol + 0.836% sodium monofluorophosphate (MFP) toothpaste (1100 ppm F) in dicalcium phosphate dihydrate base). | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of reduced caries incidence (measured by Decayed, Missing and Filled Surfaces (DMFS) scores in 2 trials, and decayed, missing and filled surfaces (dmfs) scores in 1 trial) with the use of xylitol candies/syrup compared to a control (no candy or lower concentration 2.67g/day xylitol syrup) (3 trials pooled; 2 in permanent dentition and 1 in primary dentition). In 2 trials, participants chewed candies three times a day for 5-10 minutes (frequency was not reported in the trial that tested syrup). Follow-up periods were 10 months, 1.5 years and 3 years. The concentration of xylitol in candy was 49% in the 2 | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | trials that reported concentration.<br><br>*Note*. In one of these pooled trials, the xylitol candy also contained one of two sweeteners (mannitol or polydextrose)<br><br>There was very low-certainty evidence of reduced caries incidence (measured by Decayed, Missing and Filled Surfaces (DMFS) scores and the presence of caries lesions in primary teeth) with the use of xylitol chewing gum (varied concentrations, chewing times and frequencies) compared to the use of sorbitol chewing gum at 24 months-40 months follow-up (3 trials). In the first trial, participants chewed 589mg xylitol gum five times per day for 10 min. In the second trial, participants chewed 65% xylitol gum three times per day (4.3g/day) or five times per day (8.5g/day). In the third trial, participants chewed 60.5% xylitol gum (10.42g/day) or 65% xylitol gum (10.67 g/day) 10 times per day. The follow-up periods were 2 years, 40 months and 3 years. Overall, in children aged 5-16 years, supervised consumption of chewing gum sweetened with sucrose-free polyol (xylitol only or polyol combinations) for 10-20 minutes after meals marginally reduced incidence of caries. | | |
| Newton *et al.* (2020) | Examined the difference in level of dental caries in adults and children who chew sugar-free gum (SFG), compared with those who do not chew SFG or use alternatives such as lozenges, candies, rinses, tablets and other non-chewing controls. | There was very low-certainty evidence of a significant caries preventive benefit (measured by increment of Decayed, Missing and Filled Surfaces/Teeth (DMFS/T) and decayed, missing and filled surfaces/teeth (dmfs/t)) with the use of xylitol gum compared to a control/no treatment group (8 trials). Follow-up periods were 6 months (1 trial), 9 months (1 | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | trial), 18 months (1 trial), 2 years (1 trial), 3 years (1 trial), 5 years (2 trials), and 6 years (1 trial). | | |
| Riley *et al.* (2015) | Assessed the effects of different xylitol-containing products on preventing dental caries in children and adults. | Only one trial compared xylitol (7.5 g per day) candy with control (sorbitol) candy over 36 months (assumed mixed dentition). However, the review authors were unable to use the data in analyses and the findings were therefore not reported.<br><br>None of the included trials reported on the effect of xylitol-containing candy, syrup, sucking tablets, (non-fluoride) toothpaste, tablets, or wipes (measured by increment of Decayed, Missing and Filled Surfaces (DMFS/dmfs)) in mixed dentition. | Moderate | Low |
| Sorbitol (n = 0) | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 0) | | | | |
| Sealants (n = 1) | | | | |
| Resin (n = 0) | | | | |
| Glass-ionomer (n = 0) | | | | |
| Ormocer (n = 0) | | | | |
| Hybrid (n = 0) | | | | |
| Combined (n = 0) | | | | |
| Other (n = 1) | | | | |
| Singal *et al.* (2022) | Reviewed the evidence for the remineralising and caries preventive efficacy of various CaP (calcium phosphate) derivatives. | There was very low-certainty evidence of an added caries preventive benefit (measured by the number of children with new carious lesions) with the use of Amorphous Calcium Phosphate-based sealant (ACP) compared to the use of a fluoride-based sealant (limited information provided) at 12 months follow-up (1 trial). The certainty of evidence was | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | downgraded to very low because this outcome was informed by a single trial with a sample size of 64 participants. | | |
| Laser (n = 0) | | | | |
| Subgroup: Mother of unborn/toddlers (treatment given to mothers, outcomes tested on mixed dentition of offspring) | | | | |
| Other systemic chemicals (n = 1) | | | | |
| Calcium (n = 1) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of a 27% reduction in the risk of developing caries (measured by the decayed, missing and filled teeth (dmft/DMFT) index) in the dentition of offspring with the use of non-fluoride agents (calcium supplementation, 2 g/day) in mothers compared to a placebo at 12 years follow-up (1 trial). The statistical significance of this finding was not reported. | Very low | Critically low |
| Subgroup: Combined interventions in mixed dentition | | | | |
| Topical fluoride + topical other chemicals (n = 2) | | | | |
| Gupta *et al.* (2020b) | Compared the effectiveness of combined therapy using topical fluoride along with an antimicrobial agent (Povidone Iodine/Chlorhexidine/Xylitol/Triclosan/Cetylpyridinium Chloride) versus topical fluoride monotherapy in preventing dental caries among 1- to 16-year-old children. | There was low-certainty evidence of a significantly lower caries increment (precise measure varied; mean number of decayed surfaces (ds) in 1 trial, incidence of caries (unspecified) in 2 trials, and mean increment of Decayed and Filled Surfaces (DFS) in 2 trials) following the combined use of topical fluoride (toothpaste in 4 trials, gel in 1 trial) and antimicrobial agents (chlorhexidine gel in 2 trials, povidone-iodine gel in 1 trial, and xylitol-containing toothpaste in 2 trials) compared to topical fluoride alone at 1-3 years follow-up (5 trials). Frequency and dosage of topical fluoride and antimicrobial agents varied. The review authors noted, however, that this result was driven by two studies on topical fluoride + xylitol combined therapy by the same trial authors. | Low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | *Note*. 2/5 included trials involved complex interventions (in addition to FT + xylitol, oral health education + dietary counselling was provided in 1 trial, and oral prophylaxis + restorative therapy was provided in another trial). | | |
| Sharda *et al.* (2021) | Compared the remineralising potential and caries preventive efficacy of combined therapy using CPP-ACP/bioactive glass/xylitol/ozone and topical fluoride versus topical fluoride monotherapy on high-risk individuals. | There was low-certainty evidence of a significant caries preventive benefit (measured by the mean increment of Decayed, Missing and Filled Surfaces/Teeth (DMFS/T and dmfs/t) and proportion of participants with new carious lesions) of the combined use of topical fluoride (400-1100 ppm fluoride toothpaste) and other topical chemicals (10% CPP-ACP cream in 2 trials, 3% CPP-ACP gum in 1 trial, 10% xylitol in toothpaste in two trials) compared to topical fluoride use alone at 2-3 years follow-up (5 trials). Subgroup analysis showed that this effect was largely a result of the 2 trials that included xylitol + fluoride toothpaste (the use of CPP-ACP + fluoride was not significant). This outcome was identified as a secondary outcome in the review. | Low | Critically low |
| Topical other chemicals + topical other chemicals (n = 1) | | | | |
| Rethman *et al.* (2011) | Presented evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the United States. | There was very low-certainty evidence of a significant reduction in caries increment (measured by the Decayed, Missing and Filled Surfaces (DMFS) index and the decayed, extracted and filled surfaces (defs) index) with the consumption of a sugarless confection (mints) containing arginine bicarbonate/calcium carbonate (2 mints, twice daily) compared to sugarless mints without arginine bicarbonate/calcium carbonate at 12 months follow-up (1 trial).<br><br>*Note*. It was not clear if the outcome pertained to primary | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | | and permanent dentition separately, or to mixed dentition. As such, this finding was coded under mixed dentition. | | |
| Topical other chemicals + other (n = 1) | | | | |
| Zhou *et al.* (2019) | Investigated the efficacy of strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. | The only relevant included trial reported on the effect of calcium sucrose phosphate (vs fluoride) toothpaste used via powered (vs manual) toothbrushes. The results were not presented in a way that is appropriate for the purposes of this umbrella review and limited information was provided. Therefore, the findings were excluded from data synthesis. | Low | Critically low |
| Complex combined interventions (n = 2) | | | | |
| Yu *et al.* (2021) | Assessed whether the combined use of professional fluoride application and regular fluoride toothpaste has additional benefit than using regular fluoride toothpaste alone for children under 16. | There was moderate-certainty evidence of no significant difference in caries incidence with the combined use of 5% NaF varnish applied every 6 months + fluoride toothpaste (1000-1450 ppm) + additional active intervention components (oral health education/counselling was provided in 3 trials, dietary counselling in 2 trials, supervised toothbrushing in 1 trial, and "usual care" in 1 trial) compared to control groups that received all active intervention components with the exception of the fluoride varnish, at 24-36 months follow-up (4 trials). 1/4 pooled trials reported on mixed dentition, and the remaining 3 reported on primary dentition.<br><br>*Note*. At least 2/6 included trials reported some exposure to fluoride (either water or milk). However, this was existing/background fluoride exposure, rather than part of the interventions of interest. | Moderate | Critically low |
| Figuero *et al.* (2017) | Evaluated the effect of mechanical and/or chemical plaque control methods on plaque | Some results presented in the text of this review are not consistent with results presented in the review tables. As a | Very low | Critically low |

| Author (year) | Research question | Evidence summary | Overall GRADE or certainty of evidence | Overall AMSTAR rating of review |
|---|---|---|---|---|
| | reduction and on caries increment in systemically health patients. | result of this, and the limited information provided in the review regarding the nature of the interventions and the findings, the findings were excluded from data synthesis. | | |

# Appendix K GRADE assessment results for included reviews

*Table 103 GRADE assessment results for included reviews*

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary dentition | | | | | | | | | | | |
| Attendance for dental assessment (n = 3) | | | | | | | | | | | |
| Scheduled dental appointments (n = 2) | | | | | | | | | | | |
| Fee *et al.* (2020) | RCT (2) | Moderate | 0 | -1 | -1 | N/A | 0 | 0 | -2 | | Moderate |
| Joury *et al.* (2017) | Total: RCT (5); Included: RCT (1) | Critically low | 0 | 0 | 0 | N/A | 0 | -2 | -2 | | Moderate |
| Scheduled primary care appointments (n = 1) | | | | | | | | | | | |
| Chou *et al.* (2021) | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (3) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Dental hygiene (n = 3) | | | | | | | | | | | |
| Supervised toothbrushing (n = 3) | | | | | | | | | | | |
| Hujoel *et al.* (2018) | RCT (3) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Akera *et al.* (2022) | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Dos Santos *et al.* (2018) | RCT/quasi-RCT (4) | Critically low | -1 | -1 | -1 | N/A | -2 | -2 | -7 | | Very low |
| Flossing (n = 0) | | | | | | | | | | | |
| Interdental cleaning devices (n = 0) | | | | | | | | | | | |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | |
| Systemic fluoride (n = 5) | | | | | | | | | | | |
| Milk (n = 2) | | | | | | | | | | | |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Yeung *et al.* (2015) | RCT (1) | Moderate | 0 | -1 | 0 | N/A | -1 | 0 | -2 | Yes | Very low |
| Cagetti *et al.* (2012) | Clinical trials (3) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Salt (n = 1) | | | | | | | | | | | |
| Cagetti *et al.* (2012) | Clinical trials (3) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Sugar (n = 1) | | | | | | | | | | | |
| Cagetti *et al.* (2012) | Clinical trials (3) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Supplements (n = 3) | | | | | | | | | | | |
| Tubert-Jeannin *et al.* (2011) | RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Zhou *et al.* (2019) | Total: RCT (7); non-RCT (7); Included: RCT (2); non-RCT (1) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Chou *et al.* (2021) | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (3) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Other systemic chemicals (n = 1) | | | | | | | | | | | |
| Vitamin D (n = 0) | | | | | | | | | | | |
| Calcium (n = 0) | | | | | | | | | | | |
| Sialagogues (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Zinc (n = 0) | | | | | | | | | | | |
| Topical fluoride (n = 9) | | | | | | | | | | | |
| Toothpaste (n = 2) | | | | | | | | | | | |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Walsh *et al.* (2019) | Total: RCT (96); Included: RCT (27) | Critically low | 0 | -1 | 0 | -1 | 0 | -2 | -4 | | Low |
| Santos *et al.* (2013) | RCT/non-RCT (5) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Mouthrinses (n = 0) | | | | | | | | | | | |
| Foams (n = 0) | | | | | | | | | | | |
| Gels (n = 1) | | | | | | | | | | | |
| Marinho *et al.* (2015) | RCT (27), cluster RCT (1) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Solution (n = 2) | | | | | | | | | | | |
| Oliveira *et al.* (2019) | RCT (4) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Chou *et al.* (2021) | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (3) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Slow-release fluoride devices (n = 1) | | | | | | | | | | | |
| Chong *et al.* (2018) | RCT (1) | Low | 0 | 0 | 0 | N/A | -2 | -1 | -3 | Yes | Very low |
| Varnishes (n = 3) | | | | | | | | | | | |
| Marinho *et al.* (2013) | RCT/quasi-RCT (17), cluster RCT (5) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Carvalho *et al.* (2010) | Total: Cluster RCT (2), RCT (6); Included: Cluster RCT (2), RCT (5) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Smith *et al.* (2018) | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Mixed (n = 0) | | | | | | | | | | | |
| Topical other chemicals (n = 11) | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 2) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | | | | | | | | | |
| Wang *et al.* (2017) | Total: RCT (14); Included: RCT (13) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Arginine and its derivatives (n = 0) | | | | | | | | | | | |
| CHX (n = 5) | | | | | | | | | | | |
| Walsh *et al.* (2015) | RCT (6), cluster RCT (2) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| James *et al.* (2010) | RCT/quasi-RCT (12) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Wang *et al.* (2017) | Total: RCT (14); Included: RCT (13) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Smith *et al.* (2018) | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Calcium phosphate agents (n = 3) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Wang *et al.* (2017) | Total: RCT (14); Included: RCT (13) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Singal *et al.* (2022) | Total: RCT (26); Included: RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Ozone (n = 0) | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | |
| Probiotics (n = 3) | | | | | | | | | | | |
| Hao *et al.* (2021) | RCT (10) | Critically low | 0 | -1 | -1 | N/A | -2 | -2 | -6 | | Very low |
| Jørgensen *et al.* (2016) | Total: Cluster RCT (2), RCT (5); Included: Cluster RCT (1), RCT (1) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Twetman *et al.* (2021) | Total: RCT (9); Included: RCT (7) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Propolis (n = 0) | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | |
| Riley *et al.* (2015) | Cluster RCT (2); RCT (8) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Chou *et al.* (2021) | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (3) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Wang *et al.* (2017) | Total: RCT (14); Included: RCT (13) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Sorbitol (n = 0) | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | | | | | | | | | |
| Sealants (n = 3) | | | | | | | | | | | |
| Resin (n = 2) | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | RCT (9) | Moderate | 0 | -1 | -1 | N/A | 0 | 0 | -2 | | Moderate |
| Lam *et al.* (2020) | RCT (7) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Glass-ionomer (n = 2) | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | RCT (9) | Moderate | 0 | -1 | -1 | N/A | 0 | 0 | -2 | | Moderate |
| Lam *et al.* (2020) | RCT (7) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Ormocer (n = 0) | | | | | | | | | | | |
| Hybrid (n = 0) | | | | | | | | | | | |
| Combined (n = 1) | | | | | | | | | | | |
| Akera *et al.* (2022) | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Other (n = 0) | | | | | | | | | | | |
| Laser (n = 1) | | | | | | | | | | | |
| Pagano *et al.* (2020) | RCT (7); controlled clinical trials (2) | Critically low | -1 | -1 | -1 | 0 | 0 | -2 | -5 | | Very low |
| Subgroup: Mother of unborn/toddlers (treatment given to mothers, outcomes tested on children) | | | | | | | | | | | |
| Systemic fluoride (n = 2) | | | | | | | | | | | |
| Supplements (n = 2) | | | | | | | | | | | |
| Takahashi *et al.* (2017) | RCT (1) | Moderate | 0 | -1 | -1 | N/A | 0 | 0 | -2 | Yes | Very low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Xiao *et al.* (2019) | Total: RCT (3), prospective cohort study (1), nested case-control cohort study (1); Included: RCT (2), prospective cohort study (1) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Topical other chemicals (n = 2) | | | | | | | | | | | |
| Xylitol (n = 2) | | | | | | | | | | | |
| Riggs *et al.* (2019) | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Xiao *et al.* (2019) | Total: RCT (3), prospective cohort study (1), nested case-control cohort study (1); Included: RCT (2), prospective cohort study (1) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Topical other chemicals (n = 3) | | | | | | | | | | | |
| CHX (n = 3) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Smith *et al.* (2018) | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Riggs *et al.* (2019) | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Subgroup: Combined interventions delivered to mothers of unborn/toddlers | | | | | | | | | | | |
| Topical other chemicals + topical other chemicals (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | | | | | | | | | |
| Topical other chemicals + other (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| CHX + other (n = 1) | | | | | | | | | | | |
| Riggs *et al.* (2019) | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Complex combined interventions (n = 1) | | | | | | | | | | | |
| Xiao *et al.* (2019) | Total: RCT (3), prospective cohort study (1), nested case-control cohort study (1); Included: RCT (2), prospective cohort study (1) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Subgroup: Combined interventions in primary dentition | | | | | | | | | | | |
| Topical fluoride + topical fluoride (n = 1) | | | | | | | | | | | |
| Carvalho *et al.* (2010) | Total: Cluster RCT (2), RCT (6); Included: Cluster RCT (2), RCT (5) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Topical fluoride + topical other chemicals (n = 4) | | | | | | | | | | | |
| Wang *et al.* (2017) | Total: RCT (14); Included: RCT (13) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Walsh *et al.* (2015) | RCT (6), cluster RCT (2) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Singal *et al.* (2022) | Total: RCT (26); Included: RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gupta *et al.* (2020a) | Total: RCT (5), non-RCT (1), retrospective cohort study (1); Included: RCT (5), non-RCT (1) | Critically low | -1 | -1 | -1 | 0 | -1 | -2 | -6 | | Very low |
| Topical fluoride + other (n = 7) | | | | | | | | | | | |
| Smith *et al.* (2018) | Total: Cluster RCT (3), RCT (1); Included: Cluster RCT (1), RCT (1) | Critically low | 0 | -1 | 0 | N/A | 0 | -2 | -3 | | Low |
| Lam *et al.* (2020) | RCT (7) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Dos Santos *et al.* (2018) | RCT/quasi-RCT (4) | Critically low | -1 | -1 | -1 | N/A | -2 | -2 | -7 | | Very low |
| Walsh *et al.* (2019) | Total: RCT (96); Included: RCT (27) | Critically low | 0 | -1 | 0 | -1 | 0 | -2 | -4 | | Low |
| Dos Santos *et al.* (2013) | RCT (8) | Critically low | 0 | -1 | 0 | -1 | 0 | -2 | -4 | | Low |
| Marinho *et al.* (2016) | Cluster RCT (1); RCT/quasi-RCT (36) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| de Sousa *et al.* (2019) | Cluster RCT (6), RCT (14) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |
| Systemic fluoride + topical other chemicals (n = 1) | | | | | | | | | | | |
| Jørgensen *et al.* (2016) | Total: Cluster RCT (2), RCT (5); Included: Cluster RCT (1), RCT (1) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Sealants + other (n = 1) | | | | | | | | | | | |
| Ramamurthy *et al.* (2022) | RCT (9) | Moderate | 0 | -1 | -1 | N/A | 0 | 0 | -2 | | Moderate |
| Complex combined interventions (n = 4) | | | | | | | | | | | |
| Yu *et al.* (2021) | Cluster RCT (3); RCT (3) | Critically low | 0 | 0 | 0 | 0 | 0 | -2 | -2 | | Moderate |
| de Sousa *et al.* (2019) | Cluster RCT (6), RCT (14) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |
| Chou *et al.* (2021) | Total: RCT (19), non-RCT (4), observational studies (9), systematic review (1); Included: RCT (19), non-RCT (3) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Dos Santos *et al.* (2018) | RCT/quasi-RCT (4) | Critically low | -1 | -1 | -1 | N/A | -2 | -2 | -7 | | Very low |
| Permanent dentition | | | | | | | | | | | |
| Attendance for dental assessment (n = 2) | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Scheduled dental appointments (n = 2) | | | | | | | | | | | |
| Fee *et al.* (2020) | RCT (2) | Moderate | 0 | -1 | -1 | N/A | 0 | 0 | -2 | | Moderate |
| Joury *et al.* (2017) | Total: RCT (5); Included: RCT (1) | Critically low | 0 | 0 | 0 | N/A | 0 | -2 | -2 | | Moderate |
| Scheduled primary care appointments (n = 0) | | | | | | | | | | | |
| Dental hygiene (n = 3) | | | | | | | | | | | |
| Supervised toothbrushing (n = 2) | | | | | | | | | | | |
| Hujoel *et al.* (2018) | RCT (3) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Dos Santos *et al.* (2018) | RCT/quasi-RCT (4) | Critically low | -1 | -1 | -1 | N/A | -2 | -2 | -7 | | Very low |
| Flossing (n = 0) | | | | | | | | | | | |
| Interdental cleaning devices (n = 1) | | | | | | | | | | | |
| Worthington *et al.* (2019) | RCT (35) | Low | 0 | -1 | -1 | -1 | 0 | -1 | -4 | | Low |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | |
| Systemic fluoride (n = 4) | | | | | | | | | | | |
| Milk (n = 2) | | | | | | | | | | | |
| Yeung *et al.* (2015) | RCT (1) | Moderate | 0 | -1 | 0 | N/A | -1 | 0 | -2 | Yes | Very low |
| Cagetti *et al.* (2012) | Clinical trials (3) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Salt (n = 2) | | | | | | | | | | | |
| Cagetti *et al.* (2012) | Clinical trials (3) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Sugar (n = 2) | | | | | | | | | | | |
| Cagetti *et al.* (2012) | Clinical trials (3) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Supplements (n = 2) | | | | | | | | | | | |
| Tubert-Jeannin *et al.* (2011) | RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Zhou *et al.* (2019) | Total: RCT (7); non-RCT (7); Included: RCT (2); non-RCT (1) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Other systemic chemicals (n = 1) | | | | | | | | | | | |
| Vitamin D (n = 0) | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Calcium (n = 0) | | | | | | | | | | | |
| Sialagogues (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Zinc (n = 0) | | | | | | | | | | | |
| Topical fluoride (n = 9) | | | | | | | | | | | |
| Toothpaste (n = 2) | | | | | | | | | | | |
| Walsh *et al.* (2019) | Total: RCT (96); Included: RCT (27) | Critically low | 0 | -1 | 0 | -1 | 0 | -2 | -4 | | Low |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Mouthrinses (n = 2) | | | | | | | | | | | |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Wierichs *et al.* (2015) | Total: RCT (29), non-RCT (1); Included: RCT (18), non-RCT (1) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Foams (n = 0) | | | | | | | | | | | |
| Gels (n = 3) | | | | | | | | | | | |
| Marinho *et al.* (2015) | RCT (27), cluster RCT (1) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Chan *et al.* (2022) | Clinical trials (7) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Solution (n = 4) | | | | | | | | | | | |
| Grandjean *et al.* (2021) | RCT (3) | Critically low | 0 | 0 | -1 | 0 | 0 | -2 | -3 | | Low |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Subbiah *et al.* (2018) | Total: RCT (3); Included: RCT (2) | Critically low | 0 | 0 | 0 | N/A | 0 | -2 | -2 | | Moderate |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Chan *et al.* (2022) | Clinical trials (7) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Slow-release fluoride devices (n = 1) | | | | | | | | | | | |
| Chong *et al.* (2018) | RCT (1) | Low | 0 | 0 | 0 | N/A | -2 | -1 | -3 | Yes | Very low |
| Varnishes (n = 4) | | | | | | | | | | | |
| Marinho *et al.* (2013) | RCT/quasi-RCT (17), cluster RCT (5) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Wierichs *et al.* (2015) | Total: RCT (29), non-RCT (1); Included: RCT (18), non-RCT (1) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Chan *et al.* (2022) | Clinical trials (7) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Mixed (n = 0) | | | | | | | | | | | |
| Topical other chemicals (n = 8) | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Arginine and its derivatives (n = 0) | | | | | | | | | | | |
| CHX (n = 4) | | | | | | | | | | | |
| Walsh *et al.* (2015) | RCT (6), cluster RCT (2) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Wierichs *et al.* (2015) | Total: RCT (29), non-RCT (1); Included: RCT (18), non-RCT (1) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| James *et al.* (2010) | RCT/quasi-RCT (12) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Calcium phosphate agents (n = 2) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Singal *et al.* (2022) | Total: RCT (26); Included: RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Ozone (n = 0) | | | | | | | | | | | |
| Nanomaterials (n = 0) | | | | | | | | | | | |
| Probiotics (n = 0) | | | | | | | | | | | |
| Propolis (n = 0) | | | | | | | | | | | |
| Silicates (n = 0) | | | | | | | | | | | |
| Xylitol (n = 4) | | | | | | | | | | | |
| Riley *et al.* (2015) | Cluster RCT (2); RCT (8) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| | (7), clinical controlled trials (8) | | | | | | | | | | |
| Riggs *et al.* (2019) | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Antonio *et al.* (2011) | Clinical controlled trial (1), RCT (2) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Sorbitol (n = 0) | | | | | | | | | | | |
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 2) | | | | | | | | | | | |
| Antonio *et al.* (2011) | Clinical controlled trial (1), RCT (2) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Sealants (n = 10) | | | | | | | | | | | |
| Resin (n = 8) | | | | | | | | | | | |
| Alsabek *et al.* (2021) | RCT (13) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Alirezaei *et al.* (2018) | Total: RCT (31); Included: RCT (28) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |
| Alharthy *et al.* (2022) | RCT (7), non-RCT (5) | Critically low | -1 | -1 | -1 | 0 | 0 | -2 | -5 | | Very low |
| Rashed *et al.* (2022) | RCT (4) | Critically low | 0 | -1 | 0 | -1 | 0 | -2 | -4 | | Low |
| Kashbour *et al.* (2020) | Total: RCT (11) ; Included: RCT (10) | Low | 0 | -1 | -1 | -1 | 0 | -1 | -4 | | Low |
| Ahovuo-Saloranta *et al.* (2017) | RCT (38) | Low | 0 | 0 | -1 | 0 | 0 | -1 | -2 | | Low |
| CADTH (2016) | Total: Systematic review (4), randomised controlled trials (4), retrospective cohort study (1), evidence-based clinical practice guideline (1); Included: RCT (4) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Li *et al.* (2020) | RCT (8) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |
| Glass-ionomer (n = 4) | | | | | | | | | | | |
| Kashbour *et al.* (2020) | Total: RCT (11) ; Included: RCT (10) | Low | 0 | -1 | -1 | -1 | 0 | -1 | -4 | | Low |
| Ahovuo-Saloranta *et al.* (2017) | RCT (38) | Low | 0 | 0 | -1 | 0 | 0 | -1 | -2 | | Moderate |
| Wright *et al.* (2016) | RCT (23) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| CADTH (2016) | Total: Systematic review (4), randomised controlled trials (4), retrospective cohort study (1), evidence-based clinical practice guideline (1); Included: RCT (4) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Ormocer (n = 1) | | | | | | | | | | | |
| Ahovuo-Saloranta *et al.* (2017) | RCT (38) | Low | 0 | 0 | -1 | 0 | 0 | -1 | -2 | | Moderate |
| Hybrid (n = 1) | | | | | | | | | | | |
| Wright *et al.* (2016) | RCT (23) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |
| Combined (n = 4) | | | | | | | | | | | |
| Wright *et al.* (2016) | RCT (23) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |
| CADTH (2016) | Total: Systematic review (4), randomised controlled trials (4), retrospective cohort study (1), evidence-based clinical practice guideline (1); Included: RCT (4) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Akera *et al.* (2022) | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Li *et al.* (2020) | RCT (8) | Critically low | 0 | -1 | -1 | -1 | 0 | -2 | -5 | | Very low |
| Other (n = 0) | | | | | | | | | | | |
| Laser (n = 1) | | | | | | | | | | | |
| Pagano *et al.* (2020) | RCT (7); controlled clinical trials (2) | Critically low | -1 | -1 | -1 | 0 | 0 | -2 | -5 | | Very low |
| Subgroup: Combined interventions in permanent dentition | | | | | | | | | | | |
| Topical fluoride + topical fluoride (n = 4) | | | | | | | | | | | |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Yu *et al.* (2021) | Cluster RCT (3); RCT (3) | Critically low | 0 | 0 | 0 | 0 | 0 | -2 | -2 | | Moderate |
| Wierichs *et al.* (2015) | Total: RCT (29), non-RCT (1); Included: RCT (18), non-RCT (1) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Chan *et al.* (2022) | Clinical trials (7) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Topical fluoride + topical other chemicals (n = 4) | | | | | | | | | | | |
| Gupta *et al.* (2020a) | Total: RCT (5), non-RCT (1), retrospective cohort study (1); Included: RCT (5), non-RCT (1) | Critically low | -1 | -1 | -1 | 0 | -1 | -2 | -6 | | Very low |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Singal *et al.* (2022) | Total: RCT (26); Included: RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Riley *et al.* (2015) | Cluster RCT (2); RCT (8) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Topical fluoride + other (n = 8) | | | | | | | | | | | |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Dos Santos *et al.* (2018) | RCT/quasi-RCT (4) | Critically low | -1 | -1 | -1 | N/A | -2 | -2 | -7 | | Very low |
| Walsh *et al.* (2019) | Total: RCT (96); Included: RCT (27) | Critically low | 0 | -1 | 0 | -1 | 0 | -2 | -4 | | Low |
| Konradsson *et al.* (2020) | Total: RCT (13), in-situ (7), non-RCT (1); Included: RCT (1) | Critically low | 0 | -1 | -1 | N/A | 0 | -2 | -4 | | Low |
| Marinho *et al.* (2016) | Cluster RCT (1); RCT/quasi-RCT (36) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Pagano *et al.* (2020) | RCT (7); controlled clinical trials (2) | Critically low | -1 | -1 | -1 | 0 | 0 | -2 | -5 | | Very low |
| Riggs *et al.* (2019) | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Akera *et al.* (2022) | Total: Cluster RCT (24), non-RCT (2), quasi-experiments (4), cohort studies (4); Included: Cluster RCT (2), quasi-experiment (1) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Topical fluoride + oral health instruction/education (n = 5) | | | | | | | | | | | |
| Hendre *et al.* (2017) | RCT (3) | Critically low | 0 | 0 | 0 | N/A | 0 | -2 | -2 | | Moderate |
| Oliveira *et al.* (2018) | RCT (3) | Critically low | 0 | 0 | 0 | -1 | 0 | -2 | -3 | | Low |
| Subbiah *et al.* (2018) | Total: RCT (3); Included: RCT (2) | Critically low | 0 | 0 | 0 | N/A | 0 | -2 | -2 | | Moderate |
| Zhang *et al.* (2020) | Clinical controlled trial (9) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Chan *et al.* (2022) | Clinical trials (7) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Topical other chemicals + other (n = 6) | | | | | | | | | | | |
| Hendre *et al.* (2017) | RCT (3) | Critically low | 0 | 0 | 0 | N/A | 0 | -2 | -2 | | Moderate |
| Slot *et al.* (2011) | RCT (6) | Critically low | 0 | 0 | 0 | N/A | 0 | -2 | -2 | | Moderate |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Tubert-Jeannin *et al.* (2011) | RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Riggs *et al.* (2019) | Total: RCT (12), cluster RCT (5); Included: RCT (6) | Low | 0 | -1 | -1 | 0 | 0 | -1 | -3 | | Low |
| Antonio *et al.* (2011) | Clinical controlled trial (1), RCT (2) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Sealants + other (n = 4) | | | | | | | | | | | |
| Kashbour *et al.* (2020) | Total: RCT (11); Included: RCT (10) | Low | 0 | -1 | -1 | -1 | 0 | -1 | -4 | | Low |
| Ahovuo-Saloranta *et al.* (2017) | RCT (38) | Low | 0 | 0 | -1 | 0 | 0 | -1 | -2 | | Moderate |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Pagano *et al.* (2020) | RCT (7); controlled clinical trials (2) | Critically low | -1 | -1 | -1 | 0 | 0 | -2 | -5 | | Very low |
| Zhang *et al.* (2019) | RCT (5) | Critically low | 0 | -1 | 0 | 0 | -2 | -2 | -5 | | Very low |
| Complex combined interventions (n = 3) | | | | | | | | | | | |
| Kashbour *et al.* (2020) | Total: RCT (11); Included: RCT (10) | Low | 0 | -1 | -1 | -1 | 0 | -1 | -4 | | Low |
| Antonio *et al.* (2011) | Clinical controlled trial (1), RCT (2) | Critically low | -1 | -1 | -1 | N/A | 0 | -2 | -5 | | Very low |
| Dos Santos *et al.* (2018) | RCT/quasi-RCT (4) | Critically low | -1 | -1 | -1 | N/A | -2 | -2 | -7 | | Very low |
| Mixed dentition | | | | | | | | | | | |
| Attendance for dental assessment (n = 0) | | | | | | | | | | | |
| Scheduled dental appointments (n = 0) | | | | | | | | | | | |
| Scheduled primary care appointments (n = 0) | | | | | | | | | | | |
| Dental hygiene (n = 0) | | | | | | | | | | | |
| Supervised toothbrushing (n = 0) | | | | | | | | | | | |
| Flossing (n = 0) | | | | | | | | | | | |
| Interdental cleaning devices (n = 0) | | | | | | | | | | | |
| Professional scaling or cleaning (n = 0) | | | | | | | | | | | |
| Systemic fluoride (n = 0) | | | | | | | | | | | |
| Milk (n = 0) | | | | | | | | | | | |
| Salt (n = 0) | | | | | | | | | | | |
| Sugar (n = 0) | | | | | | | | | | | |
| Supplements (n = 0) | | | | | | | | | | | |
| Other systemic chemicals (n = 1) | | | | | | | | | | | |
| Vitamin D (n = 1) | | | | | | | | | | | |
| Hujoel (2013) | Cluster RCT (11), RCT (13) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Calcium (n = 0) | | | | | | | | | | | |
| Sialagogues (n = 0) | | | | | | | | | | | |
| Zinc (n = 0) | | | | | | | | | | | |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Topical fluoride (n = 1) | | | | | | | | | | | |
| Toothpaste (n = 1) | | | | | | | | | | | |
| Figuero *et al.* (2017) | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: RCT (15), clinical controlled trials (9) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Mouthrinses (n = 1) | | | | | | | | | | | |
| Figuero *et al.* (2017) | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: RCT (15), clinical controlled trials (9) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Foams (n = 0) | | | | | | | | | | | |
| Gels (n = 0) | | | | | | | | | | | |
| Solution (n = 0) | | | | | | | | | | | |
| Slow-release fluoride devices (n = 0) | | | | | | | | | | | |
| Varnishes (n = 0) | | | | | | | | | | | |
| Mixed (n = 0) | | | | | | | | | | | |
| Topical other chemicals (n = 7) | | | | | | | | | | | |
| Antioxidants (n = 0) | | | | | | | | | | | |
| Toothpaste (n = 0) | | | | | | | | | | | |
| Antimicrobial agents (minus CHX) (n = 0) | | | | | | | | | | | |
| Arginine and its derivatives (n = 0) | | | | | | | | | | | |
| CHX (n = 2) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | clinical controlled trials (7), clinical controlled trials (8) | | | | | | | | | | |
| Figuero *et al.* (2017) | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: RCT (15), clinical controlled trials (9) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |
| Calcium phosphate agents (n = 0)<br>Ozone (n = 0)<br>Nanomaterials (n = 0)<br>Probiotics (n = 1) | | | | | | | | | | | |
| Poorni *et al.* (2019) | Total: non-randomised clinical trials (2), in-vitro trials (3); Included: non-randomised controlled trials (2) | Critically low | -1 | -1 | -1 | N/A | -2 | -2 | -7 | | Very low |
| Propolis (n = 0)<br>Silicates (n = 0)<br>Xylitol (n = 4) | | | | | | | | | | | |
| Marghalani *et al.* (2017) | Cluster RCT (3); RCT (2); non-RCT (5) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Newton *et al.* (2020) | RCT (11), pre-post (1) | Critically low | -1 | 0 | -1 | -1 | 0 | -2 | -5 | | Very low |
| Riley *et al.* (2015) | Cluster RCT (2); RCT (8) | Critically low | 0 | -1 | 0 | 0 | 0 | -2 | -3 | | Low |
| Sorbitol (n = 0) | | | | | | | | | | | |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined) (n = 0) | | | | | | | | | | | |
| Sealants (n = 1) | | | | | | | | | | | |
| Resin (n = 0) | | | | | | | | | | | |
| Glass-ionomer (n = 0) | | | | | | | | | | | |
| Ormocer (n = 0) | | | | | | | | | | | |
| Hybrid (n = 0) | | | | | | | | | | | |
| Combined (n = 0) | | | | | | | | | | | |
| Other (n = 1) | | | | | | | | | | | |
| Singal *et al.* (2022) | Total: RCT (26); Included: RCT (11) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Laser (n = 0) | | | | | | | | | | | |
| Subgroup: Mother of unborn/toddlers (treatment given to mothers, outcomes tested on mixed dentition of offspring) | | | | | | | | | | | |
| Other systemic chemicals (n = 1) | | | | | | | | | | | |
| Calcium (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |
| Subgroup: Combined interventions in mixed dentition | | | | | | | | | | | |
| Topical fluoride + topical other chemicals (n = 2) | | | | | | | | | | | |
| Gupta *et al.* (2020b) | Total: Cluster RCT (2), RCT (14); Included: Cluster RCT (2), RCT (12) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Sharda *et al.* (2021) | Total: RCT (26); Included: RCT (14) | Critically low | 0 | -1 | -1 | 0 | 0 | -2 | -4 | | Low |
| Topical other chemicals + topical other chemicals (n = 1) | | | | | | | | | | | |
| Rethman *et al.* (2011) | Total: Cluster RCT (9), RCT (42), cluster clinical | Critically low | -1 | -1 | -1 | -1 | 0 | -2 | -6 | | Very low |

| Author (year) | Primary study design included | Overall quality rating of review | Study design | Adequate randomisation | Adequate blinding of outcome ascertainment | Heterogeneity | Adequate sample size for each primary outcome | AMSTAR quality rating | GRADE score: taking account of downgrades | Single trial review | Overall GRADE or certainty of evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | controlled trials (7), clinical controlled trials (8); Included: Cluster RCT (8), RCT (33), cluster clinical controlled trials (7), clinical controlled trials (8) | | | | | | | | | | |
| Topical other chemicals + other (n = 1) | | | | | | | | | | | |
| Zhou *et al.* (2019) | Total: RCT (7); non-RCT (7); Included: RCT (2); non-RCT (1) | Critically low | -1 | -1 | 0 | 0 | 0 | -2 | -4 | | Low |
| Complex combined interventions (n = 2) | | | | | | | | | | | |
| Yu *et al.* (2021) | Cluster RCT (3); RCT (3) | Critically low | 0 | 0 | 0 | 0 | 0 | -2 | -2 | | Moderate |
| Figuero *et al.* (2017) | Total: RCT (15), clinical controlled trials (10), prospective case series (2); Included: RCT (15), clinical controlled trials (9) | Critically low | -1 | -1 | 0 | -1 | 0 | -2 | -5 | | Very low |