Primary prevention of dental caries

An evidence review

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Lisa Murphy

Louise Farragher

Kayleigh Clements

Annette Burns

Mary Archibald

Jean Long

Research. Evidence. Action.

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Health Research Board
Grattan House
67–72 Lower Mount Street
Dublin 2
D02 H638
Ireland

t 353 1 234 5000
f 353 1 661 2335

e hrb@hrb.ie
w www.hrb.ie

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Abbreviations

Abbreviation	Expanded term
ACP	amorphous calcium phosphate
AHRQ	Agency for Healthcare Research and Quality
AmF	amine fluoride
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews, version 2
APF	acidulated phosphate fluoride
ART	atraumatic restorative treatment
CENTRAL	Cochrane Central Register of Controlled Trials
CHX	chlorhexidine
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CO_2	carbon dioxide
CPP-ACP	casein phosphopeptide-amorphous calcium phosphate
d(e/m)fs	decayed, extracted/missing, and/or filled primary [teeth] surfaces (variations include dmfs, dfs, ds, and defs)
D(E/M)FS	Decayed, Extracted/Missing, and/or Filled Permanent [teeth] Surfaces (variations include DMFS, DFS, DS, and DEFS)
d(e/m)ft	decayed, extracted/missing, and/or filled primary teeth (variations include dmft, dft, and deft)
D(E/M)FT	Decayed, Extracted/Missing, and/or Filled Permanent Teeth (variations include DMFT, DFT, and DEFT)
DMFRS	Decayed, Missing, and/or Filled Root Surfaces
DoPHER	Database of Promoting Health Effectiveness Reviews
Er, Cr:YSGG	erbium, chromium-doped yttrium scandium gallium garnet
Er:YAG	erbium-doped yttrium aluminium garnet
EU	European Union
g	gram
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HRB	Health Research Board
ICDAS	International Caries Detection and Assessment System
IU	international units
JBI	Joanna Briggs Institute
kg	kilogram

MeSH	Medical Subject Headings
mg	milligram
mL	millilitre
NaF	sodium fluoride
Nd:YAG	neodymium-doped yttrium aluminium garnet
OHE	oral health education
OHI	oral health instruction
Ormocer	organically modified ceramics
PICO	population, intervention, comparator, and outcome
ppm	parts per million
PRESS	Peer Review of Electronic Search Strategies
PRIOR	Preferred Reporting Items for Overviews of Reviews
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCI	Root Caries Index
RCT	randomised controlled trial
RoB	risk of bias
SciELO	Scientific Electronic Library Online
SDF	silver diamine fluoride
SnF_2	stannous fluoride
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Glossary of terms

Term	Explanation
acidulated phosphate fluoride	Acidulated phosphate fluoride (APF) is a topical agent with a low pH that is used in the prevention of dental caries [1].
amine fluoride	An organic type of fluoride which spreads over all surfaces in the oral cavity especially quickly (due to its tenside character). Amine fluoride is strongly glycolytic (for 3–6 hours) and develops a highly bacteriostatic and bactericidal effect [2] towards oral bacteria [3–5]. The mechanism of bactericidal activity is unclear, but it is thought to involve the surfactant properties of the chemical [6]. Amine fluoride is also known to inhibit bacterial acid production [7] and block enzymes involved in bacterial metabolism [8].
amorphous calcium phosphate-based sealant	A non-crystalline form of calcium phosphate, shown to remineralise tooth structures and aid in the prevention of tooth decay. When added as a filler to sealants and composites, amorphous calcium phosphate (ACP) may aid in the remineralisation of enamel and dentine. During a carious attack, the pH in the mouth is lowered by bacteria, acid release, or food, and this drop results in ACP being converted to hydroxyapatite, which precipitates, thus replacing the hydroxyapatite lost to acid. ACP is promoted as an alternative to fluoride or an adjunct to daily fluoride for enhanced protection against caries [9,10].
amorphous calcium phosphate-resin-based sealant	An amorphous calcium phosphate-resin-based sealant is a new type of resin-based sealant which contains ACP and therefore has the capacity to release calcium and phosphate, which may make it more effective than traditional resin-based sealants in relation to caries prevention [11].
antimicrobial agents	Antimicrobial agents usually come in the form of an antibiotic that is generally administered orally and absorbed into the bloodstream through the intestine. The agent moves from the circulatory system to the intended tissue (e.g. periodontal pocket) through gingival sulcus fluid [1].
antioxidants	Antioxidants prevent free radicals from requesting electrons from normal cells, and actively donate electrons to free radicals, thereby achieving the purpose of protecting normal cells. Antioxidants can also inactivate free radicals before they attack the body's cells [12].
arginine	Arginine is an essential (indispensable) amino acid for infants and children, and is the most metabolically versatile amino acid. In addition to its role in the synthesis of nitric oxide, L-arginine serves as a precursor for the synthesis of polyamines, proline, glutamate, creatine, agmatine, and urea. In addition, regular use of products that contain an arginine bicarbonate/calcium carbonate complex can lead to a neutral pH and promote the establishment of an oral environment rich with arginolytic microbes. Supplementing the oral cavity with arginine bicarbonate/calcium carbonate compounds provides a reliable source of mineral necessary for caries prevention and remineralisation. Products that contain arginine chemistry also provide an effective desensitising strategy as well as a negative effect on *Candida albicans* growth, which destabilises dental biofilm's

Term	Explanation
	extracellular polysaccharide integrity and interferes with the biofilm adhesion on hard tooth structures [1].
bias	Bias is a systematic overestimation or underestimation of an association in research. There are many types of bias, such as selection, recall, observer, and interviewer bias. Bias is minimised through good study design and implementation [13].
blinding	Blinding is a method used in research to ensure that the people involved in a research study – participants, clinicians, and researchers – do not know which participants are assigned to each study group, or which participants experienced the exposure or outcome of interest. Blinding is used in order to ensure that knowledge of the type of exposure, treatment, or diagnosis does not affect a participant's response to the treatment, a healthcare provider's behaviour, or an interviewer's approach to data collection [13].
calcium	Calcium is a basic element with an atomic weight of 40.07. It is found in nearly all organised tissue and is essential for mineralisation of bone and teeth. The normal level in the blood is 9.0–11.5 milligrams (mg) per 100 millilitres (mL). The calcium concentration of dental plaque and the level of calcium ions in the saliva could affect the balance between demineralisation and remineralisation of enamel [1,14].
calcium phosphate	Calcium phosphate is an odourless, tasteless white powder (the various forms of which are sometimes used as abrasives in dentifrices), and is promoted as an alternative to fluoride or an adjunct to daily fluoride for enhanced protection against caries [1,9].
caries incidence	Caries incidence can be defined as the number or proportion of individuals with new caries at a specified threshold in a given population, detected during a given time period [15].
caries increment	Caries increment can be measured as the change from baseline in any standard measure of dental caries or clinical classification system, such as the decayed, missing, and filled surfaces/teeth (dmfs/t/DMFS/T) indexes or variations of these indexes, or the International Caries Detection and Assessment System (ICDAS), e.g. see [16,17].
caries prevalence	Caries prevalence can be defined as the number or proportion of individuals with caries in a given population at a specified threshold, at a particular point in time [15].
caries progression	Caries progression can be defined as an increase in the size of a carious lesion in any direction e.g. see [18].
casein phosphopeptide-amorphous calcium phosphate	Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) is a natural milk product that is promoted as an alternative to fluoride or an adjunct to daily fluoride for enhanced protection against caries [1,9].

Term	Explanation
case-control study	A case-control study is an analytic observational epidemiological study which examines volunteer subjects (cases) with an outcome (disease) back to exposure (cause) and compares their exposures with self-selected controls that do not have the disease (but are otherwise similar) in order to determine the odds that the exposure may have caused the disease. The odds ratio is the measure of choice in a case-control study. This type of study can be used to identify exposures that cause rare diseases. They contribute low-quality evidence to causality or disease aetiology. The main drawbacks in case-control studies are their potential for recall bias and that they cannot calculate incidence [13].
causality	Causality is the relation of cause and effect. The Bradford Hill criteria for causality are: strength of association or effect size; consistency of findings across studies (known as reproducibility); biological credibility (plausibility); specificity (other explanations); a temporal relationship (exposure occurred before the outcome) and biological gradient known as a dose–response relationship; coherence (consistent with other lines of evidence); and analogy (similar agents act similarly) [13].
chlorhexidine	Chlorhexidine (CHX) is an anti-infective oral prescription rinse used to prevent dental biofilm formation and subsequent gingivitis, as well as periodontal disease, and for irrigation during periodontal procedures and as an aseptic pre-rinse before dental procedures. The rinse is slowly released from tooth surfaces, dental biofilm, and oral mucosa and is thought to rupture bacterial cell membranes, leading to the rapid leakage of cell contents and cell death, reducing the number of microorganisms; however, it is not effective in the presence of blood [1].
cohort study (prospective/retrospective)	A cohort study is a form of longitudinal (analytic observational) epidemiological study in which a group of subjects, called a cohort, is followed over a period of time, and data relating to predetermined exposures and outcomes are collected on two or more occasions over this time period. The incidence (new cases) of the outcome(s) of interest is calculated in the exposed people and compared with the incidence in the non-exposed people. This comparison of incidence is known as relative risk. The data for the cohort can be collected either by following the participants into the future (prospective study) or by asking them about their past (retrospective study). However, retrospective cohort studies are limited by recall bias. One of the indicators of a high-quality cohort study is a loss to follow-up rate of less than 20%. Cohort studies contribute to causality or disease aetiology and provide, at best, moderate-quality evidence [13].
community water fluoridation	The practice of artificially fluoridating water with a precise low dose of fluoride as a public health prevention measure to protect teeth from developing caries or cavities. In Ireland, statutory regulations for fluoridation of water supplies stipulate that fluoride may be added to public water supplies, typically in the form of hydrofluorosilicic acid. In 2000, the Forum on Fluoridation recommended that the fluoride level in drinking water should be within the range of 0.6–0.8 parts per million (ppm), with a target of 0.7 ppm [19,20].

Term	Explanation
confidence interval	A confidence interval is the range of values (for example, proportions) in which the true value is likely to be found with a degree of certainty (by convention, a 95% degree; that is, the range of values will include the true value 95% of the time) [13].
confounding	Confounding is when a factor has an association with the exposure and can independently cause the outcome or disease. It can over- or underestimate an effect of interest or association. A confounding variable (also called a confounding factor or confounder) is a variable that has a relationship with both the exposure and the outcome variable. Confounding is controlled for by restricting the study population, matching the study population (for age, sex, geography, and/or socioeconomic factors), randomly selecting the study population, undertaking a stratification in the analysis (for example, by age, sex, geography, and/or socioeconomic factors), and performing regression analysis [13].
control	A control is used when completing an experiment to test an element or intervention. It is the element that remains unchanged or unaffected by other variables. A control is the point of comparison against which other test results are measured [13].
dental caries	A summary of existing literature reports that tooth mineral is lost and gained in a continuous process of demineralisation and remineralisation. Caries (dental decay) is a disease of the hard tissues of the teeth caused by an imbalance in this process over time, where there is net demineralisation of tooth structure by organic acids formed from the interactions between bacteria in dental plaque and fermentable carbohydrates (sugars). The dental caries formation process is influenced by the susceptibility of the tooth surface, the bacterial profile, the quantity of saliva, and the presence of fluoride, which promotes remineralisation and inhibits demineralisation of the tooth structure [21,22].
DMFT and dmft	DMFT is the sum of the number of decayed, missing (due to caries), or filled permanent teeth. The mean number of DMFT is the sum of individual DMFT values divided by the sum of the population. The acronym ‘dmft’ is the sum of the number of decayed, missing (due to caries), or filled primary teeth. Some countries use the acronym ‘deft’ (damaged or decayed, extracted/missing, or filled primary teeth) to assess primary teeth. Variations include ‘D(E/M)FT/d(e/m)ft’ (damaged or decayed, extracted/missing, or filled permanent/primary teeth) and ‘DFT/dft’ (decayed or filled permanent/primary teeth).
DMFS and dmfs	DMFS is the sum of the number of decayed, missing (due to caries), or filled teeth surfaces in permanent teeth. The mean number of DMFS is the sum of individual DMFS values divided by the sum of the population. The acronym ‘dmfs’ is the sum of the number of decayed, missing (due to caries), or filled teeth surfaces in primary teeth. Variations include ‘D(E/M)FS/d(e/m)fs’ (damaged or decayed, extracted/missing, or filled permanent/primary tooth surfaces) and ‘DFS/dfs’ (decayed or filled permanent/primary tooth surfaces).

Term	Explanation
flossing	Flossing is the mechanical cleansing of interproximal tooth surfaces with stringlike, waxed or unwaxed dental floss or tape. The two most frequently used methods are the spool method and the circle (or loop) method. In general, flossing is best performed by cleaning each tooth in succession, including the distal surface of the last tooth in each quadrant. Signs that suggest incorrect use include gingivitis and cuts on the interdental papillae. For those who have not adopted or will not adopt a flossing behaviour, another interproximal device may be more effective than no interproximal cleaning; a less effective device used on a regular basis is superior to irregular use of a more effective device. However, the depth the floss can reach is limited, and other devices may work deeper pockets [1].
fluoride-containing resin-based sealant	Fluoride-containing resin-based sealants are fourth-generation resin-based sealants, coming after ultraviolet-light-activated sealants, and auto-polymerised and visible-light-activated sealants. In addition to fluoride, fillers are present in fluoride-containing sealants, and this is said to increase the surface tension of fluoride-containing resin-based sealant material and may lead to poorer retention [23,24].
fluoride gels	Fluoride gels are widely used in dental surgeries and school-based caries-preventive programmes. They generally contain a higher concentration of fluoride than toothpaste and are usually applied by a dental professional, but can also be self-applied under supervision [25].
fluoridated milk	The use of milk as a vehicle for providing additional fluoride in a dental public health programme is effective because milk is already an important part of children's diets. It can be produced in a variety of liquid forms (pasteurised, ultra-high-temperature pasteurised, and sterilised) and in powder form, each containing different fluoridating compounds [26].
fluoridated salt	Fluoridated salt is a compound of sodium chloride with fluoride added; it is not considered as effective as fluoridated water [1].
fluoridated sugar	The use of sugar as a vehicle for supplementary dietary fluoride has been trialled in communities where there is little exposure to fluoride and a high prevalence of caries or caries risk [27].
fluoride supplements	Fluoride supplements are the orally administered nutritional additives of the chemical fluoride; they are often taken by individuals who do not have regular access to a fluoridated water supply, and are available as chewable tablets, drops, pills, and in combination with vitamin supplements. Fluoride supplements are very rarely prescribed due to the presence of fluoride within other water systems available to the community [1].
fluorine	Fluorine is a chemical element with the symbol F and atomic number 9. It is a member of the halogen family. Fluoride is the negative ion of the element fluorine.
foams (dental)	Fluoridated foam is another method of professional fluoride application alongside gel and varnish. Fluoridated foam was created as a safer alternative to gel in order to decrease fluoride intake by children [28].

Term	Explanation
glass ionomer	A glass ionomer is a type of sealant made from glass ionomer cements (a combination of silicate and polyacrylate cement system), which may be used as the original chemically cured type or as the light-cured type, which is modified with resin – for example, for rapid initiation of the curing process (resin-modified glass ionomers) [29].
glass ionomer cement	A glass ionomer cement is a material used to cement indirect restorations, to line deep tooth preparation walls, and to restore small intracoronal cavities. It is based on the reaction of silicate glass powder (calcium aluminofluorosilicate glass) with polyacrylic acid liquid. It has the advantage of releasing some fluoride over time. The viscosity (a liquid's resistance or inability to flow) of glass ionomer cement can range from high to low [1].
hierarchy of evidence	The hierarchy of evidence for primary epidemiological studies is, from highest to lowest quality: randomised controlled trials (RCTs), non-randomised trials, longitudinal cohort studies, case-control studies, and cross-sectional studies. Ecological or correlational studies are not usually on the hierarchy of evidence, as their role is to suggest rather than prove causal relationships [13].
I^2	index measuring the percentage of inconsistency or heterogeneity [13].
incidence	Incidence is a term used to describe the number of new cases of disease or events that develop among a population during a specified time interval [13].
interdental cleaning devices	Daily mechanical disruption and removal of dental plaque is considered important for oral health maintenance. People routinely use toothbrushes at home to remove supragingival dental plaque, but toothbrushes are unable to penetrate the interdental area where periodontal diseases first develop and are prevalent. Besides toothbrushing, which is the most common method for removing dental plaque, different interdental aids to plaque removal, such as dental floss or interdental brushes, are recommended for use in addition to toothbrushing. Floss can be used in all interdental spaces, but interdental brushes and other interdental cleaning aids require sufficient interdental space in order to be used by patients. The choice of interdental cleaning aid will depend on the size of the space to be cleaned and the ability of the patient to use the device [30].
International Caries Detection and Assessment System	The International Caries Detection and Assessment System (ICDAS II) is a clinical scoring system which enables the detection and assessment of caries activity. ICDAS II is used in clinical research, in clinical practice, and for epidemiological purposes. **Caries code and description by pit and fissure and smooth surface:** 0: Sound 1: First visual change in enamel (seen only after prolonged air drying or restricted to the confines of a pit or fissure) 2: Distinct visual change in enamel 3: Localised enamel breakdown (without clinical visual signs of dentinal involvement)

Term	Explanation
	4: Underlying dark shadow from dentin 5: Distinct cavity with visible dentin 6: Extensive distinct cavity with visible dentin **Caries associated with restoration and sealant codes** (caries secondary to treatment): Code 0: Sound tooth surface with restoration or sealant Code 1: First visual change in enamel Code 2: Distinct visual change in enamel/dentin adjacent to a restoration/sealant margin Code 3: Carious defects of <0.5 mm, with signs of code 2 Code 4: Marginal caries in enamel/dentin/cementum adjacent to restoration/sealant, with underlying dark shadow from dentin Code 5: Distinct cavity adjacent to restoration/sealant Code 6: Extensive distinct cavity with visible dentin **The suggested restoration/sealant (intervention) coding system is as follows:** 0 = Sound; that is, surface not restored or sealed (use with the codes for primary caries) 1 = Sealant, partial 2 = Sealant, full 3 = Tooth-coloured restoration 4 = Amalgam restoration 5 = Stainless steel crown 6 = Porcelain, gold, or porcelain fused to a metal alloy crown or veneer 7 = Lost or broken restoration 8 = Temporary restoration 9 = Used for the following conditions: 96 = Tooth surface cannot be examined: surface excluded 97 = Tooth missing because of caries (tooth surfaces will be coded 97) 98 = Tooth missing for reasons other than caries (all tooth surfaces will be coded 98) The codes for caries and interventions can be combined into two-digit codes. **Codes for the detection and classification of carious lesions on the root surfaces** One score will be assigned per root surface. The facial, mesial, distal, and lingual root surfaces of each tooth should be classified as follows:

Term	Explanation
	Code E: If the root surface cannot be visualised directly because of gingival recession or by gentle air drying, then it is excluded. Surfaces covered entirely by calculus can be excluded or, preferably, the calculus can be removed prior to determining the status of the surface. Code 0: The root surface does not exhibit any unusual discoloration that distinguishes it from the surrounding or adjacent root areas, nor does it exhibit a surface defect either at the cement–enamel junction or wholly on the root surface. The root surface may have a natural anatomical contour, or the root surface may exhibit a definite loss of surface continuity or an anatomical contour that is not consistent with the dental caries process. Code 1: There is a clearly demarcated area on the root surface or at the cement–enamel junction that is discoloured (light/dark brown, black) but there is no cavitation (loss of anatomical contour <0.5 mm) present. Code 2: There is a clearly demarcated area on the root surface or at the cement–enamel junction that is discoloured (light/dark brown, black) and there is cavitation (loss of anatomical contour ≥0.5 mm) present [31].
erbium laser	The erbium family of lasers has two distinct wavelengths: erbium, chromium-doped yttrium scandium gallium garnet (Er, Cr:YSGG) lasers and erbium-doped yttrium aluminium garnet (Er:YAG) lasers. The erbium wavelengths have a high affinity for hydroxyapatite and the highest absorption in water of any dental laser wavelengths. Consequently, these lasers may be used for treatment of hard dental tissue (enamel, dentine, cementum, and bone). In addition to hard tissue procedures, erbium lasers may also be used for soft tissue ablation because soft dental tissue also contains a high percentage of water. These procedures show an excellent healing response. Soft tissue applications with erbium lasers feature less haemostasis and coagulation abilities relative to carbon dioxide (CO_2) lasers [1].
mixed dentition	The teeth in the jaws after the eruption of some of the permanent teeth but before all the primary teeth are exfoliated. The mixed dentition period usually begins with the eruption of the first permanent molars and ends with the exfoliation of the last primary tooth [1].
mouth rinse	A fluid that has cleansing, germicidal, or palliative properties, which is used for rinsing the oral cavity and is then spit out [1].
nanomaterials	Nanomaterials are any materials which include very small components or features with at least one dimension less than 100 nanometres [32]. Nanomaterials have been used in dentistry in applications such as tooth sealants and fillers that use nanosized particles to improve strength and lustre, and to resist wear [33].
neodymium-doped yttrium aluminium garnet	A laser that is highly absorbed by the tissue pigment melanin as well as by haemoglobin/oxyhaemoglobin, making it an effective surgical laser for cutting and coagulating oral and dental soft tissue, having haemostasis. Neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers operate in a free-running mode; they are pumped by flashlamps [1].

Term	Explanation
odds ratio	An odds ratio is a statistic that quantifies the strength of the association between two events, A and B. The odds ratio is defined as the ratio of the odds of A in the presence of B and the odds of A in the absence of B, or equivalently (due to symmetry), the ratio of the odds of B in the presence of A and the odds of B in the absence of A.
oral health education	Oral health education (OHE) consists of any combination of learning experiences which aim to improve knowledge and thereby facilitate behaviours conducive to oral health [34].
oral health instruction	Oral health instruction (OHI) is guidance offered to patients or caregivers, such as toothbrushing or flossing instructions, which can be provided by dental hygienists or dentists [35,36].
oral-health-related quality of life	Oral-health-related quality of life is a multidimensional construct that includes a subjective evaluation of the individual's oral health, functional well-being, emotional well-being, expectations of and satisfaction with care, and sense of self. It has wide-reaching applications in survey and clinical research. It is recognised that oral diseases can have varying impacts on people and their well-being and quality of life. Dental diseases cause pain and discomfort; affect proper physical functions like chewing, talking, and smiling; and can influence an individual's social roles [37].
ormocer	Organically modified ceramics (ormocers), although composites, have been developed as an alternative to the conventional dimethacrylate-based composites. They consist of three components: organic portions, inorganic portions (glass and ceramic components), and polysiloxanes [38].
overlap	Overlap between systematic reviews occurs when a single primary study is included in more than one systematic review evaluating the same outcome. For example, Review A and Review B both synthesise evidence on tetrahydrocannabinol for ameliorating depression, and both include Primary Study C. It is important to understand the degree of overlap between reviews, because a large number of reviews on a topic may give an inaccurate impression of the size of the body of evidence if many of the reviews are not independent but are based on the same relatively small number of primary studies. It is possible to calculate the degree of overlap between reviews (known as the corrected covered area) [39].
ozone	Ozone is a natural gaseous molecule made up of three oxygen atoms. Ozone therapy presents great advantages when used as a support for conventional treatments and is indicated for use in a wide range of dental specialties. Its properties include immunostimulant, analgesic, antihypnotic, detoxicating, antimicrobial, bioenergetic, and biosynthetic actions. It is used for caries control as well as in treatment of periodontal and endodontic microbial-based lesions [1].
parts per million	The unit of measurement for fluoride in water is parts per million (ppm) or milligrams per litre (mg/L). The units are interchangeable; 1 ppm equals 1 mg/L.

Term	Explanation
permanent dentition	The usual number of 32 adult teeth that either replace or are added to the primary teeth, along with the shedding of the primary teeth [1].
placebo	'Placebo' is the name given to a substance which has no pharmacological properties but is administered as a control in testing the efficacy of a pharmacologically active preparation. Common placebos include inert tablets (sugar pills) or inert injections (sterile water or saline) which are designed to look and feel like the active substance being tested but do not contain any active ingredients [13].
polyols	Polyols are a class of sugar substitutes or non-fermentable sugars also known as 'sugar alcohols'. The most common polyols are xylitol and sorbitol [40].
prevalence	Prevalence is a term used to describe the proportion of people in a population who have a disease or condition at a specific point in time or during a specific period.
primary dentition	The 20 teeth present that erupt first and are usually replaced by the permanent teeth; primary dentition is present within the primary dentition period [1].
probiotics	The World Health Organization defined probiotics in 2001 as live microbial preparations that, when taken at an appropriate dose, are beneficial to the health of the host. Examples include *Bifidobacterium*, *Streptococcus thermophilus*, and *Lactobacillus* [41].
professional scaling or cleaning	The professional removal of deposits from the teeth [1].
propolis	Propolis is a resinous substance obtained from beehives which has antioxidant, anti-bacterial, anti-viral, antifungal, anti-tumour, and anti-inflammatory properties [42].
PROSPERO	International Prospective Register of Systematic Reviews
Q	statistic measuring variability between studies
randomised controlled trial	A randomised controlled trial (RCT) is an analytic interventional epidemiological study in which subjects are randomly assigned to one of at least two groups. The first group is the experimental group, which receives the intervention of interest, and the other group is the comparison or control group, which receives an alternative treatment (current conventional therapy or a placebo). The two groups are then followed up on to see if there are any differences between them with respect to the outcome(s) of interest. The results of the trial compare the incidence of success in the intervention group with that in the control group to assess the effectiveness of the intervention. RCTs are the most stringent study design for evaluating the effect of an intervention on an outcome [13].
RCT – parallel design	A parallel design RCT is a type of RCT where the participants are randomly allocated to one of two treatment groups and all of the participants in each group only receive one treatment for the entirety of the study. The researcher measures and compares the outcomes in the two groups at the end of the study [13].

Term	Explanation
resin	A resin material, bisphenol A glycidyl methacrylate, forms the basis for numerous resin-based dental sealants and composites. Their effectiveness is closely related to the longevity of sealant coverage (i.e. sealant retention). The development of sealants has progressed from first-generation sealants, which were activated with ultraviolet light, through to second- and third-generation sealants, which are auto-polymerised and visible-light activated, and fourth-generation sealants, which contain fluoride. First-generation sealants are no longer marketed [29].
Root Caries Index	The Root Caries Index (RCI) is one of the most frequently used conventional epidemiological indices to measure the root caries experience at the tooth/surface level. It accounts for the number of cavitated carious lesions and fillings among teeth with exposed roots [43,44].
root carious lesions	Root carious lesions are located on the root surface of the tooth and are more commonly seen in older people. Lesions are discoloured, soft, ill-defined, and may or may not be cavitated [45,46].
scheduled dental appointments	In the context of the provision of continuing dental care to patients, a 'recall visit' may be defined as the planned return of a patient who, when last seen, was in good oral health. A 'recall examination' (also referred to as a 'routine dental check-up' or an '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. There is no universally recognised definition of the term 'routine dental check-up'. However, it can be considered as involving many of the following components: clinical examination (including documenting a patient's medical history); the provision of advice; charting (including assessment and recording of any malocclusion and monitoring of periodontal status); an explanation of the risks, as well as the costs, of any required treatment; and a report. The principal function of the clinical examination component of the check-up is to detect the signs and symptoms of oral disease (in particular dental caries) and periodontal disease. It is also recommended that an examination for oral cancer, including a thorough medical and social history and a systematic examination of the oral mucosa, should form an integral part of all routine dental examinations [47].
scheduled primary care appointments	Screening for dental caries and caries risk factors in young children prior to school entry could identify carious lesions at an earlier and reversible stage and lead to interventions to treat existing carious lesions, prevent progression of carious lesions, and reduce incidence of future lesions, including lesions in the permanent dentition. Screening strategies typically include an oral health risk assessment and visual examination to identify high-risk children, including those already with caries. Primary care clinicians can play an important role in screening for dental caries because many young children routinely see a primary care clinician, starting shortly after birth, but do not see a dental health care professional until they are older [48].

Term	Explanation
sealant	A resinous material designed for application to the pits, fissures, and grooves of posterior teeth to seal surface irregularities and prevent the carious process [1].
sialagogue	A substance that increases the flow of saliva. Pilocarpine is an effective sialagogue for xerostomic patients (patients with dry mouth) with concurrent disease states [1].
silicates	A dental cement used historically as an anterior restorative material before the advent of dental composites. It is the reaction product of a powder (acid-soluble glass based on calcium oxide, silicon dioxide, aluminium oxide, and calcium difluoride) reacted with an aqueous liquid (buffered phosphoric acid). The set cement releases fluoride ions as it slowly dissolves on its surface and is considered anti-cariogenic [1].
silver diamine fluoride	Silver diamine fluoride (SDF) is a topical medicament of a metal ammine complex of silver fluoride. It is used to arrest and prevent dental caries and relieve dentinal hypersensitivity. However, it will stain most oxidizable surfaces black. Dentine and enamel without demineralisation will receive surface (pellicle) stains that can be removed by mechanical means (brushing; may need pumice polish), while demineralised tooth structure will stain more permanently black (additionally allowing for caries diagnosis). Skin and soft tissue will discolour within minutes to hours after contact and fade away (via surface shedding) within a few days. Some indications for use include xerostomia, multiple carious lesions or delay for caries treatment, behavioural management patients, anatomic niches (e.g. furcations, restoration margins, partially erupted molars), and patients with geographic or financial barriers to access [1].
slow-release fluoride devices	Devices used to provide a slow-release, more sustained presence of fluoride within the buccal cavity, showing that it is possible to sustain elevated levels of fluoride within saliva and plaque. Two types are currently in use: the co-polymer membrane and slow-dissolving fluoride glass beads [49].
sodium fluoride	Sodium fluoride (NaF) is a white, odourless powder used in 2% aqueous solution and applied topically to the teeth as a caries-preventing agent, and used as 33% NaF in kaolin and glycerin as a desensitising agent for dentinal hypersensitivity. In drinking water, 1 ppm of NaF can be used as a caries prevention substance (although this use is controversial) [1].
solution	A homogeneous mixture of two or more substances in a liquid or solid. In pharmacy, a solution is usually non-alcoholic. Solutions containing alcohol are called elixirs, tinctures, spirits, and essences [1].
sorbitol	Sorbitol is a common sugar substitute or sugar alcohol. A non-fermentable sugar, it is commonly used as a sugar substitute in chewing gum [40].
stannous fluoride	Stannous fluoride (SnF_2) is a fluoride salt often used in toothpaste and mouth rinses to prevent and slow the progression of dental caries. In many cases, it can cause extrinsic staining. Newer formulations promise less stain. However, better home-care will show reduced stain levels [1].

Term	Explanation
supervised toothbrushing	The supervised use of a brush of varying designs to brush teeth and gingivae for mechanical removal of dental biofilm [1].
systemic fluoride	Fluorides that are ingested and become incorporated into forming tooth structures. Systematic fluorides can also act locally by providing topical protection as fluoride is present in the saliva, which continually bathes the teeth [50].
toothpaste	A pharmaceutical compound used in conjunction with a toothbrush to clean and polish the teeth. Contains a mild abrasive, a detergent, a flavouring agent, a binder, and occasionally deodorants and various medicaments designed as caries preventives (e.g. antiseptics) [1].
topical fluoride	The salt of hydrofluoric acid (usually sodium or tin salts) that may be applied in a solution to exposed tooth surfaces to prevent dental caries and promote remineralisation. They come in a variety of types, such as gels or varnishes, as well as rinses, and can be applied using trays, mouth rinses, or brush-on or paint-on techniques [1].
ultraviolet light	Ultraviolet light is the light beyond the range of human vision, at the short end of the light spectrum. It occurs naturally in sunlight. It converts precursors in the skin to vitamin D. Ultraviolet light irradiation inhibits the growth of microorganisms, and has demonstrated an antimicrobial action against various pathogens [1,51].
varnishes	Varnishes are usually solutions of natural gums, synthetic resins, or rosin [1].
vitamin D	The group of lipid-soluble sterol compounds capable of preventing rickets and associated with preventing a range of other disorders. Adequate intake of vitamin D increases dietary calcium absorption and bone resorption, enabling the body to maintain proper blood calcium and phosphorus levels [1].
xylitol	Xylitol is a sugar alcohol (polyol) that may inhibit caries activity and the growth and transmission of *Streptococcus mutans*; xylitol contains 2.4 calories per gram of carbohydrates [1].
zinc	Zinc is a metallic element with atomic number 30 that often appears in dental alloys (e.g. dental amalgam, gold alloys), rapidly forms zinc oxide in the presence of oxygen, and is also an essential mineral and is found in dietary supplements and cold remedies [1].

Executive summary

Purpose

The purpose of this overview of reviews is to provide evidence to assist with the development of clinical guidelines on the prevention of caries using individual-based primary prevention interventions prior to the development of any dental decay/dental caries in some or all teeth.

Research questions

The review questions are:

1. What is the evidence from systematic reviews regarding the effectiveness of individual-based interventions to prevent carious lesions in primary teeth?
2. What is the evidence from systematic reviews regarding the effectiveness of individual-based interventions to prevent carious lesions in permanent teeth?
3. What is the evidence from systematic reviews regarding the effectiveness of individual-based interventions to prevent carious lesions in mixed dentition?

Methods

The literature searches for this overview of reviews included searches of 3 clinical databases, 11 systematic review resources, 3 search engines, and 6 resources for open access/grey/preprint material. Reference and citation chasing was carried out, as was searching for and following up on review protocols and summaries. Initial searches retrieved 5,375 results, and reference/citation/protocol chasing retrieved 5,517 papers. Screening of article titles and abstracts was carried out by two screeners. Full-text screening was carried out by the same two researchers and an information specialist. In addition to the standard exclusion criteria used in the first stages of screening (exclude on study type, intervention, date, etc.), three criteria from an adapted version of the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews, version 2) instrument were used during full-text screening: inadequate research question considering population, intervention, comparator, and outcome (PICO); inadequate literature search; and inadequate risk of bias/quality assessment. Two reviewers used the adapted version of AMSTAR 2 to assess the methodological quality of each full-text review. We used an adapted version of the Joanna Briggs Institute data extraction form for systematic reviews and research syntheses to extract data on the descriptive characteristics and findings of each included systematic review. We have experiencing of using this extraction form in previous evidence reviews we have conducted in this area. We extracted and documented the following data from each included review in tabular format: citation details; objectives of the review; participants; setting; interventions and comparators; search information; primary 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; results by outcome(s); and commentary on the use of GRADE (Grading of Recommendations, Assessment, Development and Evaluation). We then summarised the main findings and applied a modified GRADE algorithm to all included systematic reviews to assess the certainty of evidence. We used Pieper *et al.*'s methodology to assess overlap of primary studies for each outcome reported on for each intervention type.

Findings

Of the initial 5,129 papers retrieved by database searches, 93 were put forward for data extraction, and of the 4,380 papers retrieved by reference/citation/protocol chasing, an additional 7 papers were put forward for data extraction. In total, 93 papers were sent forward for data extraction. Extraction involved

a more detailed reading of the papers, at which point we excluded 27 papers, leaving 66 systematic reviews to be included in this overview of reviews. Of these systematic reviews, 38 evaluated the effectiveness of interventions for caries prevention in primary dentition, 44 evaluated the effectiveness of interventions for caries prevention in permanent dentition, and 12 evaluated the effectiveness of interventions for caries prevention in mixed dentition (23 reviews reported on more than one dentition type). The findings from many systematic reviews were obtained in the context of existing exposure to caries-preventive agents or activities among participants in the primary studies being evaluated (e.g. community water fluoridation, and existing or historical exposure to fluoride toothpaste); these contextual activities are not always declared. In addition, the comparators with which the interventions are compared with vary. We extracted this information when it was reported and present it alongside the relevant findings in Section 4. The methodological quality of many of the systematic reviews included in this review was lower than desired, with 60 (91%) of the 66 systematic reviews classified as either low or critically low quality using an adapted version of AMSTAR 2. Notably, 44 (67%) systematic reviews were deemed to be of critically low quality.

A synopsis of the key findings is presented in this Executive summary, more detailed information is included in Section 4 of the main report, and a standardised summary of each review is presented in Appendix H. The presence or absence of community water fluoridation was not considered as part of the intervention effect in this review.

Primary dentition

The certainty of the evidence reported in the systematic reviews on caries prevention in primary dentition, as assessed using a modified GRADE algorithm, ranged from very low to moderate. However, relative to low- and very low-certainty evidence, very few outcomes were considered to be of moderate certainty; the evidence for the majority of outcomes across the intervention categories reported on in primary dentition was judged to be of low or very low certainty.

We found evidence from one or more systematic reviews for 14 categories of singular interventions for caries prevention in primary dentition. The comparators used varied within and across the systematic reviews. Overall, there was consistent, or slightly inconsistent but predominantly positive, evidence for a significant caries-preventive effect of fluoridated milk (two systematic reviews), fluoride supplements (two systematic reviews), fluoride toothpaste (two systematic reviews), fluoride gel (one systematic review), fluoride solutions (one systematic review), antimicrobial agents (minus CHX; one systematic review), calcium phosphate agents (one systematic review), probiotics (three systematic reviews), and laser interventions (one systematic review). However, the total evidence in favour of four of these (fluoride solutions, antimicrobial agents (minus CHX), calcium phosphate agents, and laser interventions) consisted of a single primary trial included in one systematic review. Moreover, in comparison with fluoride supplements and probiotic interventions, the volume of evidence in favour of fluoridated milk, fluoride toothpaste, and fluoride gel interventions was very low (approximately two or three trials included in one or two systematic reviews).

There were two categories of interventions for which the evidence was mixed: namely, fluoride varnish (two systematic reviews) and chlorhexidine ((CHX); four systematic reviews). In the case of fluoride varnish, however, the evidence varied according to the outcome measure, with a predominantly significant caries-preventive effect of fluoride varnish application on the increment of caries, but no significant effect on the proportion of participants developing one or more new carious lesions.

The remaining three categories of singular interventions for which we identified systematic review evidence for caries prevention in primary dentition were xylitol, resin-based sealants, and glass ionomer sealants. The evidence for xylitol was drawn from four systematic reviews that predominantly indicated

no significant benefit of xylitol for caries prevention when compared with a placebo or no treatment. The evidence for resin-based sealants was drawn from only three primary trials included in two systematic reviews. Neither review presented evidence from standalone interventions comparing resin-based sealants with no sealant; rather, the comparisons were between different types of resin-based sealants or between a resin-based sealant and a glass ionomer sealant, and no significant differences were observed. The evidence for glass ionomer sealants consisted of a single trial included in one systematic review, which showed no significant caries-preventive effect of glass ionomer sealants compared with no sealant.

The body of evidence on the effectiveness of combined interventions (i.e. interventions in which participants received two or more active intervention components) for caries prevention in primary dentition was fragmented, with high variation in the nature of the interventions and outcomes measured. Notably, evidence for combined interventions involving topical fluoride and another non-fluoride topical chemical indicated no caries-preventive benefit of combining topical fluoride (toothpaste or mixed forms) with CHX gel, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), or povidone-iodine . The evidence for caries prevention at the individual, tooth, and tooth surface level predominantly indicated no clinical benefit of combining fluoride varnish with other types of intervention components. The evidence for the effectiveness of combining fluoride toothpaste with oral health education (OHE) indicated a significant caries-preventive effect of high-concentration (rather than low-concentration) fluoride toothpaste plus OHE. The evidence for combined interventions involving sealants predominantly indicated a significant caries-preventive benefit of combining sealant application with some form of OHE or oral health instruction (OHI). The evidence on the effectiveness of complex interventions (i.e. interventions involving three or more active components) was inconsistent, likely due to variation in the intervention components included in the trials, the dose/concentration of chemicals used, and the outcomes measured.

Finally, we found evidence from one or more systematic reviews for three categories of singular interventions delivered to pregnant women or new mothers for caries prevention in the primary dentition of their children: fluoride supplements (two systematic reviews), xylitol (one systematic review), and CHX agents (two systematic reviews). None of these reviews reported a caries-preventive effect of the interventions being evaluated. However, the volume of evidence was very low.

Permanent dentition

The certainty of the evidence reported in the systematic reviews on caries prevention in permanent dentition, as assessed using a modified GRADE algorithm, ranged from very low to moderate. However, only six out of the 44 systematic reviews on this dentition type reported evidence of moderate certainty; the evidence for the majority of outcomes in permanent dentition was judged to be of low or very low certainty.

We found evidence from one or more systematic reviews for 21 categories of singular interventions for caries prevention in permanent dentition. The comparators used varied within and across the systematic reviews. Overall, there was consistent, or slightly inconsistent but predominantly positive, evidence for a significant caries-preventive effect of fluoridated milk (one systematic review), fluoridated sugar (one systematic review), fluoride mouth rinses (two systematic reviews), fluoride gels (three systematic reviews), fluoride solutions (four systematic reviews), slow-release fluoride devices (one systematic review), polyols (one systematic review), and organically modified ceramic (ormocer) sealants (one systematic review). However, the total evidence in favour of fluoridated milk, fluoridated sugar, slow-release fluoride devices, polyols, and ormocer sealants consisted of a single primary trial included in one systematic review.

There were eight categories of interventions for which the evidence was mixed: namely, fluoride supplements (one systematic review), fluoride toothpaste (two systematic reviews), fluoride varnish (four systematic reviews), CHX (four systematic reviews), calcium phosphate agents (two systematic reviews), resin-based sealants (six systematic reviews), glass ionomer sealants (four systematic reviews), and combined sealants (four systematic reviews). However, the evidence for fluoride supplements appeared to vary depending on the comparator, with a significant benefit associated with fluoride supplements compared with no supplements, but no significant benefit when comparing fluoride supplements with the application of fluoride varnish. The evidence for fluoride varnish appeared to vary according to the outcome measure, with a predominantly significant caries-preventive effect of fluoride varnish application on caries incidence according to dentistry-specific epidemiological indicators (e.g. the Decayed, Missing, and/or Filled Surfaces (DMFS) and Decayed, Missing, and/or Filled Teeth (DMFT) indexes) and on the incidence of root caries, but no significant effect on the proportion of participants developing one or more new carious lesions.

The evidence for CHX varied according to the mode of delivery (e.g. varnish, gel, or mouth rinse), outcome measure (e.g. coronal or root caries), and/or mode of application (e.g. self-application or professional application). The evidence for calcium phosphate agents was limited and variable in relation to the comparators, the mode of calcium phosphate delivery (e.g. mouth rinse, toothpaste, or cream), and the direction of the effect. Although the evidence for resin-based sealants was inconsistent, it appeared to vary according to the comparator, with a significant caries-preventive benefit associated with the application of a resin-based sealant when compared with no sealant application, but no significant benefit when compared with the application of fluoride varnish. The body of evidence for glass ionomer sealants was substantial and did not favour the application of glass ionomer sealants over the application of a resin-based sealant, the application of fluoride varnish, or no sealant application. In most analyses in this intervention category, a resin-based sealant was the comparator, and on some occasions, the results favoured resin-based sealants over glass ionomer sealants. The evidence for combined sealants was inconclusive, likely due to variation in the comparators and outcome measures across the systematic reviews.

The remaining five categories of standalone interventions for which we identified systematic review evidence on the topic of caries prevention in permanent dentition were: scheduled dental appointments (one systematic review), supervised toothbrushing (two systematic reviews), xylitol (three systematic reviews), hybrid sealants (one systematic review), and laser interventions (one systematic review). No significant caries-preventive effects were observed for these interventions. However, the total evidence on both hybrid sealants and laser interventions consisted of a single trial included in one systematic review, and the volume of evidence for the remaining three categories of interventions was quite low (approximately two to four trials included in one to three systematic reviews).

The most notable findings on the effectiveness of combined interventions for caries prevention in permanent dentition pertained to interventions involving fluoride mouth rinse used under supervised conditions as part of school-based mouthrinsing programmes; the results of three pooled analyses in one systematic review showed a significant effect on DMFT and DMFS scores, but not on the proportion of participants developing one or more new carious lesions. The evidence for the effectiveness of topical fluoride combined with some form of OHE or OHI indicated a significant caries-preventive benefit for both the root and crown associated with this type of combined intervention. Finally, the evidence indicated a significant benefit of delivering complex interventions for caries prevention in permanent dentition. However, the volume of evidence was very low, and the nature of these interventions varied.

Mixed dentition

The certainty of the evidence reported in the systematic reviews on caries prevention in mixed dentition, as assessed using a modified GRADE algorithm, ranged from very low to moderate. However, only one out of the 12 systematic reviews on this dentition type reported evidence of moderate certainty; the evidence for all other outcomes in mixed dentition was judged to be of low or very low certainty.

We found evidence from one or more systematic reviews for five categories of singular interventions for caries prevention in mixed dentition. The comparators used varied within and across the systematic reviews. Overall, there was evidence in favour of four interventions: vitamin D (one systematic review), probiotics (one systematic review), xylitol (four systematic reviews), and sealants other than resin-based, glass ionomer, ormocer, and hybrid (one systematic review). However, the total evidence in favour of probiotics and other types of sealants consisted of a single trial included in one systematic review. The remaining intervention for which there was systematic review evidence in mixed dentition was CHX. One systematic review team presented evidence indicating no significant caries-preventive effect of CHX varnish application compared with no varnish application.

The evidence from two systematic reviews that reported on combined interventions involving topical fluoride and another non-fluoride topical chemical indicated a significant caries-preventive effect of either fluoride toothpaste or gel combined with another non-fluoride topical chemical (either CHX, povidone-iodine, xylitol, or CPP-ACP).

Conclusions

Overall, this overview of 66 systematic reviews on the primary prevention of dental caries has revealed a fragmented body of research, with a substantial proportion of single-trial outcomes and a low and very low degree of certainty in the evidence for the majority of the interventions. Following a systematic quality assessment, the methodological quality of the included systematic reviews is very low.

Relative to all other types of interventions, and taking the volume of evidence for each intervention category into account, the evidence for caries prevention in primary dentition was strongest for fluoride supplements. The evidence for caries prevention in permanent dentition was strongest for fluoride mouth rinse, fluoride gels, and fluoride solutions. The evidence for caries prevention in mixed dentition was strongest for vitamin D and xylitol (although it is important to note that the volume of evidence in the mixed dentition category was generally very low). However, further high-quality, adequately powered RCT research is required; in the meantime, conclusions may only be drawn narrowly, if at all, with respect to the most effective approach by which to prevent dental caries using individual-based primary prevention interventions prior to the development of any dental decay/dental caries.

Importantly, when the best available evidence consists of systematic reviews of critically low methodological quality and mostly findings of low and very low certainty, the development of clinical guidelines for the primary prevention of dental caries requires a greater reliance on clinical expertise, particularly in relation to preventive measures for which there is a strong clinical consensus.

1 Introduction

1.1 Background

Oral health refers to the health of the whole mouth (including the teeth, gums, tongue, palate, lips, and throat) and can be affected by disease, developmental abnormalities, and injuries [52]. Oral diseases, although largely preventable, remain among the most common noncommunicable diseases globally, with an estimated 3.5 billion cases of oral disease occurring in 2019 [53]. Good oral health is crucial in allowing individuals to perform essential daily functions, including eating, breathing, and speaking, and can affect self-confidence, well-being, and the ability to socialise and work without pain, discomfort, and embarrassment. Oral health varies over the life course from early life to old age, and is key to general good health and to supporting individuals to function as full members of society [54].

Management of oral health in Ireland is currently being reoriented from focusing on interventions after the occurrence of disease to being more prevention focused and targeting early interventions and prevention measures. This reorientation aligns with the Irish national oral health policy *Smile agus Sláinte* [55] (see Figure 1), which was published in 2019, and the recent World Health Organization (WHO) global strategy on oral health, which was adopted by WHO member states in May 2022 [54].

1.1.1 Ireland

The primary goal of the 2019 Irish national oral health policy [55] is to provide supports to enable every individual to achieve their personal best oral health, including ensuring that an appropriately accessible and adaptable oral health care service is available throughout a person's life. The second goal is to reduce oral health inequalities across the Irish population by enabling vulnerable groups to access oral health care and improve their oral health. The policy has three strategic strands [55]:

- Health and oral health promotion and protection programmes
- Oral health care service provision, and
- Evaluation of oral health in the population (clinical surveillance programme).

The goals of the policy are evidence informed and align with Department of Health and other Irish government policies, including the Healthy Ireland framework for 2013–2025 [56], as well as with international policies and approaches endorsed by the WHO and the European Union (EU) [55].

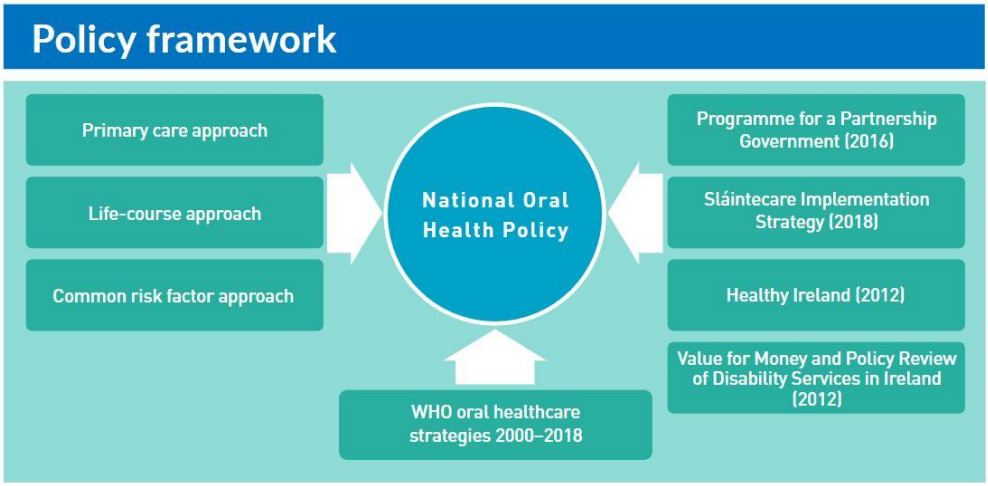

Figure 1 National oral health policy framework

Source: Department of Health, 2019 [55]

The three strategic strands of the national oral health policy are outlined in Figure 2. The first strategic strand emphasises national, community, and individual prevention and protection programmes supported by appropriate national regulation. The policy endorses a 'primary care approach', where most oral health care is delivered by the individual's choice of local oral health care professional. This approach emphasises prevention, local access, person- and family-centred care, and patient choice [55].

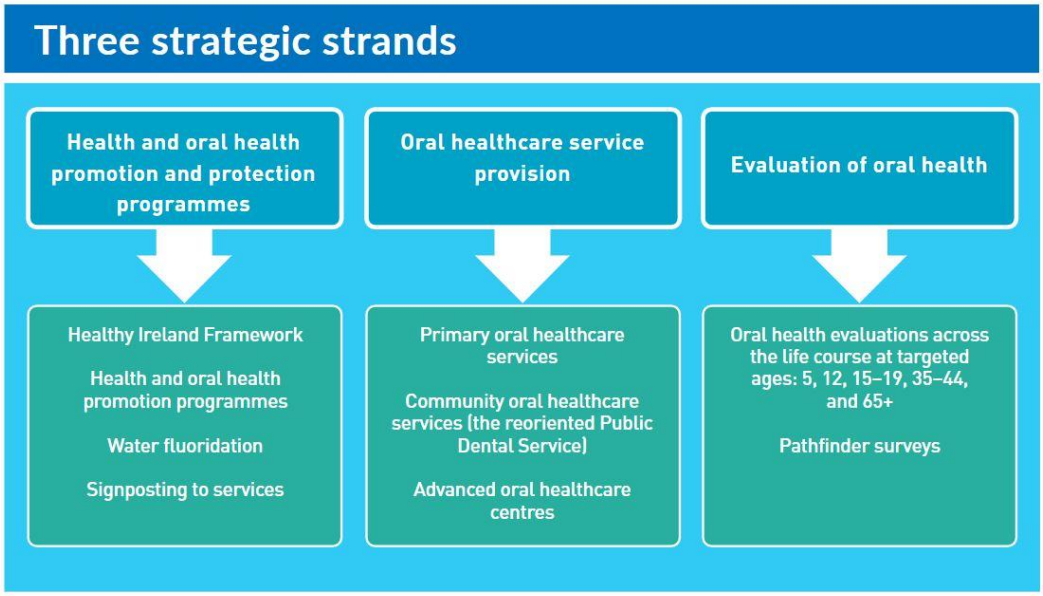

Figure 2 Strategic strands of the national oral health policy

Source: Department of Health, 2019 [55]

The Healthy Ireland framework for 2013–2025 is based around four key goals [56]:

- To increase the proportion of people who are healthy at all stages of life
- To reduce health inequalities
- To protect the public from threats to health and well-being, and

- To create an environment where every individual and sector of society can play their part in achieving a healthy Ireland.

1.1.2 The EU

The EU has introduced Regulation (EU) 2017/852 [57] to implement the 2013 United Nations Minamata Convention on Mercury [58], which aims to protect human health and the environment from mercury pollution. Regulation (EU) 2017/852 is an environmental regulation rather than a health regulation, and its purpose is to reduce the amount of mercury used in many industries and professional sectors, including dentistry (Article 10). *Smile agus Sláinte: National Oral Health Policy* considers Regulation (EU) 2017/852 on mercury by providing for the phase-down of dental amalgam, in line with international policy on reducing mercury use. The national oral health policy does this through its emphasis on health promotion, prevention, and the expansion of primary oral health care services for members of the public of all ages. In parallel, it supports education and the broadening of skills for dental professionals. The services proposed in *Smile agus Sláinte* support the preferred use of alternative materials and restorations, rather than dental amalgam, throughout the life course. In the new system of service provision, amalgam will only be used in exceptional cases. The reduction in the use of traditional filling materials requires an overt change in the delivery of oral health care services, which to date have emphasised dental amalgam restoration as a central intervention. However, reduction in the use of dental amalgam involves more than just the substitution of amalgam fillings with an alternative restorative material. In the future, prevention, non-intervention, and minimal intervention will be the preferred actions.

1.1.3 WHO

The WHO global strategy on oral health will inform the development of a new global action plan, including a framework for tracking progress with targets to be achieved by 2030. The four overarching goals set out in the strategy to guide member states are to [53]:

1. Develop ambitious national responses to promote oral health
2. Reduce oral diseases, other oral conditions, and oral health inequalities
3. Strengthen efforts to address oral diseases and conditions as part of universal health coverage, and
4. Consider the development of targets and indicators, based on national and subnational contexts, building on WHO guidance, to prioritise efforts and assess the progress made by 2030.

The global strategy includes six strategic objectives on oral health governance, oral health promotion and oral disease prevention, the oral health care workforce, oral health care, oral health information systems, and oral health research agendas.

1.1.4 Burden of disease

Based on the Global Burden of Disease study 2017, 2.3 billion and 532 million people are estimated to have untreated caries in permanent teeth and deciduous teeth, respectively. Untreated caries are defined in this study as cases where “a lesion in a pit or fissure, on a smooth tooth surface, has an unmistakable cavity, undermined enamel, or a detectably softened or floor or wall (coronal caries), or feel soft or leathery to probing (root caries)” [59 p363]. Generally, more economically developed countries have the lowest burden of untreated dental caries overall. However, the burden of dental caries in permanent teeth is reported to be highest in upper- and lower-middle-income countries. Globally, the prevalence of untreated caries peaked in those aged 5 years for deciduous teeth and in those aged 20–24 years in the case of permanent teeth [59].

These findings offer an opportunity for policy-makers to identify successful oral health strategies and strengthen them; introduce and monitor different approaches where oral diseases are increasing; plan integration of oral health in the agenda for prevention of noncommunicable diseases; and estimate the cost of providing universal coverage for dental care.

1.2 Purpose of the review

The purpose of this overview of reviews is to provide evidence to assist with the development of clinical guidelines on the prevention of caries in Ireland using individual-based primary prevention interventions prior to the development of any dental decay/dental caries in some or all teeth. Addressing the research questions in an international context ensures that the findings of this review are informed by international best practice. Prevention of caries remains a public health challenge and many interventions for the prevention of dental caries have been shown to be only partially successful [60,61]. Moreover, there is no published overview of systematic reviews summarising interventions to prevent caries and their effectiveness across primary, permanent, and mixed dentition. The evidence from this review will be used to inform the National Clinical Guidelines Group of Dental Caries with respect to the prevention of dental caries using individual-based interventions and will provide the missing piece of the jigsaw, as the Health Research Board (HRB) has already published evidence on the management of non-cavitated and cavitated caries [62]. These forthcoming clinical guidelines will be applicable for the whole population and are for all dental professions working in Ireland.

Primary prevention interventions include modalities such as an array of fluoride interventions either administered by dental professionals or other non-dental but appropriate adults, or used by the patients themselves. Examples include fluoride toothpastes, fluoride mouth rinses, fluoride varnishes, and fluoride gels. In addition, chlorhexidine (CHX), as well as professionally administered preventive measures such as sealants, are included. Oral health promotion and behavioural change programmes (including dietary interventions) and community water fluoridation programmes are not included.

2 Research questions

The Department of Health in Ireland required answers to the following three questions:

1. What is the evidence from systematic reviews regarding the effectiveness of individual-based interventions to prevent carious lesions in primary teeth?
2. What is the evidence from systematic reviews regarding the effectiveness of individual-based interventions to prevent carious lesions in permanent teeth?
3. What is the evidence from systematic reviews regarding the effectiveness of individual-based interventions to prevent carious lesions in mixed dentition?

The population of interest is people with some or all teeth that are caries free. The interventions of interest include professional scaling or cleaning, fluoridated salt and milk, fluoride supplements, fluoride toothpastes, fluoride mouth rinses, fluoride varnishes, fluoride foams, fluoride gels, and slow-release fluoride devices. In addition, CHX, as well as professionally administered preventive measures such as sealants, were included. The comparator was to each other, multiple interventions used in combination, or a placebo. We nominated a wide set of outcomes to measure in this overview of reviews at the outset, based on examples of the main outcomes from our previous review by Long *et al*. [62]. We applied date limits from 2010 to mid-June 2022 based on Joanna Briggs Institute (JBI) guidance for overviews of reviews or umbrella reviews [63]. The language limitations are a necessity, as none of the researchers speaks another language fluently. The date and language limits are dealt with in more detail in Section 3.8.

3 Methods

3.1 Review design

This evidence review uses the overview of reviews (or umbrella review) design to examine the evidence base for interventions to prevent dental carious lesions in humans. An overview of reviews synthesises findings from multiple systematic reviews, enabling reviewers to examine the evidence reported on the effectiveness of interventions and identify whether the evidence base is consistent or contradictory. Undertaking an overview of reviews requires a systematic and transparent plan that follows a set of methods consistent with the approach adopted in a systematic review. According to McKenzie and Brennan, "Overviews involve the systematic retrieval and identification, assessment of bias, and integration of results from multiple systematic reviews. They have the potential to confer many benefits and opportunities. Notably, overviews capitalise on previous research synthesis efforts bringing efficiencies that may lessen research waste" [64 p185]. The purpose of this review is to inform the development of clinical guidelines for dental practice in Ireland.

3.2 Definition of an overview of reviews

There have been numerous attempts to define the parameters of an overview of reviews. However, a recent consensus has emerged to agree on the key elements. The definition of an 'overview of reviews', as cited in Gates *et al.* [65] and developed by the Cochrane Collaboration [66], comprises five key elements. An overview of reviews:

1. Contains a clearly formulated objective designed to answer a specific research question, typically about a healthcare intervention
2. Intends to search for and include only systematic reviews (with or without meta-analyses)
3. Uses explicit and reproducible methods to identify multiple systematic reviews that meet the overview of reviews' inclusion criteria, and to assess the quality/risk of bias (RoB) of these systematic reviews
4. Intends to collect, analyse, and present the following data from included systematic reviews: descriptive characteristics of the systematic reviews and their included primary studies; the RoB of primary studies; quantitative outcome data; and certainty of evidence for predefined, clinically important outcomes, and
5. Discusses findings as they relate to the purpose, objective(s), and specific research question(s) of the overview of reviews, including a summary of the main results, the overall completeness and applicability of the evidence, the quality of the evidence, potential biases in the overview process, and agreements and/or disagreements with other reviews.

3.3 Why we chose an overview of reviews design

We chose an overview of reviews design because we knew from our previous reviews by Keane *et al*. [67] and Long *et al.* [62] that the literature is heavily populated with systematic reviews that are relevant to our research questions. According to Aromataris and Munn:

> If current, multiple, good-quality, systematic reviews exist about a given topic or question, any reviewer should reconsider the need to conduct yet another [systematic] review addressing the same issue. Rather, these [existing systematic reviews] may be the basis to conduct an overview of reviews [umbrella review] and summarize or synthesize the findings of systematic reviews already available. [63 p362]

Overviews of reviews have become feasible mainly due to the increasing volume of systematic reviews that are published on a regular basis in many subject areas. According to Hunt *et al.*, it was estimated that 22 new systematic reviews were published every day in 2018 [68].

3.4 Overview of reviews as an evidence-based product for policy-makers

Systematic reviews are a recognised evidence-based product that are often used by policy-makers in their deliberations and decision-making. As systematic reviews are the exclusive unit of analysis in overviews of reviews, this means that overviews of reviews can contribute to evidence-based policy-making. According to Aromataris and Munn, "With the ever-increasing number of systematic reviews published daily, umbrella reviews [overviews of reviews] have a clear role in evidence-based healthcare and evidence-informed decision-making" [69 p139].

3.5 What type of outputs can we derive from an overview of reviews?

According to Aromataris *et al.*, "…if current, multiple, good quality, systematic reviews exist about a given topic or question, any reviewer should reconsider the need to conduct yet another review addressing the same issue. Rather, these may be the basis to conduct an Umbrella Review and summarize or synthesize the findings of systematic reviews already available" [63 p362].

According to McKenzie and Brennan:

> The purposes of overviews include (but are not limited to) mapping the available evidence, examining the effects of different interventions for the same condition or population, examining the effects of the same intervention for different conditions or populations (also referred to as multiple-indication reviews) or examining reasons for discordance of findings and conclusions across reviews. Overviews are more suited to some purposes than others, and careful consideration of whether they are the appropriate type of review (overview of systematic reviews or systematic review of primary studies) is required. [64 p185]

3.6 Our overall methodological approach to undertaking this work

Our approach to undertaking this overview of reviews was based on guidance published by Gates *et al.,* which includes important pointers on anticipating and addressing the main challenges posed for reviewers when embarking on an overview of reviews [65]. The guidance by Gates *et al.* builds on and updates previous guidance [70]. Gates *et al.*'s guidance is based on an analysis of 77 guidance documents, which were developed and used by 34 research groups with extensive experience in designing and implementing overviews of reviews [65]. The analysis of the 77 guidance documents is supplemented by an examination of additional literature to provide a comprehensive overview of relevant issues pertaining to the conduct of overviews of reviews [65].

Each step taken in designing and implementing an overview of reviews requires careful consideration by reviewers, and decisions taken should, to a large extent, be based on evidence, as such decisions will ultimately affect the credibility of the findings. According to McKenzie and Brennan, "The choice of methods used in overviews may affect the trustworthiness of the findings, coverage of the evidence, and usability and usefulness of the overview, amongst other outcomes. Decisions as to which methods to use are best informed by methods research, along with theoretical considerations" [64 p186].

According to Gates *et al.,* "The decision about whether to only include Cochrane systematic reviews or to also include non-Cochrane systematic reviews can be a balance between ensuring quality and coverage of all-important interventions" [65 p15].

We have used the decision tool developed by Pollock *et al.* to inform our decisions on including reviews in our overview of reviews [71]. This decision tool contains four questions to assist in our decision-making:

1. Do Cochrane systematic reviews likely examine all relevant intervention comparisons and available data?
2. Do the Cochrane systematic reviews overlap?
3. Do the non-Cochrane systematic reviews overlap?
4. Are researchers prepared and able to avoid double-counting outcome data from overlapping systematic reviews by ensuring that each primary study's outcome data are extracted from overlapping systematic reviews only once?

Guidance is provided to help researchers answer each question, and empirical evidence is provided regarding the advantages, disadvantages, and potential trade-offs of the different inclusion decisions.

We have included both Cochrane and non-Cochrane reviews in this overview of reviews, as we know from our previous reviews [62,67] that both types of review evaluate relevant interventions. In addition, a review undertaken by the Scottish Dental Clinical Effectiveness Programme, which has been used to develop dental guidelines in the United Kingdom (UK), also included both Cochrane and non-Cochrane reviews [72].

According to Pollock *et al.*, it is important to decide prior to undertaking an overview of reviews "what action will be taken if there are overlapping reviews (reviews containing the same trials)" [73 p16].

To address the issue of overlapping reviews in this overview of reviews, we included the most recent update of each living review, and we calculated the corrected covered area as a measure of overlap. The latter approach is recommended by Pieper *et al.*, who contend that "all producers of overviews should analyse the overlaps and report their analysis. Reporting should be done even if the amount of overlap is small and unlikely to have an impact on the conclusion. Otherwise, consumers will not know whether there is no meaningful overlap or if the authors simply did not [take] account of it. Consequently, overlaps should be reported by default" [39 p375].

3.7 Protocol and reporting guidelines

A full protocol was prepared for this review, which was registered in advance on PROSPERO (reference number: CRD42022352754) [74]. The review is reported in accordance with the Preferred Reporting Items for Overviews of Reviews (PRIOR) guidelines; please see Appendix B for the PRIOR checklist [75].

3.8 Eligibility criteria

Our eligibility criteria are presented in Table 1. The population of interest was people with some or all teeth that were caries free. We relied on systematic reviewers' determination of caries free teeth in primary studies. The interventions of interest included professional scaling or cleaning, fluoridated salt and milk, fluoride supplements, fluoride toothpastes, fluoride mouth rinses, fluoride varnishes, fluoride foams, fluoride gels, and slow-release fluoride devices. In addition, CHX, as well as professionally administered preventive measures such as sealants, were included. No limits were placed in relation to intervention duration, frequency, mode of delivery (e.g. dental professional, parent, or self) intensity, dose, or follow-up duration. In addition, no limits were placed on the complexity of interventions; systematic reviews that reported on the delivery on combined or complex interventions were included, provided that one or more components of the intervention being evaluated was eligible for inclusion in this overview of reviews. A complete overview of the interventions of interest is illustrated in Figure 3. The majority of these interventions were identified as a result of expertise we acquired when conducting

previous evidence reviews in this substantive area, as well as from guidance we received from the Chief Dental Officer in Ireland prior to commencing the overview. When screening eligible reviews, we identified a small number of additional interventions and added these to our list of interventions. The comparator was a no treatment group, a placebo, or any alternative treatment/intervention. We nominated a wide set of outcomes to measure in this overview of reviews at the outset, based on examples of the main outcomes from our previous review by Keane *et al*. [67]. In relation to study design, only systematic reviews of trials and/or prospective cohort studies were included. We made this choice because randomised controlled trials (RCTs) are regarded as the gold standard trial methodology for evaluating the effectiveness of interventions, and RCTs, non-randomised controlled trials, and prospective cohort studies are studies that offer evidence for causality, and in the case of prospective cohort studies, present outcomes over a long time period. The date limits chosen were from 2010 to mid-June 2022, based on JBI guidance for overviews of reviews [76]. The language limitations were a necessity, as none of the researchers speaks another language fluently. It should be noted that we excluded single-trial reviews if the included trial was already included in another review measuring the same outcome.

Table 1 Eligibility criteria for overview of reviews

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 Studies examining caries prevention among populations that, as a result of physical/mental health condition or illness (such as cancer), or drug-based treatments for such conditions (such as radiotherapy), are at increased risk of dental caries
Intervention	The interventions of interest were those that should prevent caries (see Figure 3).	Oral health promotion, behaviour change programmes Community water fluoridation programmes Interventions targeting diet and sugar intake
Comparator	Placebo Any relevant alternative treatment No treatment	Studies with no comparator
Outcome	Any indicator of caries incidence or new caries presentation on any part of the tooth (e.g. percentage 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 D(E/M)FT* or d(e/m)ft† (or any variation of this index, e.g. DMFT/dmft, DEFT/deft, DFT/dft, or root DMFT/DMFT-root/DMFRT)	None included

Domain	Inclusion	Exclusion
	D(E/M)FS‡ or d(e/m)fs∞ (or any variation of this index, e.g. DMFS/dmfs, DEFS/defs, DFS/dfs, or root DMFS/DMFS-root/DMFRS) Root Caries Index (RCI)	
Study design	Systematic reviews of trials and/or prospective longitudinal cohort studies	Systematic reviews that did not include a population, intervention, comparator, and outcome (PICO) statement or the four aspects of PICO mentioned in the methods Systematic reviews based on searches of only one bibliographic database Systematic reviews that do not have at least one grey literature search and/or a supplementary search Systematic reviews without a quality assessment/RoB 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 checklists, not quality assessment tools) Systematic reviews of case-control studies, retrospective cohort studies, cross-sectional studies, case series studies, or ecological studies Narrative reviews Scoping reviews Primary studies
Date	2010 to mid-June 2022	Pre-2010
Language	English	Non-English languages

*D(E/M)FT = Decayed, Extracted/Missing, and/or Filled Permanent Teeth

†d(e/m)ft = decayed, extracted/missing, and/or filled primary teeth

‡D(E/M)FS = Decayed, Extracted/Missing, and/or Filled Permanent [teeth] Surfaces

∞d(e/m)fs = decayed, extracted/missing, and/or filled primary [teeth] surfaces

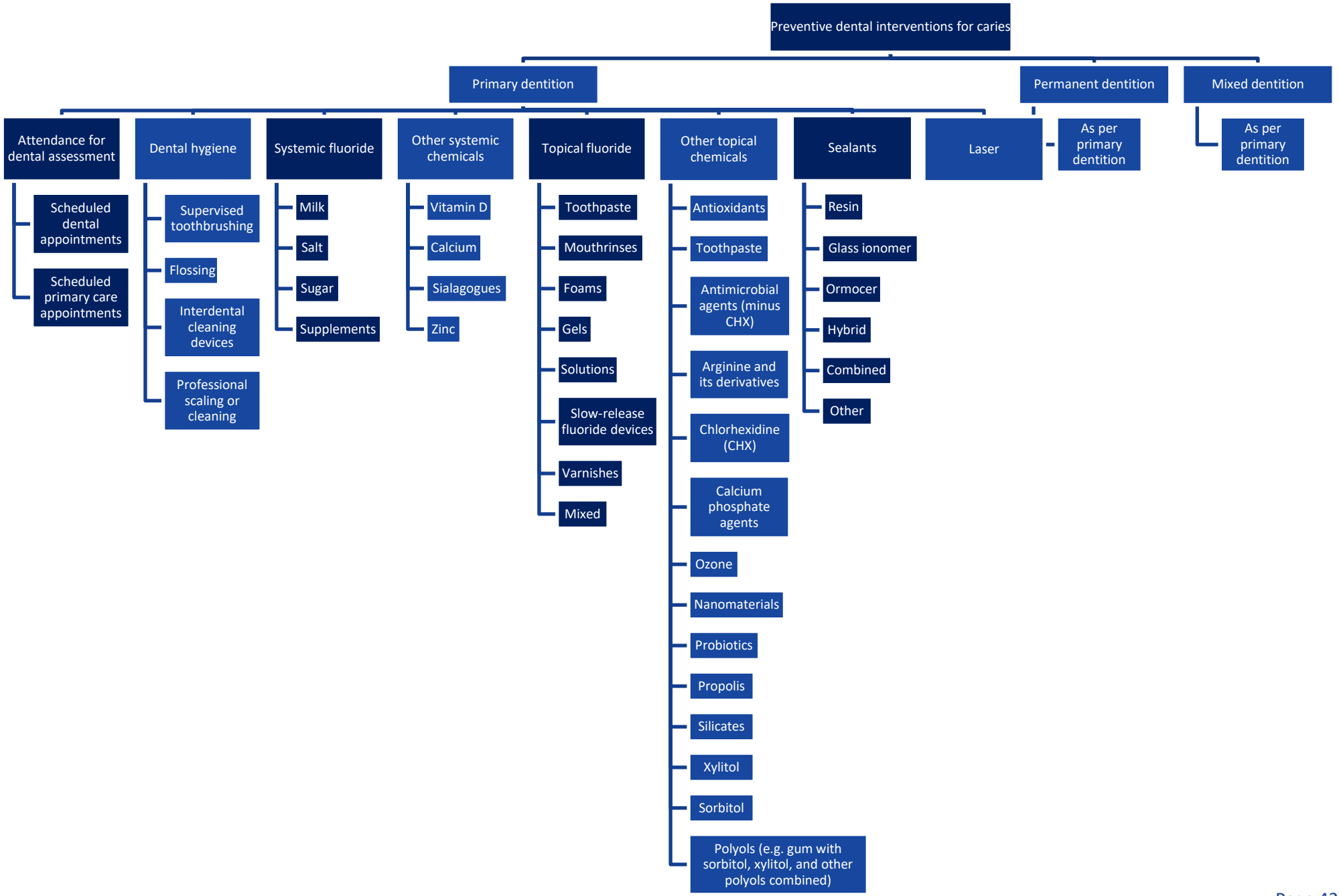
Preventive dental interventions for caries
Primary dentition
Permanent dentition
Mixed dentition
Attendance for dental assessment
Dental hygiene
Systemic fluoride
Other systemic chemicals
Topical fluoride
Other topical chemicals
Sealants
Laser
As per primary dentition
As per primary dentition
Scheduled dental appointments
Scheduled primary care appointments
Supervised toothbrushing
Flossing
Interdental cleaning devices
Professional scaling or cleaning
Milk
Salt
Sugar
Supplements
Vitamin D
Calcium
Sialagogues
Zinc
Toothpaste
Mouthrinses
Foams
Gels
Solutions
Slow-release fluoride devices
Varnishes
Mixed
Antioxidants
Toothpaste
Antimicrobial agents (minus CHX)
Arginine and its derivatives
Chlorhexidine (CHX)
Calcium phosphate agents
Ozone
Nanomaterials
Probiotics
Propolis
Silicates
Xylitol
Sorbitol
Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined)
Resin
Glass ionomer
Ormocer
Hybrid
Combined
Other

Figure 3 Grouping of preventive dental interventions classified by intervention

3.9 Search methods for identification of studies

3.9.1 Identifying research evidence

The planned structure of the literature search for this review included a comprehensive search of databases and other resources to identify as many of the relevant published syntheses on the review topic as possible. Following the selection of a set of papers that met the inclusion criteria, reference, citation, and protocol 'chasing' was undertaken to attempt to identify any further relevant research. The references from the previous review by Keane *at al.* on a related topic were also screened [67]. In addition, a final database search was undertaken at the end of the process. The literature search strategies were adapted by an information specialist (LF) and based on the search strategy developed in Long *at al.* [62]. The strategies were peer reviewed by a second information specialist (CL).

The type of evidence required to carry out an overview of reviews is limited to systematic reviews only [76]. Therefore, the type of evidence sources to be used for the information search focused on sources likely to contain systematic reviews and meta-analyses, as well as standard clinical evidence resources. The range of sources was as wide as possible given the time frame of the project, and included systematic review databases/registries, clinical databases, systematic review summary resources, preprint resources, and open access resources.

Aromataris *et al*. suggest that a broad search is appropriate for an overview of reviews [76]. This was the approach used for this search. The aim of the search strategy was to maximise sensitivity (capturing as much relevant material as possible, at the cost of including irrelevant material) over specificity (all material captured is relevant, at the cost of excluding some relevant material). A multiple-stage screening process was used to filter out the irrelevant material (title/abstract and full-text screening) in preference to using a more tightly focused search process that might inadvertently exclude relevant papers.

While the work of Cooper *et al*. [77] has shown that the current guidance on overviews of reviews lacks a specific definition of a comprehensive search, it was intended that using searches of databases, grey literature sources, and reference/citation/protocol chasing would satisfy the general requirements of a comprehensive literature search and reduce publication bias.

3.9.2 Literature search concepts

The two basic concepts around which the search was constructed are dental caries and prevention. The population of interest in this case was patients of any age or demographic at risk of caries. The intervention was any intervention for caries prevention, and the comparator was any alternative intervention. Outcomes were not included as a search concept, as the outcomes were not strictly defined in the PICO parameters, and, more importantly for the search process, outcomes may not necessarily be included in the database-indexed fields of an article and so may not be 'findable'. The *Cochrane Handbook for Systematic Reviews of Interventions* notes that it may not be helpful to include all aspects of a research question in a search strategy and recommends basing the search on population (or condition), intervention, and study design [78].

The two main concepts for our search were combined to capture papers referring to any interventions, materials, or strategies used to prevent carious lesions in primary, permanent, and mixed dentition (Figure 4). A further broad concept was included in the search: the concept of evidence syntheses, including systematic reviews, syntheses of empirical research, and meta-analyses.

Search limits in the form of date and publication type were also included. The term 'review' encompasses many types of reviews [79]. Not all of these types of reviews would have contributed meaningful data to the analysis for this overview of reviews, and only reviews that satisfied the adapted AMSTAR 2 (A

MeaSurement Tool to Assess systematic Reviews, version 2) (Appendix E) instrument were included in the final analysis. However, the search strategy aimed to capture any type of review or synthesis (which were then screened with close attention to detail in the review screening process), rather than to only search for 'systematic reviews' – a term that is occasionally omitted in actual systematic reviews and that is also used in reviews that are, based on their methods and results, clearly not systematic.

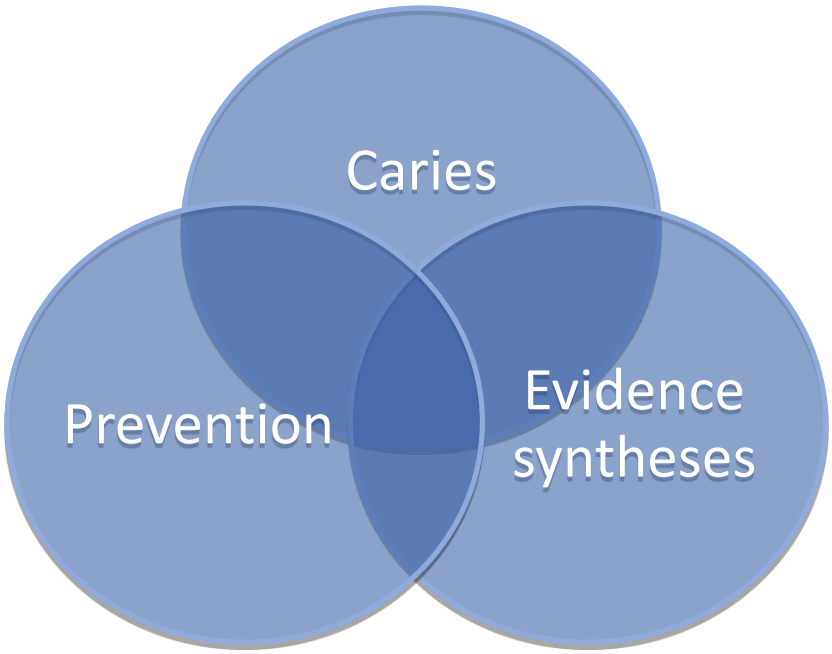

Figure 4 Graphic representation of search concepts

3.9.3 Information sources

A range of information resources was used, including clinical databases, systematic review/health technology assessment resources, search engines, open access and preprint repositories, and relevant website searches.

The literature searches for this review included searches of 3 clinical databases (Ovid MEDLINE, EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scientific Electronic Library Online (SciELO)), 11 systematic review resources (the Cochrane Library, Epistemonikos, the Campbell Collaboration, the Agency for Healthcare Research and Quality (AHRQ) Systematic Review Data Repository, the Database of Abstracts of Reviews of Effects, the Database of Promoting Health Effectiveness Reviews (DoPHER), JBI Evidence Synthesis journal, the International Health Technology Assessment Database, McMaster University's Health Evidence database, Social Systems Evidence, and Health Systems Evidence), 3 search engines (Google, Google Scholar, and DuckDuckGo), and 6 resources for open access/grey/preprint material (Core.ac.uk, Osf.io, Research Square, medRxiv, bioRxiv, and website searches). PROSPERO, the International Prospective Register of Systematic Reviews, was searched as a part of the supplemental searches in order to retrieve and follow up on relevant protocols for reviews.

Search engines were used as a supplemental resource to capture papers that were not indexed in databases, or where the information relevant to this review was not included in the indexed/searchable fields. The first 100 results from search engine searches were screened. The use of search engines in literature searching is not without problems, but the searches were documented as well as possible [80–82]. However, the transparency and reproducibility of searches in search engines is limited by the

structure of the search engines themselves, with changing web content and unknown or changing algorithms [78].

Relevant websites were searched, including national and international dentistry association sites. While reviews are not typically hosted on these sites, new publications in relevant fields are frequently noted or referenced, and any mention of a relevant review was followed up on.

A complete list of the resources used is set out in Appendix A.

3.9.4 Search terminology

The initial search strategy was constructed in Ovid MEDLINE. For both prevention and dental caries, synonyms, related relevant terms, and thesaurus/controlled vocabulary terms were sourced using PubMed PubReMiner [83], websites of dental organisations, known relevant articles, and the National Library of Medicine's Medical Subject Headings (MeSH) Browser [84]. Search terms included controlled vocabulary (MeSH terms) and 'free terms' or keywords. Boolean operators, adjacencies, and wildcards were used to focus the search terms. After testing the search terms using MEDLINE searches, the two sets of search terms (prevention and dental caries) were combined. The Canadian Health Libraries Association's systematic review filter was added to the search [85] and a date limit of 2010–2022 was also added, as per the JBI guidance on date limits for overviews of reviews. This search strategy is described in Appendix A.

Regarding publication date cut-offs, the JBI guidance for overviews of reviews suggests that a cut-off date of research published in the past 10 years will be likely to capture primary research published within approximately the previous 30 years [76]. In line with this guidance, a date range of 2012–2022 for published research was selected and implemented in the literature search. For some searches, such as the Ovid MEDLINE search, the earlier date of 2010 was set so as to include e-publications and 'online first' or 'early cite' papers and to allow for some variation in indexing of papers as preprints.

The search strategy was translated for use in the other databases (such as EBSCO CINAHL) and resources. For some evidence sources used, complex Boolean searching was not possible and abbreviated searches were used instead.

The search concepts were combined using Boolean operators in those databases where this facility is available (for example, MEDLINE and CINAHL). The broad structure of the search was as follows: ((((All terms for caries) AND (All terms for dental [prevention])) AND (Systematic review filter)) AND (date limit)).

For information resources not providing Boolean search options, the terms were combined in the search facility provided, where available. In some cases, abbreviated searches were carried out where more structured searches were not possible.

Some terminology that was included in the search would appear to be redundant – it may duplicate other terms used or may return no results. The inclusion was deliberate and was designed to show that terms were included and returned no results, rather than these terms being omitted with no knowledge gained as to whether they would be useful or not [86]. These terms may also play a role in future iterations of this or related work.

The search strategy was informally peer reviewed by a second information specialist (CL) using the headings of the Peer Review of Electronic Search Strategies (PRESS) checklist (outlined in the PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration document) [87].

3.9.5 Search limiters

The eligibility criteria for this review included a specification that papers in languages other than English would not be examined. However, a language limit was not used within the search strategy. The databases used primarily index English-language research, and the addition of a language filter was not considered necessary, as the expected low number of non-English papers would be more accurately filtered out in the screening process.

No limits were included for subject ages; this review included research on adults, children, and participants of non-specified ages. Further examination of dentition type (primary, permanent, and mixed) was established more precisely in the data extraction and synthesis process rather than through the search process.

3.9.6 Supplemental searching

3.9.6.1 Protocol/reference/citation searching

There is evidence that reference searching would likely be useful; a previously published Cochrane review examined the use of reference searching for systematic reviews and found positive results, but these were derived from weak study designs [88]. Reference and citation searching of studies retrieved from initial searches has been incorporated into the search plans of previous HRB reviews, with variable but generally positive results. The process is not without drawbacks (it is time-consuming; it may result in a bubble effect where the same authors reference and cite each other; and there are differences in the 'retrievability' of citations between journal articles, with digital object identifier numbers used in cross-referencing, and reports, where citations are not so easily identified) but it can be useful, especially to retrieve newly published articles, including those not indexed in databases (e.g. reports, grey literature) or articles indexed in databases other than the ones used in the search strategy.

Supplemental searching was carried out in the period from October to December 2022 by the information specialist (LF). The database/research data platform Dimensions and Google Scholar were used to extract article citations and references of all included papers [89]. Relevant papers were identified during the screening process and were tracked to find the related systematic reviews where these had been published. A brief search in PROSPERO was used to identify other protocols that may be relevant. The results of these searches were deduplicated. Preliminary screening was carried out by the information specialist (LF) using the inclusion/exclusion criteria from the earlier screening process, and the pre-screened results were then examined by the researchers (JL and LM).

3.9.6.2 Screening of a previous HRB review

A related HRB review by Keane *et al*. was published in 2020 [67]. The references from that review were screened by an experienced researcher (JL) for potential reviews that would match the inclusion criteria of the present overview of reviews.

3.9.6.3 Search dates

Initial database searches were carried out in mid-June 2022. Supplemental searches, comprising protocol follow-up and reference and citation searching of reviews selected from the screening process, were carried out between 19 October and 21 December 2022.

3.9.6.4 Search data management

Search results were exported to EPPI-Reviewer Web for deduplication and screening. Screening was carried out in several steps [90]. Data extraction was carried out in Microsoft Word, as described in Section 3.11.

3.10 Screening

3.10.1 Screening stage 1: title and abstract screening

All database search results (5,375) were imported into EPPI-Reviewer Web for title and abstract screening by two members of the review team (LM and JL) using the eligibility criteria outlined in Table 1, based on the review's PICO criteria. The reasons for exclusion included search dates, study type, population, intervention, intervention intent (caries management), and duplication. Citations and abstracts were retained if not enough information was provided to decide on inclusion.

The research team decided to use EPPI-Reviewer Web's priority screening function to improve the efficiency of title and abstract screening. Priority screening uses text mining to make screening for systematic reviews more efficient by prioritising the abstracts shown to the reviewer. The priority screening function pushes the more relevant studies towards the beginning of the screening process and pushes the less relevant ones towards the end. As a result, the relevant abstracts can be found earlier in the screening process, and the review can proceed more quickly through to the full-text retrieval and screening phases. Priority screening of titles and abstracts was undertaken by two members of the review team (JL and LM) in order to ensure that each reference was reviewed by two reviewers.

For the purposes of this review, EPPI-Reviewer Web's priority screening was set to the 'Multiple: auto complete (code level)' reconciliation mode. Using this option, EPPI-Reviewer Web marked the coding as complete if there was agreement between the two reviewers. Differences between reviewers were reconciled through discussion and consensus between the two reviewers. This process continued until all abstracts had been screened.

3.10.2 Screening stage 2: full-text screening

Following title and abstract screening, relevant articles were retrieved for full-text screening. Each full-text paper was independently reviewed by two reviewers (JL and LM) using the eligibility criteria outlined in Table 1. Papers were excluded if they did not match three domains of the adapted AMSTAR 2 (Appendix E) criteria: inadequate or absent PICO, inadequate or absent literature search, and inadequate or absent RoB assessment/quality assessment. The PICO did not have to be formally presented as a table, but the population/patient group, the interventions and comparators, and the outcomes relating to these aspects had to be described in the review's rationale section or methods section.

Papers that did not include an adequate literature search were excluded at this stage. The concept of an 'adequate' literature search is not set, and given the variety of resources appropriate for different topics, deciding what comprises an adequate or comprehensive search is not an exact science [77]. In this case, an adequate search was taken to include, at a minimum: at least two databases used, an attempt to describe the search (varying from including a few keywords to a complete listing of all search strategies used), and at least one grey literature or supplemental search method used. The supplemental search methods can include the use of trial registries, hand-searching of journals, reference and citation chasing, contact with subject experts, contact with authors, etc. As searches of the Cochrane Library include searches of both Cochrane systematic reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) (which derives records from, among other resources, ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform), the use of the Cochrane Library in searches is technically allowed as a supplemental search as well as a database search. It must be stressed that these three literature factors were used as parameters to establish minimum standards for searches to include systematic reviews in this overview of systematic reviews. These factors should not be taken to indicate a comprehensive search, which should have included and reported the elements described in the extended version of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-S) reporting guide for reporting literature searches [91].

The quality assessment exclusion criteria were that a quality assessment must be completed using a standard tool and that the result of the quality assessment for each primary study must have been reported by each domain on the selected tool. Reviews that used study design checklists were excluded. Reviews that did not provide a quality assessment for each included primary study were also excluded.

At all stages of the review, records that were published in a language other than English (e.g. from English-language abstracts or keywords) were retained to recognise that the English-language literature is not the total extent of the research on this topic. The papers and reasons for exclusion are given in Appendix C.

3.10.3 Screening stage 3: screening during data extraction

Papers meeting the eligibility criteria were forwarded to the data extraction stage of the review process (n=95). Each full-text paper was independently extracted by a reviewer and the extraction corroborated by another reviewer (MA and LM) using the eligibility criteria outlined in Table 1. During extraction, 27 papers were removed, as they were found upon closer inspection not to fit the criteria of the review, leaving 66 systematic review papers. The papers and reasons for exclusion are given in Appendix C; reasons for exclusion included incorrect study design (including scoping reviews), excluded topic or intervention (for example, papers that initially appeared to investigate caries but were in fact about post-orthodontic white spot lesions), or exclusion on inadequate RoB/quality assessment, as per the adjusted AMSTAR 2 criteria.

3.10.4 Screening stage 4: supplemental search results

As noted in Section 3.9.6 on supplemental searching, the results of supplemental searches (reference and citation chasing and protocol follow-up) were initially screened by the information specialist (LF). Initial screening was done by title and abstract. The results of this screening were then compared with the database search results. Any of these results arising from supplemental screening which had also arisen in the database search results, and had been screened previously, were excluded. A final set of potential results was screened on title and abstract by one of two researchers (JL and KC). The full text of all papers marked as included was retrieved, screened, and extracted as described in Sections 3.9 and 3.10.

The flow of information for the review is illustrated in the PRISMA flow chart in Figure 5.

3.11 Assessing the quality of included systematic reviews

According to Gates *et al.*:

> There is no agreement on which tool might be best to use (e.g., AMSTAR, AMSTAR 2, or ROBIS [Risk of Bias in Systematic Reviews]) to assess methodological quality, or how to use them in the context of an overview of reviews. It can be difficult to distinguish between methodological quality and the quality of reporting, and poor reporting in the systematic reviews can make assessment challenging. Authors often have difficulty interpreting and coming to agreement with assessments on the available tools. It is unclear whether authors should assess systematic reviews in their entirety or only the components that are relevant to the overview question, and what to do with systematic reviews that include other embedded reviews. When overview quality is being used to choose between overlapping systematic reviews, authors need to be careful to not exclude potentially relevant information. When overlapping systematic reviews use different methodologies and come to discordant conclusions, it can be hard to tell whether their methods are appropriate. [65 p15]

We used the AMSTAR 2 instrument to assess the quality and RoB of all reviews that met our inclusion criteria. The AMSTAR 2 instrument is relatively new, having been developed by Shea *et al*. (2017) [92] to

build on the original AMSTAR instrument, which was designed to appraise systematic reviews that exclusively included RCTs. AMSTAR 2 was developed in order to enable the appraisal of systematic reviews of randomised and non-randomised studies of healthcare interventions. We chose to use AMSTAR 2 rather than AMSTAR because, based on our previous review experience [67], we knew that relevant reviews would contain both randomised and non-randomised studies. Therefore, the AMSTAR 2 instrument was an appropriate assessment tool to use in our overview of reviews.

The AMSTAR 2 instrument contains 16 items to appraise the quality and the RoB in systematic reviews [92]. Two reviewers (MA and LM) used an adapted version of AMSTAR 2 to assess each full-text review (Appendix E). Differences between reviewer appraisals were resolved through discussion and consensus.

We piloted AMSTAR 2 on four systematic reviews while carrying out research for our overview of reviews, *Management of non-cavitated and cavitated caries in primary, permanent, and mixed dentition: An evidence review* [62]. Following this, we made several adjustments to the tool. We retained the text of the questions as per AMSTAR 2; however, we adjusted the scoring of Questions 1, 4, and 8 to provide consistent and more appropriate judgement of the parameters being scrutinised. We also added text to further explain what is required when assessing Questions 1–4, Questions 8 and 9, and Questions 11–16 in order to ensure that all reviewers were making decisions using the same parameters.

According to Shea *et al*., "Responses to AMSTAR 2 items should not be used to derive an overall score. We accept that an overall score may disguise critical weaknesses that should diminish confidence in the results of a systematic review, and we recommend that users adopt the rating process based on identification of critical domains, or some variation based on these principles" [92 p6]. Shea *et al.* suggest seven critical domains in the AMSTAR 2 instrument that reviewers may use to assess critical flaws in systematic reviews (Table 2) and recommend assigning a confidence rating to each systematic review using the schema shown in Table 3 [92]. We assigned an overall quality rating to each review using the seven critical domains and rating schema suggested by Shea and colleagues.

Table 2 Critical domains in AMSTAR 2

	Critical domain
1	Protocol registered before commencement of the review (item 2)
2	Adequacy of the literature search (item 4)
3	Justification for excluding individual studies (item 7)
4	Risk of bias assessment of the individual studies included in the review (item 9)
5	Appropriateness of meta-analytical methods (item 11)
6	Consideration of the risk of bias when interpreting the results of the review (item 13)
7	Assessment of presence and likely impact of publication bias (item 15)

Source: Shea *et al.*, 2017 [92]

Table 3 Rating 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.

Source: Shea *et al.*, 2017 [92]

3.12 Collecting and presenting data on descriptive characteristics of included systematic reviews (and primary studies)

According to Gates *et al.*:

> Overview authors are challenged with data extraction at two levels, first the level of the systematic review, and then potentially the level of the primary study. When relying on the reporting of the included systematic reviews, authors may struggle when these are poorly reported and missing important details. Overview authors need to carefully check systematic reviews for errors in data extraction, as these errors will lead to errors in the overview of reviews. They also need to decide how to deal with systematic reviews with missing information of relevance to the overview of reviews. Going back to the primary studies can be time consuming, but not doing so can lead to a loss of information. [65 p16]

Furthermore, Gates *et al.* stated that "descriptive characteristics of the systematic reviews should be presented narratively and/or in a table in adequate detail to support each systematic review's inclusion in the overview of reviews and inform the applicability of their findings" [65 p12].

We used an adapted version of the JBI data extraction form for systematic reviews and research syntheses to extract data on the descriptive characteristics and findings of each included systematic review (Appendix G). We have experiencing of using this extraction form in previous evidence reviews we have conducted in this area. One review author undertook the data extraction for each review (MA or LM) and a second author validated it (KC or LM). We extracted and documented in tabular format the following data from each included review: citation details; objectives of the review; participants; setting; interventions and comparators; search information; primary study date range; number of primary studies; study design; RoB tool used; RoB assessment, including publication bias; analysis methods; outcomes assessed; results by outcome(s); and commentary on bias, heterogeneity, and the use of GRADE (Grading of Recommendations, Assessment, Development and Evaluation) (Appendix H). We then applied the GRADE approach to each of the relevant outcomes in each systematic review (Appendix K) and summarised the main findings (Appendix J) (see Section 3.14).

3.13 Collecting, analysing, and presenting outcome data

According to Gates *et al.*:

> Many difficulties may arise when collecting, analysing, and presenting findings at the overview level, because of inconsistency in methodology and reporting of findings across systematic reviews. For example, the included systematic reviews and their primary studies may use heterogeneous outcome measures. Additionally, the included systematic reviews may be incompletely reported, or may not report data on subgroups of interest. Overlapping systematic reviews might present discordant results or present similar data in different ways (e.g., different summary measures), and it can be complex and time-consuming to ensure that data from single studies are not over-represented. Interpretation of measures of overlap (e.g., matrices and corrected covered area) can be a challenge when the number of primary studies is large. To perform analyses of interest, overview authors might need to go back to individual studies or concede that the available information is incomplete. It may not always be appropriate or feasible to conduct meta-analyses in overviews, and network meta-analyses and informal indirect comparisons are usually not appropriate. However, narrative synthesis can become complex and open to bias if not adequately described. There is a concern that synthesis errors at the systematic review level could result in errors at the overview level. [65 p16]

We nominated a wide set of a priori outcomes to measure in this overview of reviews. Our reasoning for this decision was based on our previous work on reviewing the dental literature, where we found that systematic reviews tended to focus on different outcomes in the prevention of caries in human teeth [67]. In addition, the ultimate objective of our work was to identify the different interventions that tackle the same condition (i.e. carious lesions) but that are assessed using different outcomes. As characterised by Lunny *et al*., "Overviews of systematic reviews synthesise the results of multiple systematic reviews. Overviews are typically broader in scope than systematic reviews and may examine different interventions for the same condition, the same intervention for different conditions, or the same intervention for the same condition but focusing on different outcomes" [93 p2].

Table 1 describes the outcomes of interest to this overview of reviews. However, occasionally one or more of these outcomes were presented as secondary outcomes in the included systematic reviews. In our data extraction document (Appendix H), we noted which outcomes were presented as secondary outcomes in each systematic review. In relation to our outcomes, we distinguished between general epidemiological indicators of caries incidence (e.g. proportion of participants with new carious lesions) and dentistry-specific epidemiological indicators (e.g. the Decayed, Extracted/Missing, and/or Filled Surfaces (D(E/M)FS) and Decayed, Extracted/Missing, and/or Filled Teeth (D(E/M)FT) indexes and their

variations). This distinction was applied when assessing the overlap of primary studies included in more than one systematic review. The outcomes of interest are dealt with in more detail in Table 4. We note that the International Caries Detection and Assessment System (ICDAS) tool is not included as an outcome measure per se. ICDAS was used in systematic reviews and primary studies either as a means by which to determine baseline caries among participants or as a threshold by which to identify new caries post-intervention (i.e. caries incidence) rather than as a distinct outcome measure in and of itself.

Table 4 Overview of review outcomes

General epidemiological measures	Dentistry-specific epidemiological measures
Any indicator of caries incidence or new caries presentation on any part of the tooth (e.g. percentage 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	D(E/M)FT or d(e/m)ft (or any variation of this index, e.g. DMFT/dmft, DEFT/deft, DFT/dft, and root DMFT/DMFT-root/DMFRT) D(E/M)FS or d(e/m)fs (or any variation of this index, e.g. DMFS/dmfs, DEFS/defs, DFS/dfs, and root DMFS/DMFS-root/DMFRS) RCI

When extracting outcome data from systematic reviews, we prioritised quantitative syntheses (i.e. meta-analyses) over narrative syntheses. We only extracted and summarised narrative syntheses when no quantitative synthesis was performed. We used a narrative synthesis approach to analyse the data in our overview of reviews, taking account of any discordant findings, highlighting overlaps, and assigning a certainty of evidence rating.

Finally, we extracted information (when reported) from systematic reviews pertaining to any background exposure that participants in the primary studies may have had to caries-preventive agents (such as community water fluoridation, fluoride toothpaste, etc.) that were not considered part of the intervention being delivered to prevent caries but which may have enhanced the effect of the intervention.

3.14 Assessing the certainty of evidence of outcome data

The Cochrane Collaboration recommends using the GRADE framework to facilitate the transparent rating of the quality (or certainty) of evidence for systematic reviews [94,95]. In the literature, applying the GRADE approach is typically referred to as assessing the quality of the evidence. However, in order to clarify the distinction between assessing the methodological quality of the individual reviews (using AMSTAR 2) and assessing the quality of the evidence for the outcome(s) from each systematic review, we will henceforth refer to the GRADE approach as an assessment of the certainty of the evidence.

The GRADE approach has been traditionally applied to rating the certainty of evidence in single systematic reviews, primarily reviews that include a meta-analysis. However, the application of GRADE in systematic reviews can vary due to the subjective reasoning of reviewers, and this can have implications for the overviews of reviews that rely on the GRADE assessments reported in single systematic reviews. In addition, there appears to be a lack of consensus on how best to apply a GRADE assessment when undertaking an overview of reviews. The following extract from Gates *et al.* elaborates these difficulties quite succinctly:

> It may not be possible or appropriate to simply extract existing GRADE appraisals from the included systematic reviews. The reviews might not include GRADE appraisals for the outcomes or populations of interest or be missing details on each of the GRADE considerations. Different

> systematic reviews with the same studies that have made different decisions about handling data (analysis) and appraising study quality may come to different GRADE conclusions, especially related to the study limitations, consistency, and precision domains. Different researchers rating systematic reviews could come to different conclusions, due to the subjectivity of the GRADE approach. If re-doing the GRADE for each systematic review, authors are likely to encounter difficulty due to an absence of guidance on how to apply GRADE in the context of an overview, incomplete reporting at the level of the systematic review, and a lack of familiarity with the contributing primary studies. [65 p16]

Despite these difficulties elaborated on in the literature, we believed it was important to assess the certainty of the evidence in an overview of reviews that may be used to inform the development of clinical guidelines. And, to some extent, we found some agreement with our views. For example, according to Pollock *et al*., "An essential part of an overview is the assessment of the quality of evidence arising from the included reviews, and the [GRADE] approach is the framework recommended by the Cochrane Handbook [for Systematic Reviews of Interventions] to facilitate transparent rating of quality of evidence" [96 p106].

However, to reiterate an earlier point, there is a lack of clear guidance on how to best apply GRADE within the conduct of an overview of reviews. For example, Pollock *et al*., who sought to apply GRADE in an overview of Cochrane reviews, stated: "Within our overview, reviewers found that current GRADE guidance was insufficient to make reliable and consistent judgements" [96 p106].

In an effort to overcome some of these challenges to applying GRADE in an overview of reviews, Pollock *et al*. [96] developed an algorithm to grade the certainty of evidence in their overview based on four key criteria. The HRB added an additional criterion (study design), as we included randomised, quasi-randomised, and non-randomised trials, as well as cohort studies and quasi-experiments, in this overview of reviews. The criteria are as follows:

1. The design of the included studies
2. The risk of bias within the trials contributing participants to the analysis with respect to:
    a) randomisation, and
    b) blinding of outcome ascertainment.
3. The statistical inconsistency or heterogeneity within the analysis, as determined by the I^2 statistic or the Q statistic
4. The number of participants included in the analysis, considering imprecision based on sample size and confidence intervals around outcomes of interest, and
5. The methodological quality of the review as determined by our selection of critical domains from the quality assessment tool (our adapted version of the AMSTAR 2 instrument).

Gionfriddo [97] and Murad *et al.* [98] have criticised the work of Pollock et *al.*[96] for modifying the GRADE assessment into an algorithm comprising a concrete set of rules for assessing the certainty of evidence in an overviews of reviews. To paraphrase the critiques elaborated on by Gionfriddo [97] and Murad *et al.* [98], the algorithm developed by Pollock *et al*. undermines the subjective strength of the existing GRADE assessment for systematic reviews, as the rating of the certainty of evidence is, by necessity, a matter of judgement. In response, Pollock *et al.* offered the following reply:

> We postulate that what has prompted much of the debate from both Gionfriddo (2016), and Murad *et al*. (2016) is the extent to which the purpose of rating evidence differs in an overview,

> as compared with guidelines or recommendations [for single systematic reviews]. Although Cochrane recommends use of GRADE to rate quality of evidence within overviews and while our algorithm built on our understanding of the GRADE approach, perhaps our algorithmic approach has moved so far from GRADE that it can no longer be labelled as such. However, regardless of name, our methodological approach has potentially got implications for assessment of quality of evidence within future overviews, with advantages relating to efficiency, reproducibility, and transparency. [99 p240]

We concur with the views expressed by Pollock *et al.* regarding the advantages of using their algorithm to rate the certainty of evidence in an overview of reviews relating to efficiency, reproducibility, and transparency. We believe that these properties are important in the context of assessing evidence to inform clinical guidelines, as the application of this algorithm can help to reduce subjectivity. In addition, other teams of reviewers undertaking overviews of reviews have applied the modified GRADE algorithm to assess the certainty of evidence with little difficulty reported in the application of the algorithm [100,101].

Following on from the considerations outlined above, we decided to use the algorithm developed by Pollock *et al.* [96] to rate the certainty of evidence in our overview of reviews on strategies to manage dental caries in humans and have used it again in this overview of reviews. We applied the modified GRADE algorithm to all caries prevention systematic reviews that met our inclusion criteria.

According to the guidance on this algorithm provided in Pollock *et al.* [96], each review starts with a ranking of high certainty and can receive one downgrade for a serious methodological concern on any one of the GRADE criteria (inclusion of non-RCTs in the systematic review; high RoB in randomisation or blinding for >75% of included studies; high heterogeneity (I^2 >75%); a sample size of between 100 and 199 participants; and 'no' on one of the AMSTAR 2 items selected as a critical domain) or two downgrades for a very serious methodological concern on either of two GRADE criteria (a sample size of <100 participants and 'no' on two or more of the AMSTAR 2 items selected as critical domains).

Regarding the heterogeneity criterion, many systematic reviews conducted more than one pooled analysis, and therefore reported more than one I^2 value. Where this occurred, we selected the highest I^2 value reported in order to grade the level of statistical inconsistency or heterogeneity. Similarly, with respect to the sample size criterion, many systematic reviews reported more than one sample size with respect to our nominated outcomes. Where this occurred, we selected the largest sample size reported for considering imprecision based on sample size and confidence intervals around outcomes of interest.

Regarding the methodological quality criterion, we used the seven critical domains in the AMSTAR 2 instrument that were nominated by Pollock *et al.* [96] (see Table 2). In addition, we included study design in the modified GRADE algorithm and applied a downgrade for the inclusion of non-randomised or cohort studies. Our modifications are modest and do not materially change the principles of the formula proposed by Pollock *et al.* [96]. A full elaboration of how we applied the GRADE algorithm is outlined in Table 5.

We examined a variety of different interventions to prevent caries, some of which permitted blinding for the operator while others did not permit blinding. Cochrane Oral Health Group systematic reviews appear to retain blinding in their assessment of bias and grading of the certainty of evidence; therefore, for consistency, we also did the same, as otherwise the clinical guidelines for dental operators in Ireland would not be compatible with international guidelines.

Table 5 Formula for applying a GRADE level of evidence to overviews of reviews and number of downgrades determined using the algorithm

Area assessed	Study design	RoB (randomisation)	RoB (outcome ascertainment)	Heterogeneity	Imprecision (based on sample size)	AMSTAR 2 review quality
Method of assessment	Randomised study designs	Example used and reported in Pollock *et al.* [96]. Proportion of study participants included in the pooled analysis from primary trials or studies judged to have low RoB for randomisation.	Example used and reported in Pollock *et al.* [96]. Proportion of study participants included in the pooled analysis from primary trials or studies judged to have low RoB for observer blinding.	Statistical heterogeneity or inconsistency, assessed by, for example, I^2 or Q statistic.	Adequate number of participants included in the pooled analysis.	The overall rating of the methodological quality of each systematic review is based on scoring in the critical and non-critical domains. The critical domains used and reported in Pollock *et al.* [96] were the responses to AMSTAR 2 questions 1–4: a priori research design, search characteristics, independence of study selection, and data extraction. However, we chose the seven AMSTAR 2 items suggested by Shea *et al*. [92] as critical domains (see Table 2).
No downgrade (no serious limitations)	Only randomised study designs included	≥75% of study participants included in the pooled analysis from primary trials or studies judged to have low RoB for randomisation.	≥75% of study participants included in the pooled analysis from primary trials or studies judged to have low RoB for observer blinding.	I^2 ≤75%	≥200	7/7 are all 'yes' on AMSTAR 2 (i.e. low RoB), with 0–2 non-critical weaknesses.

Area assessed	Study design	RoB (randomisation)	RoB (outcome ascertainment)	Heterogeneity	Imprecision (based on sample size)	AMSTAR 2 review quality
Downgrade 1 level (serious limitations)	Inclusion of non-randomised or cohort study designs	<75% of study participants included in the pooled analysis from primary trials or studies judged to have low RoB for randomisation.	<75% of study participants included in the pooled analysis from primary trials or studies judged to have low RoB for observer blinding.	I^2 >75%	100–199	6/7 are all 'yes' and 1 is 'partial' or 'no' on AMSTAR 2, with or without non-critical weaknesses.
Downgrade 2 levels (very serious limitations)	N/A	N/A	N/A	N/A	1–99	≤5/7 are 'yes', and the remainder are 'partial' or 'no' on AMSTAR 2, with or without non-critical weaknesses.
Notes		If RoB for randomisation in individual trials was not reported in the review, we assumed that less than 75% of participants had low RoB.	If RoB for outcome ascertainment in individual trials was not reported in the review, we assumed that less than 75% of participants had low RoB.	N/A if no meta-analysis was conducted; where more than one I^2 value was reported, we used the highest for GRADE; if I^2 value was not reported, it was assumed to be greater than 75%; if sensitivity analysis was conducted, we used the I^2 value from the sensitivity analysis over the main analysis.	If the review authors conducted more than one meta-analysis, we used the meta-analysis with the highest sample size for GRADE; if reviews included multiple comparisons under a single outcome and no pooled analysis, we summed the total sample size for that outcome for GRADE; reviews that did not report a sample size	A 'partial yes' in an AMSTAR 2 critical or non-critical domain was counted as a 'no', except for a 'partial yes' given to a Cochrane review in critical domain 1 (protocol established prior to undertaking the review). Cochrane review authors are required to prepare a review protocol. Therefore, if adequate information pertaining to the protocol was not

Area assessed	Study design	RoB (randomisation)	RoB (outcome ascertainment)	Heterogeneity	Imprecision (based on sample size)	AMSTAR 2 review quality
					were downgraded by two.	provided in a Cochrane review, the review received a 'partial yes' on AMSTAR 2 but was not downgraded.

Source: Adapted from Pollock *et al*., 2016 [96]

The number of downgrades that can be applied using the modified GRADE algorithm ranges from zero to eight (one possible downgrade on each of six criteria in the GRADE algorithm, or two possible downgrades on two of the six criteria), and these ratings can be applied within the standard GRADE level of evidence [96]. Table 6 presents an illustration of the framework we used to interpret the certainty evidence in this overview of reviews.

Table 6 Application of GRADE level of evidence to overview of reviews from number of downgrades determined using the modified algorithm

GRADE level of evidence	Number of downgrades (derived from objective assessment)
High	Score awarded when 0 downgrades are applied
Moderate	Score awarded when 1 or 2 downgrades are applied
Low	Score awarded when 3 or 4 downgrades are applied
Very low	Score awarded when 5 or more downgrades are applied

Source: Pollock *et al.*, 2016 [96]

Reviews that included only one primary study were automatically downgraded to 'very low certainty' regardless of their performance on other GRADE criteria. Some worked examples of applying the modified GRADE algorithm are: one downgrade due to inconsistency or because heterogeneity is not or cannot be dealt with appropriately; two downgrades due to imprecision based on inadequate sample size within pooled analysis; or two downgrades because of the review quality (i.e. a 'no' on two or more of the AMSTAR 2 critical domains).

Systematic reviews often reported on more than one outcome. In the included reviews some outcomes were informed by two or more trials and others were informed by one trial. For single trial outcomes, we took into account the participant sample size, as reported in the included reviews. For this, we borrowed from the modified GRADE algorithm criterion for imprecision based on population size. That is, the certainty of evidence from single trials with a sample size of between 100 and 199 was downgraded by one (e.g. from low-certainty to very low-certainty, if the evidence from the relevant systematic review was not initially graded as being of very low certainty), and the certainty of evidence from single trials with a sample size of 99 and below was downgraded by two (e.g. from moderate-certainty to very low-certainty) or by one (i.e. from low-certainty to very low-certainty, if the evidence from the relevant systematic review was initially graded as low). The certainty of evidence from single trials with a sample size of 200 and above was not downgraded on the basis of sample size. Take, for example, a systematic review in which the overall evidence has been graded as being of moderate certainty; if one of the outcomes within that systematic review was reported from a single trial with a sample size of 64 participants, the certainty of evidence for that single-trial outcome would be downgraded by two grades to very low.

3.15 Interpreting outcome data and drawing conclusions

According to Gates *et al.*:

> Interpreting data and drawing conclusions can be difficult. The included systematic reviews (and their included primary studies) may use heterogeneous outcome measures which can limit the ability to draw useful conclusions. Procedural variation at the systematic review and overview levels (e.g., study selection, data extraction) can lead to different conclusions from the same set of data. It can be difficult to provide interpretation of analyses of multiple interventions; multiple comparisons from different systematic reviews that are included in the same overview; discordant results and conclusions across the included systematic reviews. Authors need to

> consider the methods used in the systematic reviews and overview and decide how best to highlight uncertainties and gaps that remain. [65 p16]

To address these challenges highlighted by Gates *et al.,* we will use the six-item framework proposed by Lunny *et al.* (2018) to synthesise our interpretations and conclusions [93]. Therefore, we:

1. Elaborate on our interpretation and conclusions
2. Summarise the results from included systematic reviews
3. Assess and report on heterogeneity
4. Assess and report on RoB in the reviews
5. Assess and report on overlap of primary studies included in more than one systematic review, and
6. Assess and report on discordant results, interpretations, and conclusions among the included reviews.

Pieper *et al.* developed a methodology to assess the overlap of primary studies between systematic reviews of the same interventions [39]. They title this measure the 'corrected covered area'. We used this measure for each effectiveness outcome in order to assess the overlap of the same primary studies across more than one systematic review. Pieper *et al.* grade the percentage of overlap as low (1–5%), moderate (6–10%), high (11–15%), and very high (16% or over) so that reviewers can categorise the overlap [39]. We reduced the potential level of overlap by excluding single-trial reviews if the included trial was already included in another review measuring the same outcome.

As mentioned in Section 3.13, we grouped outcomes into general epidemiological indicators of caries prevention or dentistry-specific epidemiological indicators of caries prevention (see Table 4), and we used this distinction for assessing the overlap of primary studies between systematic reviews of the same interventions and outcomes. Within the dentistry-specific outcomes group, we assessed the overlap of primary studies separately for tooth surface indexes (e.g. DMFS) and tooth indexes (e.g. DMFT), where possible. For some overlap assessments, distinguishing between tooth surface and whole tooth indexes was not feasible because many reviews included both indexes in pooled analyses. In these instances, we assessed the overlap of primary studies for these indexes together as a single outcome. Finally, we assessed the overlap of primary studies separately for outcomes related to the prevention of crown caries and outcomes related to the prevention of root caries. The results of the overlap are presented in the text of the results and in Tables 8–70. The calculations of the individual overlaps are available on request.

3.16 Differences between protocol and review

In order to determine the adequacy of the literature search in each systematic review, in our protocol we stated that an adequate search must include, at a minimum, at least two databases used, an attempt to describe the search (varying from including a few keywords to a complete listing of all search strategies used), and at least one supplemental search method used, which could include use of trial registries, hand-searching of journals, reference and citation chasing, contact with subject experts, contact with authors, and searches of the Cochrane Library, including searches of both Cochrane systematic reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). We modified these criteria slightly to require at least one supplemental or grey literature search method. This decision was made because we observed during screening that some review authors had conducted a supplemental search only while others had conducted a grey literature search only. To be more inclusive, we adjusted our requirement for review authors to have conducted with a supplemental search or a grey literature search.

In relation to outcomes of interest, in our protocol we identified a wide set of outcomes at the outset and listed them in our eligibility table. When conducting this overview of reviews, we distinguished between

general epidemiological indicators and dentistry-specific epidemiological indicators of new caries (Table 4). This further categorisation of outcomes could only be made once we had identified all systematic reviews relevant to our research questions and extracted the relevant outcome data. In addition, although the distinction between primary and secondary outcomes of interest was not initially outlined in our protocol, we later made the decision to distinguish between direct indicators of caries incidence (e.g. caries incidence rate, caries increment), which we considered to be the primary outcomes of interest, and indirect or proxy indicators of the potential initiation of caries (e.g. high plaque or mutans streptococci levels), which we considered to be secondary outcomes. However, once the volume of evidence available on direct indicators of caries incidence (or primary outcomes) became evident, we took the decision to analyse and report on these outcomes only. Nevertheless, we did extract all data relating to any secondary outcomes of interest in each of the included systematic reviews. This information is findable in the detailed structured summaries of the systematic reviews in Appendix H.

Finally, in relation to assessing the certainty of the evidence (i.e. GRADE), in our protocol we indicated that we would nominate 4 out of the 16 items in the AMSTAR 2 instrument as critical domains, as these items had been nominated in our overview of reviews, *Management of non-cavitated and cavitated caries in primary, permanent, and mixed dentition: An evidence review* [62]. These were items 11–14. However, we instead selected the seven critical domains nominated by Shea *et al*. [92] (items 2, 4, 7, 9, 11, 13, and 15) as recommended by one of the peer reviewers (Professor Tanya Walsh).

4 Findings

4.1 Results of searching and screening

Our database searches identified 5,129 records, of which 814 were duplicates, leaving 4,315 records for title and abstract screening. We excluded 3,879 records on title and abstract screening, leaving 436 records for full-text screening. Following full-text screening, we excluded 350 records, leaving 86 records for extraction. We included an additional 4,380 records from supplemental searches, resulting in an additional 7 papers being included after full-text screening. In total, 93 papers were sent forward for data extraction. Extraction involved a more detailed reading of the papers, at which point we excluded 27 papers, leaving 66 systematic reviews to be included in this overview of reviews. These 66 reviews are identified in Appendix D.

The PRISMA flow chart in Figure 5 outlines the flow of information throughout the searching and screening process. Details of results from each individual part of the search process can be found in the search table in Appendix A, and studies excluded at full text, with their reason(s) for exclusion, are presented in Appendix C. The presence or absence of community water fluoridation was not considered as part of the intervention effect in this review, as it will be considered in a future review.

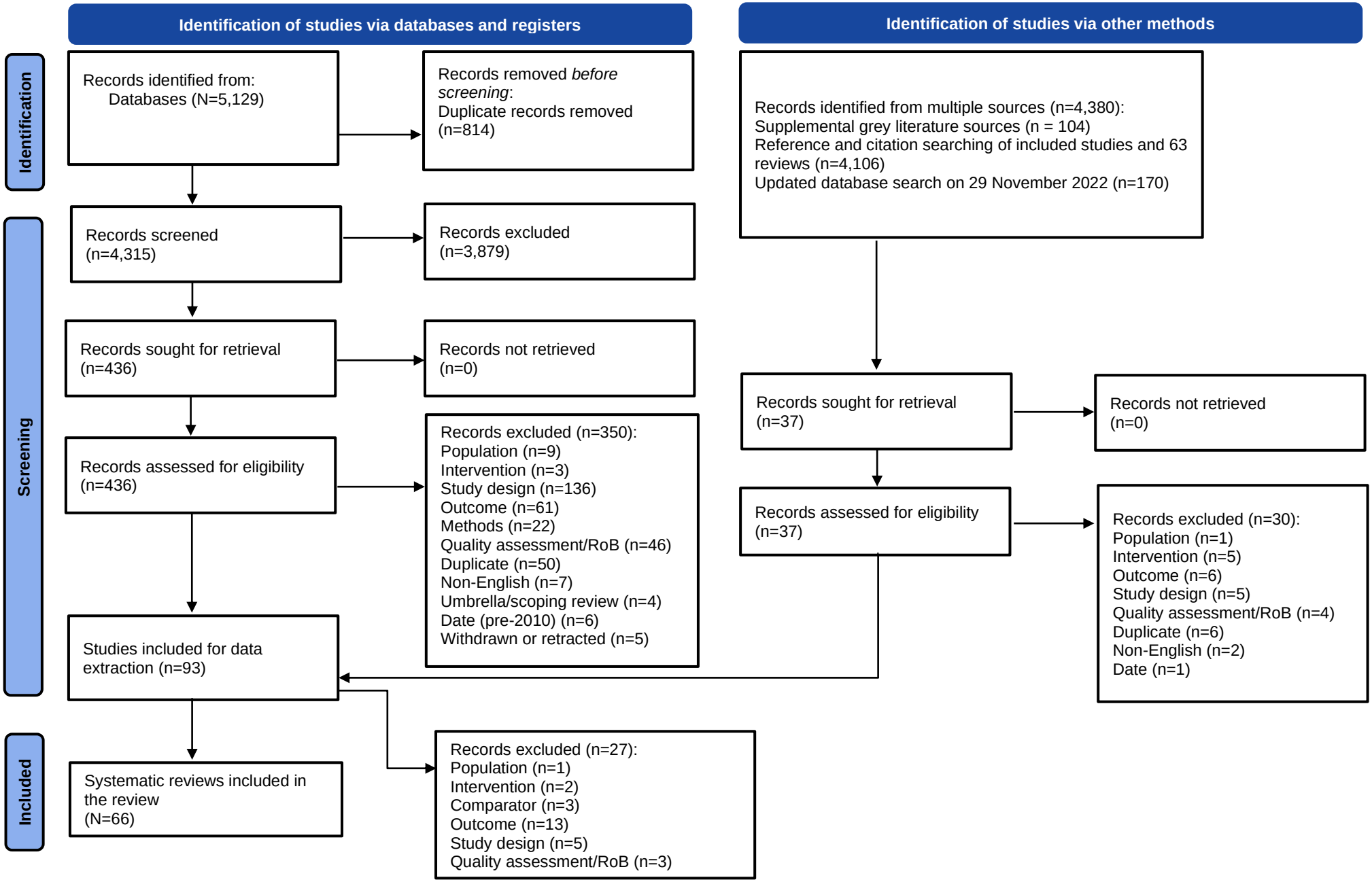

Figure 5 PRISMA flow diagram

4.2 Classification of systematic review papers

The evidence presented in this section is organised by type of dentition (primary, permanent, or mixed), then by type of intervention (Figure 3). Our 66 included systematic reviews comprised 38 reviews covering primary dentition, 44 reviews covering permanent dentition, and 12 reviews covering mixed dentition. Twenty-three reviews reported on more than one dentition type.

We classified reviews according to the stated intervention arm and not according to the comparator, even when a comparator constituted one of our intervention categories in and of itself. For instance, a sealant-based intervention in which fluoride varnish was the comparator was classified under the sealant intervention category in the appropriate dentition type. As noted previously in Section 3.8, no limits were placed on the complexity of interventions. In other words, all interventions, whether singular or combined were considered for inclusion. As such, in all three dentition types, we created a subcategory for combined interventions, which we defined as interventions in which participants received two or more active intervention components. Under the combined intervention subcategory in each dentition type, we further distinguished between combined interventions that involve two active intervention components delivered in combination, and complex interventions, which we defined as interventions involving three or more active components. Combined interventions were grouped and classified according to common intervention components (see Section 4.5.4 for a description). These classifications were made after we have extracted all data related to the nature of the interventions being evaluated in each systematic review. In both the primary and mixed dentition types, we created subcategories for interventions delivered to pregnant women/mothers for caries prevention in the primary or mixed dentition of their children.

Several systematic reviews reported the results of pooled analyses which included both trials that delivered singular interventions and trials that delivered combined or complex interventions. If the majority of pooled trials involved the delivery of a singular intervention, then the review was classified under the relevant intervention in the relevant dentition type. Alternatively, if the majority of pooled trials involved the delivery of a combined intervention, then the review was classified under combined interventions in the relevant dentition type.

We coded interventions as combined interventions in the reviews where review authors explicitly stated or implied that participants in the included trials received more than one active component. Finally, reviews that reported background exposure to other preventive measures (e.g. exposure to fluoridated toothpaste, water, etc.) were not coded as combined interventions, but this exposure was acknowledged when reporting the findings of these reviews.

4.3 Summarisation and synthesis of extracted data

The extracted data will be used to inform clinical guidelines, and these guidelines require a high level of accuracy and detail. With this purpose in mind, we have presented the extracted data in two formats: a detailed structured summary of each systematic review in extraction sheets, and a high-level summary of each systematic review, taking account of the certainty of the evidence, which is presented in Sections 4.5–4.7. We provide a detailed structured summary of each systematic review in Appendix H.

In Sections 4.5–4.7, we present a very high-level summary of the outcomes of interest to this overview of reviews and compare findings testing the same interventions. A tabular representation of these high-level summaries can be found in Appendix J. We integrated the GRADE (or certainty) level of evidence for outcomes within each of the high-level summaries of evidence. Table 7 presents a summary of the overlap of primary studies evaluating the same intervention for the same outcomes across one or more systematic reviews using the Pieper *et al.* [39] corrected covered area method.

Table 7 Overlap of primary studies evaluating the same intervention for the same outcomes across one or more systematic reviews

Corrected covered area	Overlap	Number of outcomes by intervention
1–5%	Slight	4
6–10%	Moderate	1
11–15%	High	7
≥15%	Very high	16

In 7 out of the 66 included systematic reviews, the reported findings were not usable for the purposes of this overview of reviews [30,102–107]. In five of these reviews, the nature of the outcome (i.e. caries incidence or caries progression) was not clear, and in the remaining two reviews, the nature of the intervention was either unclear or not described in a way that made the findings applicable to this overview of reviews. These reviews are identified throughout the results section where appropriate and their structured summaries are available in Appendix H.

In the detailed structured summaries and the high-level summaries of the included systematic reviews, we also extracted information pertaining to background exposure to any caries-preventive agents that were not considered part of the intervention of interest but may still have affected the outcome of the trials being reported on (e.g. background fluoride exposure). We present this information where appropriate throughout the results section.

Finally, in 9 out of the 66 systematic reviews included in this overview of reviews, the outcome of interest to this overview of reviews was identified as a secondary outcome [25,102,108–114]. We recognise that in systematic reviews, a secondary outcome will not be prioritised in the search strategy, screening process, data extraction, or evidence synthesis in the same comprehensive manner as a primary outcome would be. As such, when summarising and synthesising the extracted data for this overview of reviews, we noted when one of our outcomes of interest was identified in a systematic review as a secondary outcome, as those findings should be interpreted with caution.

4.4 Characteristics of reviews and primary studies

It was not possible to present the characteristics of systematic reviews and primary studies by each dentition type (primary, permanent, or mixed) because many of the included systematic reviews reported on more than one dentition type and did not analyse the characteristics of primary studies by dentition type. For this reason, we present the characteristics (such as sample size, age, gender, country of origin, and study design) of all included systematic reviews and primary studies together.

The total number of participants was reported in 63 of the 66 systematic reviews and ranged from 180 to 106,694 participants (Appendix I). One systematic review reported the total number of teeth included in the review. Sixty-two out of the 66 systematic reviews provided information pertaining to the ages of all participants included in the review (e.g. mean age, age range). The participants' ages ranged from 0 to 101 years. Gender was not reported in 46 out of the 66 included systematic reviews. Of the 20 systematic reviews that provided information pertaining to gender, 1 included only females and 8 did not report a gender breakdown but rather indicated the number of primary studies that included males only, females only, or both males and females. In the 11 remaining systematic reviews that reported on gender, the percentage of female participants ranged from 35% to 94%. Fifty-four of the 66 included reviews reported the study countries where the research was completed, and there was a good global spread of countries examining aspects of primary, permanent, and/or mixed dentition: Africa (Egypt, Madagascar, Nigeria, South Africa, Tanzania, Uganda, Zimbabwe); the Americas (Argentina, Belize, Brazil, Canada, Chile,

Colombia, Costa Rica, Cuba, Greenland, Guatemala, Puerto Rico, Suriname, the United States of America (USA), Venezuela); Asia (Cambodia, China, Hong Kong, India, Indonesia, Iran, Israel, Japan, Jordan, Kuwait, Malaysia, Myanmar, Pakistan, the Philippines, Russia, Saudi Arabia, Syria, Taiwan, Thailand, Turkey); Europe (Austria, Belarus, Belgium, Bulgaria, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Kosovo, Latvia, Lithuania, the Netherlands, Norway, Poland, Portugal, Romania, Scotland, Serbia, Spain, Sweden, Switzerland, the UK), and Oceania (Australia, the Marshall Islands, New Zealand). The collection of all primary studies included in the systematic reviews were published between 1924 and 2021, and the primary study designs were: 694 RCTs; 81 cluster RCTs; 28 non-RCTs; 40 controlled clinical trials; 7 cluster controlled clinical trials; 4 studies specified as nested case-control or prospective cohort studies; 9 design unspecified observational studies; 1 pre-post study; and 4 quasi-experiments. Four reviews did not distinguish between the number of RCTs and quasi-RCTs, reporting a total of 69 RCTs/quasi-RCTs. One review did not distinguish between the number of RCTs and non-RCTs, reporting on 5 RCTs/non-RCTs. Across 22 of the included systematic reviews, 169 of the primary studies reported the sources of funding for their research.

4.5 Primary dentition

4.5.1 Introduction

Thirty-eight systematic reviews reported on the primary prevention of caries in primary dentition: 3 reviews reported on the effectiveness of attendance for dental assessment, 3 reported on the effectiveness of dental hygiene activities, 5 reported on the effectiveness of systemic fluoride, 1 reported on the effectiveness of other systemic chemicals, 9 reported on the effectiveness of topical fluoride, 11 reported on the effectiveness of other topical chemicals, 3 reported on the effectiveness of sealants, and 1 reported on the effectiveness of lasers. In addition, 5 reviews reported on the effectiveness of interventions delivered to pregnant women/mothers on the primary dentition of their children, 16 reviews reported on the effectiveness of combined interventions for caries prevention in primary dentition, and 3 reviews reported on the effectiveness of combined interventions for caries prevention delivered to pregnant women/mothers on the primary dentition of their children. Several reviews appeared in multiple intervention categories because they included a range of primary studies spanning a number of intervention types. In seven reviews, the findings were either not usable for the purposes of this overview of reviews or no primary studies on the intervention of interest were found. These reviews are identified, where appropriate, throughout the results section on primary dentition.

4.5.2 Methodological quality of reviews and their primary studies

We reported in Section 3.11 that we assigned the seven critical domains in the adapted AMSTAR 2 quality assessment tool nominated by Shea *et al*. [92]. These domains were: whether the protocol was established prior to the conduct of the review (item 2); if the review authors conducted a comprehensive literature search (item 4); if review authors included a list of excluded studies and their reasons for exclusion (item 7); if the review authors used a satisfactory technique for assessing the RoB in the individual studies that were included in the review (item 9); if the methods used for statistical combination of primary study results were appropriate (item 11); if RoB was considered when interpreting results (item 13); and if review authors conducted an assessment of the presence and likely impact of publication bias (item 15). The quality of the 38 included systematic reviews with respect to methodology varied, but was predominantly critically low (Appendix F).

Twelve out of the 38 systematic reviews on primary dentition did not establish any protocol prior to carrying out the review, and 16 of the reviews only partially established a protocol prior to review (item 2); however, 13 out of those 16 reviews were Cochrane reviews, and it is well established that Cochrane review authors are required to prepare a review protocol. (As noted in Table 5, a 'partial yes' on this item in the adapted AMSTAR 2 instrument did not negatively affect quality assessment for Cochrane reviews.) Thirty-seven out of the 38 systematic reviews on primary dentition received a 'yes' rating in relation to the comprehensiveness of the literature search (item 4) and 1 review received a 'partial yes' rating on this item. Fifteen reviews did not provide a list of excluded studies and the reasons for exclusion (item 7). Four reviews either did not use a satisfactory technique for assessing the RoB in individual studies (item 9) or received a 'partial yes' rating on this item. Twenty-five reviews on primary dentition did not use appropriate methods for the statistical combination of results from primary studies (item 11; this item was not applicable to the remaining 13 reviews). Eight out of the 38 systematic reviews on primary dentition did not take RoB into account when interpreting the findings (item 13). Finally, seven reviews on primary dentition did not carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review (item 15; this item was not applicable to 26 reviews).

Overall, 4 out of the 38 systematic reviews on primary dentition were judged to be of high quality, indicating that they had no critical or non-critical flaws. One out of the 38 reviews was judged to be of

moderate quality, indicating that it had no critical flaws but did have at least one non-critical weakness. Twelve out of the 38 systematic reviews were judged to be of low quality, indicating that they had one critical flaw; these reviews either did not establish a protocol prior to review, did not provide a list of excluded studies and their reasons for exclusion, did not use appropriate methods for the statistical combination of result from primary studies, or had no discussion of RoB in relation to meta-analyses. The remaining 21 reviews on primary dentition were assessed as being of critically low quality, indicating that they had more than one critical flaw. The critical flaws for critically low-quality reviews varied, with the more common critical flaws being that the review authors did not establish a protocol prior to review, did not provide a list of excluded studies and their reasons for exclusion, did not use appropriate methods for the statistical combination of result from primary studies, and did not carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review.

4.5.3 GRADE rating

The GRADE (or certainty) of evidence is presented alongside each of the outcomes in Section 4.5.5, and the number of downgrades applied and reasons for downgrading are presented in Appendix K. In primary dentition, four reviews presented moderate-certainty evidence, as assessed using the modified GRADE algorithm. This indicates that we are moderately confident in the effect estimate; that is, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different [115]. The reasons for downgrading to moderate certainty of evidence were inadequate randomisation, inadequate blinding of outcome ascertainment, and quality rating on the adapted AMSTAR 2 instrument. Fifteen reviews presented low-certainty evidence, indicating that our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect [115]. The reasons for downgrading to low certainty of evidence included study design, inadequate randomisation, inadequate blinding of outcome ascertainment, inadequate sample size, and quality rating on the adapted AMSTAR 2 instrument. Twenty-three reviews presented very low-certainty evidence, indicating that we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect [115]. The reasons for downgrading to very low certainty of evidence included study design, inadequate randomisation, inadequate blinding of outcome ascertainment, high heterogeneity, inadequate sample size, and quality rating on the adapted AMSTAR 2 instrument.

Of note, outcomes within the same review could be graded at different levels of certainty. As a result, several reviews reported evidence at more than one level of certainty (i.e. outcomes of moderate-certainty and outcomes of very low-certainty could be reported in the same review). There were no reviews on primary dentition without any downgrades, and therefore no reviews that presented high-certainty of evidence. It can be understood that reviews with moderate-certainty evidence had one to two inadequacies, whereas reviews with low-certainty evidence had three to four inadequacies and reviews with very low-certainty evidence had five or more inadequacies. Therefore, the GRADE score is used as a summary indicator of the certainty of evidence for the individual outcomes in each review. As mentioned in Section 3.14, the GRADE score takes account of the methodological quality score of each systematic review and its primary studies.

Three systematic reviews included in this overview of reviews were single-trial reviews, and so the certainty of evidence in these reviews was automatically downgraded to very low. All three reported on outcomes in primary dentition. As mentioned in the previous paragraph, 4 out of the 38 systematic reviews on primary dentition reported moderate-certainty evidence; 2 of these reviews presented moderate-certainty evidence from single trials and the remaining 2 reviews presented moderate-certainty evidence from two or more trials.

4.5.4 Classification of combined interventions

As mentioned in Section 3.8, we classified all systematic reviews according to the types of interventions being evaluated. Nineteen reviews in total included trials that delivered combined interventions for caries prevention in primary dentition. Sixteen out of the 19 systematic reviews of combined interventions reported on the effectiveness of combined interventions delivered to children (some reviews reported on the effects of more than one combined intervention). Based on the intervention components described in the systematic reviews, we classified and subclassified combined interventions for caries prevention in primary dentition into those that involved:

- Systemic fluoride combined with one other intervention component (one review)
- Topical fluoride combined with one other intervention component, either:
  - Another form of topical fluoride (one review)
  - A non-fluoride topical chemical (four reviews), or
  - An intervention component that is neither topical fluoride nor another non-fluoride topical chemical (seven reviews), including caregiver counselling (one review), sealants (one review), supervised toothbrushing or mouthrinsing (three reviews), oral health education (OHE; one review), or several of these (one review).
- Sealants combined with one other intervention component (one review), and
- Complex interventions that included three or more intervention components for caries prevention in primary dentition (four reviews).

Three out of the 19 systematic reviews of combined interventions reported on the effectiveness of combined interventions delivered to pregnant women/mothers for caries prevention in the primary dentition of their children (one review reported on the effects of more than one combined intervention). Based on the intervention components described in the systematic reviews, we categorised combined interventions delivered to pregnant women/mothers into those that involved:

- Two forms of non-fluoride topical chemicals combined with each other (one review)
- A non-fluoride topical chemical combined with an intervention component other than another non-fluoride topical chemical (one review)
- CHX combined with an additional intervention component (one review), and
- Complex interventions that included three or more intervention components delivered to pregnant women/mothers for caries prevention in the primary dentition of their children (one review).

4.5.5 Results

4.5.5.1 Attendance for dental assessment

4.5.5.1.1 Scheduled dental appointments

We identified two systematic reviews that reported on the effects of scheduled dental appointments for caries prevention in primary dentition. Joury *et al*. [104] assessed the effectiveness of school-based dental screening compared with no screening on improving oral health in children. The results of only one primary trial were relevant to this overview of reviews. However, it was not clear whether these results pertained to the initiation of new caries or prevalence of existing caries, and so we did not extract the findings. Fee *et al*. [47] investigated the optimal recall interval of dental check-ups (fixed-length, risk-based (decided by the clinician), or no recall/patient-driven attendance) for oral health in a primary care

setting. One included trial evaluated the effect of a 24-month recall compared with a 12-month recall interval on the increment of dmfs at 2 years follow-up. However, the statistical significance of the results was reported as unclear in the systematic review itself. This trial did not compare the effects of other recall intervals of interest to the systematic review authors (namely, risk-based compared with 6-month recall, risk-based compared with 24-month recall, or 24-month recall compared with 6-month recall).

Overall, there is a **paucity of evidence** pertaining to the caries-preventive effects of different recall intervals in primary dentition.

4.5.5.1.2 Scheduled primary care appointments

We identified one systematic review on the effectiveness of scheduled primary care appointments for caries prevention in primary dentition. Chou *et al*. [48] investigated the effectiveness of various caries-preventive interventions, including primary care oral screening, on preventing and arresting dental caries in children aged under 5 years. However, **none of the included trials** compared clinical outcomes between children screened and not screened by primary care clinicians.

Overall, there is **a paucity of evidence** available to determine whether scheduled primary care appointments can reduce the risk of caries incidence in primary dentition.

4.5.5.2 Dental hygiene

4.5.5.2.1 Supervised toothbrushing

We identified three systematic reviews on the effectiveness of supervised toothbrushing for caries prevention in primary dentition. Hujoel *et al*. [116] aimed to evaluate the association between personal oral hygiene (i.e. supervised toothbrushing) and dental caries in the absence of the confounding effects of fluoride; Akera *et al*. [117] aimed to evaluate the effectiveness of school-based interventions (including supervised toothbrushing) in improving oral health among primary school children in low- and middle-income countries; and dos Santos *et al*. [118] aimed to evaluate the effectiveness of supervised toothbrushing on caries incidence in children and adolescents. However, all seven trials included in the Hujoel *et al*. review and the only trial on supervised toothbrushing in the Akera *et al*. review that was relevant to this overview of reviews reported on the effects of supervised toothbrushing for caries prevention in permanent dentition only (see Sections 4.6.5.2.1 and 4.6.5.5.9.3). Moreover, **none of the four included trials** in the dos Santos *et al*. review reported on the effectiveness of supervised toothbrushing as a standalone intervention on caries incidence in primary dentition. The evidence from the dos Santos *et al*. systematic review can be found in Section 4.5.5.5.9.2 on combined interventions involving topical fluoride.

Overall, there is **a paucity of evidence** available to determine whether supervised toothbrushing as a standalone intervention can reduce the risk of caries incidence in primary dentition.

4.5.5.2.2 Flossing

None of the included systematic reviews reported on the effectiveness of flossing for caries prevention in primary dentition.

4.5.5.2.3 Interdental cleaning devices

None of the included systematic reviews reported on the effectiveness of interdental cleaning devices for caries prevention in primary dentition.

4.5.5.2.4 Professional scaling or cleaning

None of the included systematic reviews reported on the effectiveness of professional scaling or cleaning as a standalone intervention for caries prevention in primary dentition.

Evidence on the effectiveness of combined interventions that involve professional scaling or cleaning of primary teeth can be found in Sections 4.5.5.5.9.2 and 4.5.5.9.4.3.

4.5.5.3 Systemic fluoride

4.5.5.3.1 Milk

We identified two systematic reviews on the topic of fluoridated milk for caries prevention in primary dentition.

Table 8 presents a high-level summary of treatment outcomes for this intervention category.

Yeung *et al*. [26], which was a review of a single RCT, evaluated the effect of milk fluoridation for caries prevention at a community level. The findings from the single included trial indicated very low-certainty evidence of a **significantly lower dmft increment among children who consumed 180–200 millilitres (mL) of fluoridated milk per day (2.5 milligrams (mg) of fluoride per litre of milk) using a 200 gram (g) cup when compared with children in the non-fluoridated milk group** at 3 years follow-up.

Cagetti *et al*. [119] examined the effectiveness of fluoridated food (e.g. milk, salt, and sugar) in the prevention of caries. Two of the included trials reported on the effectiveness of milk fluoridation for caries prevention in primary dentition, with one reporting on dmft increment and the other on dmfs increment. The findings from the first trial indicated very low-certainty evidence of a **significantly lower increment of dmft among children who consumed 200 mL of fluoridated milk per day (2.5 mg of fluoride per litre) when compared with children in the control group** at 21 months follow-up, resulting in a 69% reduced risk of caries initiation among children in the intervention group. The findings from the second trial indicated very low-certainty evidence of a **significantly lower increment of dmfs among children who consumed 150 mL of fluoridated milk per day (2.5 mg of fluoride per litre) compared with children who consumed standard milk** at 21 months follow-up, resulting in a 75% reduced risk of caries initiation among children in the intervention group.

Overall, there is **very low-certainty evidence from three primary trials in two systematic reviews indicating a benefit of the consumption of fluoridated milk for caries prevention** at the tooth and tooth surface levels in primary dentition. There was no overlap of primary studies across the two reviews for the included outcomes.

Table 8 Main review outcomes for fluoridated milk in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Yeung *et al.* (2015) [26]	dmft: significantly lower for fluoridated milk compared with the non-fluoridated milk group (1 trial)	High	Very low	
Cagetti *et al.* (2013) [119]	dmft: significantly lower for fluoridated milk compared with control group (1 trial) dmfs: significantly lower for fluoridated milk compared with standard milk (1 trial)	Critically low	Very low	
				dmft: no overlap dmfs: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.3.2 Salt

We identified one systematic review that aimed to evaluate the effectiveness of fluoridated salt for caries prevention in primary dentition. The review, conducted by Cagetti *et al.* [119], is described in Section 4.5.5.3.1. However, **none of the included primary trials** evaluated the use of this intervention.

As such, there is **a paucity of evidence** available to determine the benefit of salt fluoridation for caries prevention in primary dentition.

4.5.5.3.3 Sugar

We identified one systematic review on the effectiveness of fluoridated sugar for caries prevention in primary dentition. Cagetti *et al*. [119] identified one trial on the effectiveness of sugar fluoridation for caries prevention. However, this trial reported on permanent dentition only (see Section 4.6.5.3.3 on the effect of fluoridated sugar on permanent dentition).

As such, there is **a paucity of evidence** available to determine whether sugar fluoridation can reduce the risk of caries incidence in primary dentition.

4.5.5.3.4 Supplements

We identified three systematic reviews on the effectiveness of fluoride supplements (mainly fluoride tablets) for caries prevention in primary dentition. Table 9 presents a high-level summary of treatment outcomes for this intervention category.

Zhou *et al*. [103] investigated the efficacy of various strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. However, the effectiveness of fluoride supplements

was not possible to determine because the meta-analysis in Zhou *et al*.'s review was conducted to test the effectiveness of fluoride as 1 mg NaF [sodium fluoride] tablets **or** fluoride together with sodium bicarbonate and potassium dihydrogen phosphate. The results were excluded from data synthesis as we could not determine which type of fluoride-based intervention was being evaluated.

Tubert-Jeannin *et al*. [111] evaluated the effectiveness of fluoride tablets for caries prevention in children. The findings from two trials comparing fluoride tablets to no tablets were synthesised narratively. The first trial indicated low-certainty evidence of **no significant difference in final caries experience (measured by the dmft index) following the consumption of fluoride tablets (1 mg sodium fluoride (NaF)) once per day compared with no tablet consumption** at 2–3 years follow-up. The second trial, however, indicated very low-certainty evidence of **significantly higher dmft and dmfs prevented fractions following the consumption of fluoride tablets (0.5 mg NaF, 1 tablet per day) or fluoride drops (0.25 mg NaF, 2 drops per day) compared with no fluoride supplementation** at 2 years follow-up, resulting in a 65–73% reduced risk of caries initiation among participants in the intervention group. Participants in this trial were a sample of children with a cleft lip and/or palate. The review authors noted that participants had exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. Data from two additional trials in the Tubert-Jeannin *et al*. review comparing fluoride tablets with the use of topical fluoride were pooled and indicated low-certainty evidence of **no added benefit of the administration of fluoride tablets compared with the use of topical fluoride (e.g. mouth rinse, varnish, toothpaste) in final caries experience (as indicated by the dmfs prevented fraction)** at 2–3 years follow-up. In one of the pooled trials, 0.25 mg NaF sucking tablets were administered twice per day, and in the other, 1 mg NaF chewing tablets were administered once per day. The review authors noted that participants in both trials had exposure to fluoridated water, and participants in one trial had access to fluoride toothpaste. However, this was considered background fluoride exposure rather than part of the intervention of interest.

Chou *et al*. [48] investigated the effect of various caries-preventive interventions, including dietary fluoride supplementation, on preventing and arresting dental caries in children aged under 5 years. The findings from four non-RCTs (which were synthesised narratively) indicated very low-certainty evidence of **significantly higher dmft reduction among participants in the fluoride supplement groups compared with participants in the control groups that received no fluoride supplementation**. The mean dmft percentage reduction ranged from 32% to 69%. The specific nature of the intervention in the four trials, including the type and frequency of dietary fluoride supplementation, is not described in the systematic review. It should be noted that information provided by the review authors indicated that the majority of the primary trials included in their review involved the delivery of combined interventions (i.e. interventions consisting of two or more active intervention components). However, the nature of the interventions delivered in these four trials in particular was not adequately described, and so while the findings are presented here under singular interventions, it is possible that some or all four of these trials delivered combined interventions involving fluoride supplementation and an additional intervention component. The findings from another single RCT described in more detail in Chou *et al*.'s review on the effectiveness of fluoride drops indicated very low-certainty evidence of **significantly higher dmft and dmfs reductions following the use of 0.25 mg fluoride drops or chews (consumption frequency not reported) in Taiwanese children with cleft lips compared with no fluoride drops or chews**. The mean percentage reduction ranged from 52% to 72% for dmft and from 51% to 81% for dmfs. The length of follow-up in the five primary trials on fluoride supplementation was not made explicit in the review; however, the review authors stated that follow-up periods for all included trials ranged from 1 to 3 years.

Overall, **the low- and very low-certainty evidence associated with the use of fluoride supplementation compared with no supplementation for caries prevention in primary dentition is inconsistent**. In one

review, all five trials indicated a caries-preventive benefit of fluoride supplementation compared with no supplementation, and this was noted by the systematic review authors to be particularly applicable to children identified as being at high risk of developing new caries. When fluoride tablets were compared with the use of topical fluoride in a pooled analysis of two trials conducted in the other systematic review that provided evidence for this intervention, there was no clear evidence of a greater beneficial effect of fluoride tablets on primary teeth. In addition, it should be noted that the primary studies included in the Tubert-Jeannin *et al*. [111] and the Chou *et al*. [48] reviews were predominantly conducted between the 1960s and 1980s. There was very high and high overlap of primary studies between the included reviews for dmfs and dmft outcomes, respectively.

Table 9 Main review outcomes for fluoride supplements in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Zhou *et al.* (2019) [103]	None usable	Critically low	N/A	
Tubert-Jeannin *et al.* (2011) [111]	dmft: no significant difference for 1 mg NaF tablets compared with no tablets (1 trial) and significantly lower for 0.5 mg NaF tablets compared with no tablets (1 trial) dmfs: significantly lower for 0.5 mg NaF tablets compared with no tablets (1 trial); no significant difference for fluoride tablets compared with topical fluoride (2 trials, pooled)	Low	Low Very low Very low Low	
Chou *et al.* (2021) [48]	dmft: significantly higher reduction in supplement groups compared with control groups (4 trials, narrative synthesis); significantly higher reduction with drops or chews compared with no supplementation (1 trial) dmfs: significantly higher reduction with drops or chews compared with no supplementation (1 trial)	Critically low	Very low	dmfs: very high overlap dmft: high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.3.5 Combined interventions involving systemic fluoride

We identified one systematic review that reported on the effectiveness of combined interventions involving systemic fluoride for caries prevention in primary dentition. Table 10 presents a high-level summary of treatment outcomes from this review.

Jørgensen *et al*. [120] reviewed the available literature on the prevention of caries in early childhood through biofilm engineering with probiotic bacteria. The review included a single trial that delivered a combined intervention involving fluoridated milk and probiotics. The findings indicated low-certainty evidence of a **significantly lower increment of dmfs and a significantly higher proportion of children remaining caries free following the consumption of probiotic-containing (*Lactobacillus rhamnosus*) fluoridated milk 5 days per week over 21 months compared with the consumption of non-fluoridated milk without probiotics** at 21 months follow-up.

Table 10 Main review outcomes for combined systemic fluoride and other topical chemicals in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Jørgensen *et al.* (2016) [120]	dmfs: significantly lower for fluoridated milk containing probiotics compared with non-fluoridated milk without probiotics (1 trial) Percentage of children remaining caries free: significantly higher for fluoridated milk containing probiotics compared with non-fluoridated milk without probiotics (same trial)	Low	Low	defs: no overlap Percentage of children remaining caries free: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.4 Other systemic chemicals

4.5.5.4.1 Vitamin D

None of the included systematic reviews reported on the effectiveness of vitamin D-based interventions for caries prevention in primary dentition.

4.5.5.4.2 Calcium

None of the included systematic reviews reported on the effectiveness of calcium-based interventions for caries prevention in primary dentition.

4.5.5.4.3 Sialagogues

We identified one systematic review on the effectiveness of sialagogues for caries prevention in primary dentition. Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including sialagogues) on the market in the USA. However, **none of the included trials** evaluated the use of sialagogues (e.g. pilocarpine, cevimeline).

As such, there is **a paucity of evidence** available to determine the benefit of these agents for caries prevention in primary dentition.

4.5.5.4.4 Zinc

None of the included systematic reviews reported on the effectiveness of zinc-based interventions for caries prevention in primary dentition.

4.5.5.5 Topical fluoride

4.5.5.5.1 Toothpaste

We identified two systematic reviews on the effectiveness of fluoride toothpaste as a standalone intervention for caries prevention in primary dentition. Both reviews investigated the **effectiveness of different fluoride concentrations** for caries prevention in both primary and permanent dentition and reported on similar outcomes post-intervention, specifically the proportion of children developing caries, or caries increment. Table 11 presents a high-level summary of treatment outcomes for this intervention category.

Walsh *et al*. [21] presented low-certainty evidence from a single RCT on fluoride toothpaste as a standalone intervention, which showed a **significantly lower proportion of children developing new caries in the higher-fluoride toothpaste intervention group (fluoride concentration of 1450 parts per million (ppm)) compared with the lower-fluoride toothpaste group (440 ppm fluoride)** at 5 years follow-up. The review authors indicated that there was a possibility of contamination from co-intervention in this trial. The review 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.

Santos *et al*. [122] presented low-certainty evidence from three pooled trials of a **significantly lower proportion of children developing caries in primary teeth in the higher-fluoride toothpaste group (1000–1500 ppm fluoride) compared with the lower-fluoride toothpaste group (<600 ppm fluoride)**. The follow-up period was not specified in the review. However, the review authors reported that the shortest trial period in the review was 2 years. It should be noted that when extracting information pertaining to the nature of the interventions described in the Walsh *et al*. review, it became evident that two out of the three trials that Santos *et al*. included in their review involved the delivery of combined interventions, but this was not made explicit in the Santos *et al*. review. It should also be noted that, like Walsh *et al*., Santos *et al*. reported on dmfs/dmft increment as an outcome in their review. However, the findings were based on almost all the same trials that reported on this outcome in the Walsh *et al*. review. As mentioned previously, these outcomes were not extracted from the Walsh *et al*. review due to uncertainty related to the nature of what was being measured (caries incidence or caries progression). Therefore, the results on

caries increment in the Santos *et al*. review have also not been included in this evidence synthesis. For completion, however, the findings were extracted and can be found in Appendix H.

While no systematic review included in this overview of reviews evaluated the effectiveness of fluoride toothpaste compared with a control or placebo toothpaste as a standalone intervention for caries prevention in primary dentition, there is **some low-certainty evidence of a dose–response relationship in the caries-preventive effect of fluoride toothpaste**, in that the use of higher-fluoride toothpaste appears to decrease the risk of caries initiation compared with the use of low-fluoride toothpaste. There was a very high level of overlap of primary studies in these two reviews in relation to the outcome of the proportion of children developing new caries.

Evidence from these two reviews and other reviews on the effectiveness of combined interventions that involve the use of fluoride toothpaste on primary teeth can be found in Section 4.5.5.5.9.

Table 11 Main review outcomes for fluoridated toothpaste in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Walsh *et al.* (2019) [21]	Percentage developing caries: significantly lower in the higher-fluoride toothpaste group compared with the lower-fluoride toothpaste group (1 trial)	Low	Low	
Santos *et al.* (2013) [122]	Percentage developing caries: significantly lower in the higher-fluoride toothpaste group compared with the lower-fluoride toothpaste group (3 pooled trials)	Critically low	Low	
				Percentage developing caries: very high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.5.2 Mouth rinses

None of the included systematic reviews reported on the effectiveness of fluoride-based mouth rinse interventions for caries prevention in primary dentition.

4.5.5.5.3 Foams

None of the included systematic reviews reported on the effectiveness of fluoride-based foam interventions for caries prevention in primary dentition.

4.5.5.5.4 Gels

We identified one systematic review on the effectiveness of fluoride gels for caries prevention in primary dentition.

Table 12 presents a high-level summary of treatment outcomes from this review.

Marinho *et al*. [25] investigated the effectiveness and safety of fluoride gels in preventing dental caries in the child and adolescent population. The findings from three pooled trials indicated low-certainty evidence of a **significantly higher d(e/m)fs prevented fraction associated with the use of fluoride gel compared with a placebo/no treatment** at approximately 3 years follow-up, resulting in a 20% reduced risk of caries initiation among children in the intervention group. None of the pooled trials reported on the d(e/m)ft index. Two of the trials involved self-application of fluoride gel, and one involved professional application of fluoride gel. The concentration of fluoride was 5000 ppm (applied approximately 85 times per year) and 12500 ppm (applied approximately 130 times per year) in the self-application trials, and 4500 ppm (applied twice per year) in the professional-application trial. It should be noted that one of the three 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 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. It should also be noted that two out of the three pooled trials reported exposure to additional forms of fluoride (via water, tablets, and/or toothpaste). However, this was considered background fluoride exposure rather than part of the intervention of interest. The findings from one of the three pooled trials also indicated very low-certainty evidence of a **significantly lower proportion of children not remaining caries free on primary tooth surfaces in the fluoride gel group (5000 ppm of acidulated phosphate fluoride (APF), applied approximately 76 times per year) compared with the placebo group** at 1.5 years follow-up. It should be noted that this particular outcome was identified as a secondary outcome in Marinho *et al*.'s review.

Overall, there is **some low- and very low-certainty evidence that the application of fluoride gel is associated with a reduced likelihood of developing caries in primary teeth**. However, the authors of the only systematic review to focus on fluoride gel as a standalone intervention reported that they were less certain of the evidence in primary dentition relative to that in permanent dentition, as fewer trials were available to analyse in the former (see Section 4.6.5.5.4 for results in permanent dentition).

Table 12 Main review outcomes for fluoride gels in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Marinho *et al.* (2015) [25]	d(e/m)fs: significantly lower for fluoride gel compared with placebo or no treatment control (3 pooled trials)	Low	Low	d(e/m)fs: no overlap Percentage of children not remaining caries free: no overlap
	Percentage of children not remaining caries free: significantly lower for fluoride gel (APF) compared with placebo group (1 of the above pooled trials)		Very Low	

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.5.5 Solutions

We identified two systematic reviews that aimed to evaluate the effectiveness of fluoride-based solutions for caries prevention in primary dentition. Table 13 presents a high-level summary of treatment outcomes for this intervention category.

Chou *et al*. [48] investigated the effect of various caries-preventive interventions, including silver diamine fluoride (SDF) solution, on preventing and arresting dental caries in children aged under 5 years. However, **none of the included trials** evaluated the caries-preventive efficacy of this agent.

Oliveira *et al*. [123] investigated whether SDF is superior to placebo or no treatment in preventing the development of carious lesions in primary teeth. Only one out of the four trials included in Oliveira *et al*.'s review focused on preventing the initiation of new carious lesions (the remaining three applied SDF solution to existing carious lesions). The findings from that trial indicated very low-certainty evidence of a **10%, 38%, and 69% decrease in caries incidence on primary tooth surfaces in the three test groups (12% SDF applied yearly, biannually, and quarterly, respectively) compared with the no treatment control group** at 2 years follow-up. However, only the differences between quarterly compared with yearly SDF application, and quarterly compared with no SDF application, were statistically significant. The review authors noted that at baseline, participants in all trials included in the review were regularly exposed to some sort of topical fluoride product (either fluoride toothpaste or 0.2% NaF mouth rinse). However, this was considered background fluoride exposure rather than part of the intervention of interest.

While there is **some very low-certainty evidence that the use of SDF solution is associated with a reduced likelihood of developing carious lesions in primary teeth**, this evidence was collected from a single trial in one systematic review. As such, there is **a paucity of evidence available on the effectiveness of fluoride-based solutions** in preventing caries in primary teeth.

Table 13 Main review outcomes for fluoride solutions in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Chou *et al.* (2021) [48]	None reported	Critically low	N/A	
Oliveira *et al.* (2019) [123]	Caries incidence: significant decrease for SDF compared with the no treatment group (1 trial)	Critically low	Very low	
				Decrease in caries incidence: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.5.6 Slow-release fluoride devices

We identified one systematic review on the effectiveness of slow-release fluoride devices for caries prevention in primary dentition. Chong *et al*. [49] aimed 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. However, the single trial included in this review reported only on permanent dentition (see Section 4.6.5.5.5 on slow-release fluoride devices for permanent dentition).

As such, there is **a paucity of evidence** available to determine whether slow-release fluoride devices can reduce the risk of caries incidence in primary dentition.

4.5.5.5.7 Varnishes

We identified three systematic reviews on the effectiveness of fluoride varnishes for caries prevention in primary dentition.

Table 14 presents a high-level summary of treatment outcomes for this intervention category.

Smith *et al*. [124] systematically reviewed the evidence for interventions, including fluoride varnish interventions, to prevent early childhood caries in Indigenous children from high-income countries. However, **none of the included trials** evaluated the caries-preventive efficacy of fluoride varnish as a standalone intervention in primary dentition. Evidence on the effectiveness of the combined intervention that involves the use of fluoride varnish on primary teeth in this trial can be found in Section 4.5.5.5.9.2.

Marinho *et al*. [108] evaluated the effectiveness and safety of fluoride varnishes in preventing dental caries in the child and adolescent population. The findings indicated low-certainty evidence of a **significantly lower d(e/m)fs increment (10 pooled trials) and a significantly lower d(e/m)ft increment (2 pooled trials) in children following the application of fluoride varnish (applied at least once per year) compared with either no treatment or a placebo varnish** at nearest to 3 years follow-up. The pooled results indicated a 37% reduction in d(e/m)fs increment and a 65% reduction d(e/m)ft increment following the intervention. The findings are presented here in the section on standalone fluoride varnish interventions because most of the pooled trials did not involve combined interventions. However, it should be noted that 2 out of the 10 pooled trials reported some form of non-fluoride tooth prophylaxis prior to administering the varnish. In addition, 8 out of the 10 pooled trials reported some existing exposure to fluoride (via water, mouth rinses, tablets, toothpaste, milk, or an unspecified source). However, this was considered background exposure rather than part of the intervention of interest. It should also be noted that 4 out of the 10 pooled trials on d(e/m)fs increment were combined interventions involving OHE or oral health instruction (OHI), and 1 out of the 2 pooled trials on d(e/m)ft increment was a combined intervention involving OHI. Marinho *et al*. also presented findings from five pooled trials indicating low-certainty evidence of **no significant difference in the proportion of children developing one or more new caries on primary teeth between the fluoride varnish group (applied at least once per year) and the placebo/no treatment control group**. The precise follow-up period for this analysis was not specified. It should be noted that this particular outcome was identified as a secondary outcome in Marinho *et al*.'s review. Also, three out of the five pooled trials reported some existing exposure to fluoride (via water, mouth rinses, toothpaste, or milk). However, this was considered background exposure rather than part of the intervention of interest. In addition, two out of the five pooled trials on this outcome delivered combined interventions involving oral health counselling.

Carvalho *et al*. [125] evaluated whether conclusive evidence exists that the professional application of fluoride varnish decreases dental caries incidence in preschool children. The findings indicated low-certainty evidence from five trials (synthesised narratively), all showing a **significantly lower increment of dmfs following the application of 5% NaF varnish (four trials) or 1% difluorsilano varnish (one trial) compared with no treatment or OHE** at mainly 2 years follow-up (one trial followed up after 9 months). Fluoride varnish was applied every 6 months in four of the trials and every 4 months in one trial. The use of this intervention resulted in a 30–63% reduced likelihood of caries incidence in primary teeth across the trials. Conversely, there was low-certainty evidence from a sixth trial showing **no significant difference in the increment of dmfs following the application of 5% NaF varnish every 6 months compared with no treatment** at 2 years follow-up. It should be noted that six out of a total of eight included trials in Carvalho *et al*.'s review reported some existing exposure to fluoride (via water, toothpaste, or tablets). However, this was considered background exposure rather than part of the intervention of interest.

Overall, **there is low-certainty evidence of a caries-preventive benefit of the application of fluoride varnish on primary teeth**. There is some inconsistency in the findings, and much of the evidence is based on trials in which participants were exposed to other forms of fluoride and/or additional intervention components, mainly some form of education or instruction around oral health. There was also a high

degree of overlap of primary studies in relation to d(e/m)fs or dmfs increment, but no overlap in relation to the other included outcomes.

Table 14 Main review outcomes for fluoride varnishes in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Smith *et al.* (2018) [124]	None reported	Low	N/A	
Marinho *et al.* (2013) [108]	d(e/m)fs: significantly lower for fluoride varnish compared with no treatment or placebo varnish (10 pooled trials) d(e/m)ft: significantly lower for fluoride varnish compared with no treatment or placebo varnish (2 pooled trials) Percentage of children developing caries: no significant difference for fluoride varnish compared with placebo or no treatment control group (5 pooled trials)	Low	Low	
Carvalho *et al.* (2010) [125]	dmfs: significantly lower for 5% NaF varnish or 1% difluorsilano varnish compared with no treatment or OHE (5 trials, narrative synthesis); no significant difference for 5% NaF varnish compared with no treatment (1 trial)	Critically low	Low	
				d(e/m)fs or dmfs: high overlap d(e/m)ft: no overlap Percentage of children developing caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.5.8 Mixed forms of topical fluoride

None of the included systematic reviews pooled findings on various forms of topical fluoride as standalone interventions for caries prevention in primary dentition. Evidence from reviews that report pooled analyses of mixed types of topical fluoride can be found in Section 4.5.5.5.9.1 on combined interventions.

4.5.5.5.9 Combined interventions involving topical fluoride

4.5.5.5.9.1 Topical fluoride together with another topical fluoride

We identified one systematic review that reported on the effectiveness of a combined intervention involving two forms of topical fluoride for caries prevention in primary dentition. Table 15 presents a high-level summary of treatment outcomes from this review.

Carvalho *et al*. [125] evaluated whether conclusive evidence exists that the professional application of fluoride varnish decreases dental caries incidence in preschool children. The findings from a single primary trial indicated very low-certainty evidence of a **lower increment of dmfs following the combined use of 5% NaF varnish applied every 6 months together with 0.025% NaF toothpaste in comparison with a control group that received oral health counselling** at 2 years follow-up. The review authors reported a 15% reduced risk of caries in the intervention group. However, **the statistical significance of the result was not reported in the review**. It should be noted that 27% of the participants in this trial reported regularly using fluoride tablets. However, this was considered background fluoride exposure rather than part of the intervention of interest.

Table 15 Main review outcomes for multiple types of combined topical fluoride interventions in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Carvalho *et al.* (2010) [125]	dmfs: lower for 5% NaF varnish together with 0.0255% NaF toothpaste compared with a control group receiving oral health counselling (1 trial)	Critically low	Very low	
				dmfs: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.5.9.2 Topical fluoride together with other topical chemicals

We identified four systematic reviews that reported on the effectiveness of combined interventions involving topical fluoride and any other non-fluoride topical chemical for caries prevention in primary dentition. Table 16 presents a high-level summary of treatment outcomes from reviews that reported on these interventions.

Walsh *et al*. [126] assessed the effects of oral products (toothpastes, mouth rinses, varnishes, gels, gums, and sprays) containing CHX on the prevention of dental caries in children and adolescents. Two trials identified in this review delivered combined interventions involving the use of CHX gel and fluoride toothpaste. The pooled findings indicated low-certainty evidence of **no significant difference in dmft scores following the combined use of 0.12% CHX gel applied once daily together with twice daily toothbrushing with a 0.304% fluoride toothpaste in comparison with no gel together with twice daily toothbrushing with a 0.304% fluoride toothpaste** at 2 years follow-up. In addition, the review authors noted that OHI and dietary advice were provided to caregivers in both trials.

Wang *et al*. [127] assessed the effectiveness of non-fluoride agents for caries prevention in primary dentition. Four trials identified in this review involved combined interventions and were reported narratively. The findings from one trial indicated low-certainty evidence of **a significant reduction in the**

increment of defs following the combined use of fluoride toothpaste (fluoride concentration not reported) together with consumption of confections containing arginine (concentration not reported) four times per day in comparison with the combined use of fluoride toothpaste together with consumption of control confections at both 6 months and 1 year follow-up. The findings from a second trial indicated low-certainty evidence of a **slight (albeit likely not significant) decrease in the proportion of participants developing new caries in primary teeth following the combined use of 10% CPP-ACP paste applied once daily together with twice daily toothbrushing with fluoride toothpaste (fluoride concentration not reported) in comparison with twice daily toothbrushing with fluoride toothpaste alone** at 2 years follow-up. Two other trials of a combined intervention involving CHX gel and fluoride toothpaste were presented; these were the same two trials reported on in Walsh *et al*. [126]. The only difference was that Wang *et al*. reported a different outcome than Walsh *et al*. did: Wang *et al*. reported on the proportion of children developing new caries post-intervention. The findings, however, were similar across outcomes; the caries rate in both the intervention and control groups in both trials was very low.

Singal *et al*. [9] reviewed the evidence for the remineralising and caries-preventive efficacy of various calcium phosphate derivatives. One trial identified in this review delivered a combined intervention involving CPP-ACP paste and fluoride toothpaste. The findings indicated low-certainty evidence of **no significant difference in dmfs scores following the combined use of 10% CPP-ACP paste together with 1000 ppm fluoride toothpaste (frequency of use not reported) in comparison with the use of 1000 ppm fluoride toothpaste alone**. The follow-up period for this primary trial was not reported in the review.

Gupta *et al*. [128] compared the effectiveness of the combined use of topical fluoride and povidone-iodine with topical fluoride alone for the prevention of dental caries among children aged 1–12 years. The findings from three pooled trials indicated very low-certainty evidence **no significant difference in the risk of caries incidence (measured by the presence or absence of new carious lesions) between the combined intervention group that used topical fluoride (mixed) together with povidone-iodine in comparison with the group that used topical fluoride alone**. The follow-up period was not made explicit; however, the review authors indicated that it was at least 1 year. The combined interventions applied in the three trials were: (1) 1.23% APF gel together with a 10% povidone-iodine solution every week for 1 month, after which the gel and povidone-iodine were applied alternately every 3 months for 1 year; (2) a combination of 1.23% APF gel, a 2 mL povidone-iodine application, oral prophylaxis (scaling and cleaning), and complete restorative therapy (one treatment); and (3) 5% NaF varnish together with 1% povidone-iodine applied three times per year.

Overall, there is **very low- to moderate-certainty evidence** indicating no benefit of the combined use of:

1. CHX gel together with fluoride toothpaste, in comparison with toothbrushing alone
2. CPP-ACP paste together with fluoride toothpaste, in comparison with toothbrushing alone, or
3. Topical fluoride (mixed; APF gel or NaF varnish) together with povidone-iodine , in comparison with topical fluoride alone.

The very low-certainty evidence for the combined use of arginine confection and fluoride toothpaste is based on one trial only. There was no overlap of primary studies across the four reviews for the same outcomes.

Table 16 Main review outcomes for combined topical fluoride and other topical chemicals in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Walsh *et al.* (2015) [126]	dmft: no significant difference for CHX gel together with fluoride toothpaste compared with fluoride toothpaste alone (2 pooled trials)	Low	Low	
Wang *et al.* (2017) [127]	defs: significant reduction for fluoride toothpaste together with arginine confections compared with fluoride toothpaste and control confections (1 trial) Percentage of children developing new caries: slight decrease for CPP-ACP together with fluoride toothpaste compared with fluoride toothpaste alone (1 trial); no significant reducing potential for CHX gel together with fluoride toothpaste compared with fluoride toothpaste alone (2 trials, narrative synthesis)	Low	Low Moderate Low (for consistency with Walsh *et al.* (2015) as using the same trial evidence)	
Singal *et al.* (2022) [9]	dmfs: no significant difference for CPP-ACP paste together with fluoride toothpaste compared with fluoride toothpaste alone (1 trial)	Critically low	Low	
Gupta *et al.* (2020) [128]	Caries incidence: no significant difference for topical fluoride (mixed) together with povidone-iodine compared with topical fluoride alone (3 pooled trials)	Critically low	Very low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				dmft: no overlap dmfs/defs: no overlap Caries incidence/percentage developing new caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.5.9.3 Topical fluoride together with other interventions

We identified seven systematic reviews that evaluated the effectiveness of some form of topical fluoride plus an additional active intervention component besides topical fluoride and other topical chemicals for caries prevention in primary dentition. Table 17 presents a high-level summary of treatment outcomes from reviews that reported on these interventions.

Three out of the seven reviews focused on fluoride varnish, three focused on fluoride toothpaste, and one review focused on fluoride mouth rinse. The fluoride mouth rinse review, which was conducted by Marinho *et al*. [109], evaluated the combined effectiveness of the use of fluoride mouth rinse and school-based supervised rinsing. However, this review did not identify any trials evaluating this combined intervention on primary dentition; the evidence identified in this review pertained only to permanent dentition and is described in Section 4.6.5.5.9.3.

In relation to combined interventions involving fluoride varnish, Smith *et al*. [124] systematically reviewed the evidence for interventions to prevent early childhood caries in Indigenous children from high-income countries. The review included a single trial that delivered a combined intervention involving fluoride varnish. The findings indicated moderate-certainty evidence of a **significantly lower increment of dmfs following the combined use of 5% NaF varnish applied at baseline and again at 4- and 6-month intervals together with caregiver counselling, compared with caregiver counselling alone,** at 2 years follow-up. The precise nature of the caregiver counselling intervention component was not described.

Lam *et al*. [129] assessed the evidence on the effectiveness of different sealants in the prevention and arrest of pit-and-fissure occlusal caries in the primary molars of children. The review included two trials that delivered combined interventions involving fluoride varnish. The findings from one trial indicated very low-certainty evidence of a **significantly lower caries incidence rate following the combined use of 5% NaF varnish together with application of light-cured fissure sealants in comparison with the use of fluoride varnish alone** at 1 year follow-up. This effect, however, was **not statistically significant at 2 years follow-up**. The findings from the second trial indicated very low-certainty evidence of **no significant difference in the caries incidence rate in participants following the combined use of fluoride varnish together with resin infiltration in comparison with the combined use of fluoride varnish (concentration of fluoride not reported) together with resin-based sealants** at 2 years follow-up. In the same trial, a subgroup analysis indicated very low-certainty evidence of **no significant difference in the caries incidence rate in participants following the combined use of fluoride varnish together with resin-based sealants in comparison with the use of fluoride varnish alone** at 2 years follow-up.

de Sousa *et al*. [130] assessed the effectiveness of fluoride varnish in reducing the risk of developing new dentine carious lesions in preschoolers. Although this review did not describe the included interventions as combined interventions per se, the descriptions of the interventions provided by the review authors indicated that a majority of the 20 trials analysed across the pooled analyses involved combined interventions of fluoride varnish together with either: OHE (5 trials), both OHE and supervised toothbrushing (2 trials), dietary counselling (4 trials), and/or fluoridated toothpaste (2 trials). The findings from 16 pooled trials (10 of which involved various types of combined interventions) indicated very low-certainty evidence of **no significant difference in the proportion of children developing new dentine carious lesions following the use of fluoride varnish compared with no varnish** at 1–3 years follow-up. The fluoride varnish interventions varied, with 13 trials using 5% NaF, 2 trials using 0.1% difluorsilano varnish, and 1 trial using 0.9% difluorsilano varnish. Fluoride varnish was applied at 6-month intervals in 15 trials, and at 3-month intervals in 1 trial. The findings from 11 pooled trials (7 of which involved various types of combined interventions) indicated very low-certainty evidence of **significantly lower dmfs scores following the use of fluoride varnish compared with a control** at 1–3 years follow-up, resulting in a 24%

reduced risk of developing caries among participants in the intervention group. The fluoride varnish interventions varied, with 8 trials using 5% NaF, 1 trial using 0.1% difluorsilano varnish, and 1 trial using 0.9% difluorsilano varnish. Fluoride varnish was applied at 6-month intervals in nine trials, and at 3-month intervals in two trials. It should be noted that at least 17 out of the 20 trials included in the de Sousa *et al*. review reported some other exposure to fluoride (via water, toothpaste, or tablets). However, this was considered background fluoride exposure rather than part of the intervention of interest. The findings from five pooled trials (two of which involved various types of combined interventions) indicated very low-certainty evidence of **no significant difference in dmft scores following the use of fluoride varnish applied at 6-month intervals compared with a control** at 1–3 years follow-up. The fluoride varnish interventions involved 5% NaF in four trials and 0.1% difluorsilano varnish in one trial. Evidence from three additional trials testing complex interventions (which are described separately in the de Sousa *et al*. review) can be found in Section 4.5.5.10 on complex interventions in primary dentition.

In relation to combined interventions involving fluoride toothpaste, dos Santos *et al*. [118] assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. The review included a single trial that reported on a combined intervention involving fluoride toothpaste. The findings indicated very low-certainty evidence of a **significantly higher proportion of children remaining caries free, and a significantly lower increment of both dmfs and dmft, following the combined use of fluoride toothpaste (500 ppm fluoride) together with supervised toothbrushing in kindergartens compared with occasional instruction for teeth cleaning once every 3–4 months** at 27–29 months follow-up. The participating families in both groups were provided with fluoride toothpaste.

Walsh *et al*. [21] compared the effectiveness of toothpastes of different fluoride concentrations for preventing dental caries in children, adolescents, and adults. Two trials included in the review reported on the effectiveness of combined interventions involving fluoride toothpaste, with divergent findings. The findings from one trial indicated very low-certainty evidence of **no significant difference in the proportion of children developing new caries between the test group (which involved the use of high-fluoride toothpaste (1450 ppm fluoride) together with supervised toothbrushing) and the control group (which involved the use of low-fluoride toothpaste (250 ppm fluoride) together with supervised toothbrushing)** at 22 months follow-up. The findings from the other trial indicated low-certainty evidence of a **significantly lower proportion of children developing new caries in the test group (which involved the use of high-fluoride toothpaste (1055 ppm fluoride) together with supervised toothbrushing) and the control group (which involved the use of low-fluoride toothpaste (550 ppm fluoride) together with supervised toothbrushing)** at 3 years follow-up.

dos Santos *et al*. [131] assessed the effectiveness of low-fluoride and standard fluoride toothpastes for caries prevention in the primary dentition of preschool children. Although this review did not describe the included interventions as combined interventions per se, the descriptions of the interventions provided by the review authors indicated that seven out of the eight included trials in the review evaluated **the effectiveness of fluoride toothpaste use together with OHE**. In relation to low-fluoride toothpaste, the findings from two pooled trials indicated low-certainty evidence of a **significantly lower increment of dmfs following the use of low-fluoride toothpaste (<600 ppm fluoride) compared with a control**, resulting in a 40% reduced risk of developing new caries on teeth surfaces among those in the intervention group. However, the findings from two pooled trials indicated low-certainty evidence of **no significant difference in the increment of dmft following the use of low-fluoride toothpaste compared with a control**. Moreover, the findings from two pooled trials indicated low-certainty evidence of **no significant difference in the proportion of children developing new caries following the use of low-fluoride toothpaste compared with a control**. In relation to standard fluoride toothpaste, the findings from five pooled trials indicated low-certainty evidence of a **significantly lower increment of dmfs**

following the use of standard fluoride toothpaste (1000–1500 ppm fluoride) compared with a control, resulting in a 31% reduced risk of developing new caries on teeth surfaces among those in the intervention group. The findings from a single trial indicated low-certainty evidence of **a significantly lower increment of dmft following the use of standard fluoride toothpaste compared with a control**, resulting in a 16% reduced risk of developing new caries among those in the intervention group. Finally, the findings from two pooled trials indicated low-certainty evidence of a **significantly lower proportion of children developing new caries following the use of standard fluoride toothpaste compared with a control**. The follow-up periods of the trials included in the dos Santos *et al*. review were not reported in the review. However, the review authors indicated that they only included trials with a follow-up period of at least 1 year.

Overall, in relation to fluoride varnish, there is very low-certainty **evidence of no added benefit of using fluoride varnish in combination with sealant application**. There is **moderate-certainty evidence indicating a caries-preventive effect of fluoride varnish in combination with caregiver counselling**. There is **very low-certainty evidence on the effectiveness of fluoride varnish combined with other varied active intervention components, indicating a significant difference favouring fluoride varnish at the tooth surface level** in primary dentition; however, de Sousa *et al*. speculated that the difference **may be clinically irrelevant**. At the **individual level and whole tooth level, there was no significant effect of varied types of combined interventions all involving fluoride varnish** for caries prevention in primary dentition. In relation to fluoride toothpaste, the **low- and very low-certainty evidence in relation to fluoride toothpaste combined with supervised toothbrushing is inconsistent** across three individual primary trials. There is **low-certainty evidence in relation to fluoride toothpaste combined with OHE favouring the combination of standard fluoride toothpaste (1000–1500 ppm fluoride) plus OHE** over low-fluoride toothpaste (<600 ppm fluoride) plus OHE.

There was a slight overlap of primary studies across four reviews in relation to the dmfs outcome, but there was no overlap in relation to the other included outcomes.

Table 17 Main review outcomes for topical fluoride combined with other intervention components in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Marinho *et al.* (2016) [109]	None reported	Low	N/A	
Smith *et al.* (2018) [124]	dmfs: significantly lower for 5% NaF varnish together with caregiver counselling compared with caregiver counselling alone (1 trial)	Low	Moderate	
Lam *et al.* (2020) [129]	Caries incidence: significantly lower for 5% NaF varnish together with sealants compared with fluoride varnish alone (1 trial); no significant difference for resin infiltration together with fluoride varnish compared with resin-based sealants together with fluoride varnish (1 trial); no significant difference for resin-based sealants together with fluoride varnish compared with fluoride varnish alone (subgroup analysis in second trial)	Critically low	Very low	
de Sousa *et al.* (2019) [130]	Percentage of children developing new caries: no significant difference for fluoride varnish compared with no varnish (16 pooled trials) dmfs: significantly lower for fluoride varnish compared with control (11 pooled trials) dmft: no significant difference for fluoride varnish compared with control groups (5 pooled trials)	Critically low	Very low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
dos Santos *et al.* (2018) [118]	Percentage of children remaining caries free: significantly higher for fluoride toothpaste together with supervised toothbrushing compared with occasional instruction (1 trial) dmfs: significantly lower for fluoride toothpaste together with supervised toothbrushing compared with occasional instruction (same trial) dmft: significantly lower for fluoride toothpaste together with supervised toothbrushing compared with occasional instruction (same trial)	Low	Very low	
Walsh *et al.* (2019) [21]	Percentage of children developing new caries: no significant difference for 1450 ppm fluoride toothpaste together with supervised toothbrushing compared with 250 ppm fluoride toothpaste together with supervised toothbrushing (1 trial); significantly lower for 1055 ppm fluoride toothpaste together with supervised toothbrushing compared with 550 ppm fluoride toothpaste together with supervised toothbrushing (1 trial)	Low	Very low Low	
dos Santos *et al.* (2013) [131]	Percentage of children developing new caries: no significant difference for low-fluoride toothpaste compared with control (2 pooled trials); significantly	Critically low	Low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
	lower for standard fluoride toothpaste compared with control (2 pooled trials) dmfs: significantly lower for low-fluoride toothpaste compared with control (2 pooled trials); significantly lower for standard fluoride toothpaste compared with control (5 pooled trials) dmft: no significant difference for low-fluoride toothpaste compared with control (2 pooled trials); significantly lower for standard fluoride toothpaste compared with control (1 trial)			
				Caries incidence, or percentage of children developing new caries: no overlap dmfs: slight overlap dmft: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.6 Other topical chemicals

4.5.5.6.1 Antioxidants

None of the included systematic reviews reported on the effectiveness of topical antioxidant agents for caries prevention in primary dentition.

4.5.5.6.2 Toothpaste

None of the included systematic reviews reported on the effectiveness of non-fluoride toothpaste that contained other active agents for caries prevention in primary dentition.

4.5.5.6.3 Antimicrobial agents (minus CHX)

We identified two systematic reviews on the effectiveness of topical antimicrobial agents for caries prevention in primary dentition. Table 18 presents a high-level summary of treatment outcomes for this intervention category.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including antimicrobial agents, mainly triclosan and povidone-iodine) on the market in the USA. However, **none of the included trials** evaluated the use of triclosan, and while four trials reported on the effectiveness of 10% povidone-iodine compared with fluoride foam or saline, they focused predominantly on secondary prevention (or management) of caries, and there is limited information provided in the review in relation to primary prevention of caries.

Wang *et al*. [127] assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. The findings indicated moderate-certainty evidence from a single trial of **significantly lower dmft and dmfs scores following the application of 0.3% triclosan varnish twice per year compared with no treatment** at 1 year follow-up.

Overall, there is **a paucity of evidence** available to determine the benefit of antimicrobial agents (minus CHX) for caries prevention in primary dentition. There was no overlap of primary studies across the two reviews for the included outcomes.

Table 18 Main review outcomes for antimicrobial agents (minus CHX) in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	None reported	Critically low	N/A	
Wang *et al.* (2017) [127]	dmfs: significantly lower for 0.3% triclosan varnish compared with no treatment (1 trial) dmft: significantly lower for 0.3% triclosan varnish compared with no treatment (same trial)	Low	Moderate	
				dmfs: no overlap dmft: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.6.4 Arginine and its derivatives

None of the included systematic reviews reported on the effectiveness of arginine-based interventions for caries prevention in primary dentition.

4.5.5.6.5 CHX

We identified five systematic reviews on the effectiveness of CHX for caries prevention in primary dentition. Table 19 presents a high-level summary of treatment outcomes for this intervention category.

Smith *et al*. [124] systematically reviewed the evidence for interventions, including interventions involving CHX, to prevent early childhood caries in Indigenous children from high-income countries. However, **none of the included trials** evaluated the caries-preventive efficacy of CHX applied to the primary teeth of children. One trial evaluated the application of CHX varnish to mothers' teeth and evaluated the outcomes in the primary dentition of their children. This evidence, and evidence from two other reviews on the effectiveness of the application of CHX varnish to mothers' teeth for caries prevention in the primary dentition of their children, is described in Sections 4.5.5.9.3 and 4.5.5.9.4 on interventions delivered to pregnant women/mothers.

Walsh *et al*. [126] assessed the effects of CHX-containing oral products (toothpastes, mouth rinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. The findings from three pooled trials indicated low-certainty evidence of **no significant difference in the dmfs/dmft-molar index between participants in the CHX varnish groups (1% CHX varnish applied every 3 months over 2 years in one trial, and 40% CHX varnish applied every 6 months over approximately 3 years in the other two trials) and participants in the no treatment/placebo groups** at 2 years follow-up. None of the included trials evaluated the effectiveness of other CHX products as standalone interventions for caries prevention in primary dentition. Evidence on the effectiveness of a combined intervention

delivered in one trial included in the Walsh *et al*. review that involved the use of CHX gel on primary teeth can be found in Section 4.5.5.5.9.2.

James *et al*. [132] assessed the effectiveness of CHX varnish for preventing caries in the permanent and primary teeth of children and adolescents compared with placebo or no treatment. The findings from a single trial indicated very low-certainty evidence of a **significantly lower increment in the dmfs-molar index following the application of 40% CHX varnish every 6 months compared with the application of a placebo varnish** at 2 years follow-up, resulting in a 37.3% reduced risk of developing caries among children in the intervention group. It should be noted that all trials included in this review, including the trial described here, reported some other exposure to fluoride (via water, toothpaste, or mouth rinse). However, this was considered background fluoride exposure rather than part of the intervention of interest.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including CHX) on the market in the USA. The findings from a single trial indicated very low-certainty evidence of **no significant difference in dft increment following the professional application of 1% CHX gel on 3 consecutive days every 3 months compared with no gel application** at 18 months follow-up. It should be noted that participants in both groups also had exposure to fluoride toothpaste; however, this was considered background fluoride exposure rather than part of the intervention of interest. Rethman *et al*. also reported on the effectiveness of CHX varnish and mouth rinses. However, the results of trials that focused on primary dentition were pooled with the results of trials that focused on permanent dentition. These findings were therefore coded as mixed dentition and the evidence is presented in Section 4.7.5.6.5.

Wang *et al*. [127] assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. The findings indicated moderate-certainty evidence from four trials (synthesised narratively) of a **significantly lower increment in various indexes of dental caries (dmfs in one trial, dmfs-molar in two trials, dmft in one trial, and defs in two trials) following the application of CHX products (gel or varnish) compared with a placebo/no CHX application** at 2–3 years follow-up. In relation to form and concentration of CHX and frequency of application, one trial applied 1% CHX gel four times per year, two trials applied 40% CHX varnish every 6 months, and one trial applied 1% CHX-thymol varnish every 2 months.

Overall, **the very low- to moderate-certainty evidence in relation to the effectiveness of CHX varnish and gel (40% and 1%) for caries prevention in primary dentition is inconsistent**. Moreover, there is **a paucity of evidence to determine the effectiveness of other CHX products** for caries prevention in primary dentition. The overlap of primary studies was very high for three of the four outcomes (namely surface indexes for 1% and 40% CHX gel or varnish, and whole tooth indexes for 1% CHX gel or varnish). There was, however, no overlap for the remaining outcome: whole tooth indexes for 40% CHX gel or varnish.

Table 19 Main review outcomes for CHX in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Smith *et al.* (2018) [124]	None reported	Low	N/A	
Walsh *et al.* (2015) [126]	dmfs/dmft-molar: no significant difference for CHX varnish compared with no treatment/placebo group (3 pooled trials)	Low	Low	
James *et al.* (2010) [132]	dmfs-molar: significantly lower for CHX varnish compared with placebo varnish (1 trial)	Critically low	Very low	
Rethman *et al.* (2011) [121]	dft: no significant difference for CHX gel compared with no gel (1 trial)	Critically low	Very low	
Wang *et al.* (2017) [127]	dmfs (1 trial); dmfs-molar (2 trials); dmft (1 trial); and defs (2 trials): all significantly lower for CHX gel or varnish compared with placebo/no CHX application (4 trials, narrative synthesis; 2 trials reported on more than 1 outcome)	Low	Moderate	dmfs/dmft-molar, defs, or dmfs 1% CHX gel: very high overlap dmfs/t-molar/dmfs-molar/defs/dmfs-molar/dmfs-molar 40% CHX varnish: very high overlap dmfs/dmft-molar/dft/dmft 1% CHX gel: very high overlap

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				dmfs/dmft-molar 40% CHX varnish: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.6.6 Calcium phosphate agents

We identified three systematic reviews on the effectiveness of calcium phosphate agents for caries prevention in primary dentition. Table 20 presents a high-level summary of treatment outcomes for this intervention category.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including calcium phosphate agents) on the market in the USA. However, **none of the included trials** reported on the effectiveness of calcium phosphate agents for caries prevention in primary dentition.

Singal *et al*. [9] reviewed the evidence for the remineralising and caries-preventive efficacy of various calcium phosphate derivatives. However, **none of the included trials** reported on the effectiveness of calcium phosphate derivatives in a standalone intervention for caries prevention in primary dentition. The findings from this review in relation to calcium phosphate agents in combination with topical fluoride can be found in Section 4.5.5.5.9.2 on combined interventions for primary dentition.

Wang *et al*. [127] assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. The findings from a single trial indicated very low-certainty evidence of a **significantly lower increment of dmft following the use of CPP-ACP mousse twice per day compared with a placebo or use of fluoride varnish** at 1 year follow-up. This review also included the proportion of participants who developed new caries as an outcome; however, the only trial that reported on this outcome tested a combined intervention involving CPP-ACP. The findings can be found in Section 4.5.5.5.9.2 on combined interventions for primary dentition.

Overall, there is **a paucity of evidence** available to determine the effectiveness of calcium phosphate agents delivered in standalone interventions for caries prevention in primary dentition. There was no overlap of primary studies across the three reviews for the included outcomes.

Table 20 Main review outcomes for calcium phosphate agents in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	None reported	Critically low	N/A	
Singal *et al.* (2022) [9]	None reported	Critically low	N/A	
Wang *et al.* (2017) [127]	dmft: significantly lower for CPP-ACP mousse compared with placebo or fluoride varnish (1 trial)	Low	Very low	
				dmft: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.6.7 Ozone

None of the included systematic reviews reported on the effectiveness of ozone-based interventions for caries prevention in primary dentition.

4.5.5.6.8 Nanomaterials

None of the included systematic reviews reported on the effectiveness of nanomaterials for caries prevention in primary dentition.

4.5.5.6.9 Probiotics

We identified three systematic reviews on the effectiveness of probiotics for caries prevention in primary dentition. Table 21 presents a high-level summary of treatment outcomes for this intervention category.

Hao *et al*. [41] examined the effectiveness and safety of *Bifidobacterium* in preventing caries. The findings indicated very low-certainty evidence from two trials (which were synthesised narratively) of **no significant difference in the occurrence of new deciduous tooth caries following the consumption of 100 g or 300 g of *Bifidobacterium* delivered using slow-release tablets/pacifiers compared with placebo tablets/pacifiers** in primary teeth at 2 years and 4 years follow-up. It should be noted that although these are presented as two different trials in the review, the intervention was delivered to the same group of participants who were followed up after 2 years and again after 4 years.

Jørgensen *et al*. [120] reviewed the available literature on the prevention of caries in early childhood through biofilm engineering with probiotic bacteria. The findings indicated very low-certainty evidence from a single trial of a **significantly lower increment of decayed surfaces (ds) following the consumption of probiotic lozenges containing three *Streptococcus*-derived strains compared with the consumption of placebo lozenges** at 1 year follow-up. However, the review authors noted that the results in this trial were obtained in spite of the fact that **approximately 80% of the families reported supervised toothbrushing twice daily, and despite a far-from-optimal level of compliance with the administration of the probiotic lozenges**. Jørgensen *et al.* also presented findings from another trial that delivered a combined intervention involving the consumption of *Lactobacillus rhamnosus*, and this evidence is presented in Section 4.5.5.3.5 on combined interventions on primary dentition.

Twetman and Jørgensen [113] examined the preventive effect of probiotic supplements on the development of early childhood caries. The findings indicated low-certainty evidence from seven pooled trials showing a **significantly lower caries increment at the tooth and/or surface level (the pooled trials measured variations of the dmfs and dmft indexes) following the consumption of probiotics compared with consumption of a placebo** at 6–24 months follow-up. The seven pooled trials varied in relation to the type of bacteria (*Streptococcus*/*Lactobacillus*/*Bifidobacterium*), the mode of delivery, the amount consumed, and the frequency of consumption. Six out of the seven trials used probiotic milk (two trials involved consumption of 50 mL of powdered milk once per day, three trials involved consumption of 150 mL of powdered or fresh milk on weekdays, and one trial involved consumption of 200 mL of powdered milk on weekdays), and one trial involved the consumption of probiotic tablets (consumed once per day). It should be noted that this outcome was identified as a secondary outcome in Twetman and Jørgensen's review. It should also be noted that at least one of the pooled trials involved a combined intervention in which the milk consumed by participants contained both probiotics and 2.5 mg/kilogram (kg) of fluoride.

Overall, although there is some inconsistency in the findings, **the low- and very low-certainty evidence predominantly indicates a significant caries-preventive benefit of probiotics for caries prevention in primary dentition**. However, the trials included in the body of evidence vary greatly in relation to the type of probiotic bacteria consumed, the amount consumed, and the frequency of consumption. There was a high degree of overlap of primary studies in relation to ds and dmfs/dmft outcomes. There was, however, no overlap in relation to caries incidence.

Table 21 Main review outcomes for probiotics in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Hao *et al.* (2021) [41]	Caries incidence: no significant difference for *Bifidobacterium* compared with placebo tablets/pacifiers (2 trials, narrative synthesis)	Critically low	Very low	
Jørgensen *et al.* (2016) [120]	ds: significantly lower for probiotic lozenges containing three *Streptococcus*-derived strains compared with placebo lozenges (1 trial)	Low	Very low	
Twetman and Jørgensen (2021) [113]	dmfs/dmft: significantly lower for probiotics compared with placebo (7 pooled trials)	Critically low	Low	
				ds or dmfs/dmft: high overlap Caries incidence: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.6.10 Propolis

None of the included systematic reviews reported on the effectiveness of propolis for caries prevention in primary dentition.

4.5.5.6.11 Silicates

None of the included systematic reviews reported on the effectiveness of silicates for caries prevention in primary dentition.

4.5.5.6.12 Xylitol

We identified four systematic reviews on the effectiveness of xylitol for caries prevention in primary dentition. Table 22 presents a high-level summary of treatment outcomes for this intervention category.

Riley *et al*. [133] evaluated the effects of different xylitol-containing products on preventing dental caries in children and adults. The findings from four trials were synthesised narratively due to variation in the mode of delivery and outcome measures. The findings from a single trial indicated very low-certainty evidence of a **significant difference in the mean number of decayed primary teeth following the consumption of 8.00 g of xylitol syrup per day compared with the consumption of 2.67 g of xylitol syrup per day** at 1 year follow-up, resulting in a 58% reduced risk of new caries in the group that received the

higher amount of xylitol syrup. The findings from a second trial, however, indicated low-certainty evidence of **no preventive benefit (i.e. no difference in dmfs increment) following the consumption of xylitol sucking tablets (0.48–1.00 g per day) compared with no tablet consumption** at 2 years follow-up. The prevented fraction, however, was marginally significant and indicated a 53% reduced risk of new caries in favour of xylitol sucking tablets. The findings from a third trial indicated very low-certainty evidence of **no preventive benefit of xylitol tablets (200–600 mg per day administered via a slow-release pacifier or crushed up on a spoon) compared with control tablets** at 2 years follow-up. The outcome measure in this trial was slightly different to caries increment as a continuous outcome measure: it was the dichotomous presence or absence of an increment in dmfs. Finally, the findings from a fourth trial indicated very low-certainty evidence of **no preventive benefit (dichotomous presence or absence of dmfs increment) following the use of two xylitol wipes to clean the teeth and the gums, three times per day (4.2 g of xylitol per day), compared with control wipes** at 1 year follow-up. None of Riley *et al*.'s included trials reported on the preventive effectiveness of xylitol-containing lozenges or (non-fluoride) toothpaste in primary dentition. One trial reported on the effectiveness of xylitol-containing candy in mixed dentition; this evidence can be found in Section 4.7.5.6.12.

Chou *et al*. [48] investigated the effect of various caries-preventive interventions, including xylitol-based interventions, on preventing and arresting dental caries in children aged under 5 years. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the increment of dmfs following the consumption of xylitol tablets (one 0.5 mg tablet at bedtime for 6 months, followed by two tablets daily) compared with no xylitol tablets** at 2 years follow-up. Similarly, the findings from a second trial indicated very low-certainty evidence of **no significant difference in the risk of developing new caries (i.e. lower increment of dmfs and lower incidence of caries) following the use of xylitol wipes (two at a time, three times per day every 3 months for 1 year, with an estimated daily dosage of 4.2 g) compared with the use of placebo wipes**. The review authors indicated that in an on-treatment subgroup analysis of children who completed the study, xylitol was associated with a significantly lower dmfs increment and a significantly lower risk of caries incidence compared with a placebo. The follow-up period for this trial was not made explicit. However, the review authors indicated that follow-up periods for all included trials ranged from 1 to 3 years.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including xylitol) on the market in the USA. The review authors identified two trials on the effectiveness of xylitol for caries prevention in primary dentition. The findings from one trial, however, were pooled in a meta-analysis with trials evaluating permanent dentition. These findings were therefore coded under mixed dentition and the evidence is presented in Section 4.7.5.6.12. The other trial identified by Rethman *et al*. is the same trial on xylitol syrup (8.00 g compared with 2.67 g of syrup per day) as that described in Riley *et al*.'s review, which can be found at the beginning of this section. Although the two reviews reported the same direction of findings from this trial, the follow-up period in the trial was described differently: 10 months follow-up in Rethman *et al*. and 1 year follow-up in Riley *et al*. In addition, the nature of the outcome measure used in that trial was described differently in the two reviews: Riley *et al*. indicated the mean number of new decayed primary teeth, whereas Rethman *et al*. indicated the dmfs increment. For the purposes of this overview of reviews, we prioritised the follow-up period and outcome measure reported in Riley *et al*.'s review, because their review focused on xylitol-based interventions only, whereas Rethman *et al*.'s review focused on a multitude of caries-preventive agents.

Wang *et al*. [127] assessed the effect of non-fluoride agents on the prevention of dental caries in primary dentition. The findings from three trials were presented narratively due to variation in the mode of delivery and outcome measures. The findings from two trials indicated moderate-certainty evidence of **no**

significant difference in dmfs scores following the consumption of xylitol compared with no treatment or placebo at 24–30 months follow-up. One of these trials also reported low-certainty evidence of **no significant difference in the percentage of children with new caries** between the treatment and control groups. In these two trials, participants consumed either 0.5–1.0 g xylitol tablets once per day for 6 months and then twice per day for 1.5 years, or three 7.8 g xylitol gummy bears per day. The findings from a third trial indicated very low-certainty evidence of a **significantly lower proportion of children with new caries following the use of six xylitol wipes per day (with total consumption of 4.2 g of xylitol per day) compared with the use of placebo wipes** at 12 months follow-up. It should be noted that this trial is the same trial on xylitol wipes as that described in the Chou *et al*. review. However, Chou *et al*. reported on the non-significant result from the main analysis conducted by the trial authors as well as the significant result from the subgroup analysis, whereas the subgroup analysis was the only analysis reported in the Wang *et al*. review.

Overall, the **very low- to moderate-certainty body of evidence on xylitol-based interventions for caries prevention in primary teeth is inconsistent** and highly variable in relation to the mode of xylitol delivery, the amount of xylitol delivered, and the frequency of consumption. The findings from reviews in which xylitol-based interventions were delivered to pregnant women/mothers and the outcomes tested on the primary dentition of their children are described in Sections 4.5.5.9.2 and 4.5.5.9.4.1 on single interventions and combined interventions, respectively, delivered to pregnant women/mothers.

There was very high and complete overlap of primary studies in relation to dmfs and caries incidence outcomes, respectively. There was no overlap in relation to the mean number of decayed primary teeth.

Table 22 Main review outcomes for xylitol in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Riley *et al.* (2015) [133]	Mean decayed: significant difference for 8.00 g of xylitol syrup compared with 2.67 g of xylitol syrup (1 trial)	Low	Very low	
	dmfs: no difference for xylitol sucking tablets compared with no tablets (1 trial); no benefit (in dichotomous presence/absence of dmfs increment) for xylitol tablets compared with control tablets (1 trial) or for xylitol wipes compared with control wipes (1 trial)		Low Very low Very low	
Chou *et al.* (2021) [48]	dmfs: no significant difference for xylitol tablets compared with no xylitol tablets (1 trial), or for xylitol wipes compared with placebo wipes (1 trial)	Critically low	Very low	
	Caries incidence: significantly lower for xylitol wipes compared with placebo wipes (1 trial)			
Rethman *et al.* (2011) [121]	dmfs: significantly lower for 8.00 g of xylitol syrup compared with 2.67 g of xylitol syrup (1 trial)	Critically low	Very low	
Wang *et al.* (2017) [127]	dmfs: no significant difference for xylitol tablets compared with no treatment/placebo (2 trials, narrative synthesis)	Low	Moderate	
	Percentage of children with new caries: no significant difference for xylitol tablets compared with no treatment/placebo (1		Low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
	trial; one of the previous 2 trials); significantly lower for xylitol wipes compared with placebo wipes (1 trial)		Very low	
				Mean decayed: no overlap dmfs: very high overlap Caries incidence, or percentage of children with new caries: complete overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.6.13 Sorbitol

None of the included systematic reviews reported on the effectiveness of sorbitol as a standalone intervention for caries prevention in primary dentition.

4.5.5.6.14 Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined)

We identified one systematic review that aimed to report on the effectiveness of polyols for caries prevention in primary dentition. Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including polyols) on the market in the USA. However, **none of the included trials** reported on the effectiveness of polyols.

Overall, there is **a paucity of evidence** available to determine whether the use of polyols can reduce the risk of caries incidence in primary dentition.

4.5.5.7 Sealants

4.5.5.7.1 Resin

We identified two systematic reviews on the effectiveness of resin-based sealants for caries prevention in primary dentition. Table 23 presents a high-level summary of treatment outcomes for this intervention category.

Ramamurthy *et al*. [134] evaluated the effectiveness of sealants compared with no sealant or a different type of sealant in preventing pit-and-fissure caries on the occlusal surfaces of primary molars in children. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the risk of children developing one or more new carious lesions following the application of an auto-polymerised resin-based sealant compared with the application of a light polymerised resin-based sealant** at 2–3 years follow-up. The trial did not report on caries increment, which was also one of the primary outcomes in the review. Ramamurthy *et al*. also included two trials that compared the effectiveness of fluoride-releasing resin-based sealants with resin-based sealants on reducing the 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 reported in the primary trials, and so the findings were not reported in the review. In addition, none of the trials included in the Ramamurthy *et al*. review compared the effectiveness of flowable resin composite with another type of sealant on caries incidence or increment.

Lam *et al*. [129] assessed the evidence on the effectiveness of different sealants in the prevention and arrest of pit-and-fissure occlusal caries in the primary molars of children. The findings from a single trial indicated very low-certainty evidence of a **significantly lower caries incidence rate following the application of a resin-based sealant compared with the application of a glass ionomer (or resin-modified glass ionomer) sealant** at 6 months follow-up. This finding, however, was **no longer statistically significant at 18 months** follow-up. The findings from another single trial also indicated very low-certainty evidence of **no significant difference in caries incidence following the application of a resin-based sealant compared with the application of a fluoride-containing resin-based sealant or the application of ACP resin-based sealant** at 2 years follow-up. Finally, the findings from a third single trial indicated very low-certainty evidence of **no significant difference in caries incidence following the application of an auto-polymerised resin-based sealant compared with the application of a light-curing resin-based sealant** at 2 years follow-up. None of the trials included in the Lam *et al*. review examined the effectiveness of resin-based sealants compared with no sealant, and none compared the effectiveness of an ACP resin-based sealant or fluoride-containing resin-based sealant with no sealant in primary dentition.

Overall, **neither of these two reviews reported on the effectiveness of resin-based sealants compared with no sealant** as a standalone intervention on primary dentition. There is **very low-certainty evidence from reviews of standalone resin-based sealant interventions suggesting no additional benefit of resin-based sealants over and above other sealants**. The findings from both of these reviews, as well as other reviews that described combined interventions involving the use of sealants on primary dentition, are presented in Sections 1.1.1.1.1.1 and 4.5.5.7.7 on combined interventions. There was a very high level of overlap of primary studies in relation to caries incidence or risk of new caries across the two reviews.

Table 23 Main review outcomes for resin sealants in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Ramamurthy *et al.* (2022) [134]	Risk of new caries: no significant difference for auto-polymerised resin-based sealant compared with polymerised resin-based sealant (1 trial)	High	Very low	
Lam *et al.* (2020) [129]	Caries incidence: significantly lower for resin-based sealant compared with glass ionomer (or resin-modified glass ionomer) sealant at 6 months, but no difference at 18 months (1 trial); no significant difference for resin-based sealant compared with fluoride-containing resin-based sealant or ACP resin-based sealant (1 trial); no significant difference for auto-polymerised resin-based sealant compared with light-curing resin-based sealant (1 trial)	Critically low	Very low	
				Risk of new caries, or caries incidence: very high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.7.2 Glass ionomer

The same systematic reviews that evaluated the effectiveness of resin-based sealants for caries prevention in primary dentition were identified for glass ionomer-based sealants. Table 24 presents a high-level summary of treatment outcomes for this intervention category.

None of the included trials in Ramamurthy *et al*.'s review [134] compared the effectiveness of glass ionomer-based sealants with no sealant in a standalone intervention. One trial reported in this review compared the effectiveness of glass ionomer-based sealants with resin-based sealants on the incidence of new dental caries in second primary molars. However, Ramamurthy *et al*. were unable to determine the outcome due to inadequate information reported in the trial, and so they did not report the findings.

The findings from Lam *et al*. [129] on glass ionomer-based sealants came from a single trial, which indicated low-certainty evidence of **no significant difference in caries incidence following the application of a glass ionomer sealant compared with no sealant application** at 12 months follow-up.

The findings from both of these reviews, as well as other reviews that described combined interventions involving the use of sealants on primary dentition, are presented in Sections 4.5.5.7.7 and 4.5.5.5.9.3 on combined interventions.

Overall, there is **a paucity of evidence** available to determine the effectiveness of glass ionomer-based sealants as a standalone intervention for caries prevention in primary dentition. There was no overlap of primary studies across the two reviews for the included outcomes.

Table 24 Main review outcomes for glass ionomer sealants in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Ramamurthy *et al.* (2022) [134]	None reported	High	N/A	
Lam *et al.* (2020) [129]	Caries incidence: no significant difference for glass ionomer-based sealant compared with no sealant (1 trial)	Critically low	Low	
				Caries incidence: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.7.3 Ormocer

None of the included systematic reviews reported on the effectiveness of organically modified ceramic (ormocer) sealants for caries prevention in primary dentition.

4.5.5.7.4 Hybrid

None of the included systematic reviews reported on the effectiveness of hybrid sealants for caries prevention in primary dentition.

4.5.5.7.5 Combined

We identified one systematic review on the effectiveness of combined sealants for caries prevention in primary dentition. Akera *et al*. [117] evaluated the effectiveness of school-based interventions, including the application of sealants, in improving oral health compared with no intervention or usual practice among primary school children in low- and middle-income countries. However, the single trial included in this review only reported on permanent dentition (see Section 4.6.5.7.5 on combined sealants in permanent dentition).

As such, there is **a paucity of evidence** available to determine the effectiveness of combined sealants for caries prevention in primary dentition.

4.5.5.7.6 Other

None of the included systematic reviews reported on the effectiveness of other types of sealants for caries prevention in primary dentition.

4.5.5.7.7 Combined interventions involving sealants

We identified one systematic review that reported on the effectiveness of a combined intervention involving sealants for caries prevention in primary dentition. Table 25 presents a high-level summary of treatment outcomes from this review.

Ramamurthy *et al*. [134] evaluated the effectiveness of sealants compared with no sealant or a different type of sealant in preventing pit-and-fissure caries on the occlusal surfaces of primary molars in children. The findings from a single trial indicated very low-certainty evidence of a **significantly lower risk of developing one or more new carious lesions among children allocated to receive fluoride-releasing resin-based sealants together with recommendations related to oral hygiene and diet, compared with children in the control group who received oral hygiene and dietary recommendations alone,** at both 1 and 2 years follow-up. 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 findings from a second single trial indicated moderate-certainty evidence of **no significant difference in the risk of developing one or more new carious lesions among children allocated to receive glass ionomer-based sealants together with motivation and OHI, compared with those in the no intervention group,** at 12–30 months follow-up. In the same trial, however, there was moderate-certainty evidence of a **significantly lower increment of dmft among participants in the sealant intervention group compared with participants in the control group** at 1 year follow-up.

The findings from a third single trial indicated low-certainty evidence of a **significantly lower risk of developing one or more new carious lesions among children allocated to receive glass ionomer-based sealants together with a demonstration on proper toothbrushing technique, compared with those in the no sealant group who received the same instruction and demonstration**, at both 6 months and 1 year follow-up. In this trial, participants were instructed to use a low-fluoride toothpaste. The same trial, however, also reported very low-certainty evidence of **no significant difference in caries increment (precise index unspecified) on the occlusal surfaces of first primary molars in the sealant intervention group compared with the control group** at 1 year follow-up.

Overall, evidence of **moderate- to very-low certainty indicated a likely caries-preventive benefit associated with the combined use of sealants and some form of education or instruction** in relation to oral health. However, the evidence is drawn from only three primary trials.

Table 25 Main review outcomes for combined interventions involving sealants in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Ramamurthy *et al.* (2022) [134]	Caries incidence: significantly lower for fluoride-releasing resin-based sealants together with oral hygiene and diet recommendations compared with oral hygiene and diet recommendations alone (1 trial); no significant difference for glass ionomer-based sealants together with motivation and OHI compared with no intervention (1 trial); significantly lower for glass ionomer-based sealants together with a toothbrushing technique demonstration compared with no sealant group that received the toothbrushing demonstration only (1 trial)	High	Very low Moderate Low	Caries incidence: no overlap
	Mean number of new cavitated occlusal lesions: significantly lower compared with control group (1 trial)		Very low	Mean number of new cavitated occlusal lesions: no overlap
	Caries increment (index unspecified): no significant difference for sealant intervention group compared with control group (1 trial)		Low	Caries increment (index unspecified): no overlap
	dmft: significantly lower for glass ionomer-based sealants together with motivation and OHI compared with control group (1 trial)		Moderate	dmft: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.8 Lasers

We identified one systematic review that evaluated the effectiveness of lasers for caries prevention in primary dentition. Table 26 presents a high-level summary of treatment outcomes from this review.

Pagano *et al*. [135] evaluated whether the use of lasers at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries, improved fluoride uptake, and retention of sealant materials by improving traditional etching procedures. The findings from a single trial indicated very low-certainty evidence of a **significantly lower incidence of caries in the first and second primary molars following the use of a neodymium-doped yttrium aluminium garnet (Nd:YAG) laser compared with no treatment** at 1 year follow-up.

Table 26 Main review outcomes for lasers in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Pagano *et al.* (2020) [135]	Caries incidence: significantly lower for Nd:YAG laser compared with no treatment (1 trial)	Critically low	Very low	
				Caries incidence: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.9 Interventions delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

4.5.5.9.1 Systemic fluoride: supplements

We identified two systematic reviews on the effectiveness of fluoride supplements taken by pregnant women/mothers for caries prevention in the primary dentition of their children. Table 27 presents a high-level summary of treatment outcomes for maternal fluoride supplement interventions.

Takahashi *et al*. [136] **evaluated the effects of pregnant women taking fluoride supplementation (tablets in the only included trial) compared with no fluoride supplementation during pregnancy** to prevent caries in the primary teeth of their children. The intervention delivered in the only trial included in this review involved pregnant women consuming one dose (2.2 mg) of sodium fluoride (NaF) tablets once daily beginning in the fourth month of pregnancy, and their children receiving fluoride drops from birth until they were aged 2 years and a single 0.5 mg tablet daily for children aged 2–3 years. The findings indicated very low-certainty evidence of **no significant difference in the number of children with any caries or in the mean difference in dfs between participants in the intervention and participants in the control group who received a placebo tablet** at both 3 years and 5 years follow-up.

Xiao *et al*. [137] systematically reviewed the scientific evidence relating to the association between prenatal oral health care, reduced carriage of *Streptococcus mutans*, and early childhood caries prevention. The only trial included in Xiao *et al*.'s review that was relevant to our overview of reviews is the same trial as that described in Takahashi *et al*.'s review, and both reviews reported the same outcome.

Overall, there is **very low-certainty evidence of a caries-preventive effect associated with maternal fluoride supplementation in the primary teeth of children**. However, the evidence is based on a single trial reported in two systematic reviews. There was a complete overlap of primary studies across the two reviews.

Table 27 Main review outcomes for fluoridated supplements delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Takahashi *et al.* (2017) [136]	Number of children with caries: no significant difference for NaF tablets compared with placebo tablet (1 trial) dfs: no significant difference for NaF tablets compared with placebo tablet (same trial)	High	Very low	
Xiao *et al.* (2019) [137]	dmfs: no significant difference for NaF tablets compared with placebo tablet (1 trial)	Critically low	Very low	
				d(m)fs: complete overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.9.2 Topical other chemicals: xylitol

We identified two systematic reviews on the effectiveness of xylitol-based interventions given to pregnant women/mothers for caries prevention in the primary dentition of their children. Table 28 presents a high-level summary of treatment outcomes for xylitol-based maternal interventions.

None of the trials included in the Xiao *et al*. review [137] (described in the previous section) reported on xylitol-based prenatal interventions for caries prevention in children.

Riggs *et al*. [110] 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 until they were aged 6 years). The findings from two single trials (which were not pooled) indicated low- and very low-certainty evidence of **no significant difference in the risk of caries incidence following maternal consumption of xylitol chewing gum compared with the application of CHX varnish, or with the consumption of chewing gum containing both CHX and xylitol**. The intervention delivered in the first trial involved mothers chewing xylitol gum beginning 3 months after the birth of their child and continuing until the child was aged 3 years (average daily dose of xylitol: 6–7 g; average consumption frequency: four times per day) compared with three applications of CHX varnish 6, 12, and 18 months after the birth. The outcome measured was dmft index (low-certainty evidence), and the reported follow-up period was when the child was aged 2 years. The intervention delivered in the second trial involved

mothers chewing one piece of xylitol chewing gum for 5 minutes, three times per day (650 mg of xylitol per day, commencing 6 months postpartum up until 18 months postpartum) compared with consumption of chewing gum containing 532.5 mg of xylitol, 5.0 mg of CHX, and 141.9 mg of NaF. The outcomes were any caries incidence and defs scores (very low-certainty evidence), and the reported follow-up period was when the child was aged 4 years.

Overall, there is **some low- and very low-certainty evidence of no caries-preventive benefit of maternal consumption of xylitol chewing gum** compared with the application of CHX varnish or the consumption of chewing gum containing CHX, xylitol, and NaF. However, the evidence is drawn from only two trials. There was no overlap of primary studies across the two reviews for the included outcomes.

Table 28 Main review outcomes for xylitol delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Xiao *et al.* (2019) [137]	None reported	Critically low	N/A	
Riggs *et al.* (2019) [110]	defs: no significant difference for xylitol gum compared with gum containing 532.5 mg xylitol, 5.0 mg CHX, and 141.9 mg NaF (1 trial) Caries incidence: no significant difference for xylitol gum compared with gum containing 532.5 mg xylitol, 5.0 mg CHX, and 141.9 mg NaF (same trial) dmft: no significant difference for xylitol gum compared with CHX varnish (1 trial)	Low	Very low	defs: no overlap Caries incidence: no overlap dmft: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.9.3 Other topical chemicals: CHX

We identified three systematic reviews on the effectiveness of CHX given to pregnant women/mothers for caries prevention in the primary dentition of their children.

Table 29 presents a high-level summary of treatment outcomes for CHX-based maternal interventions.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including CHX) on the market in the USA. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the increment of dfs following the application of 10% CHX varnish to mothers' dentition (four weekly applications 6 months after delivery, followed by a single application once every 6 months) compared with the application of a placebo varnish** at 4 years follow-up.

Smith *et al*. [124] systematically reviewed the evidence for interventions, including CHX-based interventions, to prevent early childhood caries in Indigenous children from high-income countries. The findings from a single trial indicated moderate-certainty evidence of **no significant difference in the number of new carious surfaces in the primary dentition of children whose mothers received four weekly applications of 10% CHX varnish and a single application when their child was aged 12, 18, and 24 months, compared with a placebo varnish**. The outcome was assessed at 18–20 months follow-up. The precise timing of the weekly applications of 10% CHX was not made explicit in the review.

Riggs *et al*. [110] (described in the previous section) also aimed to assess the effectiveness of the use of CHX applied to mothers' dentition. However, **none of the included trials** reported on the effectiveness of CHX applied to mothers' dentition as a standalone intervention for caries prevention in the primary dentition of their children. The trials included in Riggs *et al*.'s review that reported on interventions of this nature tested combined interventions involving CHX. Information pertaining to this evidence can be found in Section 4.5.5.9.4.3 on combined interventions delivered to pregnant women/mothers.

Overall, there is **some very low- and moderate-certainty evidence of no caries-preventive benefit of the application of 10% CHX varnish to mothers' dentition** compared with application of placebo varnish. However, the evidence is drawn from only two trials. There was no overlap of primary studies across the three reviews for the included outcomes.

Table 29 Main review outcomes for CHX delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	dfs: no significant difference for 10% CHX varnish compared with placebo varnish (1 trial)	Critically low	Very low	
Smith *et al.* (2018) [124]	Caries incidence: no significant difference for 10% CHX varnish compared with placebo varnish (1 trial)	Low	Moderate	
Riggs *et al.* (2019) [110]	None reported	Low	N/A	
				dfs: no overlap Caries incidence: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.9.4 Combined interventions delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

4.5.5.9.4.1 Other topical chemicals together with other topical chemicals

We identified one systematic review that reported on the effectiveness of a combined intervention involving two forms of topical non-fluoride chemicals delivered to pregnant women/mothers for caries prevention in the primary dentition of their children.

Table 30 presents a high-level summary of treatment outcomes from this review.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents on the market in the USA. The findings from a single trial indicated very low-certainty evidence of a **significantly lower increment of dmf following maternal consumption of xylitol gum four times per day (6–7 g per day) from 3 months postpartum to 2 years postpartum together with the application of 40% CHX varnish on mothers' dentition, compared with the application of fluoride varnish (concentration and frequency unspecified),** at 5 years follow-up.

Table 30 Main review outcomes for combined other topical chemicals delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	dmf: significantly lower for xylitol gum together with 40% CHX varnish compared with fluoride varnish (1 trial)	Critically low	Very low	dmf: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.9.4.2 Other topical chemicals together with other interventions

We identified one systematic review that reported on the effectiveness of a combined intervention involving a non-fluoride topical chemical plus an additional intervention component delivered to pregnant women/mothers for caries prevention in the primary dentition of their children.

Table 31 presents a high-level summary of treatment outcomes from this review.

Rethman *et al*. [121] (the systematic review described in the previous section) reported findings from a single trial that delivered a combined intervention involving topical chemicals and a form of OHE. The findings indicated very low-certainty evidence of a **significantly lower increment of defs following the application of 1% CHX gel on mothers' dentition together with the delivery of a preventive programme up to 3 years postpartum, compared with the delivery of a preventive programme alone,** at 5 years follow-up. Information pertaining to the precise nature of the intervention was limited in the review.

Table 31 Main review outcomes for combined other topical chemicals together with other intervention components delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	defs: significantly lower for 1% CHX gel together with preventive programme compared with preventive programme alone (1 trial)	Critically low	Very low	defs: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.9.4.3 CHX together with other interventions

We identified one systematic review that reported on the effectiveness of a combined intervention involving CHX plus an additional non-topical chemical intervention component delivered to pregnant women/mothers for caries prevention in the primary dentition of their children. Riggs *et al*. [110] 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 until they were aged 6 years). Riggs *et al*. conducted a meta-analysis of three trials to examine the effect of maternal consumption of either CHX or iodine-NaF together with prophylaxis (teeth cleaning), compared with a placebo, for caries presence in the primary dentition of children. However, the precise nature of the intervention was unclear given the fact that the data were pooled. Therefore, the findings were excluded from our data synthesis.

4.5.5.9.4.4 Complex interventions delivered to pregnant women/mothers

We identified one systematic review that reported on the effectiveness of a complex intervention involving several intervention components delivered to pregnant women/mothers for caries prevention in the primary dentition of their children.

Table 32 presents a high-level summary of treatment outcomes from this review.

Xiao *et al*. [137] systematically reviewed the scientific evidence relating to the association between prenatal oral health care, reduced carriage of *Streptococcus mutans*, and early childhood caries prevention. The review authors included a single trial that delivered a complex intervention consisting of multiple intervention components delivered to both mothers and their children. The intervention, referred to as 'primary-primary prevention', involved four scheduled primary care appointments. The first visit (during pregnancy) involved a dental examination, individual preventive self-care OHI, instruction on avoiding microbe transmission, caries aetiology education, and referral for dental treatment if needed. The second visit (>8 months gestational age) involved education about infection related to maternal–child caries transmission. The third visit (postnatal visit when the child was aged 0–3 years) involved an oral exam for both mother and child, as well as OHI. The final visit (postnatal visit when the child was aged 3–4 years) involved children's OHI, primary teeth cleaning, and topical fluoride and CHX varnish application. The findings indicated very low-certainty evidence of a **significantly lower proportion of children with new caries and significantly lower dmfs scores in the children of mothers who received the primary-primary prevention intervention compared with mothers who received no intervention** at both 3 years and 5 years follow-up.

Table 32 Main review outcomes for complex combined interventions delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Xiao *et al.* (2019) [137]	Percentage of children with new caries: significantly lower for complex intervention compared with no intervention (1 trial) dmfs: significantly lower for complex intervention compared with no intervention (same trial)	Critically low	Very low	Percentage of children with new caries: no overlap dmfs: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.5.5.10 Complex interventions in primary dentition

We identified four systematic reviews that reported on the effectiveness of complex interventions that included three or more intervention components for caries prevention in primary dentition. Table 33 presents a high-level summary of treatment outcomes from the reviews that reported on these interventions.

Yu *et al*. [138] assessed whether the combined use of professional fluoride application and regular fluoride toothpaste has any additional benefit over using regular fluoride toothpaste alone for children aged under 16 years. The findings indicated moderate-certainty evidence from six pooled trials of **no significant difference in increment of d(e/m)fs following the combination of the application of fluoride varnish (5% NaF in five trials and 0.9% difluorosilane in one trial, applied every 6 months), the use of fluoride toothpaste (1000–1450 ppm), and the delivery of additional active intervention components (in five out of six trials)**. These included oral health education (OHE) and/or oral health counselling in five trials, dietary counselling in two trials, supervised toothbrushing in two trials, and usual care in one trial. The comparator groups in four out of five trials received all active intervention components except for the fluoride varnish, and in one trial, the comparator was usual care. The follow-up periods ranged from 2 to 3 years. There was no evidence from subgroup analyses to suggest that dentition type (primary or mixed dentition), caries risk at baseline, or the length of follow-up could affect the caries-preventive effect of the added use of fluoride varnish. It should be noted that, from the information provided in the review, at least two out of the six trials included in the Yu *et al*. review reported some other exposure to fluoride (in either water or milk). However, this was considered background fluoride exposure rather than part of the intervention of interest.

de Sousa *et al*. [130] assessed the effectiveness of fluoride varnish in reducing the risk of developing new dentine carious lesions in preschoolers. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the proportion of children developing new caries following the combination of the application of 5% NaF varnish every 6 months, the delivery of OHE, the provision of dietary counselling, and the use of 500 ppm fluoride toothpaste, compared with the no treatment group,** at 2 years follow-up. The findings from another single trial indicated very low-certainty evidence of **no significant difference in the proportion of children developing new caries following the combination of the application of 5% NaF varnish every 6 months, the delivery of oral health advice, the provision of dietary counselling, and the use of 1450 ppm fluoride toothpaste**, **compared with oral health advice alone,** at 3 years follow-up. Finally, the findings from a third single trial indicated very low-certainty evidence of **no significant difference in the increment of dmft following the combination of the application of 5% NaF varnish, the delivery of OHE, and the delivery of dietary counselling, compared with the combination of the use of a placebo water-based coloured solution, the delivery of OHE, and the delivery of dietary counselling,** at 2 years follow-up.

Chou *et al*. [48] investigated the effect of primary care oral screening and preventive interventions on preventing and arresting dental caries in children aged under 5 years. One of the pooled analyses included data from trials that delivered complex interventions. The findings from 13 pooled trials indicated very low-certainty evidence of a **significantly lower increment of dmfs/dmft following the application of topical fluoride together with additional active intervention components, compared with a placebo or no topical fluoride,** at 1–3 years follow-up. The type and concentration of fluoride varied greatly. Six trials used 5% NaF varnish, one trial used 1.23% APF foam, one trial used 0.9% difluorsilano varnish, one trial used 1.5% ammonium fluoride varnish, two trials used 50 mg/mL Duraphat toothpaste, one trial used 0.5 mL Profluorid varnish, and one trial used a 22,600 parts per litre fluoride varnish. The frequency of application was every 6 months in 11 trials, every 4 months in 1 trial, and every 3 months in 1 trial. Notably, 12 out of the 13 pooled trials delivered combined interventions, one-half of which involved three or more active intervention components delivered to the participating children and a parent or caregiver. The most common additional intervention components were parental OHE (eight trials), parental toothbrushing training/instruction (three trials), the provision of fluoride toothpaste and toothbrushes (four trials), and supervised toothbrushing (three trials).

dos Santos *et al*. [118] assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. The review included a single trial that reported on a complex intervention. The findings indicated very low-certainty evidence of a **significantly higher proportion of children remaining caries-free and a significantly lower increment of deft following an intervention consisting of 30-minute oral hygiene instruction sessions, practical demonstration and application of toothbrushing technique on 5 consecutive school days (which was repeated twice per year by a dental hygienist and a research assistant), and daily school-supervised toothbrushing by a research assistant with 500 ppm fluoride toothpaste. The comparison group received 30-minute oral hygiene instruction sessions on 5 consecutive school days, which was repeated twice per year by a dental hygienist and a research assistant**. At 4 years follow-up, the proportion of children who remained caries free in their primary teeth was 14.0% in the intervention group, compared with 9.4% in the control group.

Overall, the body of **evidence on the effectiveness of complex interventions for caries prevention in primary dentition is inconsistent**, likely due to the high variation in the intervention components included in the primary trials, the frequency of engagement in different intervention components, the dose/concentration of any chemicals used, and the outcomes measured, as well as due to the variation in the certainty of evidence. There was a high overlap and slight overlap of primary studies for the dmfs/defs

outcomes and dmft/deft outcomes, respectively. There was no overlap of primary studies for caries incidence.

Table 33 Main review outcomes for complex interventions in primary dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Yu *et al.* (2021) [138]	d(e/m)fs: no significant difference for the combined use of fluoride varnish, fluoride toothpaste, and delivery of additional active intervention components compared with various comparators (6 pooled trials)	Critically low	Moderate	
de Sousa *et al.* (2019) [130]	Percentage of children developing new caries: no significant difference for the combined use of fluoride varnish, delivery of OHE, delivery of dietary counselling, and 500 ppm fluoride toothpaste compared with no treatment (1 trial); no significant difference for the combined use of fluoride varnish, delivery of oral health advice, delivery of dietary counselling, and 1450 ppm fluoride toothpaste compared with oral health advice alone (1 trial) dmft: no significant difference for the combined use of fluoride varnish, delivery of OHE, and delivery of dietary counselling compared with the combination of a placebo water-based coloured solution, delivery of OHE, and delivery of dietary counselling (1 trial)	Critically low	Very low	
Chou *et al.* (2021) [48]	dmfs/dmft: significantly lower for topical fluoride together with additional active intervention components compared with placebo or no topical fluoride (13 pooled trials)	Critically low	Very low	
dos Santos *et al.* (2018) [118]	Percentage of children remaining caries free: significantly higher for complex intervention compared with oral health hygiene instruction alone (1 trial) deft: significantly lower for complex intervention compared with oral health hygiene instruction alone (1 trial)	Low	Very low	
				Caries incidence (percentage of children with caries or percentage

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				of children remaining caries free): no overlap dmft or deft: slight overlap dmfs or defs: high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6 Permanent dentition

4.6.1 Introduction

Forty-four systematic reviews reported on the permanent prevention of caries in permanent dentition: 2 reviews reported on the effectiveness of attendance for dental assessment, 3 reviews reported on the effectiveness of dental hygiene activities, 4 reviews reported on the effectiveness of systemic fluoride, 1 review reported on the effectiveness of other systemic chemicals, 9 reviews reported on the effectiveness of topical fluoride, 8 reviews reported on the effectiveness of other topical chemicals, 10 reviews reported on the effectiveness of sealants, and 1 review reported on the effectiveness of lasers. In addition, 24 reviews reported on the effectiveness of combined interventions for caries prevention in permanent dentition. In eight reviews, the findings were either not usable for the purposes of this overview of reviews or no primary studies on the intervention of interest were found. These reviews are identified throughout the results on permanent dentition where appropriate.

4.6.2 Methodological quality of reviews and their primary studies

We reported in Section 3.11 that we assigned seven critical domains in the adapted AMSTAR 2 quality assessment tool. The quality of the 44 included systematic reviews with respect to methodology varied, but was predominantly critically low (Appendix F).

Forty-one out of the 44 systematic reviews on permanent dentition did not establish any protocol prior to carrying out the review, and 18 of the reviews only partially established a protocol prior to review (item 2); however, 14 out of those 18 reviews were Cochrane reviews, and it is well established that Cochrane review authors are required to prepare a review protocol. As noted in Table 5, a 'partial yes' on this item in the adapted AMSTAR 2 instrument did not negatively affect quality assessment for Cochrane reviews. Twenty out of the 44 systematic reviews on permanent dentition received a 'yes' rating in relation to the comprehensiveness of the literature search (item 4) and 1 review received a 'partial yes' rating on this item. Twenty reviews did not provide a list of excluded studies and the reasons for exclusion (item 7). Five reviews either did not use a satisfactory technique for assessing the RoB in individual studies (item 9) or received a 'partial yes' rating on this item. Thirty-two reviews on permanent dentition did not use appropriate methods for the statistical combination of results from primary studies (item 11; this item was not applicable to the 11 reviews, leaving only 1 review on permanent dentition that received a 'yes' rating for this item). Nine out of the 44 systematic reviews did not take RoB into account when interpreting the findings (item 13). Finally, ten reviews on permanent dentition did not carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review (item 15; this item was not applicable to 27 reviews).

Overall, 2 out of the 44 systematic reviews on permanent dentition were judged to be of high quality, indicating that they had no critical or non-critical flaws. One out of the 44 reviews was judged to be of moderate quality, indicating that it had no critical flaws but did have at least one non-critical weakness. Fourteen out of the 44 systematic reviews were judged to be of low quality, indicating that they had one critical flaw; these reviews either did not establish a protocol prior to review, did not provide a list of excluded studies and their reasons for exclusion, or did not use appropriate methods for the statistical combination of result from primary studies. The remaining 27 reviews on permanent dentition were assessed as being of critically low quality, indicating that they had more than one critical flaw. The critical flaws for critically low-quality reviews varied, with the more common critical flaws being that the review authors did not establish a protocol prior to review, did not provide a list of excluded studies and their reasons for exclusion, did not use appropriate methods for the statistical combination of result from

primary studies, and did not carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review.

4.6.3 GRADE rating

The GRADE (or certainty) of evidence is presented alongside each of the outcomes in Section 4.6.5, and the number of downgrades applied and reasons for downgrading are presented in Appendix K. In permanent dentition, five reviews presented moderate-certainty evidence, as assessed using the modified GRADE algorithm. This indicates that we are moderately confident in the effect estimate; that is, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different [115]. The reasons for downgrading to moderate certainty of evidence were inadequate randomisation, inadequate blinding of outcome ascertainment, and quality rating on the adapted AMSTAR 2 instrument. Nineteen reviews presented low-certainty evidence, indicating that our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect [115]. The reasons for downgrading to low certainty of evidence included study design, inadequate randomisation, inadequate blinding of outcome ascertainment, high heterogeneity, and quality rating on the adapted AMSTAR 2 instrument. Twenty presented very low-certainty evidence, indicating that we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect [115]. The reasons for downgrading to very low-certainty of evidence included study design, inadequate randomisation, inadequate blinding of outcome ascertainment, high heterogeneity, inadequate sample size, and quality rating on the adapted AMSTAR 2 instrument.

Of note, outcomes within the same review could be graded at different levels of certainty. As a result, several reviews reported evidence at more than one level of certainty (i.e. outcomes of moderate-certainty and outcomes of very low-certainty could be reported in the same review). There were no reviews on permanent dentition without any downgrades, and therefore no reviews that presented high-certainty of evidence. It can be understood that reviews with moderate-certainty evidence had one to two inadequacies, whereas reviews with low-certainty evidence had three to four inadequacies and reviews with very low-certainty evidence had five or more inadequacies. Therefore, the GRADE score is used as a summary indicator of the certainty of evidence for the individual outcomes in each review. It is important to note that the GRADE score takes account of the methodological quality score of each systematic review and its primary studies.

Three reviews included in this overview of reviews were single-trial reviews, and so the certainty of evidence in these reviews was automatically downgraded to very low. Two of these reported on outcomes in permanent dentition. As mentioned in the previous paragraph, 5 out of the 44 systematic reviews on permanent dentition reported moderate-certainty evidence; 1 of these reviews presented moderate-certainty evidence from a single trial only and the remaining 4 reviews presented moderate-certainty evidence from 2 or more trials.

4.6.4 Classification of combined interventions

As mentioned in Section 3.8, we classified all systematic reviews according to the types of interventions being evaluated. Twenty-four reviews in total included trials that delivered combined interventions for caries prevention in permanent dentition (some reviews reported on the effects of more than one combined intervention). Based on the intervention components described in the systematic reviews, we classified and subclassified combined interventions for caries prevention in permanent dentition into those that involved:

- Topical fluoride combined with one other intervention component, either:

  - Another form of topical fluoride (four reviews)
  - A non-fluoride topical chemical (four reviews)
  - OHI or OHE (five reviews), or
  - An intervention component that is neither topical fluoride nor another non-fluoride topical chemical (eight reviews), including systemic fluoride (one review), professional prophylaxis (one review), laser (one review), and supervised toothbrushing or mouthrinsing (four reviews) (the results in one of the eight reviews were not usable).
- A non-fluoride topical chemical combined with one other intervention component (five reviews), including OHI (one review), systemic fluoride (one review), professional prophylaxis (one review), or several of these (two reviews)
- Sealants combined with one other intervention component (four reviews), including OHE (one review), laser (two reviews), or several combined interventions (one review), and
- Complex interventions that included three or more intervention components for caries prevention in permanent dentition (three reviews).

4.6.5 Results

4.6.5.1 Attendance for dental assessment

4.6.5.1.1 Scheduled dental appointments

We identified two systematic reviews that reported on the effects of scheduled dental appointments on the prevention of caries in permanent dentition. Table 34 presents a high-level summary of treatment outcomes for this intervention category.

Joury *et al*. [104] assessed the effectiveness of school-based dental screening compared with no screening on improving oral health in children. The results of only one trial were relevant to the purposes of this overview of reviews. However, it was not clear whether these results pertained to the initiation of new caries or the prevalence of existing caries, and so the findings were not extracted.

Fee *et al*. [47] investigated the **optimal recall interval of dental check-ups** (fixed-length, risk-based (decided by the clinician), or no recall/patient-driven attendance) for oral health in a primary care setting. **It was unclear from the evidence, which was of very low certainty and taken from a single trial, whether there was a significant difference in DMFS increment between a 24- and a 12-month recall period** at 2 years follow-up. The findings from another single trial indicated moderate-certainty evidence of **little to no difference in the number of permanent tooth surfaces with any caries between the 6-month and risk-based recall intervals** at 4 years follow-up. There was also moderate-certainty evidence from the same trial of **little to no difference in the number of permanent tooth surfaces with any caries when comparing a 24-month recall interval with either a 6-month or a risk-based recall interval** at 4 years follow-up. This trial did not compare the effect of a 24-month recall interval with a 12-month recall interval on caries incidence in permanent dentition.

Overall, there is a **paucity of evidence** pertaining to the caries-preventive effects of different recall intervals in permanent dentition. There was no overlap of primary studies across the two reviews for the included outcomes.

Table 34 Main review outcomes for scheduled dental appointments in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Joury *et al.* (2017) [104]	None usable	Critically low	N/A	
Fee *et al.* (2020) [47]	DMFS: unclear if there was a significant difference between a 24- and a 12-month recall period (1 trial) Permanent tooth surfaces with caries: little to no difference between 6-month and risk-based recall intervals and between 24-month and either 6-month or risk-based recall intervals (same trial)	High	Moderate	DMFS: no overlap Permanent tooth surfaces with caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.1.2 Scheduled primary care appointments

None of the included systematic reviews reported on the effectiveness of scheduled primary care appointments for caries prevention in permanent dentition.

4.6.5.2 Dental hygiene

4.6.5.2.1 Supervised toothbrushing

We identified two systematic reviews on the effectiveness of supervised toothbrushing for caries prevention in permanent dentition. Table 35 presents a high-level summary of treatment outcomes for this intervention category.

Hujoel *et al*. [116] evaluated the association between **personal oral hygiene (i.e. supervised toothbrushing**) and dental caries in the absence of the confounding effects of fluoride. The findings from three pooled trials indicated low-certainty evidence of **no significant difference in DMFS scores between the supervised oral hygiene and control groups** at 29–36 months follow-up. Oral hygiene was supervised daily in school in two of the pooled trials, and every 2 weeks in the third. The review authors noted that the findings were robust to sensitivity analyses, even when including the results of non-randomised studies.

dos Santos *et al*. [118] evaluated the effectiveness of supervised toothbrushing on caries incidence in children and adolescents. The findings from a single trial indicated very low-certainty evidence of **no significant difference in increment of DMFS or DMFT following an intervention involving daily school-based supervised toothbrushing with non-fluoride toothpaste compared with no intervention** at 21 months follow-up.

Overall, there is **low- and very low-certainty evidence indicating no caries-preventive benefit of supervised toothbrushing** without the addition of fluoride toothpaste or other preventive interventions in permanent dentition. The findings from reviews that described combined interventions involving supervised toothbrushing on permanent dentition are presented in Sections 4.6.5.5.9.3 and 4.5.5.6.94.6.5.9 on combined and complex interventions. There was no overlap of primary studies across the two reviews for the included outcomes.

Table 35 Main review outcomes for supervised toothbrushing in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Hujoel *et al.* (2018) [116]	DMFS: no significant difference for supervised oral hygiene compared with control group (3 pooled trials)	Critically low	Low	
dos Santos *et al.* (2018) [118]	DMFS: no significant difference for daily supervised toothbrushing compared with no intervention (1 trial) DMFT: no significant difference for daily supervised toothbrushing compared with no intervention (same trial)	Low	Very low	
				DMFS: no overlap DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.2.2 Flossing

None of the included systematic reviews reported on the effectiveness of flossing for caries prevention in permanent dentition.

4.6.5.2.3 Interdental cleaning devices

We identified one systematic review on the effectiveness of interdental cleaning devices for caries prevention in permanent dentition. Worthington *et al*. [30] evaluated the effectiveness of various types of interdental cleaning devices used at home in addition to toothbrushing, compared with toothbrushing alone, for preventing and controlling periodontal diseases, caries, and plaque. However, the review authors indicated that 51% of the included trials involved training or supervised instruction on using the device being evaluated, and that there was an insufficient number of trials in any one meta-analysis to make subgroup analyses meaningful. As the distinction between trials that involved training and those that did not was not made explicit in the review, the findings were excluded from our data synthesis.

As such, there is **a paucity of evidence** available to determine whether interdental cleaning devices can reduce the risk of caries incidence in permanent dentition.

4.6.5.2.4 Professional scaling or cleaning

None of the included systematic reviews reported on the effectiveness of professional cleaning or scaling for caries prevention in permanent dentition. Evidence on the effectiveness of combined interventions that involve professional scaling or cleaning of permanent teeth can be found in Sections 4.6.5.5.9.3 and 4.6.5.6.15.

4.6.5.3 Systemic fluoride

4.6.5.3.1 Milk

We identified two systematic reviews on the topic of fluoridated milk for caries prevention in permanent dentition. Yeung *et al*.'s [26] review of a single RCT evaluated the effect of milk fluoridation for caries prevention at a community level. The findings from this single trial indicated very low-certainty evidence of a **significantly lower increment of DMFT among children who consumed 180–200 mL of fluoridated milk per day (2.5 mg of fluoride per litre) using a 200 g cup compared with children in the non-fluoridated milk group** at 3 years follow-up.

Cagetti *et al*. [119] examined the effectiveness of fluoridated food (e.g. milk, salt, and sugar) in the prevention of caries. However, **none of the included trials** evaluated the caries-preventive benefit of only fluoridated milk in permanent dentition.

As such, there is **a paucity of evidence** available to determine the benefit of milk fluoridation for caries prevention in permanent dentition. There was no overlap of primary studies across the two reviews for the included outcomes. Table 36 presents a high-level summary of treatment outcomes for this intervention category.

Table 36 Main review outcomes for fluoridated milk in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Yeung *et al.* (2015) [26]	DMFT: significantly lower for fluoridated milk compared with non-fluoridated milk (1 trial)	High	Very low	
Cagetti *et al.* (2013) [119]	None usable	Critically low	N/A	
				DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%)

4.6.5.3.2 Salt

We identified one systematic review that aimed to evaluate the effectiveness of fluoridated salt for caries prevention in permanent dentition. This review was conducted by Cagetti *et al*. [119] and was described in the previous section. However, **none of the included trials** evaluated the use of this intervention.

As such, there is **a paucity of evidence** available to determine the benefit of salt fluoridation for caries prevention in permanent dentition.

4.6.5.3.3 Sugar

We identified one systematic review that evaluated the effectiveness of fluoridated sugar for caries prevention in permanent dentition. Table 37 presents a high-level summary of treatment outcomes from this review.

Cagetti *et al*. [119] presented findings from a single trial indicating very low-certainty evidence of a **significantly lower increment of DMFT among participants who consumed fluoridated sugar (10 ppm fluoride) compared with participants in the control group** at 18 months follow-up. In this trial, fluoridated sugar was used as an ingredient in tea and porridge.

Table 37 Main review outcomes for fluoridated sugar in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Cagetti *et al.* (2013) [119]	DMFT: significantly lower for fluoridated sugar compared with control group (1 trial)	Critically low	Very low	
				DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.3.4 Supplements

We identified two systematic reviews on the effectiveness of fluoride supplements for caries prevention in permanent dentition. Table 38 presents a high-level summary of treatment outcomes for this intervention category.

One of these reviews, conducted by Zhou *et al*. [103], investigated the efficacy of various strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. However, the effect of fluoride supplements was not possible to determine because the meta-analysis in Zhou *et al*.'s review was conducted to test the effectiveness of fluoride as 1 mg NaF [sodium fluoride] tablets **or** fluoride together with sodium bicarbonate and potassium dihydrogen phosphate.

Tubert-Jeannin *et al*. [111] evaluated the effectiveness of the administration of various types of fluoride supplements for caries prevention in children. There was low-certainty evidence from two separate pooled analyses showing **significantly higher DMFS (three pooled trials) and DMFT (three pooled trials) prevented fractions following the use of fluoride supplements compared with no supplements** at 2–3 years follow-up, resulting in a 24% and 29% reduced risk of developing caries as measured by DMFS and DMFT, respectively. In the pooled analysis on DMFS increment, two trials involved the use of fluoride tablets taken one to two times per day at school, and one involved the use of fluoride supplements diluted in a liquid resulting in a solution, which was swallowed once per day at school. The review authors noted that participants in two of the pooled trials that reported on DMFS had some other exposure to fluoride (via fluoridated water in one trial and an unspecified source of fluoride in the other trial) and participants in one of the trials that reported on DMFT had background exposure to an unspecified source of fluoride. However, this was considered background fluoride exposure rather than part of the intervention of interest. In one of these trials, the caries-preventive effect (measured via the DMFS index) of APF tablets (1 mg fluoride) administered once or twice per day remained significant at lengthier follow-up periods, resulting in a 25% and 28% reduced risk of developing caries at 55 months and 72 months follow-up, respectively. In the pooled analysis on DMFT increment, two trials involved the use of fluoride tablets taken once per day at school, and one involved the use of fluoride supplements diluted in a liquid resulting in a solution, which was swallowed once per day at school. The review authors noted that participants in one of the pooled trials had some other exposure to fluoride (via an unspecified source). However, this was considered background fluoride exposure rather than part of the intervention of interest.

The Tubert-Jeannin *et al*. review also reported low-certainty evidence from four pooled trials indicating **no significant difference in DMFS prevented fraction when the effectiveness of fluoride supplements was compared with that of topical fluoride mouth rinse** at 2–3 years follow-up. Two of these trials involved the use of fluoride tablets administered once per day at school, and two involved the use of fluoride lozenges administered either once per day or three to six times per day at school. The review authors noted that participants in three of the pooled trials had some other exposure to fluoride (via water and/or toothpaste). However, this was considered background fluoride exposure rather than part of the intervention of interest.

Overall, there is **low-certainty evidence of a caries-preventive effect of fluoride supplements when compared with no supplements**. However, this benefit may not persist over and above that of fluoride mouth rinse. There was no overlap of primary studies across the two reviews for the included outcomes.

Table 38 Main review outcomes for fluoride supplements in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	Certainty of evidence†	Overlap of primary studies‡
Zhou *et al.* (2019) [103]	None usable	Critically low	N/A	
Tubert-Jeannin *et al.* (2011) [111]	DMFS: significantly lower for fluoride supplements compared with no supplements (3 pooled trials); no significant difference for fluoride supplements compared with topical fluoride mouth rinse (4 pooled trials) DMFT: significantly lower for fluoride supplements compared with no supplements (3 pooled trials)	Low	Low	
				DMFS: no overlap DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.4 Other systemic chemicals

4.6.5.4.1 Vitamin D

None of the included systematic reviews reported on the effectiveness of vitamin D-based interventions for caries prevention in permanent dentition.

4.6.5.4.2 Calcium

None of the included systematic reviews reported on the effectiveness of calcium-based interventions for caries prevention in permanent dentition.

4.6.5.4.3 Sialagogues

We identified one systematic review on the effectiveness of sialagogues for caries prevention in permanent dentition. Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including sialagogues) on the market in the USA. However, **none of the included trials** evaluated the use of sialagogues (e.g. pilocarpine, cevimeline).

As such, there is **a paucity of evidence** available to determine the benefit of these agents for caries prevention in permanent dentition.

4.6.5.4.4 Zinc

None of the included systematic reviews reported on the effectiveness of zinc-based interventions for caries prevention in permanent dentition.

4.6.5.5 Topical fluoride

4.6.5.5.1 Toothpaste

We identified two systematic reviews on the effectiveness of fluoride toothpaste as a standalone intervention for caries prevention in permanent dentition.

Table 39 presents a high-level summary of treatment outcomes for this intervention category.

Walsh *et al*. [21] compared the effects of toothpastes of different fluoride concentrations for preventing dental caries in children, adolescents, and adults. The findings from two pooled trials indicated low-certainty evidence of **no significant difference in the proportion of children developing new caries in immature permanent dentition in the 250 ppm fluoride toothpaste group compared with children in the 0 ppm fluoride toothpaste group** at 2 years follow-up. It should be noted that in both trials, participants used fluoride mouth rinse and were exposed to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. The findings from seven pooled trials also indicated low-certainty evidence **of a lower (but not significantly lower) proportion of children developing new caries in immature permanent dentition in the 1000–1250 ppm fluoride toothpaste group compared with children in the 0 ppm fluoride toothpaste group** at 1–5 years follow-up. It should be noted that one of these pooled trials tested a combined intervention involving fluoride toothpaste and supervised toothbrushing. In addition, participants in at least six out of the seven pooled trials had additional exposure to fluoride (in water, mouth rinse, or salt; additional fluoride exposure was not reported on in the seventh trial). Again, however, this was considered background fluoride exposure rather than part of the intervention of interest. Finally, the findings from a single trial indicated low-certainty evidence of a **significantly lower proportion of children developing new caries in immature permanent dentition in the group that used 1450–1500 ppm fluoride toothpaste compared with the group that used 0 ppm fluoride toothpaste** at 3 years follow-up. Participants in this trial were exposed to fluoridated water, which again was considered background fluoride exposure rather than part of the intervention of interest. None of the included trials reported on the effect of fluoride concentration on the proportion of children developing new caries in mature permanent dentition.

Zhang *et al*. [139] synthesised the best available clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. The findings from a network meta-analysis of nine trials indicated low-certainty evidence of a **significant caries-preventive effect (as indicated by scores on both the Decayed Root (D-Root) and Decayed or Filled Root (DF-Root) indexes) following the daily use of 1100–1500 ppm fluoride toothpaste compared with a control** at 2 years follow-up. Daily use of 1100–1500 ppm fluoride toothpaste was one of three significant self-applied fluoride interventions out of a total of seven self-applied interventions examined in Zhang *et al*.'s review. It should be noted that, because trials involving five professionally applied and seven self-applied topical fluoride agents or combinations were included in the meta-analysis, not all of the nine pooled trials would have evaluated the effectiveness of daily use of 1100–1500 ppm fluoride toothpaste.

Overall, there is **some low-certainty evidence of a dose–response relationship in the caries-preventive effect of fluoride toothpaste in permanent dentition**, with the strength of the effect increasing with the concentration of fluoride in toothpastes. However, more trials are required to test higher-concentration fluoride toothpaste interventions as standalone interventions. There was no overlap of primary studies across the two reviews for the included outcomes. Evidence from the above two reviews and other

reviews on the effectiveness of combined interventions that involve the use of fluoride toothpaste on permanent teeth can be found in Section 4.6.5.5.9.

Table 39 Main review outcomes for fluoridated toothpaste in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Walsh *et al.* (2019) [21]	Percentage of children developing new caries: no significant difference for 250 ppm fluoride toothpaste compared with 0 ppm fluoride toothpaste (2 pooled trials); lower (but not significantly) for 1000–1250 ppm fluoride toothpaste compared with 0 ppm fluoride toothpaste (7 pooled trials); significantly lower for 1450–1500 ppm fluoride toothpaste compared with 0 ppm fluoride toothpaste (1 trial)	Low	Low	
Zhang *et al.* (2020) [139]	D-Root: significant caries-preventive effect for 1100–1500 ppm fluoride toothpaste compared with control (network meta-analysis of 9 trials) DF-Root: significant caries-preventive effect for 1100–1500 ppm fluoride toothpaste compared with control (same network meta-analysis of 9 trials)	Low	Low	
				Percentage of children developing new caries: no overlap D-Root: no overlap DF-Root: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.2 Mouth rinses

We identified two systematic reviews on the effectiveness of fluoride mouth rinse as a standalone intervention for caries prevention in permanent dentition. Table 40 presents a high-level summary of treatment outcomes for this intervention category.

The review by Zhang *et al*. [139], described in the previous section, reported findings from a network meta-analysis of nine trials indicating low-certainty evidence of **no significant caries-preventive effect (as indicated by scores on both the D-Root and DF-Root indexes) following the daily use of 0.05% NaF mouth rinse** compared with a control at 2 years follow-up. However, the findings did indicate low-certainty evidence of a **significant caries-preventive effect (as indicated by scores on both the D-Root and DF-Root indexes) following the daily use of 0.2% NaF mouth rinse compared with a control** at 2 years follow-up. Daily use of 0.2% NaF mouth rinse was one of three significant self-applied fluoride interventions out of a total of seven self-applied interventions examined in Zhang *et al*.'s review.

Wierichs and Meyer-Lueckel [140] evaluated the results of clinical studies investigating chemical agents to reduce initiation of root carious lesions or inactivate existing ones. The findings from four pooled trials indicated very low-certainty evidence of **significantly lower Decayed, Missing, and/or Filled Root Surfaces (DMFRS) scores (i.e. lower initiation of new root carious lesions) among participants who used NaF mouth rinse (225–900 ppm fluoride; frequency of use not reported) compared with those who used a placebo mouth rinse** at 2–3 years follow-up.

Overall, there is **low- and very low-certainty evidence from two reviews suggesting a root caries-preventive effect of NaF mouth rinse** compared with a control or placebo mouth rinse. There was also a very high overlap of primary studies in the two reviews for the included outcomes. Evidence on the effectiveness of combined interventions that involve the use of fluoride mouth rinse on permanent teeth can be found in Section 4.6.5.5.9.

Table 40 Main review outcomes for fluoride mouth rinse in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Zhang *et al.* (2020) [139]	D-Root: no significant preventive effect with 0.05% NaF mouth rinse compared with control (network meta-analysis of 9 trials); significant preventive effect with 0.2% NaF mouth rinse compared with control (network meta-analysis of 9 trials) DF-Root: no significant preventive effect with 0.05% NaF mouth rinse compared with control (network meta-analysis of 9 trials); significant preventive effect with 0.2% NaF mouth rinse compared with control (same network meta-analysis)	Low	Low	
Wierichs and Meyer-Lueckel (2015) [140]	DMFRS: significantly lower for NaF mouth rinse (225–900 ppm fluoride) compared with placebo mouth rinse (4 pooled trials)	Critically low	Very low	
				D-Root, DF-Root, or DMFRS: very high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.3 Foams

None of the included systematic reviews reported on the effectiveness of fluoride foams for caries prevention in permanent dentition.

4.6.5.5.4 Gels

We identified three systematic reviews on the effectiveness of fluoride gels for caries prevention in permanent dentition. Table 41 presents a high-level summary of treatment outcomes for this intervention category.

Marinho *et al*. [25] investigated the effectiveness and safety of fluoride gels in preventing dental caries in the child and adolescent population. The concentration of fluoride across all 28 trials included in this review ranged from 2425 ppm fluoride (stannous fluoride (SnF_2)) to 12500 ppm fluoride (amine fluoride (AmF) and NaF), with most trials using 12300 ppm fluoride APF gel concentration. The frequency of application was required to be at least once per year but varied greatly across the included trials. The findings from 25 pooled trials indicated low-certainty evidence of a **significantly lower increment of DMFS among participants in the fluoride gel group compared with the placebo/no treatment control group** at 3 years follow-up, resulting in a 28% reduced risk of developing caries in the intervention group. It should be noted that 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, Marinho *et al*. 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 participant exposure to additional forms of fluoride (via 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 1 out of the 25 pooled trials tested the effectiveness of a combined intervention involving OHI together with supervised toothbrushing with fluoridated toothpaste. One of the trials included in the above meta-analysis of 25 trials also reported low-certainty evidence that **when comparing two fluoride gel groups (2425 ppm SnF_2 and 4500 ppm NaF) with the placebo group, there was a significantly lower proportion of children developing one or more new caries in permanent tooth surfaces and a significantly lower change in the proportion of participants not remaining caries free on permanent tooth surfaces** at 1.5 years and 3.0 years follow-up. It should be noted that these latter two outcomes were identified as secondary outcomes in the review. It should also be noted that participants in the trial had access to fluoride toothpaste. However, this was considered background fluoride exposure rather than part of the intervention of interest.

Marinho *et al*.'s review also reported findings from 10 pooled trials indicating low-certainty evidence of a **significantly lower increment of DMFT among participants in the fluoride gel groups compared with the placebo/no treatment control groups** at 3 years follow-up, resulting in a 32% reduced risk of developing caries in the intervention groups. It should be noted that 9 of the 10 pooled trials reported the performance of some form of prior (professional or self-performed) tooth prophylaxis before administering the gel. 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.

The network meta-analysis of nine trials conducted by Zhang *et al*. [139], describe in the previous section, indicated low-certainty evidence of a **significant caries-preventive effect (as indicated by scores on both the D-Root and DF-Root indexes) following the semi-annual professional application of 1.2% APF gel compared with a control** at 2 years follow-up.

Chan *et al*. [141] evaluated the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years and over. The findings from a single trial indicated very low-certainty evidence of a **significant root caries-preventive effect among community-dwelling older adults following semi-annual application of 1.23% APF gel compared with application of a placebo gel** at 2 years follow-up, resulting in a 32% reduced risk of developing new root caries among participants in the intervention group.

Overall, there is **low- and very low-certainty evidence of a strong caries-preventive effect associated with the application of fluoride gel** compared with a placebo or no treatment. There was no overlap of primary studies across the three reviews for the included outcomes. Evidence on the effectiveness of

combined interventions that involve the use of fluoride gel on permanent teeth can be found in Section 4.6.5.5.9.

Table 41 Main review outcomes for fluoride gels in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Marinho *et al.* (2015) [25]	DMFS: significantly lower for fluoride gel groups compared with placebo/no treatment control group (25 pooled trials) DMFT: significantly lower for fluoride gel groups compared with placebo/no treatment control group (10 pooled trials) Percentage developing new caries: significantly lower for two fluoride gel groups (2425 ppm SnF_2 and 4500 ppm NaF) compared with placebo group (1 trial) Percentage not remaining caries free: significantly lower change for two fluoride gel groups (2425 ppm SnF_2 and 4500 ppm NaF) compared with placebo group (1 trial)	Low	Low	
Zhang *et al.* (2020) [139]	D-Root: significant caries-preventive effect for 1.2% APF gel compared with control (network meta-analysis of 9 trials) DF-Root: significant caries-preventive effect for 1.2% APF gel compared with control (same network meta-analysis)	Low	Low	
Chan *et al.* (2022) [141]	Root caries: significant root caries-preventive effect for 1.23% APF gel compared with placebo gel (1 trial)	Critically low	Very low	
				DMFS: no overlap DMFT: no overlap

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				Percentage developing new caries, or not remaining caries free: no overlap D-Root or DF-Root: no overlap Root caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.5 Solutions

We identified four systematic reviews that evaluated the effectiveness of fluoride-based solutions for caries prevention in permanent dentition. Table 42 presents a high-level summary of treatment outcomes for this intervention category.

Grandjean *et al*. [142] evaluated the effectiveness of SDF in preventing and arresting root carious lesions in elders. The findings from three pooled trials indicated low-certainty evidence of a **significantly lower mean number of new root carious surfaces among older adults following the use of SDF compared with a control** at 24 months follow-up. The concentration of fluoride and frequency of use was not reported. The results remained significant at 30–36 months follow-up (two pooled trials).

The review by Zhang *et al*. [139], described previously, presented findings from a network meta-analysis of nine trials indicating low-certainty evidence of a **significant caries-preventive effect (as indicated by scores on both the D-Root and DF-Root indexes) following both the annual professional application of 38% SDF solution and the annual application of 38% SDF solution followed by potassium iodide** (to prevent discolouration), compared with a control, at 2 years follow-up.

Subbiah and Gopinathan [143] evaluated the effectiveness of SDF in preventing and arresting caries in elderly adults. The findings from a single trial indicated moderate-certainty evidence of **significantly lower DMFRS scores following the use of 38% SDF every 12 months compared with a control, with the use of CHX, or with the use of fluoride varnish** at 3 years follow-up, resulting in a 71%, 57%, and 64% reduced risk of developing new caries when the use of SDF was compared with a control, CHX, and fluoride varnish, respectively. The findings from another single trial also indicated moderate-certainty evidence of **significantly lower DMFRS scores among participants in the 38% SDF group compared with those in the control group** at 24 months follow-up. It should be noted, however, that limited information pertaining to the standalone intervention component of this particular trial was available in the systematic review.

The review by Chan *et al*. [141], described previously, presented findings from three pooled trials indicating low-certainty evidence of a **significantly lower mean number of new root carious lesions following the annual application of 38% SDF compared with a control** among samples of community-dwelling and institutionalised older adults at 2 years follow-up. The risk of developing new root caries among community-dwelling older adults was reduced by 25–47% and 52–62% at 24 and 30 months follow-up, respectively. In institutionalised older adults, the risk of developing new root caries was reduced by 71% at 3 years follow-up. In addition, the application of SDF with or without potassium iodide application showed no statistically significant differences in the prevention of root caries.

Overall, there is **moderate- and low-certainty evidence of a significant root caries-preventive effect associated with the application of 38% SDF among older adults**. There was a complete overlap and high overlap of primary studies in relation to the outcomes of mean number of new root carious lesions/surfaces and D-Root/DF-Root/DMFRS scores, respectively. Evidence from three of these four reviews, as well as other reviews, on the effectiveness of combined interventions that involve the use of fluoride-based solutions on permanent teeth can be found in Section 4.6.5.5.9.

Table 42 Main review outcomes for fluoride solutions in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Grandjean *et al.* (2021) [142]	Mean number of new root carious surfaces: significantly lower for SDF compared with a control (3 pooled trials)	Critically low	Low	
Zhang *et al.* (2020) [139]	D-Root: significant preventive effect for both 38% SDF solution and 38% SDF solution together with potassium iodide compared with control (network meta-analysis of 9 trials) DF-Root: significant preventive effect for both 38% SDF solution and 38% SDF solution together with potassium iodide compared with control (same network meta-analysis)	Low	Low	
Subbiah and Gopinathan (2018) [143]	DMFRS: significantly lower for 38% SDF compared with a control, with CHX, and with fluoride varnish (1 trial); significantly lower for 38% SDF compared with control group (1 trial)	Critically low	Moderate	
Chan *et al.* (2022) [141]	Mean number of new root carious lesions: significantly lower for 38% SDF compared with a control (3 pooled trials)	Critically low	Low	
				Mean number of new root carious lesions or surfaces: complete overlap D-Root, DF-Root, or DMFRS: high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.6 Slow-release fluoride devices

We identified one systematic review on the effectiveness of slow-release fluoride devices for caries prevention in permanent dentition. Table 43 presents a high-level summary of treatment outcomes from this review.

Chong *et al*. [49], in a single-trial review, 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. The findings indicated very low-certainty evidence of a **significantly lower increment of both DMFS and DMFT following the use of a slow-release fluoride device (glass beads with fluoride) compared with a control (glass beads without fluoride)** among children from disadvantaged backgrounds.

Although there is very low-certainty evidence from one trial indicating a caries-preventive benefit associated with the use of slow-release fluoride devices, there is **a paucity of evidence available to make a conclusive determination as to the effectiveness of this intervention**.

Table 43 Main review outcomes for slow-release fluoride devices in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Chong *et al.* (2018) [49]	DMFS: significantly lower for slow-release fluoride device compared with a control (1 trial) DMFT: significantly lower for slow-release fluoride device compared with a control (same trial)	Moderate	Very low	DMFS: no overlap DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.7 Varnishes

We identified four systematic reviews on the effectiveness of fluoride varnishes for caries prevention in permanent dentition. Table 44 presents a high-level summary of treatment outcomes for this intervention category.

Marinho *et al*. [108] evaluated the effectiveness and safety of fluoride varnishes in preventing dental caries in child and adolescent populations. The concentration of fluoride in the varnish in most of the trials included in the review was 22600 ppm fluoride. The findings from 13 pooled trials indicated low-certainty evidence of a **significantly lower increment of DMFS following the application of fluoride varnish at least once per year compared with placebo varnish or no treatment** at nearest to 3 years follow-up, resulting in a 43% reduction in DMFS increment among participants in the intervention group.

The findings are presented here in standalone fluoride varnish interventions because most of the pooled trials did not involve combined interventions. However, it should be noted that 5 out of the 13 pooled trials delivered combined interventions involving supervised mouthrinsing (2 trials) or OHE/OHI (3 trials), and 1 trial delivered a complex intervention involving the combination of supervised toothbrushing, OHI, and dietary advice. It should also be noted that 5 out of the 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 (via water, mouth rinses, toothpaste, milk, or an unspecified source). However, this was considered background exposure rather than part of the intervention of interest.

Similarly, the findings from five pooled trials indicated low-certainty evidence of a **significantly lower increment of DMFT following the application of fluoride varnish at least once per year compared with placebo varnish or no treatment** at nearest to 3 years follow-up, resulting in a 44% reduction in the increment of DMFT among participants in the intervention group. The findings are presented here in standalone fluoride varnish interventions because most of the pooled trials did not involve combined interventions. However, it should be noted that two out of the 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 (via water, mouth rinses, toothpaste, or an unspecified source). However, this was considered background exposure rather than part of the intervention of interest. It should also be noted that one out of the five pooled trials delivered combined interventions involving OHI, and one trial delivered a complex intervention involving the combination of supervised toothbrushing, OHI, and dietary advice.

The Marinho *et al*. review also presented low-certainty evidence from five pooled trials of **no significant difference in the proportion of children developing one or more new caries on permanent teeth between the fluoride varnish group (applied at least once per year) and the placebo/no treatment control group**. The precise follow-up period for this analysis was not specified. It should be noted that this outcome was identified as a secondary outcome in the review. It should also be noted that one out of the five included pooled trials reported some form of non-fluoride tooth prophylaxis prior to the administration of varnish, and all five pooled trials reported some existing exposure to fluoride (via water, mouth rinses, toothpaste, or milk). However, this was considered background exposure rather than part of the intervention of interest. In addition, one out of the five pooled trials on this outcome delivered a combined intervention involving oral health counselling.

Zhang *et al*.'s review [139], which has been described previously, presented findings from a network meta-analysis of nine trials indicating low-certainty evidence of a **significant caries-preventive effect (as indicated by scores on both the D-Root and DF-Root indexes) following the quarterly professional application of 5% NaF varnish** compared with a control at 2 years follow-up.

Wierichs and Meyer-Lueckel [140] evaluated the results of clinical studies investigating the efficacy of chemical agents in reducing the initiation of root carious lesions or inactivating existing ones. The findings from two pooled trials indicated very low-certainty evidence of **significantly lower DMFRS scores (i.e. lower initiation of new root carious lesions) among participants who received professionally applied 38% SDF varnish (frequency of application not reported) compared with the application of a placebo varnish** at 2–3 years follow-up.

The review by Chan *et al*. [141], described previously, presented findings from a single trial indicating very low-certainty evidence of a **significantly lower mean number of teeth with coronal caries following the semi-annual application of 5% NaF varnish compared with no treatment** among a sample of institutionalised older adults at 12 months follow-up. The risk of developing new root caries was reduced by 15 times in the intervention group. The findings from a second single trial indicated very low-certainty

evidence of a **significantly higher root caries preventive fraction following the application of 5% NaF varnish every 3 months compared with water** at 3 years follow-up. The risk of developing root caries was 64% lower in the intervention group. The duration of treatment was not reported in the review.

Overall, while there is some inconsistency in the findings related to the caries-preventive effect of fluoride varnish in permanent teeth, **most of the low- and very low-certainty evidence on this topic indicates that the application of fluoride varnish is an effective means by which to prevent caries** in permanent dentition. There was a very high overlap of primary studies for the D-Root/DF-Root/DMFRS outcomes, but no overlap for other included outcomes. Evidence from reviews on the effectiveness of combined interventions that involve the use of fluoride varnish on permanent teeth can be found in Section 4.6.5.5.9.

Table 44 Main review outcomes for fluoride varnishes in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Marinho *et al.* (2013) [108]	DMFS: significantly lower for fluoride varnish compared with placebo varnish or no treatment (13 pooled trials) DMFT: significantly lower for fluoride varnish compared with placebo varnish or no treatment (5 pooled trials) Percentage of children developing new caries: no significant difference for fluoride varnish compared with placebo/no treatment control group (5 pooled trials)	Low	Low	
Zhang *et al.* (2020) [139]	D-Root: significant preventive effect for 5% NaF varnish compared with control (network meta-analysis of 9 trials) DF-Root: significant preventive effect for 5% NaF varnish compared with control (same network meta-analysis)	Low	Low	
Wierichs and Meyer-Lueckel (2015) [140]	DMFRS: significantly lower for 38% SDF varnish compared with placebo varnish (2 pooled trials)	Critically low	Very low	
Chan *et al.* (2022) [141]	Mean number of teeth with coronal caries: significantly lower for 5% NaF varnish compared with no treatment (1 trial) Root caries: significantly lower for 5% NaF varnish compared with water (1 trial)	Critically low	Very low	
				DMFS: no overlap DMFT: no overlap

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				Percentage developing new caries: no overlap D-Root, DF-Root, or DMFRS: very high overlap Mean number of teeth with coronal caries: no overlap Root caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.8 Mixed forms of topical fluoride

None of the included systematic reviews pooled findings on various forms of topical fluoride as standalone interventions for caries prevention in permanent dentition. Evidence from reviews on the effectiveness of combined interventions that involve the use of mixed types of topical fluoride on permanent teeth can be found in Section 4.6.5.5.9.

4.6.5.5.9 Combined interventions involving topical fluoride

4.6.5.5.9.1 Topical fluoride together with another topical fluoride

We identified four systematic reviews that reported on the effectiveness of a combined intervention involving two topical fluoride intervention components for caries prevention in permanent dentition. Table 45 presents a high-level summary of treatment outcomes from the reviews that reported on these interventions.

Yu *et al*. [138] assessed whether the use of professional fluoride application in combination with the use of regular fluoride toothpaste has an additional benefit compared with the use of regular fluoride toothpaste alone for children aged under 16 years. However, **none of the included trials** evaluated the use of a combined topical fluoride intervention for caries prevention in permanent dentition. Evidence from this review can be found in Section 4.7.5.10 on complex interventions in mixed dentition.

Zhang *et al*. [139] synthesised the best available clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. The findings from a network meta-analysis of nine trials indicated low-certainty evidence of **no significant difference in root caries prevention (as indicated by scores on both the D-Root and DF-Root indexes) following the combined daily self-application of 1100–1500 ppm fluoride toothpaste together with an amine fluoride (AmF)/SnF_2 mouth rinse (250 ppm fluoride) compared with a control** at 2 years follow-up. Alternatively, the findings from the same analysis did indicate low-certainty evidence of a **significant difference in root caries prevention (as indicated by scores on both the D-Root and DF-Root indexes) following the combined daily use of 1100–1500 ppm fluoride toothpaste and 0.05% NaF mouth rinse (250 ppm fluoride) compared with a control** at 2 years follow-up. Combined use of fluoride toothpaste and fluoride mouth rinse was one of three significant self-applied fluoride interventions out of a total of seven self-applied interventions in Zhang *et al*.'s review.

Wierichs and Meyer-Lueckel [140] evaluated the results of clinical studies investigating the use of chemical agents to reduce initiation of root carious lesions or inactivate existing ones. The findings from two pooled trials indicated very low-certainty evidence of **no significant difference in the initiation of new root carious lesions (measured by change in DMFRS in one trial and by change in RCI in the other trial) between the intervention group that used a combination of AmF/SnF_2-containing toothpaste (1400 ppm fluoride) together with AmF/SnF_2 mouth rinse (250 ppm fluoride), and the control group that used a combination of NaF-containing toothpaste (1400 ppm fluoride) and NaF mouth rinse (250 ppm fluoride),** at both 5 months and 2 years follow-up.

Chan *et al*. [141] evaluated the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years and over. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the mean number of new root carious lesions between the group that received an annual combined application of 5% NaF varnish together with 38% SDF compared with a control** in a sample of institutionalised older adults at 3 years follow-up.

Overall, the **low- and very low-certainty evidence on the effectiveness of using a combination of different types of topical fluoride treatments for caries prevention in permanent dentition is inconsistent**. However, it appears that fluoride toothpaste combined with NaF mouth rinse may be

effective for caries prevention, whereas fluoride toothpaste combined with AmF/SnF_2 mouth rinse may not. Very low-certainty evidence taken from a single trial indicated **no significant caries-preventive effect of applying fluoride varnish in combination with a fluoride solution**. There was no overlap of primary studies across the four reviews for the included outcomes.

Table 45 Main review outcomes for multiple types of combined topical fluoride interventions in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Yu *et al.* (2021) [138]	None reported	Critically low	N/A	
Zhang *et al.* (2020) [139]	D-Root: no significant preventive effect for 1100–1500 ppm fluoride toothpaste together with AmF/SnF_2 mouth rinse compared with a control (network meta-analysis of 9 trials); significant difference in preventive effect for 1100–1500 ppm fluoride toothpaste together with 0.05% NaF mouth rinse compared with a control (network meta-analysis of 9 trials) DF-Root: no significant preventive effect for 1100–1500 ppm fluoride toothpaste together with AmF/SnF_2 mouth rinse compared with a control (network meta-analysis of 9 trials); significant difference in preventive effect for 1100–1500 ppm fluoride toothpaste together with 0.05% NaF mouth rinse compared with a control (same network meta-analysis)	Low	Low	
Wierichs and Meyer-Lueckel (2015) [140]	DMFRS: no significant difference for AmF/SnF_2-containing toothpaste together with AmF/SnF_2 mouth rinse compared with control group (1/2 pooled trials)§ RCI: no significant difference for AmF/SnF_2-containing toothpaste together with AmF/SnF_2 mouth rinse compared with control group (1/2 pooled trials)§	Critically low	Very low	
Chan *et al.* (2022) [141]	Mean number of new root carious lesions: no significant difference for 5% NaF varnish together with 38% SDF compared with a control (2 pooled trials)	Critically low	Very low	
				D-Root, DF-Root, DMFRS, or RCI: no overlap

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				Mean number of new root carious lesions: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

§Due to pooling, all trials were included in the overlap for all outcomes.

4.6.5.5.9.2 Topical fluoride together with other topical chemicals

We identified four systematic reviews that reported on the effectiveness of combined interventions involving topical fluoride and any other topical chemical for caries prevention in permanent dentition. Table 46 presents a high-level summary of treatment outcomes from the reviews that reported on these interventions.

Gupta *et al*. [128] compared the effectiveness of the combined use of topical fluoride and povidone-iodine with topical fluoride alone for the prevention of dental caries among children aged 1–12 years. However, the results from the relevant trial on the combined effect of topical fluoride together with povidone-iodine on the initiation of new carious lesions in permanent dentition could not be used in our review, as data from a retrospective cohort study was included in the pooled analysis.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including sialagogues) on the market in the USA. The findings from a single trial indicated very low-certainty evidence of a **significantly lower increment of DMFS following the combined use of dicalcium phosphate dihydrate together with 0.243% NaF toothpaste (twice daily), compared with the use of 0.243% NaF toothpaste only,** at 2 years follow-up. The review authors reported that participants in this trial were exposed to low levels of fluoride in community water. However, this was considered background fluoride exposure rather than part of the intervention of interest. The findings from a second trial indicated very low-certainty evidence of **no significant difference in increment of RCI following the initial application of 5% CHX gel followed by daily use of 1% CHX gel together with 0.1% NaF gel, compared with the application of 0.1% NaF gel alone,** at 18 months follow-up.

Singal *et al*. [9] reviewed the evidence for the remineralising and caries-preventive efficacy of various calcium phosphate derivatives. The findings from a single trial indicated very low-certainty evidence of **no significant difference in DMFS or DMFT scores following the combined use of CPP-ACP paste together with fluoride toothpaste (concentration of chemicals and frequency of use were not specified) compared with the use of fluoride toothpaste alone**. It should be noted that the review authors provided limited information pertaining to the primary trial, including information pertaining to the follow-up period.

Riley *et al*. [133] evaluated the effects of different xylitol-containing products on preventing dental caries in children and adults. The findings from two pooled trials indicated moderate-certainty evidence of a **significantly lower increment of DFS following the combined use of fluoride toothpaste containing 10% xylitol (twice daily brushing) compared with a control** at 30–36 months follow-up, resulting in a 13% reduced risk of developing caries. In one trial, participants used 0.243% NaF toothpaste (1100 ppm fluoride), and in the other, participants used 0.836% sodium monofluorophosphate toothpaste (1100 ppm fluoride). It should be noted that in both trials, participants had some exposure to fluoride (via low-fluoride water and/or fluoridated salt). However, this was considered background fluoride exposure rather than part of the intervention of interest.

Overall, the **very low-certainty evidence on the effectiveness of fluoride toothpaste combined with calcium phosphate agents is inconsistent**. However, the trials that involved these combined interventions tested different forms of calcium phosphate (dicalcium phosphate dihydrate in toothpaste and CPP-ACP paste). Regarding the combined use of **fluoride and xylitol in toothpaste, there is moderate-certainty evidence from two pooled trials of a caries-preventive effect**. When the use of **fluoride gel is combined with CHX gel, there is very low-certainty evidence of no caries-preventive effect**. However, this evidence is drawn from only a single trial. There was no overlap of primary studies across the four reviews for the included outcomes.

Table 46 Main review outcomes for topical fluoride combined with other topical chemicals in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Gupta *et al.* (2020) [128]	None usable	Critically low	N/A	
Rethman *et al.* (2011) [121]	DMFS: significantly lower for dicalcium phosphate dihydrate together with 0.243% NaF toothpaste compared with 0.243% NaF toothpaste only (1 trial) RCI: no significant difference for 5% CHX gel followed by daily 1% CHX gel together with 0.1% NaF gel compared with 0.1% NaF gel alone (1 trial)	Critically low	Very low	
Singal *et al.* (2022) [9]	DMFS: no significant difference for CPP-ACP paste together with fluoride toothpaste compared with fluoride toothpaste alone (1 trial) DMFT: no significant difference for CPP-ACP paste together with fluoride toothpaste compared with fluoride toothpaste alone (same trial)	Critically low	Very low	
Riley *et al.* (2015) [133]	DFS: significantly lower for fluoride toothpaste containing 10% xylitol compared with a control (2 pooled trials)	Low	Moderate	
				DMFS or DFS: no overlap DMFT: no overlap RCI: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.9.3 Topical fluoride together with other interventions

We identified eight systematic reviews that evaluated the effectiveness of some form of topical fluoride plus an additional active intervention component besides topical fluoride and other topical chemicals for caries prevention in permanent dentition. Table 47 presents a high-level summary of treatment outcomes from reviews that reported on these interventions.

Konradsson *et al*. [105] examined the scientific evidence for the efficacy of stabilised SnF_2 dentifrice in relation to dental caries, dental erosion, and dentine hypersensitivity when compared with standard fluoride dentifrices in patients with, or at risk of, these three dental conditions. Konradsson *et al*. noted that two independent examiners examined the outcomes of interest. However, the results varied greatly between the examiners, and the findings of one examiner appear to be excluded from a table in their review for one intervention arm. Therefore, the findings from this review were excluded from our data synthesis. For completeness, we extracted the data reported in the review, which can be found in the extraction file in Appendix H.

Zhang *et al*. [139] synthesised the best available clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. The findings from a network meta-analysis of nine trials indicated low-certainty evidence of **no significant caries-preventive effect (as indicated by scores on both the D-Root and DF-Root indexes) associated with the daily use of 1100–1500 ppm fluoride toothpaste together with systemic fluoride (consumption of 1.66 mg NaF tablets) compared with a control** at 2 years follow-up.

dos Santos *et al*. [118] evaluated the effects of supervised toothbrushing on caries incidence in children and adolescents. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the cumulative survival rate of occlusal first permanent molar surfaces with no caries between the intervention group (who received daily supervised toothbrushing using 1000 ppm fluoride toothpaste) compared with the control group who received no intervention** at 3 years follow-up. It should be noted that, in the review, there was no information pertaining to the number of participants included in the trial. It should also be noted that, while participants in the control group did not receive the intervention, they did receive an oral hygiene kit containing a toothbrush, 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*. [21] compared the effectiveness of toothpastes of different fluoride concentrations for preventing dental caries in children, adolescents, and adults. The findings from two pooled trials indicated low-certainty evidence of **no significant difference in the proportion of children developing new caries following the combined use of higher-fluoride toothpaste (1450–1500 ppm fluoride) together with supervised toothbrushing compared with the combined use of lower-fluoride toothpaste (1000–1200 ppm fluoride) together with supervised toothbrushing** at 3 years follow-up. Walsh *et al*. 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.

Marinho *et al*. [109] evaluated the combined effect of the use of fluoride mouth rinse and school-based supervised rinsing. The findings from 35 pooled trials indicated low-certainty evidence of **a large caries-preventive benefit (lower DMFS scores) associated with the use of fluoride mouth rinse under supervised conditions as part of school-based mouthrinsing programmes compared with placebo/no treatment** at nearest to 3 years follow-up, resulting in a DMFS prevented fraction of 27%. It should be noted that in 15 out of the 35 pooled trials, participants were reported to have exposure to fluoride (via water, toothpaste, varnish, tablets, or unspecified systemic fluoride sources). However, this was considered background fluoride exposure rather than part of the intervention of interest. In addition, 1 out of the 35 pooled trials involved the delivery of a complex intervention in which participants in both

groups received OHI and professional prophylaxis in addition to the supervised use of fluoride mouth rinse. In addition, the findings from 13 pooled trials indicated low-certainty evidence of a moderate to large **caries-preventive benefit (lower DMFT scores) associated with the use of fluoride mouth rinse under supervised conditions compared with placebo/no treatment** at nearest to 3 years follow-up, resulting in a DMFT prevented fraction of 23%. It should be noted that in 1 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. Across all trials in both pooled analyses, the frequency of supervision of mouth rinse use varied from daily to fortnightly, and the concentration of fluoride in mouth rinse was primarily either 230 ppm or 900 ppm fluoride. Finally, the findings from three pooled trials indicated low-certainty evidence of **no significant difference in the proportion of children who developed one or more new caries on permanent teeth between the supervised fluoride mouth rinse intervention groups and the placebo/no treatment control groups** at 2–3 years follow-up. It should be noted that this particular outcome was identified as a secondary outcome in the review. It should also be noted that 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.

Pagano *et al*. [135] evaluated whether the use of lasers at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries, improved fluoride uptake, and retention of sealant materials by improving traditional etching procedures. The findings from a single trial indicated very low-certainty evidence of a **significantly lower number of cases with new caries following the combined use of 1.23% APF gel (frequency of use was not reported) and Nd:YAG laser compared with the use of fluoride gel alone** at 1 year follow-up.

Riggs *et al*. [110] 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 until they were aged 6 years). The findings from two pooled trials indicated low-certainty evidence of a **significantly lower increment of DMFS following the combined use of iodine-NaF solution (six applications in one trial and three applications in the other) together with professional prophylaxis at baseline and at follow-up (at 6 months and 1 year) compared with a placebo** at 1–3 years follow-up. It should be noted that this outcome was identified as a secondary outcome in the review. It should also be noted that one of these pooled trials involved the delivery of a complex intervention in which the participants received OHE at baseline and at follow-up.

Akera *et al*. [117] evaluated the effectiveness of school-based interventions, including the application of sealants, in improving oral health compared with no intervention or usual practice among primary school children in low- and middle-income countries. The findings from a single trial indicated very low-certainty evidence of a **significantly lower net increment of DMFT among participants in the intervention group (who received daily supervised toothbrushing with 0.3 mL of fluoride toothpaste (1450 ppm fluoride)) compared with a control group**. The precise follow-up period was not specified but appeared to be at least 2 years. Conversely, there was **no significant difference in DMFT scores** between the intervention and control groups in the same trial.

Overall, four reviews presented **low- and very low-certainty evidence related to the use of topical fluoride (toothpaste or mouth rinse) under supervised conditions, with inconsistent findings**. The use of **fluoride mouth rinse under supervised conditions appeared to have a significant effect on the increment of DMFT and DMFS, but not on the proportion of participants who developed new caries**. There was **very low-certainty evidence of a caries-preventive effect of the combined use of fluoride gel and laser**. However, this evidence came from a single trial. There was low-certainty evidence of **no caries-preventive effect of the combined use of fluoride toothpaste and consumption of fluoride tablets**.

There was low-certainty evidence of a **caries-preventive benefit associated with the use of a fluoride-based solution in combination with professional prophylaxis**. There was no overlap of primary studies for any of the included outcomes.

Table 47 Main review outcomes for topical fluoride combined with other intervention components in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Konradsson *et al.* (2020) [105]	None usable	Critically low	N/A	
Zhang *et al.* (2020) [139]	D-Root: no significant preventive effect for 1100–1500 ppm fluoride toothpaste together with systemic fluoride (1.66 mg NaF tablets) compared with a control (network meta-analysis of 9 trials) DF-Root: no significant preventive effect for 1100–1500 ppm fluoride toothpaste together with systemic fluoride (1.66 mg NaF tablets) compared with a control (same network meta-analysis)	Low	Low	
dos Santos *et al.* (2018) [118]	Cumulative survival rate of tooth surfaces: no significant difference for supervised toothbrushing using 1000 ppm fluoride toothpaste compared with no intervention group (1 trial)	Low	Very low	
Walsh *et al.* (2019) [21]	Percentage of children developing new caries: no significant difference for higher-fluoride (1450–1500 ppm) toothpaste together with supervised toothbrushing compared with lower-fluoride (1000–1200 ppm) toothpaste together with supervised toothbrushing (2 pooled trials)	Low	Low	
Marinho *et al.* (2016) [109]	DMFS: large caries-preventive benefit for supervised use of fluoride mouth rinse compared with placebo/no treatment (35 pooled trials) DMFT: moderate to large caries-preventive benefit for supervised use of fluoride mouth rinse compared with placebo/no treatment (13 pooled trials)	Low	Low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
	Percentage of children developing new caries: no significant difference for supervised use of fluoride mouth rinse compared with placebo/no treatment control groups (3 pooled trials)			
Pagano *et al.* (2020) [135]	Percentage with new caries: significantly lower for 1.23% APF gel together with Nd:YAG laser compared with fluoride gel alone (1 trial)	Critically low	Very low	
Riggs *et al.* (2019) [110]	DMFS: significantly lower for iodine-NaF solution together with professional prophylaxis compared with placebo (2 pooled trials)	Low	Low	
Akera *et al.* (2022) [117]	DMFT: significantly lower DMFT net increment for supervised toothbrushing with 0.3 mL of fluoride toothpaste (1450 ppm fluoride) compared with a control group (1 trial); no significant difference in DMFT scores in the same trial	Critically low	Very low	
				D-Root or DF-Root: no overlap Cumulative survival rate of tooth surfaces: no overlap Percentage with new caries: no overlap DMFS: no overlap DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.5.9.4 Topical fluoride together with OHE and/or OHI

We identified five systematic reviews that evaluated the effectiveness of some form of topical fluoride combined with OHI/OHE for caries prevention in permanent dentition.

Table 48 presents a high-level summary of treatment outcomes from the reviews that reported on these interventions.

Hendre *et al*. [144] examined the evidence regarding the effectiveness of SDF in arresting or preventing root caries in older adults. The findings from a single trial indicated low-certainty evidence of a **significantly lower mean number of new root carious surfaces following the annual application of 38% SDF together with provision of OHI compared with a control (water) together with provision of OHI** at 3 years follow-up, resulting in a 71% reduced risk of developing new root caries among participants in the intervention group. In the same trial, there was low-certainty evidence of a **significantly lower mean number of new root carious surfaces following the quarterly application of 5% NaF varnish together with provision of OHI compared with a control (water) together with provision of OHI** at 3 years follow-up, resulting in a 64% reduced risk of developing new root caries among participants in the intervention group. In addition, there was very low-certainty evidence from another single trial of a **significantly lower mean number of new root carious surfaces following the annual application of 38% SDF solution on sound exposed root surfaces together with provision of OHI compared with a control (water) together with provision of OHI** at 2 years follow-up, resulting in a 25% reduced risk of developing new root caries among participants in the intervention group. This effect was amplified when tailored biannual OHE was added to the combined SDF and OHI intervention, resulting in a 47% reduced risk at 2 years follow-up.

Oliveira *et al*. [145] examined the scientific evidence on the effect of SDF for preventing and arresting dental caries on exposed root surfaces in adults' teeth. The findings from three pooled trials indicated low-certainty evidence of a **significantly lower mean number of new carious lesions following the annual application of 38% SDF solution together with provision of OHI compared with a placebo together with provision of OHI** at 2 years follow-up. The same effect was found at 1 year (two pooled trials) and ≥30 months (two pooled 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.

Subbiah and Gopinathan [143] evaluated the effectiveness of SDF in preventing and arresting caries in elderly adults. The findings from a single trial indicated moderate-certainty evidence of **significantly lower DMFRS scores following the application of 38% SDF solution (frequency of application was not reported) together with provision of OHI compared with the provision of OHI alone** at 2 years follow-up, resulting in a 25% reduced risk of developing new root caries among participants in the intervention group. There was also moderate-certainty evidence from the same trial indicating **significantly lower DMFRS scores following the combination of annual application of 38% SDF solution, provision of OHI, and provision of biannual OHE compared with the provision of OHI alone** at 2 years follow-up, resulting in a 47% reduced risk of developing new root caries among participants in the intervention group.

Zhang *et al*. [139] synthesised the best available clinical evidence on the benefits of professionally applied and self-applied topical fluoride treatments for the prevention of root caries. The findings from a network meta-analysis of nine trials indicated low-certainty evidence of a **significant root caries-preventive effect (as indicated by scores on both the D-Root and DF-Root indexes) following the annual professional application of 38% SDF solution together with the provision of OHE compared with a control** at 2 years follow-up.

Chan *et al*. [141] evaluated the effectiveness of professionally applied fluoride therapy in preventing and arresting dental caries in older adults aged 60 years and over. The findings from a single trial, which was included in the review conducted by Hendre *et al*. indicated very low-certainty evidence of a **significantly lower mean number of new carious lesions following the combination of annual application 38% SDF solution, the provision of OHI, and the biannual provision of OHE compared with a control** in

community-dwelling older adults at 2 years follow-up, resulting in a 47% reduced risk of developing new root carious lesions among participants in the intervention group.

Overall, there is **very low- to moderate-certainty evidence of a significant caries-preventive effect associated with the combined use of topical fluoride (38% SDF solution or 5% NaF varnish) together with OHI and/or OHE** when compared with a control/placebo or with the provision of OHI/OHE alone. There was a very high and high degree of overlap for the mean number of new root carious lesions and DMFRS/D-Root/DF-Root outcomes, respectively.

Table 48 Main review outcomes for combined topical fluoride and OHI/OHE in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Hendre *et al.* (2017) [144]	Mean number of new root carious surfaces: significantly lower for 38% SDF together with provision of OHI compared with a control (water) together with provision of OHI (1 trial); significantly lower for 5% NaF varnish together with provision of OHI compared with a control (water) together with provision of OHI (same trial); significantly lower for 38% SDF on sound exposed root surfaces together with provision of OHI compared with a control (water) together with provision of OHI (1 trial)	Critically low	Low Low Very low	
Oliveira *et al.* (2018) [145]	Mean number of new carious lesions: significantly lower for 38% SDF together with provision of OHI compared with a placebo together with provision of OHI (3 pooled trials)	Critically low	Low	
Subbiah and Gopinathan (2018) [143]	DMFRS: significantly lower for 38% SDF together with provision of OHI compared with provision of OHI alone (1 trial)	Critically low	Moderate	
Zhang *et al.* (2020) [139]	D-Root: significant preventive effect for 38% SDF solution together with the provision of OHE compared with a control (network meta-analysis of 9 trials) DF-Root: significant preventive effect for 38% SDF solution together with the provision of OHE compared with a control (same network meta-analysis)	Low	Low	
Chan *et al.* (2022) [141]	Mean number of new carious lesions: significantly lower for 38% SDF solution, the provision of OHI, and the biannual provision of OHE compared with a control (1 trial)	Critically low	Very low	
				Mean number of new root carious lesions: very high overlap DMFRS, D-Root, or DF-Root: high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.6 Other topical chemicals

4.6.5.6.1 Antioxidants

None of the included systematic reviews reported on the effectiveness of antioxidants for caries prevention in permanent dentition.

4.6.5.6.2 Toothpaste

None of the included systematic reviews reported on the effectiveness of non-fluoride toothpaste for caries prevention in permanent dentition.

4.6.5.6.3 Antimicrobial agents (minus CHX)

We identified one systematic review on the effectiveness of topical antimicrobial agents for caries prevention in permanent dentition. Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including antimicrobial agents, mainly triclosan and povidone-iodine) on the market in the USA. However, **none of the included trials** evaluated the use of triclosan for caries prevention in permanent dentition. Four of the included trials evaluated the effect of 10% povidone-iodine compared with fluoride foam or saline on coronal caries. However, these trials focused predominantly on secondary prevention of caries, and there is limited information provided in the review in relation to primary prevention of caries in permanent dentition.

Overall, there is **a paucity of evidence** available to determine the benefit of antimicrobial agents (minus CHX) for caries prevention in permanent dentition.

4.6.5.6.4 Arginine and its derivatives

None of the included systematic reviews reported on the effectiveness of arginine-based interventions for caries prevention in permanent dentition. Evidence from a review on the effectiveness of combined interventions that involve the use of arginine on permanent teeth can be found in Section 4.6.5.6.15.

4.6.5.6.5 CHX

We identified four systematic reviews on the effectiveness of CHX for caries prevention in permanent dentition. Table 49 presents a high-level summary of treatment outcomes for this intervention category.

Walsh *et al*. [126] assessed the effects of CHX-containing oral products (toothpastes, mouth rinses, varnishes, gels, gums, and sprays) on the prevention of dental caries in children and adolescents. The findings from two pooled trials indicated low-certainty evidence of **no significant difference in the increment of DMFS between the CHX varnish groups (10% CHX varnish applied every week for 1 month and then at 3- and 6-month recall intervals for 3 years in one trial, and 40% CHX varnish applied every 6 months over approximately 30 months in the other trial) and the no treatment/placebo group** at 30–36 months follow-up. It should be noted that in one of the pooled trials, participants received comprehensive caries advice and demonstrations of oral hygiene techniques.

The review by Wierichs and Meyer-Lueckel [140] (described previously) presented findings from three pooled trials indicating very low-certainty evidence of **significantly lower DMFRS scores (i.e. lower initiation of new root carious lesions) among participants who received professionally applied CHX varnish (1% or 10%; frequency of application not reported) compared with those who received a placebo varnish** at 1–3 years follow-up.

James *et al*. [132] evaluated the effectiveness of CHX varnish at preventing caries in the permanent and primary teeth of children and adolescents compared with placebo or no treatment. The findings from six parallel-group trials synthesised narratively indicated very low-certainty evidence of **no significant**

difference in the increment of DMFS following the application of CHX varnish compared with a placebo varnish or a control at 2–3 years follow-up. The concentration of CHX was 1% in three trials, 10% in one trial, and 40% in two trials, and it was applied every 1–2 months in one trial, every 3 months in three trials, and every 6 months in two trials. However, four other split-mouth trials that were synthesised narratively and that reported on the same outcome yielded inconsistent results. Two trials indicated very low-certainty evidence **in favour of CHX varnish (1% varnish applied every 4 months in the first trial, and 40% varnish applied every 3–4 months in the second trial) compared with a placebo varnish or a control** at 2 years follow-up. The first trial assessed the effect of CHX varnish for preventing caries on the occlusal surfaces of first permanent molars, and the second trial assessed the effect of CHX varnish for preventing caries on the first and second permanent molars. Alternatively, two other trials indicated very low-certainty evidence of **no significant caries-preventive effect of CHX varnish (1% CHX varnish applied every 3 months in the first trial, and every 2 weeks for 2.5 months in the second trial) compared with placebo varnish** at 1–2 years follow-up. The first trial assessed the effect of CHX varnish for preventing caries on the approximal surfaces of premolar and molar teeth in two quadrants of the mouth, and the second trial assessed the effect of CHX varnish for preventing caries on the occlusal surfaces of first permanent molars. James *et al*.'s review also presented findings from a single trial indicating very low-certainty evidence of **no significant difference in the approximal increment of DMFS following the 3-monthly application of 1% CHX-thymol varnish compared with the 3-monthly application of 0.1% fluoride varnish** at 3 years follow-up. It should be noted that all trials included in this review reported some exposure to fluoride (via water, toothpaste, or mouth rinse). However, this was considered background fluoride exposure rather than part of the intervention of interest.

The review by Rethman *et al*. [121], described previously, presented results from four pooled trials indicating very low-certainty evidence of **no significant difference in caries incidence (measured via DMFS increment in three trials, and incidence rate in one trial) between participants who used CHX mouth rinse compared with those who received a placebo mouth rinse or a control** at 2–5 years follow-up (2 years in three trials and 5 years in one trial). The frequency of mouth rinse use was every day in two trials, every day for 5 days and then every third week in one trial, and daily for 1 month followed by weekly use for 5 months in one trial. The concentration of CHX was 0.12% in two trials and 0.05% in one trial; the concentration of CHX was not reported in one trial. It should be noted that in the primary trial in which concentration of CHX was not reported, participants received a combined intervention involving mouth rinse consisting of CHX and fluoride followed by toothbrushing twice per day with toothpaste having the same composition of active ingredients as the mouth rinse. It should also be noted that in three out of the four pooled trials, participants were reported to have some exposure to fluoride (via toothpaste or varnish). However, this was considered background fluoride exposure rather than part of the intervention of interest. In relation to CHX varnish, the findings from a single trial indicated very low-certainty evidence of a **significant reduction in RCI between participants who received a 1:1 CHX-thymol varnish at 1, 3, 6, and 12 months and those who received a placebo varnish** at 1 year follow-up. It should be noted that in this trial, 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.

In relation to CHX gel, the Rethman *et al*. review identified and narratively synthesised four trials, yielding inconsistent results. Two trials indicated very low-certainty evidence of a **significantly lower increment of approximal D(E)FS following the professional application of 1% CHX gel four times per year compared with the application of a placebo gel** at 3 years follow-up. It should be noted that in both trials, the gel was applied via professional flossing. It should also be noted that in both trials, participants were reported to have some exposure to fluoride (via water, toothpaste, tablets, and/or mouth rinse). However, this was considered background fluoride exposure rather than part of the intervention of interest. Alternatively,

the findings from two other trials indicated very low-certainty evidence of **no significant caries-preventive effects associated with the use of CHX gel (measured via increment of DS in the first trial and increment of DFS in the second trial) compared with either a placebo or fluoride varnish** at 1–2 years follow-up. In the first trial, participants from the general population brushed their teeth at home with 0.5% CHX gel (frequency of brushing not reported), and in the second trial, participants at a high risk for caries used 1 mL of 1% CHX gel on 2 consecutive days every 3 months. It should be noted that in one out of the two trials, participants were reported to have some exposure to fluoride (via water and mouth rinse). However, again, this was considered background fluoride exposure rather than part of the intervention of interest.

Overall, the body of **low- and very low-certainty evidence in relation to the caries-preventive effect of CHX products on permanent teeth is inconsistent**. In relation to CHX varnish, the evidence on the DMFS index predominantly (albeit not exclusively) indicated no significant caries-preventive benefit of CHX varnish, whereas the evidence in relation to the incidence of root caries did indicate a significant benefit in favour of CHX varnish. In relation to CHX mouth rinse, the evidence from one pooled analysis of four trials indicated no caries-preventive benefit. The findings in relation to the caries-preventive effect of CHX gel for permanent dentition are divergent. However, the divergent results may be explained by how the CHX varnish was applied; in the two trials that reported a significant caries-preventive effect, CHX gel was applied via professional flossing, whereas in the other two trials it can be assumed from the (limited) information provided in the review that the gel was not applied by a professional. There was no overlap of primary studies across the four reviews in relation to any of the included outcomes. Evidence on the effectiveness of interventions that involve the use of CHX products on mixed dentition can be found in Section 4.7.5.6.5. Additionally, evidence on the effectiveness of combined interventions that involve the use of CHX products on permanent dentition can be found in Sections 4.6.5.5.9.2 and 4.6.5.6.15. Evidence on the effectiveness of combined interventions that involve the use of CHX products on mixed dentition can be found in Section 4.7.5.5.9.1.

Table 49 Main review outcomes for CHX in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Walsh *et al.* (2015) [126]	DMFS: no significant difference for CHX varnish groups compared with no treatment/placebo group (2 pooled trials)	Low	Low	
Wierichs and Meyer-Lueckel (2015) [140]	DMFRS: significantly lower for professionally applied CHX varnish compared with a placebo varnish (3 pooled trials)	Critically low	Very low	
James *et al.* (2010) [132]	DMFS: no significant difference for CHX varnish compared with placebo varnish/control (6 trials, narrative synthesis); no significant difference for CHX-thymol varnish compared with fluoride varnish (1 trial) Caries incidence: significantly lower for CHX varnish compared with placebo varnish/control (2 trials, narrative synthesis); no significant preventive effect for CHX varnish compared with placebo varnish (2 trials, narrative synthesis)	Critically low	Very low	
Rethman et al. (2011) [121]	DMFS: no significant difference for CHX mouth rinse compared with placebo mouth rinse or control (4 pooled trials) D(E)FS: significantly lower for CHX gel compared with placebo gel (2 trials, narrative synthesis) DS: no significant caries-preventive effect of 0.5% CHX gel compared with either placebo or fluoride varnish (1 trial) DFS: no significant caries-preventive effect of 1% CHX gel compared with either placebo or fluoride varnish (1 trial) RCI: significant reduction for CHX-thymol varnish compared with placebo (1 trial)	Critically low	Very low	
				1% DMFS/D(E)FS/DS: no overlap

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				1% DMRFS/RCI: no overlap 10% DMFS: no overlap 10% DMFRS: no overlap 40% DMFS: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.6.6 Calcium phosphate agents

We identified two systematic reviews on the effectiveness of calcium phosphate agents for caries prevention in permanent dentition. Table 50 presents a high-level summary of treatment outcomes for this intervention category.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including antimicrobial agents, mainly triclosan and povidone-iodine) on the market in the USA. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the increment of DFS between patients with salivary gland dysfunction who used a mouth rinse containing a casein derivative with calcium phosphate three times per day compared with patients who used 0.05% NaF mouth rinse** at 1 year follow-up. The findings from another single trial indicated very low-certainty evidence of **no significant difference in the increment of DS between participants who used toothpaste containing casein phosphopeptide (twice daily brushing for 5 minutes over the course of 12 months) and participants who brushed with fluoride toothpaste** at 2 years follow-up. Both toothpastes, however, were significantly better than a placebo.

Singal *et al*. [9] reviewed the evidence for the remineralising and caries-preventive efficacy of various calcium phosphate derivatives. The findings from a single trial indicated very low-certainty evidence of **significantly lower DMFT scores between participants who used CPP-ACP cream compared with participants in both the no treatment group and who received 5% fluoride varnish** at 1 year follow-up. It should be noted, however, that information pertaining to this trial was limited in the review, including information pertaining to the frequency of applying the CPP-ACP cream.

Overall, the **very low-certainty evidence on the effectiveness of calcium phosphate agents for caries prevention in permanent dentition is inconsistent**. This is likely because the evidence is based on only three trials reported in two systematic reviews, which tested different modes of delivery of calcium phosphate and used different comparators. There was no overlap of primary studies across the two included reviews for the included outcomes.

Table 50 Main review outcomes for calcium phosphate agents in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	DFS/DS: no significant difference for mouth rinse containing a casein derivative with calcium phosphate compared with NaF mouth rinse (1 trial); no significant difference for toothpaste containing casein phosphopeptide compared with fluoride toothpaste (1 trial)	Critically low	Very low	
Singal *et al.* (2022) [9]	DMFT: significantly lower for CPP-ACP cream compared with both no treatment and fluoride varnish groups (1 trial)	Critically low	Very low	
				DFS/DS: no overlap DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.6.7 Ozone

None of the included systematic reviews reported on the effectiveness of ozone-based interventions for caries prevention in permanent dentition.

4.6.5.6.8 Nanomaterials

None of the included systematic reviews reported on the effectiveness of nanomaterials for caries prevention in permanent dentition.

4.6.5.6.9 Probiotics

None of the included systematic reviews reported on the effectiveness of probiotics for caries prevention in permanent dentition.

4.6.5.6.10 Propolis

None of the included systematic reviews reported on the effectiveness of propolis for caries prevention in permanent dentition.

4.6.5.6.11 Silicates

None of the included systematic reviews reported on the effectiveness of silicates for caries prevention in permanent dentition.

4.6.5.6.12 Xylitol

We identified four systematic reviews on the effectiveness of xylitol for caries prevention in permanent dentition. Table 51 presents a high-level summary of treatment outcomes for this intervention category.

Riggs *et al*. [110] 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 until they were aged 6 years). However, **none of the included trials** evaluated the caries-preventive efficacy of xylitol on the permanent dentition of mothers. It should be noted that this outcome was identified as a secondary outcome in the review.

Riley *et al*. [133] evaluated the effects of different xylitol-containing products on preventing dental caries in children and adults. The findings of two trials (which were narratively synthesised) indicated moderate-certainty evidence of **no significant difference in the increment of DMFS following the consumption of xylitol lozenges (5.0 g per day in one trial, 4.7 g per day in the other trial) compared with control lozenges or no treatment** at 33 months (one trial) and 2 years (one trial) follow-up. It should be noted, from the information provided in the review, that participants were reported to have some other exposure to fluoride (via water, toothpaste, and/or a history of professionally applied fluoride). However, this was considered background fluoride exposure rather than part of the intervention of interest. Neither of the included trials reported on the preventive effect of other xylitol-containing agents, such as xylitol-containing candy, syrup, sucking tablets, (non-fluoride) toothpaste, tablets, or wipes, in permanent dentition.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including xylitol-containing agents) on the market in the USA. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the approximal increment of DMFS following the consumption of 422 mg xylitol candies (two candies consumed three times per day) compared with usual care (which included preventive varnish)** among participants at high risk for caries at 2 years follow-up.

Finally, Antonio *et al*. [146] assessed the overall caries-preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. The findings from a single trial indicated very low-certainty evidence of **no significant difference in DMFS scores or 2-year incidence of proximal enamel carious lesions between the group that consumed 42.2% xylitol lozenges (two tablets taken three times per day) compared with the control group who received OHE and application of fluoride varnish two or three times per year** at 2 years follow-up.

Overall, there is **moderate- and very low-certainty evidence of no significant caries-preventive effect of xylitol-containing agents as a standalone intervention for caries prevention in permanent dentition**. The evidence is, however, drawn from a small number of trials and, importantly, there was a very high degree of overlap of primary studies across the included reviews. The findings from reviews that describe combined interventions that involve the use of xylitol are presented in Sections 4.6.5.5.9.2 and 4.6.5.6.15 on combined interventions in permanent dentition.

Table 51 Main review outcomes for xylitol in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Riggs *et al.* (2019) [110]	None reported	Low	N/A	
Riley *et al.* (2015) [133]	DMFS: no significant difference for xylitol lozenges compared with control lozenges or no treatment (2 trials, narrative synthesis)	Low	Moderate	
Rethman *et al.* (2011) [121]	DMFS: no significant difference for xylitol candies compared with usual care (1 trial)	Critically low	Very low	
Antonio *et al.* (2011) [146]	DMFS: no significant difference for 42.2% xylitol lozenges compared with control group (1 trial)	Low	Very low	
				DMFS: very high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.6.13 Sorbitol

None of the included systematic reviews reported on the effectiveness of sorbitol for caries prevention in permanent dentition.

4.6.5.6.14 Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined)

We identified one systematic review on the effectiveness of polyols for caries prevention in permanent dentition. Table 52 presents a high-level summary of treatment outcomes for this intervention category.

Antonio *et al*. [146] assessed the overall caries-preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. However, the only relevant included trial **did not carry out any statistical tests between the 49% xylitol/maltitol and xylitol/polydextrose candy groups and the control group**, which received no additional preventive care outside routine local measures. However, there was low-certainty evidence of the **xylitol/maltitol and xylitol/polydextrose candy groups having the lowest 3-year increment of DMFS compared with the control group**.

Table 52 Main review outcomes for polyols in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Antonio *et al.* (2011) [146]	DMFS: lowest 3-year increment occurred in the xylitol/maltitol and xylitol/polydextrose candy groups compared with the control group (1 trial)	Low	Low	
				DMFS: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.6.15 Combined interventions involving other topical chemicals

We identified five systematic reviews that reported on the effectiveness of combined interventions involving non-fluoride topical chemicals plus an additional active intervention component for caries prevention in permanent dentition. Table 53 presents a high-level summary of treatment outcomes from reviews that reported on these interventions.

Hendre *et al*. [144] examined the evidence regarding the effectiveness of SDF and other caries-preventive agents in arresting or preventing root caries in older adults. The findings from a single trial indicated low-certainty evidence of a **significantly lower mean number of new root carious surfaces following the application of 1% CHX varnish together with OHI compared with a control (water) together with OHI** at 3 years follow-up, resulting in a 57% reduced risk of developing new root caries among participants in the intervention group.

Slot *et al*. [147] evaluated the literature to determine the effect of the use of CHX varnish on root caries incidence and activity. The findings from three pooled trials indicated moderate-certainty evidence of **significantly lower DMFRS scores in the groups that received application of CHX varnish together with an additional intervention component compared with the control/placebo groups** (two trials evaluated 1% CHX varnish in an elderly population and one trial evaluated 10% CHX varnish in patients with xerostomia (dry mouth)). In one out of the three pooled trials, participants received OHI 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 CHX varnish. One of the pooled trials involved the delivery of a complex intervention in which participants received a combination of OHI together with professional oral prophylaxis (both at baseline) and the application of CHX varnish. The frequency of CHX varnish application was every 3 months in two trials, and twice in the first week followed by one application at 1, 3, 6, 9, and 12 months in one trial. The follow-up periods for the three trials were 1 year, 13 months, and 3 years.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents on the market in the USA. The findings from a single trial indicated very low-certainty evidence of a **significantly lower increment of DMFS following the use of an arginine bicarbonate/calcium phosphate combination toothpaste used three times daily compared with fluoride toothpaste** at 1 year follow-up. However, the difference between the groups was smaller in magnitude at 2 years follow-up. It should be 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. The findings from another single trial indicated very low-certainty evidence of a **significantly lower RCI following the application of 1:1 CHX/thymol varnish together with the provision of OHI every 3 months compared with the provision of OHI alone** at 3 years follow-up. Rethman *et al*. [121] also reported findings from nine pooled trials indicating very low-certainty evidence of a **significant reduction in the increment of DMFS following the consumption of sucrose-free polyol chewing gum compared with no gum**. Follow-up periods were 24 months (four trials), 30 months (one trial), 36 months (three trials), and 40 months (one trial). Gum was chewed under supervised conditions in the majority of trials. The frequency of supervised gum chewing was between two and six times per day with a duration of chewing ranging from 10 to 20 minutes. In the relevant trials, the concentration of sorbitol ranged from 50.0% to 70.0%, the concentration of xylitol ranged from 4.3% to 65.0%, the concentration of mannitol ranged from 4.0% to 70.0%, and the concentration of carbamide was 2.3%. In addition, subgroup analyses showed that xylitol gum had the highest caries-preventive effect, followed by gums with a combination of polyols, followed by sorbitol gum. However, when the non-randomised trials 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 non-significant. It should be noted that in seven out of the nine pooled trials, participants were reported to have exposure to fluoride (via water, toothpaste, mouth rinse, and/or varnish). However, this was considered background fluoride exposure rather than part of the intervention of interest.

Tubert-Jeannin *et al*. [111] evaluated the effectiveness of the administration of fluoride supplements (various forms) for caries prevention in children. The findings from a single trial indicated very low-certainty evidence of **no significant difference in increment of DMFS following the combined use of 422.0 mg xylitol lozenges together with 0.5 mg NaF lozenges compared with xylitol-only lozenges** at 2 years follow-up. The review authors reported that in this trial, all the participants were encouraged to brush their teeth with fluoride toothpastes two times per 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.

Riggs *et al*. [110] 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 until they were aged 6 years). The review authors also reported on the effects of interventions for caries prevention in the permanent dentition of pregnant women/mothers. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the increment of DMFT following the application of 10% CHX varnish (four treatments (one per week for 4 weeks), commencing when children were about 6 months old, i.e. around the time of first tooth emergence) together with professional prophylaxis prior to the commencement of the trial compared with the application of placebo varnish** at 3 years follow-up. It should be noted that this outcome was identified as a secondary outcome in the review.

Overall, the **evidence on the effectiveness of combined interventions involving non-fluoride topical chemicals is inconsistent**. There is moderate- to very low-certainty evidence of a **likely, albeit not entirely consistent, caries-preventive effect of combining CHX with an additional intervention component**. However, the nature of the other component varied across the reviews. There is very low-certainty evidence of a **significant benefit of polyol chewing gum chewed under supervised conditions** for caries prevention in permanent dentition. The two remaining reviews in this body of evidence tested **different types of topical chemicals with divergent results**. There was a complete overlap of primary studies in relation to DMFRS/RCI, but no overlap in relation to the other included outcomes.

Table 53 Main review outcomes for combined interventions involving other topical chemicals in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Hendre *et al.* (2017) [144]	Mean root carious surfaces: significantly lower for 1% CHX varnish together with OHI compared with a control (water) together with OHI (1 trial)	Critically low	Low	
Slot *et al.* (2011) [147]	DMFRS: significantly lower for CHX varnish together with an additional intervention component compared with control/placebo groups (3 pooled trials)	Critically low	Moderate	
Rethman *et al.* (2011) [121]	DMFS: significantly lower for arginine bicarbonate/calcium phosphate combination toothpaste compared with fluoride toothpaste (1 trial); significantly lower for sucrose-free polyol chewing gum compared with no gum (9 pooled trials) RCI: significantly lower for 1:1 CHX/thymol varnish together with OHI compared with OHI alone (1 trial)	Critically low	Very low	
Tubert-Jeannin *et al.* (2011) [111]	DMFS: no significant difference for 422.0 mg xylitol lozenges together with 0.5 mg NaF lozenges compared with xylitol-only lozenges (1 trial)	Low	Very low	
Riggs *et al.* (2019) [110]	DMFT: no significant difference for 10% CHX varnish together with professional prophylaxis compared with placebo varnish (1 trial)	Low	Very low	
				Mean root carious surfaces: no overlap DMFRS or RCI: complete overlap DMFS: no overlap DMFT: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.7 Sealants

4.6.5.7.1 Resin

We identified eight systematic reviews on the effectiveness of resin-based sealants for caries prevention in permanent dentition. However, the findings from two reviews were not used for data synthesis in our review. Table 54 presents a high-level summary of treatment outcomes for this intervention category.

Alirezaei *et al*. [106] evaluated the ability of glass ionomer cement-based sealants and resin-based sealants to prevent the occurrence of caries, as well as their retention in standard clinical studies. The outcome relevant to this review was caries development. However, it was not clear whether this outcome related to caries initiation or caries progression, and so the findings were not included in our data synthesis.

Alharthy *et al*. [107] evaluated the retention and cariostatic effect of hydrophilic and hydrophobic resin-based sealants in primary and/or permanent teeth with a follow-up period of at least 3 months. Similar to the Alirezaei *et al*. review, it was not clear whether the outcome of interest (cariostatic effect) related to caries prevention, arrest, or remineralisation, and as such, the findings were not included in our data synthesis. The findings related to retention rate from both Alirezaei *et al*. and Alharthy *et al*. can be found in the extraction file in Appendix H.

Alsabek *et al*. [112] evaluated the effectiveness of hydrophilic resin-based sealants in preventing pit-and-fissure caries in permanent teeth. The findings from five pooled trials indicated low-certainty evidence of **no significant difference in caries incidence between teeth that received hydrophilic resin-based sealants and teeth that received standard resin-based sealants** at 6 months (four trials) and 1 year (five trials) follow-up. It should be noted that this outcome was identified as a secondary outcome in the review.

Rashed *et al*. [148] compared pit-and-fissure sealants with fluoride varnish for the prevention of caries in the first permanent molars of schoolchildren. The findings from three pooled trials indicated low-certainty evidence of **no significant difference in caries incidence on the surfaces of first permanent molars between participants who received resin-based sealants and participants who received fluoride varnish (concentration of fluoride and frequency of application not reported)** at 2 years follow-up. In addition, the findings from two pooled trials indicated low-certainty evidence of **no significant difference in the increment of DMFS on first permanent molars between participants who received resin-based sealants and participants who received fluoride varnish (concentration of fluoride and frequency of application not reported)** at 2 years follow-up.

Kashbour *et al*. [29] 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. The findings from four pooled trials indicated low-certainty evidence of **no superiority of resin-based sealants in preventing the occurrence of new dentine carious lesions on the first permanent molars of children and adolescents compared with fluoride varnish** at 2–3 years follow-up. However, the trials assessed the odds of caries at different levels (the person level in two trials, the tooth level in one trial, and the tooth surface level in one trial), which could have affected the precision of different estimates. It should be noted that one out of the four 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 mouthrinsing with a 0.5% NaF solution at school. It should also be noted that in another one of the four pooled trials, 90% of toothpastes on sale in the area where the study took place contained fluoride. However, this can be considered background fluoride exposure

rather than part of the intervention of interest. Kashbour *et al*. also included changes from baseline in DMF figures at surface, tooth, and whole mouth levels as an outcome. However, none of the included trials involving standalone resin-based sealant interventions reported on this outcome.

Ahovuo-Saloranta *et al*. [38] compared the effects of different types of fissure sealants in preventing caries in the occlusal surfaces of permanent teeth in children and adolescents who had different levels of caries incidence. The findings from seven pooled trials indicated moderate-certainty evidence of a **significantly lower incidence of carious lesions on occlusal surfaces of permanent molars or premolars that received second-, third-, and fourth-generation resin-based sealants compared with those that did not receive sealants** at 24 months follow-up. The caries-preventive effect was maintained at 36 months, 48 months, and 54 months follow-up. It should be noted that in four out of the seven pooled trials, participants had exposure to some form of fluoride (via water or toothpaste). However, this was considered background fluoride exposure rather than part of the intervention of interest. In addition, the findings from a single trial indicated moderate-certainty evidence of a **significantly lower increment of DFS following the application of auto-polymerised resin-based sealants compared with a control** at 2 years follow-up. It should be noted that participants in this trial had exposure to fluoride (via water and toothpaste). However, this was considered background fluoride exposure rather than part of the intervention of interest.

The Canadian Agency for Drugs and Technologies in Health [149] conducted a review of the evidence with respect to the clinical effectiveness (specifically caries prevention) and cost-effectiveness of dental sealants and preventive resins when applied to the permanent teeth of children and adolescents. The findings from a single trial indicated low-certainty evidence of **a significant reduction in the number of new carious lesions in permanent first molars that received resin-based sealants compared with those that received no sealant** at 1 year follow-up, and the outcome remained consistent at 3 years follow-up. However, the findings from another single trial indicated low-certainty evidence of **no significant difference in the incidence of cavitated dentine lesions between participants who received composite resin sealants on high-risk occlusal surfaces of permanent first molars compared with participants who received supervised toothbrushing** at 3 years follow-up. Participants in both trials were from low socioeconomic backgrounds. In addition, it was reported that participants in the second trial had exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest.

Li *et al*. [150] evaluated the efficacy of caries management in first permanent molars between fluoride sealant and fluoride varnish. The findings from two pooled trials indicated very low-certainty evidence of **no significant difference in caries incidence among children in the resin-based sealant group compared with children who received biannual application of 22600 ppm fluoride varnish** at 2–3 years follow-up.

Overall, **the very low- to moderate-certainty body of evidence on the caries-preventive effect of resin-based sealants in permanent dentition is inconsistent**, and varies in relation to outcome measure, comparator, and the delivery of combined interventions among the relevant trials. However, the three reviews that included fluoride varnish as a comparator all concluded that there was **no added benefit associated with resin-based sealants over and above that of fluoride varnish**. There was slight overlap of primary studies across the reviews for the caries incidence outcome, and very high overlap for the DFS/DMFS outcome. Evidence from reviews on the effectiveness of combined interventions that involve the use of resin-based sealants on permanent teeth can be found in Section 4.6.5.7.7.

Table 54 Main review outcomes for resin sealants in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Alirezaei *et al.* (2018) [106]	None usable	Critically low	N/A	
Alharthy *et al.* (2022) [107]	None usable	Critically low	N/A	
Alsabek *et al.* (2021) [112]	Caries incidence: no significant difference for hydrophilic resin-based sealants compared with standard resin-based sealants (5 pooled trials)	Critically low	Low	
Rashed *et al.* (2022) [148]	Caries incidence: no significant difference for resin-based sealants compared with fluoride varnish (3 pooled trials) DMFS: no significant difference for resin-based sealants compared with fluoride varnish (2 pooled trials)	Critically low	Low	
Kashbour *et al.* (2020) [29]	New carious lesions: no superiority of resin-based sealants compared with fluoride varnish (4 pooled trials)	Low	Low	
Ahovuo-Saloranta *et al.* (2017) [38]	Incidence of carious lesions: significantly lower for second-, third-, and fourth-generation resin-based sealants compared with no sealants (7 pooled trials) DFS: significantly lower for auto-polymerised resin-based sealants compared with control (1 trial)	Low	Moderate	
Canadian Agency for Drugs and Technologies in Health (2016) [149]	New carious lesions: significant reduction for resin-based sealants compared with no sealant (1 trial)	Critically low	Low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
	Incidence of cavitated dentine lesions: no significant difference for composite resin sealants compared with supervised toothbrushing (1 trial)			
Li *et al.* (2020) [150]	Caries incidence: no significant difference for resin-based sealant group compared with fluoride varnish group (2 pooled trials)	Critically low	Very low	
				Caries incidence, new carious lesions, or cavitated dental lesions: slight overlap DFS or DMFS: very high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.7.2 Glass ionomer

We identified four systematic reviews on the effectiveness of glass ionomer-based sealants for caries prevention in permanent dentition. Table 55 presents a high-level summary of the treatment outcomes for this intervention category.

Kashbour *et al.*'s review [29], described in the previous section, presented findings from three trials indicating low-certainty evidence of **no overall difference in the presence of new dentine carious lesions on the first permanent molars of children and adolescents following the application of glass ionomer sealants compared with fluoride varnish** at 1, 2, and 3 years follow-up. However, the review authors **reported limited information about how they reached this overall conclusion**, noting only that they were unable to perform a meta-analysis due to clinical differences between the trials. It was reported, however, that in one of the three trials, participants in both groups received OHE, and in that 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. None of the included trials of glass ionomer-based sealants reported on changes in DMFS or DMFT from baseline.

Ahovuo-Saloranta *et al.*'s review [38], described in the previous section, presented findings from a single trial indicating moderate-certainty evidence of **no significant difference in mean DFS scores between the glass ionomer-based sealant group and the no sealant group** at 2 years follow-up. None of the included trials reported on both this comparison and this outcome at the other follow-up periods of interest (1 year, 3–4 years, 5 years, 6 years, and 7 years). Several trials reported on the effectiveness of glass ionomer-based sealants compared with resin-based sealants. None reported on mean DFS (or DMFS or similar) scores; most of the findings pertained to the incidence of carious lesions on the occlusal surfaces of molars or premolars. The findings were presented according to follow-up duration (1, 2, 3–4, 5, 6, and 7 years). At the 1-year follow-up period, the findings from six pooled trials indicated moderate-certainty evidence of **no significant difference in the incidence of carious lesions on the occlusal surfaces of molars or premolars associated with the application of glass ionomer-based sealants compared with resin-based sealants (four trials compared low-viscosity glass ionomers with resin sealants and two trials compared resin-modified glass ionomers with resin sealants)**. It should be noted that one of these six 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 (via water or toothpaste). However, this was considered background exposure rather than part of the intervention of interest.

At the 2-year follow-up period, the findings from 10 pooled trials indicated moderate-certainty evidence of **no significant difference in the incidence of carious lesions on the occlusal surfaces of molars or premolars associated with the application of low-viscosity glass ionomers compared with resin-based sealants**. It should be noted that 3 out of the 10 pooled trials involved the delivery of a combined intervention: OHI at each clinic visit in 1 trial, oral prophylaxis in 1 trial, and the delivery of a complex intervention in 1 trial, whereby at each clinic visit (at 6 months and 12 months), participants received the combination of OHE, dietary counselling, brushing with fluoride toothpaste (600 ppm fluoride), and application of fluoride foam (6000 ppm fluoride). It should also be noted that 2 of the 10 pooled trials reported participant exposure to other forms of fluoride (via water or toothpaste). However, this was considered background exposure rather than part of the intervention of interest. Similarly, the findings from two pooled trials indicated moderate-certainty evidence of **no significant difference in the incidence of carious lesions on the occlusal surfaces of molars or premolars associated with the application of high-viscosity glass ionomers compared with resin-based sealants**. It should be noted that one of the two pooled trials involved the delivery of a combined intervention whereby participants in both groups received OHE at baseline. In addition, both trials reported participant exposure to fluoridated

water. However, again, this was considered background exposure rather than part of the intervention of interest. When comparing resin-modified glass ionomers with resin-based sealants, however, the findings from two pooled trials favoured the comparator, with moderate-certainty evidence of a **significantly lower incidence of carious lesions on occlusal surfaces of molars or premolars associated with the application of resin-based sealants compared with resin-modified glass ionomers** at 2 years follow-up. It should be noted that one of the two pooled trials involved the delivery of a combined intervention in which participants in both groups received OHI at baseline and used fluoridated toothpaste for the duration of the trial intervention.

At the 3–4-year follow-up period, it was not possible to conduct pooled analyses due to significant heterogeneity and divergent results among the primary trials. As such, results were presented narratively. When comparing glass ionomers with resin-based sealants, the findings from five trials (which were synthesised narratively) favoured the comparator, with moderate-certainty evidence of a **significantly lower incidence of carious lesions on occlusal surfaces of molars or premolars associated with resin-based sealants compared with glass ionomers** (three trials compared low-viscosity glass ionomers with resin-based sealants and two compared resin-modified glass ionomers with resin-based sealants). It should also be noted that one of these trials reported participant exposure to fluoridated water. However, this was considered background exposure rather than part of the intervention of interest. Alternatively, the findings from two additional trials (which were synthesised narratively) indicated moderate-certainty evidence of **no significant difference in the incidence of carious lesions on occlusal surfaces of molars or premolars associated with the application of low-viscosity glass ionomers compared with resin-based sealants**. One of these trials reported participant exposure to fluoridated water. However, again, this was considered background exposure rather than part of the intervention of interest. Only two trials reported a significant effect favouring glass ionomer-based sealants over resin-based sealants. The findings from one of those trials indicated very low-certainty evidence of a **significantly lower incidence of carious lesions on occlusal surfaces of molars or premolars associated with the application of low-viscosity glass ionomer sealants compared with second-generation resin sealants** at 44 months follow-up. The findings from the second trial indicated moderate-certainty evidence of a **significantly higher cumulative survival rate of dentine carious lesion-free pits and fissures associated with the application of atraumatic restorative treatment (ART) high-viscosity glass ionomer with light-curing** compared with the resin-composite group at 4 years follow-up. It should be noted that in both trials, participants had exposure to some form of fluoride (via water or toothpaste). However, this was considered background fluoride exposure rather than part of the intervention of interest.

At the 5-year follow-up period, the findings from a single trial indicated very low-certainty evidence of **no significant difference in the incidence of carious lesions on occlusal surfaces of molars or premolars associated with the application of high-viscosity glass ionomer sealants compared with resin-based sealants**. It should be noted that participants in this trial had exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. Likewise, at the 7-year follow-up period, the findings from a single trial indicated very low-certainty evidence of **no significant difference in the incidence of carious lesions on occlusal surfaces of molars or premolars associated with the application of low-viscosity glass ionomer sealants compared with resin-based sealants**.

Wright *et al*. [151] summarised the available evidence regarding the effect of dental sealants for the prevention of pit-and-fissure occlusal caries in the primary and permanent molars of children, adolescents, and adults compared with a control without sealants, with fluoride varnishes, or with another head-to-head comparator. The findings from nine pooled trials indicated very low-certainty evidence of **no significant difference in the presence of new carious lesions on the occlusal surfaces of**

permanent molars between participants who received glass ionomer-based sealants and participants who received resin-based sealants at 2–3 years follow-up. In addition, the findings from a single trial indicated very low-certainty evidence of **no significant difference in the presence of new carious lesions on the occlusal surfaces of permanent molars between participants who received glass ionomer-based sealants and participants who received resin-modified glass ionomer sealants** at 2–3 years follow-up. Finally, the findings from a single trial indicated very low-certainty evidence of **no significant difference in the presence of new carious lesions on the occlusal surfaces of permanent molars between participants who received glass ionomer-based sealants and participants who received polyacid-modified resin sealants** at 2–3 years follow-up.

The review by the Canadian Agency for Drugs and Technologies in Health [149], described in the previous section, presented findings from a single trial indicating low-certainty evidence of **no significant difference in the incidence of cavitated dentine lesions on high-risk occlusal surfaces of permanent molars between participants who received composite ART-high-viscosity glass ionomer cement compared with participants who received supervised toothbrushing** at 3 years follow-up. Participants in this trial were from low socioeconomic backgrounds.

The body of evidence on the preventive benefit of glass ionomer-based sealants varies in certainty (from moderate- to very low-certainty), as well as in relation to the comparators used and the follow-up time periods. Overall, however, with the exception of two single primary trials, **the evidence does not favour the use of glass ionomer-based sealants over resin-based sealants**. There was a moderate overlap of primary studies in relation to caries incidence, but no overlap in relation to DFS. Evidence from reviews on the effectiveness of combined interventions that involve the use of glass ionomer-based sealants on permanent teeth can be found in Section 4.6.5.7.7.

Table 55 Main review outcomes for glass ionomer sealants in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Kashbour *et al.* (2020) [29]	New dentinal carious lesions: no overall difference for glass ionomer sealants compared with fluoride varnish (3 trials, narrative synthesis)	Low	Low	
Ahovuo-Saloranta *et al.* (2017) [38]	DFS: no significant difference for glass ionomer-based sealants compared with no sealant (1 trial)	Low	Moderate	
	Incidence of carious lesions: no significant difference for glass ionomer-based sealants compared with resin-based sealants (6 pooled trials); no significant difference for low-viscosity glass ionomers compared with resin-based sealants (10 pooled trials); no significant difference for high-viscosity glass ionomers compared with resin-based sealants (2 pooled trials); significantly lower compared with resin-modified glass ionomers§ (2 pooled trials); significantly lower compared with glass ionomers§ (5 trials, narrative synthesis); no significant difference for low-viscosity glass ionomers compared with resin-based sealants (2 trials, narrative synthesis); significantly lower for low-viscosity glass ionomers compared with second-generation resin sealant (1 trial); no significant difference for high-viscosity glass ionomer sealants compared with resin-based sealants (1 trial); no significant difference for low-viscosity glass ionomer sealants compared with resin-based sealants (1 trial)		Moderate Moderate Moderate Moderate Moderate Moderate Moderate Very low Very low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
	Cumulative survival rate: significantly higher for ART high-viscosity glass ionomer with light-curing compared with resin composite (1 trial)		Moderate	
Wright *et al.* (2016) [151]	New carious lesions: no significant difference for glass ionomer-based sealants compared with resin-based sealants (9 pooled trials); no significant difference for glass ionomer-based sealants compared with resin-modified glass ionomer sealants (1 trial); no significant difference for glass ionomer-based sealants compared with polyacid-modified resin sealants (1 trial)	Critically low	Very low	
Canadian Agency for Drugs and Technologies in Health (2016) [149]	Incidence of cavitated lesions: no significant difference for composite ART-high-viscosity glass ionomer cement compared with supervised toothbrushing (1 trial)	Critically low	Low	
				New dentinal carious lesions, incidence of carious lesions, or incidence of cavitated lesions: moderate overlap DFS: no overlap Cumulative survival rate: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

§Intervention: resin-based sealant; comparator: glass ionomers

4.6.5.7.3 Ormocer

We identified one systematic review on the effectiveness of ormocer sealants for caries prevention in permanent dentition. Table 56 presents a high-level summary of treatment outcomes from this review.

Ahovuo-Saloranta *et al*. [38], described in the previous two sections, presented findings from a single trial in which the results favoured the comparator (low-viscosity glass ionomer sealant) over ormocer sealant, with very low-certainty evidence of a **significantly *higher* incidence of carious lesions on occlusal surfaces of molars or premolars following the application of ormocer sealant compared with the application of low-viscosity glass ionomer sealant** at 2 years follow-up. The results showed that the presence of caries was 32% in the ormocer group and 16% in the glass ionomer group. Ahovuo-Saloranta *et al*. also included increment of DMFS as an outcome; however, none of the included trials involving glass ionomer-based sealants reported on this outcome.

Table 56 Main review outcomes for ormocer sealants in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Ahovuo-Saloranta *et al.* (2017) [38]	Incidence of carious lesions: significantly higher for ormocer compared with low-viscosity glass ionomer sealants (1 trial)	Low	Very low	
				Incidence of carious lesions: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.7.4 Hybrid

We identified one systematic review on the effectiveness of hybrid sealants for caries prevention in permanent dentition. Table 57 presents a high-level summary of treatment outcomes from this review.

Wright *et al*.'s review [151], described previously, presented findings from a single trial indicating very low-certainty evidence of **no significant difference in the presence of new carious lesions on the occlusal surfaces of permanent molars among participants who received polyacid-modified resin sealants compared with participants who received resin-based sealants** at 2–3 years follow-up.

Table 57 Main review outcomes for hybrid sealants in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Wright *et al.* (2016) [151]	New carious lesions: no significant difference for polyacid-modified resin sealants compared with resin-based sealants (1 trial)	Critically low	Very low	
				New carious lesions: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.7.5 Combined

We identified four systematic reviews on the effectiveness of combined sealants for caries prevention in permanent dentition. Table 58 presents a high-level summary of treatment outcomes for this intervention category.

Wright *et al*.'s review [151], described previously, reported findings from six pooled trials indicating very low-certainty evidence of a **significantly lower number of new carious lesions on the occlusal surfaces of permanent molars among participants who received sealants compared with participants who did not receive sealants** at 2–3 years follow-up. The results showed a 76% reduced risk of caries incidence in the intervention compared with the control group. The effect was maintained at 4–7 years follow-up (three pooled trials; 79% reduced risk of caries incidence) and at 7 years or longer follow-up (two trials; 85% reduced risk of caries incidence). The **findings were similar when sealants were compared with fluoride varnish** at 2–3 years follow-up (two pooled trials; 73% reduced risk of caries incidence), 4–7 years follow-up (two pooled trials; 81% reduced risk of caries incidence), and 7 years or longer follow-up (one trial; 71% reduced risk of caries incidence).

The Canadian Agency for Drugs and Technologies in Health [149] conducted a review of the evidence with respect to the clinical effectiveness (specifically caries prevention) and cost-effectiveness of dental sealants and preventive resins when applied to the permanent teeth of children and adolescents. The findings from a single trial indicated very low-certainty evidence of **no caries-preventive effect (precise outcome measure not specified) of sealants applied to premolars compared with no sealant application** at 1 year follow-up. The type of sealant was not specified, although it is likely that the analysis involved a combination of resin-based and glass ionomer-based sealants. Overall, however, **limited information was provided** in relation to this trial in the review.

Akera *et al*. [117] evaluated the effectiveness of school-based interventions, including the application of sealants, in improving oral health compared with no intervention or usual practice among primary school children in low- and middle-income countries. The findings from a single trial indicated very low-certainty evidence of **significantly lower DMFT scores among participants who took part in a fissure sealant intervention programme compared with participants in the control group** at 7 years follow-up. It should be noted, however, that **limited information was provided** in relation to this trial in the review.

Li *et al*. [150] evaluated the efficacy of caries management in first permanent molars between fluoride sealant and fluoride varnish. The findings from six pooled trials indicated very low-certainty evidence of **no significant caries-preventive benefit (measured as incidence of new caries on the occlusal surfaces of first permanent molars in four trials, DMFS scores in one trial, and both incidence of new caries and DMFS scores in one trial) of sealant application compared with fluoride varnish** (biannual application of 22600 ppm fluoride varnish in five trials and 7700 ppm fluoride varnish in one trial) at 2–3 years follow-up. Five out of the six pooled trials used resin-based sealants on participants in the intervention group, and one trial used glass ionomer-based sealants on participants in the intervention group. The findings from three pooled trials indicated very low-certainty evidence of **no significant difference in DMFS scores (first permanent molars) between participants in the sealant group and participants in the fluoride varnish group** (biannual application of 22600 ppm fluoride varnish) at 2 years follow-up. Two out of the three pooled trials used resin-based sealants on participants in the intervention group, and one trial used resin-modified glass ionomer cement on participants in the intervention group.

Overall, the **very low-certainty body of evidence on the effectiveness of combined sealants for caries prevention in permanent dentition is inconsistent**. There was a slight overlap of primary studies across the reviews for caries incidence, but no overlap in relation to the DMFT or DMFS outcomes. Evidence from reviews on the effectiveness of combined interventions that involve the use of sealants on permanent teeth can be found in Section 4.6.5.7.7.

Table 58 Main review outcomes for combined sealants in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Wright *et al.* (2016) [151]	New carious lesions: significantly lower for sealants compared with no sealants (6 pooled trials) Caries incidence: reduced risk for sealants compared with fluoride varnish (2 pooled trials)	Critically low	Very low	
Canadian Agency for Drugs and Technologies in Health (2016) [149]	Caries: no caries-preventive effect for sealants compared with no sealants (1 trial)	Critically low	Very low	
Akera *et al.* (2022) [117]	DMFT: significantly lower for fissure sealant intervention compared with control group (1 trial)	Critically low	Very low	
Li *et al.* (2020) [150]	Incidence of new caries: no significant caries-preventive benefit for sealant application compared with fluoride varnish (5/6 pooled trials)§ DMFS: no significant caries-preventive benefit for sealant application compared with fluoride varnish (2/6 pooled trials)§; no significant difference for sealants compared with fluoride varnish (3 pooled trials)	Critically low	Very low	
				New carious lesions, caries incidence, caries, or incidence of new caries: slight overlap DMFT: no overlap DMFS: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

§Due to pooling, all trials were included in the overlap for all outcomes.

4.6.5.7.6 Other

None of the included systematic reviews reported on the effectiveness of other types of sealants for caries prevention in permanent dentition.

4.6.5.7.7 Combined interventions involving sealants

We identified four systematics review that reported on the effectiveness of combined interventions involving sealants for caries prevention in permanent dentition. Table 59 presents a high-level summary of treatment outcomes from the reviews that reported on these interventions.

Kashbour *et al*. [29] evaluated the effectiveness of dental sealants compared with fluoride varnishes, or sealants and fluoride varnishes in combination compared with fluoride varnishes alone, for preventing dental caries on the occlusal surfaces of the permanent teeth of children and adolescents. The findings from a single trial indicated very low-certainty evidence of a **significantly smaller mean increment of DMF on occlusal surfaces of first permanent molars following the application of resin-modified glass ionomer cement together with the provision of OHE (1 hour of education delivered every 3 months) compared with the biannual application of fluoride varnish together with the provision of OHE among children classified as being at high risk for caries** at 2 years follow-up. There was no statistically significant difference found among children classified as being at low risk for caries. It should be noted that participants in this trial also had exposure to fluoride toothpaste and fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest. The findings from a second trial indicated low-certainty evidence of a **slight, but not clinically important, benefit of resin-based sealant together with the provision of OHE (the frequency of education was not made explicit but appears to be every 3 months) on the increment of both DMFS and DMFT compared with the application of 0.1% fluoride varnish every 6 months (four applications in total) together with the provision of OHE** at 2 years follow-up.

Ahovuo-Saloranta *et al*. [38] compared the effects of different types of fissure sealants in preventing caries on occlusal surfaces of permanent teeth in children and adolescents who had different levels of caries incidence. The findings from a single trial (the same trial as was described in the Kashbour *et al*. review) indicated very low-certainty evidence of a **significantly smaller mean increment of DMF on occlusal surfaces of first permanent molars following the application of resin-modified glass ionomer cement together with the provision of OHE (1 hour of education delivered every 3 months) compared with the biannual application of fluoride varnish together with the provision of OHE** among children classified as being at high risk for caries at 2 years follow-up. There was no statistically significant difference found among children classified as being at low risk for caries. The findings from another single trial (the same trial as was described in the Kashbour *et al*. review but reporting on a different comparator) indicated low-certainty evidence of a **significantly lower increment of DMFS on permanent molars following the application of light-cured, fluoride-releasing resin-based sealant together with the provision of OHE compared with the provision of OHE alone** at 2 years follow-up.

Pagano *et al*. [135] evaluated whether the use of lasers at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries, improved fluoride uptake, and retention of sealant materials by improving traditional etching procedures. The findings from a single trial indicated very low-certainty evidence of a **significantly lower number of cases with new caries following the combined use of a carbon dioxide (CO_2) laser together with a sealant (sealant type not specified) compared with a control group of untreated teeth** at 4 years follow-up, resulting in a 78% reduced risk of developing new caries. It should be noted, however, that limited information was provided in relation to this trial in Pagano *et al*.'s review. The findings from another single trial indicated very low-certainty evidence of a **significantly lower number of cases with new caries following the**

combined use of an erbium-doped yttrium aluminium garnet (Er:YAG) laser together with a sealant (sealant type not specified) compared with sealant application alone at 18 months follow-up, resulting in a 56% reduced risk of developing new caries.

Zhang *et al*. [152] assessed the clinical effects of laser preparation compared with other types of chemical or mechanical preparation of the tooth surfaces used in fissure sealant placement. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the incidence of caries on permanent premolars or molars between the erbium, chromium-doped yttrium scandium gallium garnet (Er, Cr:YSGG) laser group compared with the acid etching group prior to application of a light-cure, low-viscosity, fluoride-releasing sealant** at 2 years follow-up. The findings from another single trial indicated very low-certainty evidence of **no significant difference in the incidence of caries on permanent premolars or molars between the Er:YAG laser together with acid etching group compared with the acid etching only group prior to application of a light-cured, nano-filled sealant** at 18 months follow-up.

Overall, **there is low-certainty evidence from a single trial of a significant benefit of combining sealant application with OHE compared with the delivery of OHE alone**, but the low- and very low-certainty evidence from two trials on the benefit of sealant application combined with OHE **when compared with the application of fluoride varnish is inconsistent**. The **very low-certainty evidence of the effectiveness of the combined use of sealants and lasers is inconsistent**. There was also a complete overlap of primary studies in relation to DMF on occlusal surfaces/DMFS and a very high overlap in relation to caries incidence. There was no overlap of primary studies in relation to DMFT.

Table 59 Main review outcomes for combined interventions involving sealants in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Kashbour *et al.* (2020) [29]	DMF on occlusal surfaces: significantly smaller for resin-modified glass ionomer cement together with provision of OHE compared with the biannual application of fluoride varnish together with provision of OHE (1 trial) DMFS: slight benefit for resin-based sealant together with provision of OHE compared with application of 0.1% fluoride varnish every 6 months together with provision of OHE (1 trial) DMFT: slight benefit for resin-based sealant together with provision of OHE compared with application of 0.1% fluoride varnish every 6 months together with provision of OHE (same trial as DMFS trial)	Low	Very low Low Low	
Ahovuo-Saloranta *et al.* (2017) [38]	DMF on occlusal surfaces: significantly smaller for resin-modified glass ionomer cement together with provision of OHE compared with the biannual application of fluoride varnish together with provision of OHE (1 trial) DMFS: significantly lower for light-cured, fluoride-releasing resin-based sealant together with provision of OHE compared with provision of OHE alone (1 trial)	Low	Very low Low (for consistency with Kashbour *et al*. (2020) as using the same trial evidence)	
Pagano *et al.* (2020) [135]	Percentage with new caries: significantly lower for a CO2 laser together with a sealant compared with a control group (1 trial); significantly lower for Er:YAG laser together with a sealant compared with sealant application alone (1 trial)	Critically low	Very low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Zhang *et al.* (2019) [152]	Incidence of caries: no significant difference for the Er, Cr:YSGG laser group compared with the acid etching group (1 trial); no significant difference for the Er:YAG laser together with acid etching group compared with the acid etching only group (1 trial)	Critically low	Very low	
				DMF on occlusal surfaces, or DMFS: complete overlap DMFT: no overlap Percentage with new caries, or incidence of caries: very high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.8 Lasers

We identified one systematic review that evaluated the effectiveness of lasers for caries prevention in permanent dentition. Table 60 presents a high-level summary of treatment outcomes from this review.

Pagano *et al*. [135] evaluated whether the use of lasers at sub-ablative energy induces enamel modification sufficient to improve it in the following ways: resistance against caries, improved fluoride uptake, and retention of sealant materials by improving traditional etching procedures. The findings from a single trial indicated very low-certainty evidence of **no significant difference in the number of cases with new caries in the first permanent molars following the use of a CO_2 laser alone compared with no treatment** at 4 years follow-up.

Table 60 Main review outcomes for lasers in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Pagano *et al.* (2020) [135]	New caries: no significant difference for a CO_2 laser compared with no treatment (1 trial)	Critically low	Very low	
				New caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.6.5.9 Complex interventions in permanent dentition

We identified three systematic reviews that reported on the effectiveness of complex interventions that included several intervention components for caries prevention in permanent dentition. Table 61 presents a high-level summary of treatment outcomes from the reviews that reported on these interventions.

Antonio *et al*. [146] assessed the overall caries-preventive effect of xylitol candies and lozenges according to explicit and specific selection criteria. The findings from a single trial indicated very low-certainty evidence of a **significantly lower increment of both DMFS and DMFT among participants in the intervention group who consumed one 49% xylitol candy three times every school day compared with participants in the control group at 1.5 years follow-up. Participants in both the intervention and control groups also received the combined intervention of OHE, supervised toothbrushing, sealant application, and restorative care**.

Kashbour *et al*. [29] evaluated the effectiveness of dental sealants compared with fluoride varnishes, or the effectiveness of sealants plus fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of the permanent teeth of children and adolescents. The findings from a single trial indicated very low-certainty evidence of a **significantly lower increment of DMFS at the whole mouth level between participants who received the combined intervention of application of resin-based sealant, fluoride varnish (applied semi-annually, concentration not specified), oral hygiene instruction, and supervised toothbrushing, compared with participants who received the combined intervention of fluoride varnish, oral hygiene instruction, and supervised toothbrushing** at 2 years follow-up. There was also very low-certainty evidence from the same trial of a **significantly lower likelihood of occurrence of new caries on sound occlusal surfaces in the intervention**

group compared with the control group. The review authors reported that a small proportion (5%) of participants in this trial also had exposure to fluoride tablets, and that all participants had exposure to fluoridated water. However, this was considered background fluoride exposure rather than part of the intervention of interest.

dos Santos *et al*. [118] assessed the effects of supervised toothbrushing on caries incidence in children and adolescents. The review included a single trial that reported on a complex intervention. The findings indicated very low-certainty evidence of a **significantly higher proportion of children remaining caries-free and a significantly lower increment of DMFT following an intervention consisting of 30-minute oral hygiene instruction sessions, practical demonstration and application of toothbrushing technique on 5 consecutive school days (which was repeated twice per year by a dental hygienist and a research assistant), and daily school-supervised toothbrushing by a research assistant with 1000 ppm fluoride toothpaste**. The comparison group received 30-minute oral hygiene instruction sessions on 5 consecutive school days, which was repeated twice per year by a dental hygienist and a research assistant. At 4 years follow-up, the proportion of children who remained caries free in their permanent teeth was 43.6% in the intervention group, compared with 33.0% in the control group.

Overall, **there is very low-certainty evidence from three single primary trials across three reviews of a caries-preventive effect of complex interventions on permanent teeth** that include a topical chemical intervention component (xylitol or fluoride lozenges, varnish, or toothpaste) and an educational and/or instructional intervention component, as well as supervised toothbrushing. In addition, two of the three primary trials involved the use of sealants. There was no overlap of primary studies in relation to the included outcomes across the three reviews.

Table 61 Main review outcomes for complex interventions in permanent dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Antonio *et al.* (2011) [146]	DMFS: significantly lower for the combination of 49% xylitol candy, OHE, supervised toothbrushing, sealant application, and restorative care compared with the control group (OHE, supervised toothbrushing, sealant application, and restorative care) (1 trial) DMFT: significantly lower for the combination of 49% xylitol candy, OHE, supervised toothbrushing, sealant application, and restorative care compared with the control group (OHE, supervised toothbrushing, sealant application, and restorative care) (same trial)	Low	Very low	
Kashbour *et al.* (2020) [29]	DMFS: significantly lower for combination of resin-based sealant, fluoride varnish, oral hygiene instruction, and supervised toothbrushing compared with combination of fluoride varnish, oral hygiene instruction, and supervised toothbrushing (1 trial) New caries: significantly lower for combination of resin-based sealant, fluoride varnish, oral hygiene instruction, and supervised toothbrushing compared with combination of fluoride varnish, oral hygiene instruction, and supervised toothbrushing (same trial)	Low	Very low	
dos Santos *et al.* (2018) [118]	DMFT: significantly lower for complex intervention compared with oral hygiene instruction sessions alone (1 trial) Percentage remaining caries free: significantly higher for complex intervention compared with oral hygiene instruction sessions alone (same trial)	Low	Very low	

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
				DMFS: no overlap DMFT: no overlap New caries, or percentage remaining caries free: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.7 Mixed dentition

4.7.1 Introduction

Mixed dentition systematic reviews included reviews that involved participants who had, at the time of the study, both primary and permanent teeth in their oral cavity, as well as studies that covered both the primary and permanent teeth populations, and studies that reported including human teeth that could not be classified as either primary or permanent teeth. There were 12 systematic reviews on the prevention of caries in mixed dentition: 1 review reported on the effectiveness of systematic chemicals other than fluoride, 1 review reported on the effectiveness of topical fluoride, 6 reviews reported on the effectiveness of other topical chemicals, and 1 review reported on the effectiveness of sealants. In addition, one review reported on the effectiveness of interventions delivered to pregnant women/mothers for caries prevention in the mixed dentition of their children, and six reviews reported on the effectiveness of combined interventions for caries prevention in mixed dentition. The findings presented in three reviews were not usable for the purposes of this overview of reviews. These reviews are identified throughout the results on mixed dentition where appropriate.

4.7.2 Methodological quality of reviews and their primary studies

We reported in Section 3.11 that we assigned seven critical domains in the adapted AMSTAR 2 quality assessment tool. The quality of all 12 included systematic reviews with respect to methodology was critically low (Appendix F). Two out of the 12 systematic reviews on mixed dentition did not establish any protocol prior to carrying out the review, and 5 of the reviews only partially established a protocol prior to review (item 2). As noted in Table 5, a 'partial yes' on this item in the adapted AMSTAR 2 instrument did not negatively affect quality assessment for Cochrane reviews. All 12 systematic reviews on mixed dentition received a 'yes' rating in relation to the comprehensiveness of the literature search (item 4). Six reviews did not provide a list of excluded studies and the reasons for exclusion (item 7). One review received a 'partial yes' rating on the item that relates to the use of a satisfactory technique for assessing the RoB in individual studies (item 9). Eleven reviews on mixed dentition did not use appropriate methods for the statistical combination of results from primary studies (item 11; this item was not applicable to the remaining review). One out of the 12 systematic reviews did not take RoB into account when interpreting the findings (item 13). Finally, six reviews on mixed dentition did not carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review (item 15; this item was not applicable to four reviews).

All 12 reviews were judged to be of critically low quality, indicating that they had more than one critical flaw. With the exception of the use of a satisfactory technique for assessing the RoB in the individual studies that were included in the review (item 9), every other type of critical flaw was present in the reviews for mixed dentition.

4.7.3 GRADE rating

The GRADE (or certainty) of evidence is presented alongside each of the outcomes in Section 4.7.5, and the number of downgrades applied and reasons for downgrading are presented in Appendix K. In mixed dentition, one review presented moderate-certainty evidence, as assessed using the modified GRADE algorithm. This indicates that we are moderately confident in the effect estimate; that is, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different [115]. The reason for downgrading to moderate certainty of evidence in this review was the quality rating on the adapted AMSTAR 2 instrument. Three reviews presented low-certainty evidence, indicating that our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect [115]. The reasons for downgrading to low certainty of evidence included

inadequate randomisation, inadequate blinding of outcome ascertainment, and quality rating on the adapted AMSTAR 2 instrument. Five reviews presented very low-certainty evidence, indicating that we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect [115]. The reasons for downgrading to very low certainty of evidence included study design, inadequate randomisation, inadequate blinding of outcome ascertainment, high heterogeneity, inadequate sample size, and quality rating on the adapted AMSTAR 2 instrument.

There were no reviews on mixed dentition without any downgrades, and therefore no reviews that presented high-certainty of evidence. It can be understood that reviews with moderate-certainty evidence had one to two inadequacies, whereas reviews with low-certainty evidence had three to four inadequacies and reviews with very low-certainty evidence had five or more inadequacies. Therefore, the GRADE score is used as a summary indicator of the certainty of evidence for the individual outcomes in each review. It is important to note that the GRADE score takes account of the methodological quality score of each systematic review and its primary studies.

4.7.4 Classification of combined interventions

As mentioned in Section 3.8, we classified all systematic reviews according to the types of interventions being evaluated. Six reviews on mixed dentition included trials that delivered combined interventions for caries prevention in mixed dentition. Based on the intervention components described in the systematic reviews, we classified and subclassified combined interventions for caries prevention in mixed dentition into those that involved:

- Topical fluoride combined with one other non-fluoride topical chemical (two reviews)
- A non-fluoride topical chemical combined with one other intervention component, either:
  - Another non-fluoride topical chemical (one review), or
  - Another intervention component (one review; however, the results were not usable).
- Complex interventions that included three or more intervention components for caries prevention in mixed dentition (two reviews).

4.7.5 Results

4.7.5.1 Attendance for dental assessment

4.7.5.1.1 Scheduled dental appointments

None of the included systematic reviews reported on the effectiveness of scheduled dental appointments for caries prevention in mixed dentition.

4.7.5.1.2 Scheduled primary care appointments

None of the included systematic reviews reported on the effectiveness of scheduled primary care appointments for caries prevention in mixed dentition.

4.7.5.2 Dental hygiene

4.7.5.2.1 Supervised toothbrushing

None of the included systematic reviews reported on the effectiveness of supervised toothbrushing for caries prevention in mixed dentition.

4.7.5.2.2 Flossing

None of the included systematic reviews reported on the effectiveness of flossing as an intervention for caries prevention in mixed dentition.

4.7.5.2.3 Interdental cleaning devices

None of the included systematic reviews reported on the effectiveness of interdental cleaning devices for caries prevention in mixed dentition.

4.7.5.2.4 Professional scaling or cleaning

None of the included systematic reviews reported on the effectiveness of professional scaling or cleaning for caries prevention in mixed dentition.

4.7.5.3 Systemic fluoride

4.7.5.3.1 Milk

None of the included systematic reviews reported on the effectiveness of fluoridated milk for caries prevention in mixed dentition.

4.7.5.3.2 Salt

None of the included systematic reviews reported on the effectiveness of fluoridated salt for caries prevention in mixed dentition.

4.7.5.3.3 Sugar

None of the included systematic reviews reported on the effectiveness of fluoridated sugar for caries prevention in mixed dentition.

4.7.5.3.4 Supplements

None of the included systematic reviews reported on the effectiveness of fluoride supplements for caries prevention in mixed dentition.

4.7.5.4 Other systemic chemicals

4.7.5.4.1 Vitamin D

We identified one systematic review on the effectiveness of vitamin D interventions for caries prevention in mixed dentition. Table 62 presents a high-level summary of treatment outcomes from this review.

Hujoel [153] presented low-certainty evidence from 24 pooled trials of a **significantly lower incidence of caries following the use of vitamin D supplementation compared with a control**. The specific measures used to assess caries incidence varied across the included trials, as did the follow-up period. However, the median follow-up period was 1 year. Three forms of supplementation were used across the 24 trials: vitamin D_2 was used in 15 trials, vitamin D_3 was used in 12 trials, and ultraviolet radiation was used in 6 trials. The median dose of vitamin D_2 supplementation was 3,750 international units (IU), and the median dose of vitamin D_3 was 800 IU. Either erythemal (four trials) or full-spectrum fluorescent lighting (two trials) was used in the six trials that examined ultraviolet radiation. Subgroup analyses indicated a significant caries-preventive effect of all three forms of vitamin D compared with a control.

Table 62 Main review outcomes for vitamin D in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Hujoel (2013) [153]	Incidence of caries: significantly lower for vitamin D supplementation compared with a control (24 pooled trials)	Critically low	Low	
				Incidence of caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.7.5.4.2 Calcium

None of the included systematic reviews reported on the effectiveness of calcium-based interventions for caries prevention in mixed dentition.

4.7.5.4.3 Sialagogues

None of the included systematic reviews reported on the effectiveness of sialagogues for caries prevention in mixed dentition.

4.7.5.4.4 Zinc

None of the included systematic reviews reported on the effectiveness of zinc-based interventions for caries prevention in mixed dentition.

4.7.5.5 Topical fluoride

4.7.5.5.1 Toothpaste

We identified one systematic review that evaluated the effectiveness of fluoride toothpaste for caries prevention in mixed (or undetermined and therefore assumed to be mixed) dentition. Figuero *et al*. [102] assessed the effect of mechanical and/or chemical plaque control methods, including the use of fluoride toothpaste, on plaque reduction and caries increment in systemically healthy patients. However, we noticed during data extraction that in this review, some of the results presented in the text were not consistent with results presented in the tables. As a result of this, as well as the limited information provided in the review regarding the nature of the interventions and the findings, the results were excluded from our evidence synthesis.

As such, there is **a paucity of evidence** available to determine whether fluoride toothpaste can reduce the risk of caries incidence in mixed dentition.

4.7.5.5.2 Mouth rinses

Figuero *et al*.'s review [102] was the only systematic review we identified that evaluated the effectiveness of fluoride mouth rinse for caries prevention in mixed (or undetermined and therefore assumed to be mixed) dentition. However, as described in the previous section, the results from this review were excluded from our evidence synthesis.

As such, there is **a paucity of evidence** available to determine whether fluoride mouth rinse can reduce the risk of caries incidence in mixed dentition.

4.7.5.5.3 Foams

None of the included systematic reviews reported on the effectiveness of fluoride foams for caries prevention in mixed dentition.

4.7.5.5.4 Gels

None of the included systematic reviews reported on the effectiveness of fluoride gels for caries prevention in mixed dentition.

4.7.5.5.5 Solutions

None of the included systematic reviews reported on the effectiveness of fluoride-based solutions for caries prevention in mixed dentition.

4.7.5.5.6 Slow-release fluoride devices

None of the included systematic reviews reported on the effectiveness of slow-release fluoride devices for caries prevention in mixed dentition.

4.7.5.5.7 Varnishes

None of the included systematic reviews reported on the effectiveness of fluoride varnishes for caries prevention in mixed dentition.

4.7.5.5.8 Mixed forms of topical fluoride

None of the included systematic reviews pooled findings on mixed forms of topical fluoride as standalone interventions for caries prevention in mixed dentition. However, evidence from reviews that report pooled analyses of mixed types of topical fluoride can be found in Section 4.7.5.5.9 on combined interventions involving topical fluoride.

4.7.5.5.9 Combined interventions involving topical fluoride

4.7.5.5.9.1 Topical fluoride together with other topical chemicals

We identified two systematic reviews that reported on the effectiveness of combined interventions involving topical fluoride and any other topical chemicals in mixed (or undetermined and therefore assumed to be mixed) dentition. Table 63 presents a high-level summary of treatment outcomes from reviews that reported on these interventions.

Gupta *et al*. [154] examined the effectiveness of combined therapy using topical fluoride along with an antimicrobial agent compared with topical fluoride monotherapy in preventing dental caries among children aged 1–16 years. The findings from five pooled trials indicated low-certainty evidence of a **significant caries-preventive effect (measured using the ds index in one trial, the DFS index in two trials, and caries incidence rate in two trials) associated with the combined use of topical fluoride together with antimicrobial agents compared with the use of topical fluoride alone** at 1–3 years follow-up. In relation to the type of topical fluoride, fluoride toothpaste was used in four trials and fluoride gel was used in one trial. In relation to the type of antimicrobial agents, CHX gel was used in two trials, povidone-iodine gel was used in one trial, and xylitol-containing toothpaste was used in two trials. The dose and form of fluoride and antimicrobial agents in the pooled trials were as follows: 0.304% fluoride toothpaste together with 0.12% CHX gel (one trial), 250 ppm fluoride toothpaste together with 1% CHX gel (one trial), 1.23% APF gel together with 2 mL of povidone-iodine (one trial), and toothpaste containing 1100 ppm fluoride and 10% xylitol (two trials). It should be noted that two out of the five pooled trials involved the delivery of a complex intervention. In addition to fluoride toothpaste together with xylitol, one trial

included OHE together with dietary counselling, and another trial included oral prophylaxis together with restorative therapy.

Sharda *et al*. [114] examined the remineralising potential and caries-preventive efficacy of combined therapy using CPP-ACP/bioactive glass/xylitol/ozone and topical fluoride compared with topical fluoride monotherapy on high-risk individuals. The findings from five pooled trials indicated low-certainty evidence of a **significant caries-preventive benefit (measured using the mean increment of DMFS/DMFT and dmfs/dmft, and the proportion of participants with new carious lesions) following the combined use of topical fluoride together with other topical chemicals compared with the use of topical fluoride alone** at 2–3 years follow-up. The topical fluoride used in all five trials was fluoride toothpaste (400–1100 ppm fluoride), and the antimicrobial agents used were 10% CPP-ACP cream in two trials, 3% CPP-ACP gum in one trial, and toothpaste containing 10% xylitol in two trials. It should be noted that this outcome was identified as a secondary outcome in the review. It should also be noted that three out of the five pooled trials are also included in the pooled analysis conducted in the Gupta *et al*. review described in the previous paragraph, and like what Gupta *et al*. reported, a subgroup analysis in Sharda *et al*.'s review showed that this effect was largely a result of the two trials that included toothpaste containing xylitol and fluoride.

Overall, **low-certainty evidence from two reviews indicates a caries-preventive effect of combined interventions involving the use of topical fluoride (toothpaste or gel across the included trials in the two reviews) and another non-fluoride topical chemical (CHX, povidone-iodine, xylitol, and CPP-ACP across the included trials in the two reviews).** There was a very high overlap of primary studies across the two reviews in relation to both the tooth surface index and the incidence of caries outcomes.

Table 63 Main review outcomes for topical fluoride combined with other topical chemicals in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Gupta *et al.* (2020) [154]	ds: significant caries-preventive effect for topical fluoride together with antimicrobial agents compared with use of topical fluoride alone (1/5 pooled trials)§ DFS: significant caries-preventive effect for topical fluoride together with antimicrobial agents compared with use of topical fluoride alone (2/5 pooled trials)§ Incidence of caries: significant caries-preventive effect for topical fluoride together with antimicrobial agents compared with use of topical fluoride alone (2/5 pooled trials)§	Critically low	Low	
Sharda *et al.* (2021) [114]	DMFS/DMFT and dmfs/dmft: significant preventive benefit for topical fluoride together with other topical chemicals compared with the use of topical fluoride alone (5 pooled trials) Percentage with new carious lesions: significant preventive benefit for topical fluoride together with other topical chemicals compared with the use of topical fluoride alone (5 pooled trials)	Critically low	Low	
				ds, DFS, DMFS/DMFT, or dmfs/dmft: very high overlap Incidence of caries, or percentage with new carious lesions: very high overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

§Due to pooling, all trials were included in the overlap for all outcomes.

4.7.5.6 Other topical chemicals

4.7.5.6.1 Antioxidants

None of the included systematic reviews reported on the effectiveness of antioxidants for caries prevention in mixed dentition.

4.7.5.6.2 Toothpaste

None of the included systematic reviews reported on the effectiveness of non-fluoride toothpaste for caries prevention in mixed dentition.

4.7.5.6.3 Antimicrobial agents (minus CHX)

None of the included systematic reviews reported on the effectiveness of antimicrobial agents for caries prevention in mixed dentition.

4.7.5.6.4 Arginine and its derivatives

None of the included systematic reviews reported on the effectiveness of arginine-based interventions for caries prevention in mixed dentition.

4.7.5.6.5 CHX

We identified two systematic reviews that reported on the **effectiveness of CHX** for caries prevention in mixed dentition. Table 64 presents a high-level summary of the treatment outcomes for this intervention category.

The first review was conducted by Figuero *et al*. [102]. As described in Section 4.7.5.5.1 the results from this review were excluded from our evidence synthesis.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including CHX) on the market in the USA. The findings from two pooled trials indicated very low-certainty evidence of **no significant caries-preventive effect associated with the application of 1:1 CHX/thymol varnish applied every 3 months (for 1 year in one trial and 2 years in the other trial) compared with no varnish application** at 1 and 2 years follow-up. One of the pooled trials reported on mixed dentition using the DFS and dmfs indexes, and the other trial reported on primary dentition using the dmfs index. There was no overlap of primary studies for included outcomes across the two reviews.

Table 64 Main review outcomes for CHX in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Figuero *et al.* (2017) [102]	None usable	Critically low	N/A	
Rethman *et al.* (2011) [121]	DFS: no significant caries-preventive effect for 1:1 CHX/thymol varnish compared with no varnish application (1/2 pooled trials)§ dmfs: no significant caries-preventive effect for 1:1 CHX/thymol varnish compared with no varnish application (2/2 pooled trials)	Critically low	Very low	
				DFS or dmfs: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

§Due to pooling, all trials were included in the overlap for all outcomes.

4.7.5.6.6 Calcium phosphate agents

None of the included systematic reviews reported on the effectiveness of calcium phosphate agents for caries prevention in mixed dentition.

4.7.5.6.7 Ozone

None of the included systematic reviews reported on the effectiveness of ozone-based interventions for caries prevention in mixed dentition.

4.7.5.6.8 Nanomaterials

None of the included systematic reviews reported on the effectiveness of nanomaterials for caries prevention in mixed dentition.

4.7.5.6.9 Probiotics

We identified one systematic review that reported on the effectiveness of probiotics for caries prevention in mixed (or undetermined and therefore assumed to be mixed) dentition. Table 65 presents a high-level summary of treatment outcomes from this review.

Poorni *et al.* [155] reviewed the published literature on various probiotic *Streptococcus* strains as a preventive and therapeutic method for dental caries management. Limited information was provided in the review. However, the findings from a single trial indicated very low-certainty evidence of a **significantly reduced likelihood of developing new caries associated with the consumption of *salivarius***

M18 in lozenges (two lozenges per day for 3 months) compared with a placebo. The follow-up period was not reported.

Table 65 Main review outcomes for probiotics in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Poorni *et al.* (2019) [155]	New caries: significantly reduced likelihood for consumption of *salivarius* M18 in lozenges compared with a placebo (1 trial)	Critically low	Very low	
				New caries: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.7.5.6.10 Propolis

None of the included systematic reviews reported on the effectiveness of propolis for caries prevention in mixed dentition.

4.7.5.6.11 Silicates

None of the included systematic reviews reported on the effectiveness of silicates for caries prevention in mixed dentition.

4.7.5.6.12 Xylitol

We identified four systematic reviews on the effectiveness of xylitol for caries prevention in mixed dentition. Table 66 presents a high-level summary of treatment outcomes for this intervention category.

Riley *et al*. [133] assessed the effects of different xylitol-containing products on preventing dental caries in children and adults. Only one included trial compared xylitol (7.5 g per day) candy with a control (sorbitol) candy over 3 years. The information provided about this trial in Riley *et al*.'s review was very limited, so we assumed the trial involved mixed dentition. However, the systematic review authors were unable to use the data in analyses and the findings were therefore not reported. **None of the included trials** in Riley *et al*.'s review reported on the effectiveness of xylitol-containing candy, syrup, sucking tablets, (non-fluoride) toothpaste, tablets, or wipes in mixed dentition.

Marghalani *et al*. [156] evaluated the effectiveness of xylitol in reducing dental caries in children compared with no treatment, a placebo, or preventive strategies. The findings from 10 pooled trials indicated very low-certainty evidence of a **significant caries-preventive effect (measured using mean scores or increment of DMFS/DMFT and dmfs/dmft, combined) following the consumption or use of xylitol (gum in 6 trials, toothpaste in 2 trials, lozenges in 1 trial, and wipes in 1 trial) compared with no xylitol** at at least 1 year follow-up. The dose of xylitol in gum varied across the trials: 2.50 g per day (one trial), 2.90 g per day (one trial), 4.30–8.50 g per day (one trial), 5.00 g per day (two trials), and 10.67 g per day (one trial). The dose of xylitol in toothpaste was 10% (two trials). The dose of xylitol provided in lozenges was 2.5 g per day (one trial), and the dose of xylitol provided in wipes was 4.2 g per day (one trial). The results also showed that the effect of xylitol may be greater at higher doses (greater than 4 g per day). However, this potential effect of dosage was observational, as dose was not randomised in the

included trials. It should be noted that 2 out of the 10 pooled trials delivered combined interventions, one involving supervised toothbrushing at home and at school twice per day with toothpaste containing 10% xylitol and 0.243% sodium fluoride (NaF)/silica, and the other involving supervised toothbrushing at home and at school twice per day with toothpaste containing 10% xylitol and 0.836% sodium monofluorophosphate (1100 ppm fluoride) in a dicalcium phosphate dihydrate base.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents (including xylitol) on the market in the USA. The findings from three pooled trials indicated very low-certainty evidence of a **significantly lower increment of DMFS/dmfs (DMFS in two trials and dmfs in one trial) following the consumption of xylitol candies or tablets compared with no candy or tablet consumption**. In two of the pooled trials, participants chewed candies three times per day for 5–10 minutes. In the trial on xylitol tablets, participants consumed one tablet per day for 6 months and two tablets per day thereafter. The follow-up periods were 1.5 years, 2.0 years, and 3.0 years. The concentration of xylitol in candy was 49%, and the concentration of xylitol in tablets was 0.48 g. In one of the pooled trials on xylitol candy, the candy also contained one of two sweeteners: mannitol or polydextrose. It should be noted that, according to the information provided in the review, participants in one of the pooled trials used fluoride toothpaste. However, this was considered background fluoride exposure rather than part of the intervention of interest. In addition, participants in at least two out of the three pooled trials received other unspecified preventive measures as part of routine care (the nature of any ongoing dental care was not reported in the third trial). Rethman *et al*. also reported findings from three pooled trials indicating very low-certainty evidence of a **significant caries-preventive effect (measured using DMFS scores in two trials and the presence of carious lesions in primary teeth in one trial) associated with the consumption of xylitol gum compared with the consumption of sorbitol gum**. In the first trial, participants chewed 589 mg xylitol gum five times per day for 10 minutes. In the second trial, participants chewed 65% xylitol gum three times per day (for total xylitol consumption of 4.3 g per day) or five times per day (for total xylitol consumption of 8.5 g per day). In the third trial, participants chewed 60.5% xylitol gum (for total xylitol consumption of 10.42 g per day) or 65.0% xylitol gum (for total xylitol consumption of 10.67 g per day) 10 times per day. The follow-up periods were 24, 36, and 40 months. It should be noted that, from the information provided in the review, participants in one of the pooled trials used fluoride toothpaste, and participants in one of the trials were exposed to low-fluoride water. However, this was considered background fluoride exposure rather than part of the intervention of interest.

Newton *et al*. [157] examined the difference in the level of dental caries in adults and children who chewed sugar-free gum compared with those who did not chew sugar-free gum or who used alternatives such as lozenges, candies, mouth rinses, tablets, and other non-chewing controls. The findings from eight pooled trials indicated very low-certainty evidence of a **significant caries-preventive benefit (i.e. lower increment of DMFS/DMFT and dmfs/dmft) associated with the consumption of xylitol gum compared with a control/no treatment group**, resulting in a 33% reduced risk of developing caries among those in the xylitol gum intervention group. The follow-up periods varied, ranging from 6 months (one trial) to 6 years (one trial). Xylitol gum was chewed three times per day in six trials and once per day in one trial (the frequency of chewing was not reported in one trial). The concentration of xylitol in gum was only reported in one trial (15% and 65%, depending on the intervention group).

Overall, there is **very low-certainty evidence of a significant caries-preventive effect of xylitol (delivered via candy, tablets, toothpaste, lozenges, or wipes, but particularly when delivered via chewing gum)** in analyses on mixed dentition. There was a very high degree of overlap of primary studies in relation to DMFS/DMFT and dmfs/dmft, but no overlap in relation to the incidence of carious lesions.

Table 66 Main review outcomes for xylitol in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Riley *et al.* (2015) [133]	None usable	Low	N/A	
Marghalani *et al.* (2017) [156]	DMFS/DMFT and dmfs/dmft: significant caries-preventive effect for xylitol compared with no xylitol control groups (10 pooled trials)	Critically low	Very low	
Rethman *et al.* (2011) [121]	DMFS/dmfs: significantly lower for xylitol candies or tablets compared with no candy/tablet (3 pooled trials); significant preventive effect for xylitol gum compared with sorbitol gum (2/3 pooled trials)§ Caries lesions: significant preventive effect for xylitol gum compared with sorbitol gum (1/3 pooled trials)§	Critically low	Very low	
Newton *et al.* (2020) [157]	DMFS/DMFT and dmfs/dmft: significant preventive benefit for xylitol gum compared with control/no treatment group (8 pooled trials)	Critically low	Very low	
				DMFS/DMFT or dmfs/dmft: very high overlap Caries lesions: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

§Due to pooling, all trials were included in the overlap for all outcomes.

4.7.5.6.13 Sorbitol

None of the included systematic reviews reported on the effectiveness of sorbitol for caries prevention in mixed dentition.

4.7.5.6.14 Polyols (e.g. gum with sorbitol, xylitol, and other polyols combined)

None of the included systematic reviews reported on the effectiveness of polyols for caries prevention in mixed dentition.

4.7.5.6.15 Combined interventions involving other topical chemicals

4.7.5.6.15.1 Combination of non-fluoride topical chemicals

We identified one systematic review that evaluated the effectiveness of combined non-fluoride topical chemicals in mixed (or undetermined and therefore assumed to be mixed) dentition. Table 67 presents a high-level summary of treatment outcomes from this review.

Rethman *et al*. [121] reported findings from a single trial indicating very low-certainty evidence of a **significantly lower increment of DMFS and defs following the consumption of a sugar-free confection (mints) containing arginine bicarbonate/calcium carbonate (two mints consumed twice daily) compared with the consumption of sugar-free mints without arginine bicarbonate/calcium carbonate** at 1 year follow-up. It should be noted that limited information was provided in the review. Therefore, it is unclear whether the trial authors reported on DMFS and defs separately or together. In addition, it is indicated in the review that participants in this trial had exposure to fluoride toothpaste and fluoridated salt. However, this was considered background fluoride exposure rather than part of the intervention of interest.

Table 67 Main review outcomes for combined topical chemicals in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	DMFS/defs: significantly lower for arginine bicarbonate/calcium carbonate mints compared with sugar-free mints (1 trial)	Critically low	Very low	
				DMFS/defs: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.7.5.6.15.2 Other topical chemicals together with other interventions

We identified one systematic review that evaluated the effectiveness of a non-fluoride topical chemical plus an additional active intervention component outside of topical chemicals in mixed dentition. Zhou *et al*. [103] investigated the efficacy of various strategies in caries and gingivitis prevention among children and adolescents with intellectual disabilities. The only relevant trial included in the review reported on the effectiveness of calcium sucrose phosphate (compared with fluoride) toothpaste used via powered (compared with manual) toothbrushes. However, the results were not presented in a way that is appropriate for the purposes of this overview of reviews and limited information was provided. Therefore, the findings were excluded from our data synthesis.

As such, there is **a paucity of evidence** available to determine whether combined interventions involving a non-fluoride topical chemical plus an additional active intervention component outside topical chemicals can reduce the risk of caries incidence in mixed dentition.

4.7.5.7 Sealants

4.7.5.7.1 Resin

None of the included systematic reviews reported on the effectiveness of resin-based sealants for caries prevention in mixed dentition.

4.7.5.7.2 Glass ionomer

None of the included systematic reviews reported on the effectiveness of glass ionomer sealants for caries prevention in mixed dentition.

4.7.5.7.3 Ormocer

None of the included systematic reviews reported on the effectiveness of ormocer sealants for caries prevention in mixed dentition.

4.7.5.7.4 Hybrid

None of the included systematic reviews reported on the effectiveness of hybrid sealants for caries prevention in mixed dentition.

4.7.5.7.5 Combined

None of the included systematic reviews reported on the effectiveness of combined sealants for caries prevention in mixed dentition.

4.7.5.7.6 Other

We identified one systematic review on the effectiveness of other types of sealants for caries prevention in mixed dentition. Table 68 presents a high-level summary of treatment outcomes from this review.

Singal *et al*. [9] reviewed the evidence for the remineralising and caries-preventive efficacy of various calcium phosphate derivatives. The findings from a single trial indicated very low-certainty evidence of a **significantly lower proportion of children developing new carious lesions following the application of ACP-based sealant compared with the application of fluoride-based sealant** at 1 year follow-up. It should be noted that limited information was provided on this trial in the review.

Table 68 Main review outcomes for other sealants in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRACE certainty of evidence†	Overlap of primary studies‡
Singal *et al.* (2022) [9]	Percentage developing new carious lesions: significantly lower for ACP-based sealant compared with fluoride-based sealant (1 trial)	Critically low	Very low	
				Percentage developing new carious lesions: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.7.5.8 Lasers

None of the included systematic reviews reported on the effectiveness of lasers for caries prevention in mixed dentition.

4.7.5.9 Interventions delivered to pregnant women/mothers for caries prevention in the mixed dentition of their children

We identified one systematic review that reported on the effectiveness of interventions delivered to pregnant women/mothers for caries prevention in the mixed dentition of their children. Table 69 presents a high-level summary of treatment outcomes from this review.

Rethman *et al*. [121] conducted a systematic review to develop evidence-based clinical recommendations on non-fluoride caries-preventive agents on the market in the USA. The findings from one trial on calcium supplementation indicated very low-certainty evidence of a **27% reduced risk of the development of caries in the mixed dentition of children (measured via the DMFT/dmft index) associated with maternal consumption of 2 g of calcium per day compared with a placebo** at 12 years follow-up. It should be noted that limited information was provided on this trial in the review, including information pertaining to the statistical significance of the outcome.

Table 69 Main review outcomes for interventions delivered to pregnant women/mothers for caries prevention in the mixed dentition of their children

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Rethman *et al.* (2011) [121]	DMFT/dmft: reduced risk for calcium supplement compared with placebo (1 trial)	Critically low	Very low	
				DMFT/dmft: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

4.7.5.10 Complex interventions in mixed dentition

We identified two systematic reviews that reported on the effectiveness of complex interventions that included several active intervention components for caries prevention in mixed dentition. Table 70 presents a high-level summary of treatment outcomes from the reviews that reported on these interventions.

Figuero *et al*. [102] assessed the effect of mechanical and/or chemical plaque control methods, including the use of fluoride toothpaste, on plaque reduction and caries increment in systemically healthy patients. However, for reasons described in Section 4.7.5.5, the results were excluded from our evidence synthesis.

Yu *et al*. [138] assessed whether the combination of professional fluoride application and use of regular fluoride toothpaste has an additional benefit over using regular fluoride toothpaste alone for children aged under 16 years. The findings from four pooled trials indicated moderate-certainty evidence of **no significant difference in caries incidence (precise indicator unspecified) between participants in the group that received the combination of fluoride toothpaste, fluoride varnish, and additional active intervention components compared with the group that received all intervention components minus the fluoride varnish** at 2–3 years follow-up. All trials used 5% NaF varnish together with 1000–1450 ppm fluoride toothpaste. Three out of the four pooled trials involved two additional intervention components in addition to fluoride varnish and fluoride toothpaste: OHE or oral health counselling was provided in all three of these trials, dietary counselling was provided in two of the trials, and supervised toothbrushing was provided in one of the trials. The fourth trial indicated that usual care only was provided to participants in both the intervention and control groups. It should be noted that, from the information provided in the review, at least two out of the four pooled trials reported some additional exposure to fluoride (via water or milk). However, this was considered background fluoride exposure rather than part of the intervention of interest. There was no overlap of primary studies across the two reviews in relation to the included outcome.

Table 70 Main review outcomes for complex interventions in mixed dentition

Review	Outcome measure(s)	AMSTAR 2 quality of review*	GRADE certainty of evidence†	Overlap of primary studies‡
Figuero *et al.* (2017) [102]	None usable	Critically low	N/A	
Yu *et al.* (2021) [138]	Caries incidence: no significant difference for the combination of fluoride toothpaste, fluoride varnish, and additional active intervention components compared with all intervention components minus the fluoride varnish (4 pooled trials)	Critically low	Moderate	
				Caries incidence: no overlap

*AMSTAR 2 overall methodological quality ratings: High, moderate, low, or critically low.

†GRADE certainty of evidence ratings: High, moderate, low, or very low.

‡Overlap: None (0%), slight (1–5%), moderate (6–10%), high (11–15%), very high (≥15%), or complete (100%).

5 Discussion

5.1 Summary findings

A total of 66 reviews were included in this overview of reviews on individual-based interventions to prevent carious lesions in primary dentition, permanent dentition, and mixed dentition. The findings from many systematic reviews were obtained in the context of existing exposure to caries-preventive agents or activities among participants in the primary studies being evaluated. We extracted this information when it was reported and presented it alongside the relevant findings throughout Section 4.

5.1.1 Primary dentition

We identified 38 systematic reviews on caries prevention in primary dentition, albeit evidence from 7 of these reviews could not be presented as the findings were either not usable for the purposes of this overview of reviews or no primary studies on the intervention of interest were found. The certainty of the evidence reported in the remaining 31 reviews ranged from very low to moderate, as assessed using the modified GRADE algorithm. Four of the reviews reported moderate-certainty evidence. However, the moderate-certainty outcomes in two of these reviews[124,158] were based on single trials. This left two systematic reviews that presented moderate certainty evidence from two or more trials. The review by Yu *et al*. [138] presented moderate-certainty evidence based on a pooled analysis of six trials showing no significant difference in the increment of d(e/m)fs between participants who received a complex intervention involving fluoride varnish, fluoride toothpaste, and an additional active intervention component which varied across the pooled trials, compared with participants in the comparator groups who mostly received the same intervention components with the exception of fluoride varnish. Notably, while the certainty of evidence in this case was moderate, the review was judged to be of critically low quality using our adapted version of AMSTAR 2 [92]. The review by Wang *et al*. [127] presented moderate-certainty evidence from four trials synthesised narratively showing a significantly lower increment in various indexes of dental caries following the application of CHX products (gel or varnish) compared with a placebo or no CHX application. Wang *et al*. also presented moderate-certainty evidence from two trials synthesised narratively showing no significant difference in dmfs scores following the consumption of xylitol compared with no treatment or placebo. In relation to combined interventions, the same review presented moderate-certainty evidence from two trials synthesised narratively showing no significant difference in the proportion of children developing new caries with the combined use of CHX gel and fluoride toothpaste compared to the use of fluoride toothpaste alone.

The evidence for all other outcomes in primary dentition was judged to be of low or very low certainty using the modified GRADE algorithm and should therefore be interpreted with caution.

5.1.1.1 Singular interventions

We found evidence from one or more systematic reviews for 14 categories of singular interventions for caries prevention in primary dentition. Overall, there was consistent, or slightly inconsistent but predominantly positive, evidence for a significant caries-preventive effect of fluoridated milk (two systematic reviews [26,119]), fluoride supplements (two systematic reviews [48,111]), fluoride toothpaste (two systematic reviews [21,122]), fluoride gel (one systematic review [25]), fluoride solutions (one systematic review [123]), antimicrobial agents (minus CHX; one systematic review [127]), calcium phosphate agents (one systematic review [127]), probiotics (three systematic reviews [41,113,120]), and laser interventions (one systematic review [135]). However, the total evidence in favour of fluoride solutions, antimicrobial agents (minus CHX), calcium phosphate agents, and laser interventions consisted of a single primary trial included in one systematic review. In addition, in comparison with fluoride

supplements and probiotic interventions, the volume of evidence in favour of fluoridated milk, fluoride toothpaste, and fluoride gel interventions was quite low: approximately two or three trials included in one or two systematic reviews. There were two categories of interventions for which the evidence was mixed: namely, fluoride varnish (two systematic reviews [108,125]) and CHX (four systematic reviews [121,126,127,132]). Regarding fluoride varnish, however, the evidence appeared to vary according to the outcome measure; there was a predominantly (albeit not exclusively) significant caries-preventive effect of fluoride varnish application on the increment of d(e/m)fs and d(e/m)ft, but no significant effect on the proportion of participants developing one or more new carious lesions on primary teeth.

The remaining three categories of singular interventions for which we identified systematic review evidence for caries prevention in primary dentition were xylitol, resin-based sealants, and glass ionomer sealants. The evidence for xylitol was drawn from four systematic reviews [48,121,127,133] that predominantly indicated no significant benefit of xylitol (delivered via sucking tablets, tablets, wipes, or gummy bears) for caries prevention when compared with a placebo or no treatment. There was evidence from a single trial reported in two systematic reviews [121,133], however, of a significant caries-preventive effect of high-concentration xylitol syrup compared with low-concentration xylitol syrup. The evidence for resin-based sealants was drawn from only three primary trials included in two systematic reviews [129,134]. Neither review presented evidence from standalone interventions comparing resin-based sealants with no sealant; rather, the comparisons were between different types of resin-based sealants or between resin-based sealants and glass ionomer sealants, and no significant differences were observed. The evidence for glass ionomer sealants consisted of a single trial included in one systematic review [129], which showed no significant caries-preventive effect of glass ionomer sealants compared with no sealant.

It is worth noting that the methodological quality of 12 out of the above 21 systematic reviews that evaluated the effectiveness of standalone interventions for caries prevention in primary dentition was judged to be of critically low quality using our adapted version of AMSTAR 2; the methodological quality of the remaining reviews was judged to be low (7 reviews) or high (2 reviews).

5.1.1.2 Combined interventions

The evidence on the effectiveness of combined interventions for caries prevention in primary dentition was drawn from 15 systematic reviews. Regarding combined interventions involving systemic fluoride, a single primary trial included in one systematic review [120] showed a significant caries-preventive effect of combining probiotics and fluoride in milk. In relation to combined interventions involving two forms of topical fluoride, a single primary trial reported in one systematic review [125] showed a likely caries-preventive benefit of combining the application of fluoride varnish with the use of fluoride toothpaste, albeit the statistical significance of this result was not indicated in the review.

The evidence for combined interventions involving topical fluoride and another non-fluoride topical chemical was drawn from four systematic reviews [9,126–128], and indicated no caries-preventive benefit of combining topical fluoride (toothpaste or mixed forms) with CHX gel, CPP-ACP, or povidone-iodine. One primary trial from one systematic review [127] did show a significant reduction in the increment of defs associated with the use of fluoride toothpaste combined with the consumption of confections containing arginine compared with the use of fluoride toothpaste combined with the consumption of control confections.

The evidence for combined interventions involving topical fluoride and another active intervention component besides topical chemicals was drawn from six systematic reviews [21,118,124,129–131]. Two primary trials included in one systematic review [129] showed no significant benefit of combining fluoride varnish with sealant application. The remainder of the evidence on the effectiveness of combined

interventions involving fluoride varnish for caries prevention at the individual, tooth, and tooth surface levels predominantly indicated no clinical benefit of combining fluoride varnish with other types of intervention components. The evidence in relation to combined interventions involving fluoride toothpaste was also inconsistent, particularly when fluoride toothpaste was combined with supervised toothbrushing. When fluoride toothpaste was combined with OHE, the evidence indicated a significant caries-preventive effect of high-concentration fluoride toothpaste plus OHE; the evidence for combined interventions involving low-concentration fluoride toothpaste plus OHE was inconsistent.

The evidence for combined interventions involving sealants was slightly inconsistent, but predominantly indicated a significant caries-preventive benefit of combining sealant application with some form of OHE or OHI [134].

It is worth noting that the methodological quality of 6 out of the above 13 systematic reviews that evaluated the effectiveness of combined interventions for caries prevention in primary dentition was judged to be of critically low quality using our adapted version of AMSTAR 2; the methodological quality of the remaining reviews was judged to be low (6 review) or high (1 review).

The evidence on the effectiveness of complex interventions for caries prevention in primary dentition was drawn from four systematic reviews [48,118,130,138], and the findings were inconsistent, likely due to variation in the intervention components included in the trials, the dose/concentration of chemicals used, and the outcomes measured. The methodological quality of three of the systematic reviews was judged to be critically low using our adapted version of AMSTAR 2; the methodological quality of remaining systematic review was judged to be low.

5.1.1.3 Interventions delivered to pregnant women/mothers for caries prevention in the primary dentition of their children

We found evidence from one or more systematic reviews for three categories of singular interventions delivered to pregnant women or new mothers for caries prevention in the primary dentition of their children. These interventions were: fluoride supplements (two systematic reviews [136,137]), xylitol (one systematic review [110]), and CHX (two systematic reviews [121,124]). None of these reviews reported a caries-preventive effect of the interventions being evaluated. The evidence for each of the three interventions was drawn from only two primary trials included in one or two systematic reviews. The methodological quality was judged to be critically low in two of the systematic reviews, low in two of the systematic reviews, and high in one systematic review.

In relation to combined and complex interventions delivered to pregnant women or new mothers for caries prevention in the primary dentition of their children, the evidence was scarce. Two primary trials included in one systematic review [121] reported a significant caries-preventive effect of a maternal intervention involving the use of CHX (varnish or gel) combined with an additional intervention component: the consumption of xylitol gum in one primary trial and the delivery of a preventive programme in another primary trial. Finally, a single trial included in one systematic review [137] showed a significant caries-preventive benefit associated with the delivery of a ‘primary-primary prevention’ intervention to both mothers and children. This intervention involved several intervention components over a period of approximately 4 years, including dental examination, individual preventive self-care OHI, instruction on avoiding microbe transmission, caries aetiology education, education about infection related to maternal–child caries transmission, oral examination for both mother and child, OHI delivered to children, primary teeth cleaning, and the application of topical fluoride and CHX varnish.

5.1.2 Permanent dentition

We identified 44 systematic reviews on caries prevention in permanent dentition, albeit evidence from 8 of these reviews could not be presented as the findings were either not usable for the purposes of this overview of reviews or no primary studies on the intervention of interest were found. The certainty of the evidence reported in the remaining 36 reviews ranged from very low to moderate, as assessed using the modified GRADE algorithm. Five of the reviews reported moderate certainty evidence. The moderate-certainty outcome in one of these reviews [47] was based on a single trial. This left four systematic reviews that presented moderate certainty evidence from two or more trials. The review by Ahovuo-Saloranta *et al.* [38] presented moderate-certainty evidence for both resin and glass ionomer sealants. Regarding resin-based sealants, a pooled analysis of seven trials showed a significantly lower incidence of carious lesions following the application of second-, third-, and fourth-generation resin-based sealants compared with no sealant. Regarding glass ionomer sealants, several pooled analyses showed either no significant difference in the incidence of carious lesions between the glass ionomer sealant groups and the resin-based sealant groups, or a significant difference in favour of the comparator (resin-based sealants). The review by Slot *et al.* [147] presented moderate-certainty evidence from a pooled analysis of three trials showing significantly lower DMFRS scores following the delivery of combined interventions involving CHX varnish plus professional prophylaxis compared with a control or the application of a placebo varnish. The review by Riley *et al*. [133] presented moderate-certainty evidence from a pooled analysis of 2 trials showing a significantly lower increment of DFS following the combined use of fluoride toothpaste containing 10% xylitol compared with a control. The same review also presented moderate-certainty evidence from two trials synthesised narratively showing no significant difference in the increment of DMFS following the consumption of xylitol lozenges compared with control lozenges or no treatment. Finally, the review by Subbiah and Gopinathan [143] presented moderate-certainty evidence from two trials synthesised narratively showing significantly lower DMFRS scores with the use of 38% SDF compared with a control. Notably, while the certainty of evidence was moderate, the review itself was judged to be of critically low quality using our adapted version of AMSTAR 2 [92].

The evidence for all other outcomes in permanent dentition was judged to be of low or very low certainty using the modified GRADE algorithm and should therefore be interpreted with caution.

5.1.2.1 Singular interventions

We found evidence from one or more systematic reviews for 21 categories of singular interventions for caries prevention in permanent dentition. Overall, there was consistent, or slightly inconsistent but predominantly positive, evidence for a significant caries-preventive effect of fluoridated milk (one systematic review [26]), fluoridated sugar (one systematic review [119]), fluoride mouth rinse (two systematic reviews [139,140]), fluoride gels (three systematic reviews [25,139,141]), fluoride solutions (four systematic reviews [139,141–143]), slow-release fluoride devices (one systematic review [49]), polyols (one systematic review [146]), and ormocer sealants (one systematic review [38]). However, the total evidence in favour of fluoridated milk, fluoridated sugar, slow-release fluoride devices, polyols, and ormocer sealants consisted of a single primary trial included in one systematic review.

There were eight categories of interventions for which the evidence was mixed: namely, fluoride supplements (one systematic review [111]), fluoride toothpaste (two systematic reviews [21,139]), fluoride varnish (four systematic reviews [108,139–141]), CHX (four systematic reviews [121,126,132,140]), calcium phosphate agents (two systematic reviews [9,121]), resin-based sealants (six systematic reviews [29,38,112,148–150]), glass ionomer sealants (four systematic reviews [29,38,149,151]), and combined sealants (four systematic reviews [117,149–151]). Regarding fluoride supplements, the evidence appeared to vary depending on the comparator, with a significant benefit associated with fluoride supplements compared with no supplements, but no significant benefit when

comparing fluoride supplements with the application of fluoride varnish. Moreover, the evidence for fluoride varnish appeared to vary according to the outcome measure, with a predominantly (albeit not exclusively) significant caries-preventive effect of fluoride varnish application on caries incidence according to dentistry-specific epidemiological indicators (e.g. the DMFS, DMFT, DMFRS, D-Root, and DF-Root indexes) and on the incidence of root caries, but no significant effect on the proportion of participants developing one or more new carious lesions on permanent teeth.

The evidence for CHX varied according to the mode of delivery, outcome measure, and/or mode of application. The evidence for CHX varnish predominantly (albeit not exclusively) indicated no significant difference in the increment of DMFS following the application of CHX varnish compared with a control or placebo varnish, whereas the evidence in relation to the incidence of root caries, measured via the DMFRS and RCI indexes, did indicate a significant benefit in favour of CHX varnish [21,132,140]. The evidence for CHX mouth rinse consisted of a single pooled analysis of four trials in one review [121], which showed no caries-preventive benefit of CHX mouth rinse compared with a control or placebo mouth rinse. The evidence for CHX gel from the same review was inconsistent and varied according to the mode of application; in the two trials that reported a significant caries-preventive effect, CHX gel was applied via professional flossing, but in the other two trials it can be assumed from the information provided in the review that the gel was not professionally applied.

The evidence for calcium phosphate agents was drawn from three trials reported in two systematic reviews [9,121] with inconclusive results, likely due to variation in the comparators and in the mode of calcium phosphate delivery across the three trials (mouth rinse, toothpaste, or cream).

Although the evidence for resin-based sealants was inconsistent, it appeared to vary according to the comparator; there was a significant caries-preventive benefit associated with the application of resin-based sealants when compared with no sealant application, but not when compared with the application of fluoride varnish or with supervised toothbrushing, although only one primary trial reported in one systematic review [149] compared resin-based sealants with supervised toothbrushing. The body of evidence for glass ionomer sealants was substantial, and did not favour the application of glass ionomer sealants over the application of resin-based sealants, the application of fluoride varnish, or no sealant application, although only one trial reported in one systematic review compared glass ionomer sealants with no sealant application [38]. In most analyses in this intervention category, resin-based sealants were the comparator, and on some occasions, the results favoured resin-based sealants over glass ionomer sealants. Finally, the evidence in relation to combined sealants was inconclusive, likely due to variation in the comparators and outcome measures across the systematic reviews.

The remaining five categories of standalone interventions for which we identified systematic review evidence on the topic of caries prevention in permanent dentition were: scheduled dental appointments (one systematic review [47]), supervised toothbrushing (two systematic reviews [116,118]), xylitol (three systematic reviews [121,133,146]), hybrid sealants (one systematic review [151]), and laser interventions (one systematic review [135]). No significant caries-preventive effects were observed for these interventions. However, the total evidence on both hybrid sealants and laser interventions consisted of a single trial included in one systematic review. Moreover, the volume of evidence on the remaining three categories of interventions was quite low: approximately two to four trials included in one to three systematic reviews.

It is worth noting that the methodological quality of 16 out of the above mentioned 30 systematic reviews that evaluated the effectiveness of standalone interventions for caries prevention in permanent dentition was judged to be of critically low quality using our adapted version of AMSTAR 2; the methodological

quality of the remaining reviews was judged to be low (11 reviews), moderate (1 review), or high (2 reviews).

5.1.2.2 Combined interventions

The evidence on the effectiveness of combined interventions for caries prevention in permanent dentition was drawn from 20 systematic reviews. Three systematic reviews [139–141] provided evidence on the effectiveness of combined interventions involving two forms of topical fluoride. Regarding the effectiveness of combining fluoride toothpaste and fluoride mouth rinse specifically, there was inconsistent evidence from two reviews [139,140]. However, analyses from one of these reviews [139] indicated that the effect may vary according to the type of mouth rinse: the combined use of fluoride toothpaste and NaF mouth rinse resulted in a significant caries-preventive effect, whereas the combined use of fluoride toothpaste and amine fluoride/stannous fluoride mouth rinse did not. The third review [141] presented evidence of no significant caries-preventive benefit associated with the combined use of NaF varnish and 38% SDF.

Three systematic reviews [9,121,133] provided evidence on the effectiveness of combined interventions involving topical fluoride and another non-fluoride topical chemical. Evidence for the combined effectiveness of fluoride toothpaste and calcium phosphate agents was inconclusive, but consisted of only two primary trials reported in two systematic reviews [9,121], and each evaluated a different form of calcium phosphate (dicalcium phosphate dihydrate in toothpaste and CPP-ACP paste). Only one trial reported in one systematic review [121] evaluated the effectiveness of CHX gel combined with fluoride toothpaste, and that trial found no significant caries-preventive effect of the combined intervention. The third trial [133] reported a significant caries-preventive effect of using toothpaste containing both fluoride and xylitol.

There was evidence from seven systematic reviews [21,109,110,117,118,135,139] on the effectiveness of topical fluoride combined with another active intervention component besides a topical chemical. The majority of this evidence was drawn from one systematic review [109], in which the results of three pooled analyses showed a significant effect of fluoride mouth rinse used under supervised conditions as part of school-based mouthrinsing programmes on DMFT and DMFS scores, but not on the proportion of participants developing one or more new carious lesions. There was evidence from three reviews [21,117,118] on the effectiveness of fluoride toothpaste used under supervised conditions. The findings were inconsistent but favoured no significant caries-preventive effect of supervised toothbrushing using fluoride toothpaste on permanent dentition. However, the evidence for this type of combined intervention was sparse (four trials) and variable in relation to the comparators and outcome measures. A network meta-analysis conducted by one review team [139] found no root caries-preventive effect of the combined use of fluoride toothpaste and fluoride tablets. Only one trial reported in one systematic review [135] evaluated the effectiveness of fluoride gel combined with laser interventions, and found a significantly lower number of cases with new carious lesions post-intervention compared with the use of fluoride gel alone. The final review [110] reported a caries-preventive benefit associated with the use of a fluoride solution combined with professional prophylaxis, either at baseline or on multiple occasions over a period of 1 year.

Five systematic reviews [139,141,143–145] evaluated the effectiveness of topical fluoride (NaF varnish or 38% SDF) combined with OHI/OHE for caries prevention in permanent dentition, and all five reported a significant caries-preventive benefit for both the root and crown associated with this type of combined intervention.

Five systematic reviews [110,111,121,144,147] evaluated the effectiveness of combined interventions involving non-fluoride topical chemicals and varied types of other intervention components. In relation to

combined interventions involving CHX varnish, one review [147] reported significantly lower DMFRS scores among participants who received application of CHX varnish plus an additional intervention component compared with a control or placebo, although the type of combined intervention varied across the pooled trials. In addition, two single trials reported in one of two systematic reviews [121,144] found a significant root caries-preventive effect of the combined use of CHX varnish and OHI compared with OHI alone. Taken together, these results indicate that combined interventions involving CHX varnish are effective for the prevention of root caries. Alternatively, evidence from a single trial reported in one systematic review [110] showed no significant coronal caries-preventive effect when CHX varnish was combined with professional prophylaxis compared with placebo varnish. A single trial reported in one review [121] showed a significant caries-preventive effect of the use of arginine bicarbonate and calcium phosphate combination toothpaste compared with fluoride toothpaste. Alternatively, a single primary trial reported in another review [111] found no evidence of a caries-preventive benefit associated with the consumption of lozenges containing both xylitol and fluoride when compared with the consumption of xylitol-only lozenges.

Four systematic reviews [29,38,135,152] reported on the effectiveness of combined interventions involving sealants. A single primary trial reported in one review [38] found a significant benefit of combining sealant application with the delivery of OHE compared with the delivery of OHE alone. However, the evidence from two trials reported in another review [29] on the combined effectiveness of sealant application plus OHE when compared with the combined effectiveness of the application of fluoride varnish plus OHE was inconclusive. The remaining two reviews [135,152] reported evidence from four single trials on the combined used of sealants and laser interventions with divergent results, likely due to varied intervention components and comparators.

It is worth noting that the methodological quality of 11 out of the above 20 systematic reviews that evaluated the effectiveness of combined interventions for caries prevention in permanent dentition was judged to be of critically low quality using our adapted version of AMSTAR 2; the methodological quality of the remaining 9 reviews was judged to be low.

The evidence on the effectiveness of complex interventions for caries prevention in permanent dentition was drawn from three single trials reported across three systematic reviews [29,118,146], all of which indicated a significant caries-preventive benefit of delivering complex interventions. The nature of the complex interventions varied across the three trials. However, all three included a topical chemical component (xylitol or fluoride lozenges, varnish, or toothpaste) and an educational and/or instructional component, as well as supervised toothbrushing. In addition, two of the three trials involved the use of sealants. The methodological quality of all three of the systematic reviews was judged to be low using our adapted version of AMSTAR 2.

5.1.3 Mixed dentition

We identified 12 systematic reviews on the topic of prevention of caries in mixed dentition, albeit evidence from 3 of these reviews could not be presented as the findings were not usable for the purposes of this overview of reviews. The certainty of the evidence reported in the remaining nine reviews ranged from very low to moderate, as assessed using the modified GRADE algorithm. Moderate-certainty evidence was provided in just one review [138], which reported no significant caries-preventive effect of complex interventions involving the application of fluoride varnish plus several other additional intervention components, which varied across the four pooled trials, compared with control groups that received all the same intervention components with the exception of fluoride varnish application. Although the evidence presented was of moderate certainty, the methodological quality of the review itself was judged to be critically low using our adapted version of AMSTAR 2.

The evidence for all other outcomes in mixed dentition was judged to be of low or very low certainty using the modified GRADE algorithm and should therefore be interpreted with caution.

5.1.3.1 Singular interventions

We found evidence from one or more systematic reviews for five categories of singular interventions for caries prevention in mixed dentition. Overall, there was evidence in favour of four interventions: vitamin D (one systematic review [153]), probiotics (one systematic review [155]), xylitol (three systematic reviews [121,156,157]), and sealants other than resin-based, glass ionomer, ormocer, and hybrid (one systematic review [9]). However, the total evidence in favour of probiotics and other types of sealants consisted of a single trial included in one systematic review. The remaining intervention for which there was systematic review evidence in mixed dentition was CHX. A pooled analysis of two trials conducted by one review team [121] indicated no significant caries-preventive effect of CHX varnish application compared with no varnish application. The methodological quality of all of the above reviews was judged to be critically low using our adapted version of AMSTAR 2.

5.1.3.2 Combined interventions

The evidence on the effectiveness of combined interventions for caries prevention in mixed dentition was drawn from four systematic reviews. Regarding combined interventions involving topical fluoride and another non-fluoride topical chemical, evidence from two systematic reviews [114,154] indicated a significant caries-preventive effect of combined interventions involving the use of either fluoride toothpaste or gel plus another non-fluoride topical chemical (either CHX, povidone-iodine, xylitol, or CPP-ACP). Regarding combined interventions involving two forms of non-fluoride topical chemicals, evidence from a single primary trial reported in one systematic review [121] indicated a significant caries-preventive benefit associated with the consumption of sugar-free mints containing arginine bicarbonate/calcium carbonate compared with the consumption of sugar-free mints without arginine bicarbonate/calcium carbonate. The methodological quality of all of these reviews was judged to be critically low using our adapted version of AMSTAR 2.

The evidence on the effectiveness of complex interventions for caries prevention in mixed dentition was drawn from one analysis of four pooled trials reported in one systematic review [138], which is described at the beginning of Section 5.1.3.

5.1.3.3 Interventions delivered to pregnant women/mothers for caries prevention in the mixed dentition of their children

We found evidence for only one category of singular interventions delivered to pregnant women or new mothers for caries prevention in the mixed dentition of their children. This evidence pertained to calcium supplementation, and was drawn from only a single trial reported in one systematic review [121]. The findings indicated a significantly reduced risk of new caries in the mixed dentition of children associated with maternal consumption of 2 g of calcium per day compared with a placebo. The methodological quality of this review was judged to be critically low using our adapted version of AMSTAR 2.

5.2 Comparison with other overviews of systematic reviews

We did not identify any existing overviews of reviews on caries prevention in permanent or mixed dentition, but we did find an overview of reviews on the prevention of early childhood caries. The overview by Soares *et al*. [61] included 13 systematic reviews on the prevention of dental caries in children aged under 6 years. Like our overview of reviews, Soares *et al*. judged the methodological quality of a large majority of the included systematic reviews to be critically low. Interventions positively related to the prevention of caries were: preventive dental programmes for pregnant women; advice on diet and

feeding; prenatal oral health care; integration of maternal and children's oral health promotion into nursing practice; maternal oral health programmes undertaken by non-dental health professionals; dental health education in combination with the use of fluoride for children; early preventive dental visits; and the use of fluoride varnish and toothpastes with more than 1000 ppm fluoride [61]. While health promotion interventions, behaviour change interventions, and interventions targeting diet were not evaluated in our overview of reviews, our findings of a dose–response relationship in the caries-preventive effect of fluoride toothpaste complement the findings reported by Soares *et al*. The evidence in relation to the caries-preventive effect of fluoride varnish in Soares *et al.*'s overview of reviews is not consistent with our overview findings; however, the majority of trials evaluated in the two systematic reviews that reported fluoride varnish interventions for caries prevention in primary dentition in the current overview showed a positive effect.

Notably, Soares *et al*. also emphasised the need for further evidence; while some interventions appeared to have more potential than others, there were still issues with methodological quality in relation to both the included systematic reviews and the primary studies [61].

5.3 Evidence for consensus clinical guidelines

We identified several recently published clinical guideline documents on the prevention of caries from England, Scotland, wider European collaborations, and North America.

A 2021 United Kingdom (UK) report by the National Health Service England on delivering better oral health care made recommendations for the prevention of dental caries at various ages [159]. For all children aged up to 3 years, it was strongly recommended that parents or carers brush their teeth with toothpaste containing at least 1000 ppm fluoride twice per day, and it was conditionally recommended that children be assigned a recall interval ranging from 3 to 12 months based on oral health needs and disease risk. For children aged 3–6 years, brushing with toothpaste containing at least 1000 ppm fluoride twice per day was recommended, as was the application of fluoride varnish (2.26% NaF) twice per year and a recall interval of 3–12 months. For children aged 0–6 years who are at increased risk for dental caries, toothpaste containing 1350–1500 ppm fluoride, application of fluoride varnish (2.26% NaF), and a shortened recall interval based on risk were recommended. For children aged 7–18 years, the National Health Service England recommended toothpaste containing 1350–1500 ppm fluoride, application of fluoride varnish (2.26% NaF) twice per year, and a recall interval ranging from 3 to 12 months. For children aged 7–18 years who are at increased risk for dental caries, the guidelines also recommended assisted or supervised toothbrushing (if needed), application of resin sealant to permanent teeth on eruption, and application of fluoride varnish (2.26% NaF) two or more times per year, along with other conditional and age-dependent recommendations around fluoride mouth rinse (0.05% NaF; 230 ppm fluoride) and temporary use of 2800 or 5000 ppm fluoride toothpaste. Finally, for adults, the recommendations were brushing with 1350–1500 ppm fluoride toothpaste and a recall interval ranging from 3 to 24 months. For adults at increased risk for dental caries, support with toothbrushing where required, application of fluoride varnish (2.26% NaF) twice per year, and conditional recommendations around shortened recall, daily fluoride mouth rinse (0.05% NaF; 230 ppm fluoride), and temporary use of 2800 or 5000 ppm fluoride toothpaste were also recommended [160].

In 2018, the Scottish Dental Clinical Effectiveness Programme published an evidence review and clinical guidelines on the prevention and treatment of dental caries in the primary or permanent teeth of children and adolescents, and based on the findings, made a series of recommendations to the dental profession in the UK [72]. In relation to the prevention of caries, recommendations were made in relation to toothbrushing, fissure sealants, and topical fluoride, as well as in relation to motivation and action planning and to dietary advice, interventions which were not evaluated in our overview of reviews.

Evidence for fluoride toothpaste for children was deemed to be of high quality (or certainty), and it was recommended that children and young people aged up to 18 years should brush their teeth twice daily and use toothpaste with a fluoride concentration in the range of 1000 to 1500 ppm, with 1500 ppm fluoride specified for those aged up to 10 years who are at increased risk for dental caries, and 2800 ppm fluoride for those aged 10–16 years and at increased risk for dental caries. It was concluded that fissure sealants were effective for the prevention of caries in both primary and permanent teeth. Evidence on fissure sealants was reported to be of moderate quality (or certainty), and strong recommendations were made for the application of fissure sealants to the permanent molars of all children in Scotland in order to prevent dental caries, with the suggestion that some children may also benefit from sealant application to other teeth. Evidence in relation to the comparative effectiveness of resin-based sealants compared with glass ionomer sealants was lacking in the report, but resin-based sealants have been shown to be better retained, while glass ionomer sealants may be particularly useful for newly erupted teeth. The use of both types of sealants was recommended. However, resin-based sealants were recommended as the first choice, and in cases where a child is uncooperative, glass ionomer sealants plus fluoride varnish application on fully erupted teeth was recommended [72]. In relation to topical fluoride, it was strongly recommended, based on moderate-quality (or certainty) evidence, that all children, regardless of caries risk, should have fluoride varnish applied at least twice per year, as fluoride varnish is the most effective topical fluoride agent and significantly reduces caries increment in both primary and permanent teeth. The use of other forms of topical fluoride, such as fluoride tablets, drops, gels, beads, or lozenges, is no longer encouraged in the UK as there is little evidence to support their use [72].

The US Preventive Services Task Force has also made a number of recommendations for the prevention of dental caries in children aged under 5 years [161]. Specifically, it recommends that primary care clinicians prescribe oral fluoride supplementation starting when children are aged 6 months for children whose water supply is deficient in fluoride, and that primary care clinicians apply fluoride varnish to the primary teeth of all infants and children starting at the time of primary tooth eruption. In relation to routine screening examinations for dental caries by primary care clinicians, for children aged under 5 years, the US Preventive Services Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms [161].

Finally, a Health Technology Review by the Canadian Agency for Drugs and Technologies in Health [162] reported on guidelines from the American Dental Association [163], the Scottish Dental Clinical Effectiveness Programme [72], and a Joint Expert Delphi Consensus Statement by the European Organisation for Caries Research and the European Federation of Conservative Dentistry [164], noting that all three recommend the use of dental sealants to prevent dental caries in children and adolescents. Sealants can be used as a preventive measure upon the eruption of molars and may be used alone or in combination with other treatments that protect against tooth decay. Overall, the guidelines around the use of sealants were described as rigorous, comprehensive, and clearly reported, but gaps were noted by the Canadian Agency for Drugs and Technologies in Health in relation to guidance around implementation, choice of sealant material, and selection of patients [162].

The evidence for the interventions for caries prevention that we have summarised was deemed to be of moderate- to very low-certainty using the modified GRADE algorithm. However, there is sufficient data and clinical experience to support the implementation of some of these recommendations in Ireland; for instance, the use of fluoride toothpaste to protect primary teeth and the use of fluoride mouth rinse to protect permanent teeth. The evidence for commonly recommended interventions (such as fluoride varnish) was, to some extent, supported in our overview of reviews. However, while the body of evidence for fluoride varnish in both primary and permanent dentition was strong, it was not entirely consistent. Despite the preventive evidence in relation to fluoride supplements and gels in both primary and

permanent teeth in our overview of reviews, these interventions are not widely recommended in the jurisdictions we examined.

5.4 Strengths and limitations

5.4.1 Research design

We chose an overview of reviews design for two reasons: to appropriately acknowledge and take advantage of the volume of existing systematic reviews on the prevention of caries, and to allow us to cover the full scope of relevant interventions, which would not have been possible with a traditional systematic review in the available time frame. Methods for overviews of reviews are continually evolving, and we consulted best-practice guidance provided by the leading thinkers in this area in order to develop our approach, tailoring our methods where necessary.

While our review was conducted in accordance with best-practice guidance for overviews of reviews, it is vulnerable to some of the disadvantages inherent to this form of evidence review. Most significantly, the validity of the findings in any overview of reviews is contingent on the methodological quality of the included systematic reviews. While we took several steps to screen out low-quality work (see Section 3.8 on eligibility criteria and Section 3.10 on screening), weaknesses within the body of evidence as a whole cannot be overcome by the process of conducting an overview of reviews. There may be errors in extraction of data from primary studies that were difficult or not possible to detect without scrutinising and comparing primary studies included in the systematic reviews. Moreover, there may be inconsistencies between systematic review teams in reporting the nature of interventions and/or outcome measures. For instance, there were several instances in which an intervention was appropriately described as a combined intervention in one review but was described as a standalone intervention in another review. In addition, the precise nature of an outcome measure was often described differently by different systematic review teams. We identified and appropriately dealt with these inconsistencies on a case-by-case basis to the best of our ability, guided by our priority to ensure that the findings of this overview of reviews are as valid as possible. However, these limitations should be considered when interpreting and applying the findings. The very nature of overviews of reviews means that the overview authors are one step further away from the original research than systematic review authors, and so nuances of methodology or interpretation that are important to the original research may be obfuscated in the findings of an overview of reviews.

5.4.2 Scope

A limitation of the literature search stage was the lack of non-English-language databases and resources included in the search. The use of a language limit (in the form of English-language work only) was necessary, as our review team members did not have the language skills necessary to interpret complex and technical papers in other languages, and the time frame and competing work commitments did not allow for the professional translation of papers. Based on previous experience, we determined that the use of Google Translate software would not be adequate for thorough, detailed extraction and synthesis of these papers. However, non-English-language reviews with English-language abstracts or keywords that appeared to be relevant to the topic were retained in order to ensure that this wider research was recorded and credited. These records are available in Appendix C and included works in 19 languages, representing a wide geographic span. These records were captured using English-language-based databases, and using non-English-language databases or regional databases would likely have captured considerably more of this body of work. There is some research to suggest that omitting languages other than English may not change the direction of findings significantly [165], but findings may be field- or topic-specific and it may not be possible to extrapolate from the general to the specific in this matter.

While the inclusion of an adequate search process in the reviews which make up this overview of reviews was required, the use of non-English-language databases in those searches was not mandatory. The limits of the search methods of those reviews influenced the quality of research included in our overview of reviews. The inclusion of English-only primary studies in the reviews included in this overview may compound the language bias of only including English-language reviews in our overview. However, 29 of the 66 included systematic review papers stated that there were no language restrictions in their search, and therefore non-English-language papers were included in their analyses. In addition, one review included studies published in English and German, and another review included trials published in English, Spanish, and Portuguese. The characteristics of the primary studies indicate that research came from all continents, including the Americas and Europe.

We also limited our search to systematic reviews published since 2010 (i.e. in the last 13 years). Based on expert guidance, we expected that this would yield primary research conducted in the last 30 years [63]. This allowed us to cover a comprehensive range of literature while keeping our volume of records more manageable. The final searches were carried out in mid-June 2022, and supplemental searching was carried out between October and December 2022. Therefore, reviews published after these dates could not be included.

5.4.3 Search

A strength of this overview of reviews is that the search strategy was robust and comprehensive. We did not specify particular outcomes so as to capture as wide a range of outcomes and conditions as possible; thus, the search strategy was based around the concepts of 'caries' and 'prevention'. However, it is possible that reviews which dealt with the prevention of dental diseases but did not include caries-related terms in the searchable fields of the resources used may not have been retrieved. Employing a very broad search strategy using only the general concept of dental prevention would have resulted in an unmanageable number of search results, given the time frame in which the review was to be completed. The terms used for caries were very broad, and it is expected that any review that evaluated caries prevention would have included a term for caries in the title, abstract, author keywords, and/or controlled vocabulary (Medical Subject Headings (MeSH) terms, etc.). However, not all databases use full-text searching for the search terms. For example, Ovid lists the searchable fields available in Ovid MEDLINE in its database guide; this database searches the record of the article rather than the article itself [166]. Less structured, general searches were used in many of the resources searched, and it was hoped that this would capture a wide range of results. The use of supplemental searching (reference, citation, and protocol follow-up, and screening of a previous work by the HRB authors) [67] was also expected to capture as much relevant material as possible, thereby mitigating the risk of relevant articles being missed.

5.4.4 Quality of systematic reviews and primary studies, and certainty of evidence

In designing our eligibility criteria, we aimed to limit the inclusion of systematic reviews with serious shortcomings by excluding reviews with inadequate coverage of bibliographic databases, inadequate descriptions of search methods, and inadequate appraisal of methodological quality/risk of bias of included primary studies (see Section 3.10). However, as reported in Section 4, the methodological quality of many of the systematic reviews included in this review was lower than desired, with 60 (91%) of the 66 systematic reviews classified as either low or critically low quality using an adapted version of AMSTAR 2. Notably, 44 (67%) systematic reviews were deemed to be of critically low quality. During full-text screening, we attempted to increase the transparency of the quality of primary studies included in systematic reviews by screening out studies that did not complete a quality assessment or provide detailed quality assessment results. However, the methodological quality of the 66 included systematic

reviews was hampered by the large number of primary studies that had an unclear or high risk of bias that could not be or was not controlled for in the meta-analyses via sensitivity or subgroup analysis.

Many of our included systematic reviews evaluated primary studies not related to caries prevention alongside studies that did focus on caries prevention. Taking only the primary studies in each systematic review relevant to caries prevention, a majority of the included reviews (44/66) included caries prevention RCTs only; however, a large proportion of these trials had inadequate randomisation and/or blinding of outcome assessors, leading to questions about the validity of such trials. Specifically, 35 (79%) of the systematic reviews that solely included caries prevention RCTs presented data indicating that 75% or more of all of their included primary studies had inadequate randomisation, and 26 (59%) of the reviews presented data that indicated that 75% or more of all of their included primary studies had inadequate blinding when ascertaining the outcome.

Forty-seven systematic review teams did not use appropriate methods for statistical combination of results. This quality assessment item was not applicable to 18 of the included reviews, leaving only 1 systematic review that did use appropriate methods for statistical combination of results. Twenty-one systematic review teams did not discuss the impact of heterogeneity on their results.

We dealt with these issues when grading the certainty (or quality) of evidence so that the reported certainty of evidence was realistic. We used the adapted algorithm originally developed by Pollock *et al*. [99] to grade the certainty of evidence in this overview of reviews, and we provide a transparent record of downgrades applied to each systematic review in Appendix K. Some systematic review teams had applied Grading of Recommendations, Assessment, Development and Evaluation (GRADE) to their outcomes using recommended tools. However, for consistency, we re-graded our outcomes using a systematic approach. This adjusted the GRADE classification for some reviews, and these adjustments are justified at the end of each review summary in Appendix H.

Evidence from 57 out of the 66 included reviews was graded to be of low or very low certainty using the modified GRADE algorithm, leaving 9 reviews that presented moderate-certainty evidence. Of these nine reviews, three presented other outcomes graded as low- and/or very low-certainty. This means that we have limited confidence that the estimated effect of the intervention under examination is close to the true effect in the majority of the included reviews. This reflects the relatively low quality of the existing research that makes up the body of evidence for the prevention of caries. Notably, the volume of single-trial outcomes reported across our included systematic reviews inflated the volume of evidence that was graded as very low certainty. A known strength of overviews of systematic reviews is that they can combine large volumes of systematic review data into a single synthesis [65]. However, this is only possible when the body of best available evidence is substantial enough to evaluate and draw meaningful conclusions from. We identified 66 systematic reviews that evaluated, or aimed to evaluate, the effectiveness of various interventions for the prevention of caries. Nevertheless, the volume of available evidence was often insufficient when reviews were categorised according to the type and nature (singular or combined) of the interventions being evaluated, with approximately three-quarters of the outcomes in primary dentition, more than one-half of the outcomes in permanent dentition, and almost one-third of the outcomes in mixed dentition being single-trial outcomes. Moreover, the total evidence for four interventions in primary dentition (fluoride solutions, antimicrobial agents (minus CHX), calcium phosphate agents, and laser interventions), six interventions in permanent dentition (fluoridated milk, fluoridated sugar, slow-release fluoride devices, ormocer sealants, hybrid sealants, and laser interventions), and three interventions in mixed dentition (probiotics, other types of sealants, and maternal calcium-based interventions) consisted of only a single primary trial reported in one systematic review. It is also important to consider that where more than one systematic review addressed the same

outcome, overlap was generally high, with the same RCTs being counted in multiple systematic reviews, and this can create an illusion of a stronger, deeper body of evidence than exists in reality.

5.5 Future research

There are research gaps that will need to be addressed through additional research. We note that the systematic reviews included in this overview of reviews all met the minimum quality criteria we chose in order to be included. As such, when referring to evidence gaps, we are referring to gaps in the evidence from systematic reviews that met a certain methodological standard; there may be systematic reviews available on some of the topics indicated below that did not meet our minimum quality criteria.

Regarding population, the systematic review research on the prevention of root caries in older adults was limited in comparison with systematic review research on other populations – children and adolescents in particular – which may be an avenue for future systematic review research. Moreover, although it was not possible to fully distinguish between and analyse the evidence according to biological age in this overview of reviews, systematic review evidence on caries prevention in middle adulthood appears to be lacking in comparison to that on children, adolescents, and older adults. This may be due to the paucity of primary RCT evidence for the prevention of caries in adults. In relation to interventions, most of the available systematic review evidence on caries prevention in primary and permanent dentition pertains to supervised toothbrushing; fluoride supplements and fluoridated milk, toothpaste, mouth rinse mouth rinses, gels, solutions, and varnishes; CHX; calcium phosphate agents; probiotics; xylitol; and sealant-based interventions. Systematic review evidence on the remaining 30 types of interventions that we identified was either non-existent, insufficient, or unusable. In addition, more systematic review research on standalone (as opposed to combined) interventions is required in order to better understand which active intervention components are most effective for caries prevention and for whom.

We excluded oral health promotion initiatives, including oral health education, instruction, motivation, and dietary counselling. However, the evidence on combined interventions reported in this overview often involved these oral health promotion activities, many of which indicated positive caries-preventive benefits when combining a clinical intervention with some form of oral health education, instruction, or similar. Evaluating the effectiveness of oral health promotion initiatives as standalone prevention interventions would be a fruitful avenue of research. In relation to the reporting of interventions, it is essential moving forward that systematic review authors report on the precise nature of the interventions in the trials they are evaluating, making clear how many (and which) of their included trials delivered combined or complex interventions, as well as conducting the necessary analyses in order to assess systematic differences in outcome measures according to the nature and complexity of interventions. When conducting this overview of reviews, we identified several systematic reviews that aimed to evaluate the effectiveness of a certain caries prevention intervention in a given dentition type, but could not do so, predominantly due to a lack of available evidence. Nevertheless, these systematic reviews are identified under the relevant interventions throughout the Findings chapter of this overview in order to highlight gaps in both systematic review research and primary research in the area of caries prevention.

In relation to outcomes, the systematic reviews included in this overview of reviews reported on a wide variety of outcomes, including indicators of whole tooth caries, tooth surface caries, and root caries, as well as a variety of both dentistry-specific and general epidemiological indicators of caries. However, in some systematic reviews, the nature of the outcome measure was not adequately described to allow the reader, or authors of overviews of reviews, to determine whether the review was evaluating primary prevention or secondary prevention (i.e. management) of caries. Reporting on the precise nature of the outcomes in clinical trials is essential in order to ensure that the findings can be interpreted and applied appropriately.

The methodological quality of 91% of the systematic reviews included in this overview of reviews was classified as either low or critically low, indicating that further high-quality, adequately powered RCT research is required in this field. In particular, systematic review authors who aim to conduct a meta-analysis should ensure that only trials judged to be at low risk of bias are included in meta-analyses, and where no trials with a low risk of bias are available, the findings should be synthesised narratively. This is a critical step to ensuring that the findings in favour of or against a particular intervention are valid, and therefore of use to the developers of clinical guidelines and, ultimately, to dental practitioners. Finally, the cost of preventive dental interventions in Ireland is an area in need of systematic review research.

6 Conclusion

Overall, this overview of 66 systematic reviews on the primary prevention of dental caries has revealed a fragmented body of research, with a substantial proportion of single-trial outcomes and a low and very low degree of certainty in the evidence for the majority of the interventions. Following a systematic quality assessment, the methodological quality of the included systematic reviews is very low.

Relative to all other types of interventions, and taking the volume of evidence for each intervention category into account, the evidence for caries prevention in primary dentition was strongest for fluoride supplements. The evidence for caries prevention in permanent dentition was strongest for fluoride mouth rinse, fluoride gels, and fluoride solutions. The evidence for caries prevention in mixed dentition was strongest for vitamin D and xylitol (although it is important to note that the volume of evidence in the mixed dentition category was generally very low). However, further high-quality, adequately powered RCT research is required; in the meantime, conclusions may only be drawn narrowly, if at all, with respect to the most effective approach by which to prevent dental caries using individual-based primary prevention interventions prior to the development of any dental decay/dental caries.

Importantly, when the best available evidence consists of systematic reviews of critically low methodological quality and mostly findings of low and very low certainty, the development of clinical guidelines for the primary prevention of dental caries requires a greater reliance on clinical expertise, particularly in relation to preventive measures for which there is a strong clinical consensus.

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