Measures to reduce the clinical need for dental amalgam

Evidence review

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Abbreviations

Abbreviation	Full text
ACP	Amorphous calcium phosphate
APF	Acidulated phosphate fluoride
CADTH	Canadian Agency for Drugs and Technologies in Health
CPP-APC	Casein phosphopeptide-amorphous calcium phosphate
DOH	Department of Health
EU	European Union
GI	Glass ionomer
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HEMA	2-hydroxyethyl methacrylate
HRB	Health Research Board
NaF	Sodium fluoride
ppm	Parts per million
SDF	Silver diamine fluoride
SREA	Systematic rapid evidence assessment
UK	United Kingdom
USA	United States of America

Summary

Introduction

The European Union (EU) has introduced Regulation (EU) 2017/852 in order to implement the 2013 United Nations Minamata Convention on Mercury, which aims to protect human health and the environment from mercury pollution. This 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). This EU Regulation is binding in its entirety and is directly applicable in all Member States. The Department of Communications, Climate Action and Environment published Statutory Instrument No. 533 of 2018 to implement Regulation (EU) 2017/852 and the United Nations Minamata Convention on Mercury. Since July 2018, the EU regulation has introduced a ban on amalgam use in children under 15 years of age, and in pregnant or breastfeeding women, except where deemed strictly necessary by the dental practitioner based on the specific medical needs of the patient. By July 2019, the Irish Government must submit a plan to the EU detailing Ireland*'s* approaches to the phase-down of amalgam up to 2030. The Department of Health (DOH) asked the Health Research Board (HRB) to answer a number of questions in order to provide information and evidence for the plan.

Research questions

The research questions are:

1. What are the medical or clinical grounds for exemption from the ban on amalgam across European jurisdictions?
2. What measures have other high-income (in particular European) countries reported to support the phasing out of dental amalgam?
3. What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for young people aged 16 and under?
4. What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for adults aged 16 and older?

Methods

First, the authors of this review will deal with the methods for Questions 1 and 2 and then we will outline our decision-making processes and methods chosen for Questions 3 and 4.

Questions 1 and 2

In order to answer Questions 1 and 2, we drew on an eclectic mix of both peer-reviewed and grey literature to document the reported exemptions allowed by European countries (Q1) and the reported measures taken by high-income economy (or European) countries, to support the phasing out of dental amalgam, as well as the lessons learned from these countries (Q2).

We retrieved most of these data resources during the initial scoping stages of our work. For example, we ran general searches in the search engine Google to gain an initial idea of terminology and likely key terms. Initial search terms used included combinations of 'mercury', 'dental amalgam', 'filling', and 'caries'. Further searches were carried out using the websites of national and international dental organisations, including national and international regulatory bodies. The majority of data sources we used to answer Questions 1 and 2 were grey literature or technical reports located through searches

developed by our information specialist. We drew on only a very small number of papers published in peer-reviewed journals. The data we retrieved from these documents were nested within a wider exploration of a range of issues and discussions relating to the phase-out of dental amalgam.

We extracted fragments of data from these papers when we judged the data relevant to contributing to our questions. From these fragments, we built a response to our questions using a descriptive format and, for Question 2, we organised the findings using the actions outlined in the Minamata Convention on Mercury.

Questions 3 and 4

This review employs a systematic rapid evidence assessment (SREA) approach for Questions 3 and 4, which assembles evidence in a short time frame to assist policy-makers. The SREA is a focused and limited search review of the literature which seeks to use the same methods and principles as a systematic review but reduces the scope of evidence considered in order to deliver the evidence review more quickly. We undertook the work for Questions 3 and 4 in two phases: a mapping phase and an in-depth phase. In order to progress the approach to gathering evidence for Questions 3 and 4, we agreed with the DOH to undertake a rapid descriptive mapping exercise to identify the nature and extent of the literature that examined alternatives to amalgam as a restorative solution for children and adolescents. We agreed that the mapping exercise would document the main characteristics of peer-reviewed research undertaken from 2010 to 2019 that compared dental restorative materials with amalgam in children and adolescents. This process was repeated for adults at a later stage. For the mapping exercise, we completed a focused search which was limited to four databases (Ovid MEDLINE, Embase, EBSCO CINAHL, and the Cochrane Library). Our search returned 519 systematic reviews and 3,867 randomised controlled trials which appeared to include a focus on children and adolescents. In consultation with the DOH and due to time constraints, we decided to include systematic reviews only. We were only interested in retaining reviews that focused on cariology (prevention interventions, early treatment for non-cavitated carious lesions, direct and indirect restorations for cavitated caries, and other products and processes associated with restoration). We excluded reviews that did not report comparing an intervention with a control intervention. We also excluded reviews that were not published in English and those that were published before 2010. For Cochrane reviews, we only retained the most recent versions of updated reviews. The objective of this work was to facilitate the DOH to prioritise a focused research question or inquiry that could be addressed through a subsequent in-depth review. We mapped the 48 systematic reviews on cariology in children and adolescents. Towards the end of March 2019, we presented a draft descriptive map of the characteristics of systematic reviews for Question 3 to the DOH and agreed a refined Question 3. We then applied the same process to Question 4. A second search, focusing on adults, identified 291 systematic reviews. We screened and mapped the adult reviews using the same process as employed for the childrens' and adolescents' reviews. After abstract and full-text screening, and an additional search of prevention interventions tested on children and adults, we had 48 systematic reviews on children and adolescents and 53 reviews on adults. For the purposes of the in-depth review, we extracted data from the included reviews into standardised extraction sheets developed specifically for this review. Levels of evidence (adequate, inadequate, or inconclusive) were assigned to each of the primary outcomes reported in each systematic review, using an adaptation of a schema designed by Faggion. The level of evidence assigned to each review considered the conclusions of the review authors, the results of the risk of

bias or quality assessment in the primary trials, and the review authors' stated limitations. We completed a narrative summary for each review.

The following describes the categories assigned to describe the level of evidence:

- Adequate evidence (unlikely to change)
    - When authors stated their confidence using words such as 'sound', 'high', or 'good quality' (which was rarely the case in the reviews examined), or when authors did not explicitly state that the evidence was weak, and reported some (moderate) evidence for effectiveness, the evidence was considered adequate which was more commonly the case in the reviews we examined.
- Inadequate evidence (likely to change)
    - When authors described weak or insufficient evidence (low or very low quality), or when no studies were included in the review (an empty review), the quality of evidence was considered inadequate.
- As stated above, the HRB authors added: Inconclusive evidence
    - The evidence was considered inconclusive when it was not possible to determine which intervention was better or best.

Findings

Clinical or medical justifications where dental amalgam is the only option

The only grounds for exemption from the amalgam ban were for the restoration of permanent teeth, and we found five European jurisdictions (Denmark, Finland, Norway, and Sweden), that have, or had in the past, an exemption policy. The exemptions are (or were): inability to keep the operating area dry (Denmark, Norway); too difficult to access the cavity (Denmark); a very large dental cavity (Denmark); too great a distance between the affected tooth and the proximate tooth (Denmark); restoration requires general anaesthesia (Denmark and Norway); allergy to components of mercury-free fillings (Norway); and the patient having a specific medical condition (Sweden). Finland and Sweden state that amalgam can be used when other dental filling materials cannot be used or do not provide an adequate restoration. The four chief dental officers in the United Kingdom (UK) state that amalgam can be used to address the specific needs of the adult population until practical clinical, and cost-effective alternative materials are available. A three-year time limit was placed on exemptions in Norway, which expired on 1 January 2011. At the end of December 2011, Sweden ceased its policy of exemptions.

Measures by other countries to support the phasing out of dental amalgam

The United Nations Environment Programme (2016) in its report titled *Lessons from countries phasing down dental amalgam use* advised countries to take the actions outlined in the Minamata Convention on Mercury to phase down amalgam. These actions are based mainly on the experience of other countries, in particular Norway and Sweden, and include:

1. Setting national objectives to reduce the need for dental restoration by increasing primary and secondary prevention activities, as done by the World Health Organization and in Canada, Scotland, and, more recently, Ireland. Of note, the four chief dental officers in the UK support phasing down the use of amalgam rather than phasing it out.
2. Setting national objectives and approaches for minimising the use of dental amalgam by using a step-by-step approach to phasing down the use of amalgam, as done in Denmark,

Finland, France, Germany, Hungary, the Netherlands, Norway, and Sweden. The first steps were raising awareness of the potential environmental hazards of mercury among the dental professions, the public, and other stakeholders, followed by forming a representative working group, and then identifying vulnerable populations (such as children and pregnant or breastfeeding women) and banning the use of amalgam in these populations. The last step was to allow the use of amalgam in exceptional (but justifiable) circumstances while ensuring patient consent.

3. In addition to a prevention and early treatment approach, ensuring access to reliable alternative dental restorative materials and techniques for amalgam restorations was essential. In Norway, there is a policy of minimally interventive operative dentistry which supports the use of resin composite for permanent teeth, and the use of other compounds for temporary and primary teeth restorations. Norway also introduced a Dental Biomaterials Adverse Reaction Unit to monitor adverse events from dental products.
4. Developing and testing new mercury-free materials for dental restoration is an action promoted by the World Health Organization and the United Nations Environment Programme. This action is less progressed by the countries that have progressed the implementation of mercury-free dentistry. The World Health Organization states that additional research is needed to assess the safety and adverse effects of alternative restorative materials to dental amalgam and, therefore, collaboration between material scientists, computer scientists, toxicologists, synthesis chemists, and industry is critical.
5. Educating and training dental professionals and students to use evidence-informed practice. The first step of this action is to work with the dental professions and dental schools in order to ensure an undergraduate curriculum and continuous professional development programme that is based on preventing caries, using mercury-free alternatives, and using minimally invasive techniques. In addition, resource allocation needs to be directed away from amalgam and towards embracing alternatives. The undergraduate curriculum has included training on posterior composite resin restorations using minimally invasive techniques in a number of countries, including Brazil, Canada, Iran, Ireland, Japan, Norway, Spain, Sweden, the UK, and the United States of America (USA). However, more needs to be done in some countries including Ireland to promote posterior composite resin restorations using minimally invasive techniques.
6. Realigning dental insurance policies and programmes to favour the use of quality alternatives to dental amalgam is an action taken by a number of European countries. In Sweden, dental treatment for children is fully covered, and 50% of the treatment cost is covered for adults. Amalgam fillings are not covered. In Norway, dental care is fully covered for children up to 18 years of age, and amalgam fillings are not permitted. Many other national insurance schemes already fully or partially cover mercury-free fillings (Belgium, Bulgaria, Finland, France, Hungary, Italy, and Slovenia).
7. Exemptions to the amalgam ban were permitted only for permanent tooth restoration, and we found four European jurisdictions (Denmark, Finland, Norway, and Sweden) that have (or had) an exemption policy.
8. Introducing environmental practices in dental facilities that reduce releases of mercury. Switzerland adheres to a policy of substituting less hazardous chemical substances, and mercury is included in this policy. In addition, the United Nations Environment Programme reports that there are a number of other measures that countries may take to limit dental mercury releases to the environment, such as an accurate inventory of amalgam use or the implementation of a waste management scheme that isolates amalgam scrap, capsules, or

removed amalgam and disposes of it appropriately. Canada requires all dental practices to implement a best practice waste management scheme for dental amalgam.

9. A number of EU Member States have implemented legislation to ensure mandatory installation of amalgam separators in dental practices (Austria, Belgium, the Czech Republic, France, Finland, Germany, Italy, Latvia, Malta, the Netherlands, Poland, Portugal, Slovakia, Sweden, and the UK).

Alternatives to amalgam as a restorative solution for young people aged 16 years and under

We identified two categories of interventions that evaluated prevention of caries in children and adolescents: fluoride-based technologies and non-fluoride-based technologies (such as antibacterials, minerals, and sealants). We found two early treatment intervention categories for the treatment of early non-carious lesions in children's and adolescents' teeth: remineralising agents and microinvasive strategies. We identified two intervention categories that have been evaluated in systematic reviews as late treatment responses to cavitated caries in children and adolescents: restorative procedures and techniques, and restorative materials. The categorisation of interventions allowed us to capture the similarities between the interventions and to reflect the diversity of the different techniques and materials evaluated.

We have provided an assessment of the level of evidence (adequate, inadequate, or inconclusive) for each intervention evaluated. It is important to note that when we say that the evidence for an intervention is inadequate, it generally means that the research base upon which to evaluate the intervention is inadequate, rather than that the intervention itself is inadequate. Overall, there were few interventions that systematic review authors judged as not useful (specifically, dental liners and silver-reinforced glass-ionomer cement).

Prevention of dental caries in children and adolescents

Fluoride technologies to prevent caries in children and adolescents

We identified 11 systematic reviews of fluoride technologies to prevent dental caries in children and adolescents (Table 1). Regarding the concentrations of fluoride toothpaste, there is adequate evidence from one review that fluoride concentrations of 1500 ppm and 1450 ppm prevent dental caries in primary teeth; however, the 1450 ppm concentration only showed a slight reduction. There is also adequate evidence in the same review that fluoride concentrations of 1000–1250 ppm and 1450–1500 ppm reduce caries in the permanent teeth of children and adolescents. There is inconclusive evidence regarding the application of a fluoride concentration of 1055 ppm versus 550 ppm on primary teeth in the same review, so we cannot tell which of these concentrations is more effective. In addition, this review found that the evidence is equal (inconclusive) for brushing with the higher concentrations of fluoride toothpaste – 1700–2200 ppm or 2400–2800 ppm as compared with 1450–1500 ppm – in the permanent teeth of children and adolescents, which may suggest that the effect of fluoride toothpaste plateaus at some point between 1450 ppm and 1500 ppm when applied to permanent teeth in children and adolescents. There is adequate evidence in another review to suggest that brushing with a high concentration of fluoride toothpaste (>2500 ppm) is more effective than the standard concentration (≤1500 ppm); however, two of the eight trials included in the review involved adults aged 27 years and over, and this may have skewed the results.

There is adequate evidence in one review that fluoride technologies in the form of toothpastes, mouth rinses, gels, or varnishes are effective interventions to prevent dental caries in the primary and

permanent teeth of children and adolescents aged 5–16 years. In the same review, the evidence is insufficient (and therefore inadequate) to suggest that combining two fluoride technologies is superior to using fluoride toothpaste on its own, and in a different review, the evidence is inconclusive regarding the superiority of one topical fluoride technology over another.

There is adequate evidence in one review that fluoride varnishes are effective in preventing dental caries in the primary and permanent teeth of children and adolescents. There is adequate evidence that fluoride gels are effective for permanent teeth, but there is inadequate evidence that they are effective for primary teeth. There is adequate evidence that fluoride mouth rinses are effective for permanent teeth. Finally, the evidence overall is weak (and therefore inadequate) upon which to judge the effectiveness of using fluoride supplements (tablets, drops, lozenges) to prevent dental caries in primary or permanent teeth in children and adolescents.

Non-fluoride technologies to prevent caries in children and adolescents

We found 10 systematic reviews of non-fluoride technologies to prevent dental caries in children and adolescents (Table 2). There is adequate evidence in a single review that resin-based sealants are an effective intervention to prevent dental caries in permanent teeth in children and adolescents when compared with children without sealants. The results were inconclusive when glass-ionomer-based sealants were compared with no sealant, and they were inconclusive when one type of sealant material was compared with another. A review carried out in China reported adequate evidence that resin-based sealants are an effective intervention to prevent dental caries in the permanent teeth of children and adolescents. However, the data analysed in the review are from trials undertaken with children in China only, and the likelihood of the trials being affected by bias is high, which may have led to overestimation of the effects observed, but this point is not adequately addressed by the authors.

An updated review concludes that the evidence remains inconclusive regarding whether sealants or fluoride varnish is better in preventing dental caries in the permanent teeth of young children. In addition, an earlier review reported inconclusive evidence regarding whether either resin-modified glass-ionomer cements or resin-based fissure sealants are superior in preventing dental caries in the permanent teeth of children and adolescents.

In the review by Botton *et al.* (2016), the evidence is inconclusive upon which to judge whether prior-acid etching is a better technique than self-etching to seal occlusal surfaces in primary and permanent teeth, as only five trials were included in this review and some used a small sample or showed a high dropout rate, which may impair the confidence in the evidence.

In two reviews, there is inadequate evidence upon which to judge the effectiveness of xylitol as an intervention to prevent dental caries in children and adolescents. In another review, there is inadequate evidence to promote the use of non-fluoride agents (arginine, chlorhexidine, casein phosphopeptide-amorphous calcium phosphate, triclosan, and xylitol) for preventing caries in the primary teeth of young children.

In another review, there is inadequate evidence upon which to judge the effectiveness of chlorhexidine-containing oral products (varnish or gel), while in an earlier review, there is conflicting and inconclusive evidence upon which to judge whether chlorhexidine-containing oral products (varnish or gel) are more effective or less effective than controls.

Interventions to treat dental caries in children and adolescents

Early or non-cavitated caries treatment in children and adolescents

Remineralisation agents for early caries treatment in children and adolescents

We identified seven systematic reviews of remineralisation agents for early treatment of dental caries in children and adolescents (Table 3). There is adequate evidence in four reviews that silver diamine fluoride is more effective than controls. One of the four reviews found that 38% silver diamine fluoride was more effective at arresting caries lesions when applied every six months to any coronal surface of primary teeth, compared with both 12% silver diamine fluoride solution applied every six months and 38% silver diamine fluoride solution applied every 12 months. In another review, silver diamine fluoride was more effective (adequate) than controls in arresting caries lesions in primary teeth and providing an anti-caries benefit for the entire dentition, but when silver diamine fluoride was compared with other active treatments in the same review, the evidence was inconclusive.

Results from the network meta-analysis suggest that there is a range of remineralising agents which are effective in arresting and/or reversing non-cavitated carious lesions. The combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth (adequate evidence). There is inadequate evidence that the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective treatment for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth. The evidence is inadequate to suggest that 5000 parts per million (ppm) fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective treatment for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth. Results from the study-level data show that when compared with no intervention, there is adequate evidence that 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth. There is adequate evidence that the application of 1.23% acidulated phosphate fluoride gel to facial/lingual lesions every 12 months, compared with oral health education only, was effective.

There is adequate evidence in two reviews that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth. Finally, there is adequate evidence in one review that brushing teeth with highly concentrated fluoride toothpaste is effective in slowing the progression of early caries in preschool children.

Microinvasive strategies for early treatment of caries in children and adolescents

We found four systematic reviews of microinvasive strategies for early treatment of dental caries in children and adolescents (Table 4). There is adequate evidence in two reviews that microinvasive treatment (sealing and resin infiltration) is superior to non-invasive treatment. One review found that there is adequate evidence to suggest that either sealing or infiltration, used separately, are superior to non-invasive treatment, and in the same review the evidence is inconclusive regarding the superiority of either sealing or infiltration over one another. In another review, there is inconclusive evidence that resin infiltration, by comparison with controls, is effective in arresting the progression of caries. Finally, there is adequate evidence in one review that sealants, when compared with no sealant, are better in preventing carious lesions and arresting the progression of non-cavitated carious lesions. However, the evidence for sealants versus fluoride varnish is inconclusive. The evidence is inconclusive regarding the superiority of one sealant material over another.

Late or restorative treatment cavitated caries in children and adolescents

Procedures and techniques for dental caries restoration in children and adolescents

We found seven systematic reviews of procedures and techniques for restorative treatment of dental caries in children and adolescents (Table 5).

The evidence in two reviews that the conventional restorative treatment technique is better than the atraumatic restorative treatment technique for placing restorative materials to treat caries lesions in primary and permanent teeth is inadequate and cannot support this hypothesis. The evidence provided in two reviews is inconclusive regarding the superiority of the atraumatic restorative treatment technique over the conventional technique when applying glass-ionomer cement to single-surface occlusal restorations in permanent and primary teeth, and for the survival rates of restorations of occlusoproximal cavities in primary teeth.

One review reports that there is adequate evidence for using the conventional technique when applying glass-ionomer cements to restore approximal or multi-surface cavities in primary teeth, and that there is adequate evidence to prefer resin-modified glass-ionomer cement applied using the conventional technique when restoring approximal cavities in primary teeth.

One review reported that there is inadequate evidence upon which to assess laser therapy, by comparison with mechanical methods.

A single review suggests that there is adequate evidence of a clinical advantage in choosing selective caries removal over the complete removal of caries in both primary and permanent teeth.

The evidence from one review was inadequate with respect to the use of dental cavity liners under the placement of composite resin restorations in permanent teeth for the reduction of post-operative sensitivity. Evidence from the same review is inconclusive regarding the superiority of either using or not using dental cavity liners to affect the longevity of composite resin restorations in permanent teeth. The systematic review authors suggest that there is little benefit to be gained in using dental cavity liners.

Materials for cavitated caries restoration in children and adolescents

We found six systematic reviews of restorative materials for the treatment of dental caries in children and adolescents (Table 6). When glass-ionomer cements are compared with other restorative materials, the evidence provided in four reviews is inconclusive overall in determining which material is superior for restorations in primary teeth, for preventing adjacent caries in occlusal surfaces, or for preventing or arresting secondary caries lesions in approximal surface in contact with occlusoproximal restorations in children.

There is insufficient and inadequate evidence in one review to judge whether any of the materials are effective in retrograde filling in children and adults. There is adequate evidence in one review that preformed crowns (using the Hall technique) are superior to conventional fillings for managing tooth decay in primary teeth. However, the evidence in the same review is inadequate when comparing preformed crowns with non-restorative caries management, or when comparing preformed metal crowns with preformed white crowns.

Longitudinal survival of dental restorations for children and adolescents

We identified three reviews on the longitudinal survival of dental caries treatments in children and adolescents (Table 7). In the first review, composite resin exhibited the lowest annual failure rate for

posterior restorations, and modified resin glass-ionomer cement exhibited the highest annual failure rate. Steel crowns had the highest success rate. However, the evidence is inconclusive regarding the best material for posterior restorations in primary teeth; this is due to wide ranges for failure or success and different time points for measuring. There is adequate evidence in the second review that using the atraumatic restorative treatment technique to place high-viscosity glass-ionomer cement sealants produce medium to high levels of survival, and that using the atraumatic restorative treatment technique to place high-viscosity glass-ionomer cement sealants effectively prevent caries lesions in children and adolescents. In the third review, there is inconclusive evidence that the characteristics of individual teeth had any influence on the clinical performance of pit and fissure sealants, or that all deciduous or permanent posterior teeth could be effectively sealed.

Alternatives to amalgam as a restorative solution for adults

We identified two categories of interventions that evaluated prevention of caries in adults: fluoride-based technologies, and sealants. We have also identified evaluations of early treatment interventions for the management of non-carious lesions in adult permanent teeth. For early treatment interventions, we identified five categories of interventions: remineralisation, microinvasive strategies, dental adhesives and other retention aids, restorative materials, and a combination of both remineralisation and microinvasive strategies. We also found systematic reviews that examined the survival of restorations in adults. We identified a number of studies that evaluated direct and indirect restoration treatment responses to repair cavitated caries in adults, a category we titled late treatment. Late treatment includes: restorative procedures and techniques, and restorative materials. The categorisation of interventions allowed us to capture the similarities between the interventions and to reflect the diversity of the different techniques and materials evaluated.

We completed an assessment of the level of evidence (adequate, inadequate, or inconclusive) for each type of intervention evaluated. It is important to note that when we say that the evidence for an intervention is inadequate, it generally means that the research base upon which to evaluate the intervention is inadequate, rather than that the intervention itself is inadequate.

Overall, there was one intervention (dental liners) that systematic review authors judged as not useful for adults.

Prevention of caries in adults

Fluoride technologies to prevent caries in adults

We identified two systematic reviews of fluoride technologies to prevent dental caries in adults (Table 8).

Regarding the two reviews that evaluated fluoride technologies, there is adequate evidence that brushing teeth with 1000 or 1100 ppm fluoride toothpaste reduces caries increment in decayed, missing, and filled permanent surfaces when compared with non-fluoride toothpaste in adults of all ages. In the first review, the evidence is inconclusive regarding the magnitude of the effect due to considerable variability of the effect across the included studies. In the second review, there is adequate evidence that fluoride gel is effective in preventing crown caries and reversing root caries in adults and older people, but the same review provides inadequate evidence upon which to judge the performance of fluoride mouth rinse and fluoride foam.

Sealants to prevent caries in adults

We identified three systematic reviews of sealants to prevent dental caries in adults (Table 9). From the three reviews that evaluated sealants, one 2018 review contained adequate evidence that

conventional resin-based sealants have a superior retention capacity when compared with glass-ionomer cement-based sealants, while another 2018 review contained inconclusive evidence regarding whether flowable composite sealants or conventional resin-based sealants have superior retention rates. Finally, the evidence in two other reviews is inconclusive regarding whether conventional resin-based sealants or glass-ionomer cement-based sealants, and resin-modified glass-ionomer cements or resin-based fissure sealants, respectively, perform better in terms of preventing caries in adult permanent teeth.

Interventions to treat dental caries in adults

Early treatment of non-cavitated caries in adults

Remineralisation agents for the treatment of early caries lesions in adults

We identified six reviews of remineralising agents to enable early treatment of dental caries in adults (Table 10). In five of the six reviews that evaluated remineralising agents, there is inadequate evidence upon which to judge the performance of the intervention when compared with controls. For example, there is inadequate evidence upon which to judge the effectiveness of the combination of casein phosphopeptide-amorphous calcium phosphate and fluorides when compared with fluorides monotherapy; inadequate evidence upon which to judge the effectiveness of casein phosphopeptide-amorphous calcium phosphate technologies compared with routine oral care; and inadequate evidence upon which to assess the relative effectiveness of casein phosphopeptide-amorphous calcium phosphate, fluoride products, and resins when compared with each other. In addition, we judged the evidence to be inadequate on the performance of resin-modified glass-ionomer cement, compared with fluoride-containing composite resin and with composite resin without fluoride, in reducing demineralisation in hard tooth tissues. We judged the evidence to be inconclusive in support of the claim that casein phosphopeptide-amorphous calcium phosphate is an effective remineralising agent to treat naturally occurring white spot lesions.

Microinvasive strategies for the treatment of early caries lesions in adults

We found five systematic reviews of microinvasive strategies to enable early treatment of dental caries in adults (Table 11).

There is adequate evidence in four of the five reviews evaluating microinvasive strategies that resin infiltration and sealants are effective interventions for the early treatment of caries in adult teeth. For example, there is adequate evidence that resin infiltration and resin sealants are effective microinvasive interventions to arrest the progression of non-cavitated proximal caries and that resin infiltration could arrest progression of enamel caries and caries around the enamel-dentine junction. However, there is inconclusive evidence for the therapeutic effectiveness of resin infiltration in dentine caries. There is adequate evidence that sealant or infiltration are superior to non-invasive treatment, and that either sealing or infiltration used separately are also superior to non-invasive treatment. Another review reports adequate evidence that microinvasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions and that this is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss). Two reviews regarding which microinvasive technique offers the greatest benefit found that there is inadequate evidence upon which to judge the effectiveness of non-invasive, microinvasive, and minimally invasive treatments, as all included studies had a high risk of bias and the authors of the reviews graded the the quality of evidence as being low or very low.

Adhesives and other retention aids for early treatment in adults

We located six systematic reviews of adhesives and other retention aids to enable early treatment of dental caries in adults (Table 12).

Regarding the six reviews that evaluated dental adhesives and other retention aids, there is adequate evidence that the selective enamel etching technique is better than no etching for improving the marginal adaptation, discolouration, and retention of composite restorations in non-carious cervical lesions in the adult population. When a 2-hydroxyethyl methacrylate (HEMA)-free adhesive system is compared with a HEMA-containing adhesive system, the evidence is inconclusive regarding which system is better. There is also inconclusive evidence regarding whether bevelled or non-bevelled restorations are superior in the short term.

In two reviews that evaluated adhesives, there is inadequate evidence upon which to judge the effectiveness of contemporary adhesives for the restoration of non-carious cervical lesions in permanent teeth. In contrast, another recent review compared restorations bonded with self-etch adhesives with restorations bonded with etch-and-rinse adhesives for post-operative sensitivity, retention rates, and marginal discolouration in non-carious cervical lesions. It found adequate evidence that using etch-and-rinse adhesives can result in a better reduction of marginal discolouration, when compared with using self-etch adhesives. In addition, there is adequate evidence that neither bonding strategy (either etch and rinse or self-etch) influences the risk of post-operative sensitivity. With respect to the retention of restorations, the evidence is inconclusive, as no significant differences between etch-and-rinse versus self-etch adhesives were observed.

Dental restorative materials in adults

We identifed two reviews of restorative materials to enable early treatment of dental caries in adults (Table 13). In the two reviews that evaluated dental restorative materials, there is adequate evidence that glass-ionomer cement restorations showed superior retention levels when compared with resin-based composite restorations in follow-ups after between one and five years, and the evidence is adequate to support the claim that resin composite viscosity does not influence retention rates up to three years follow-up. The quality of this evidence was judged to be moderate in both reviews based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system. There is inadequate evidence upon which to compare flowable resin composite restorations with regular resin composites on marginal discolouration and marginal adaptation, as the quality of the evidence was judged to be low.

Remineralising agents and microinvasive strategies combined for early treatment in adults

We found two systematic reviews of remineralising agents and microinvasive strategies combined to enable early treatment of dental caries in adults (Table 14). In the first review, which included evaluations of interventions with elements of both remineralising agents and microinvasive strategies, there is adequate evidence that the combination of sealants and 5% sodium fluoride varnish is effective for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth; that the combination of resin infiltration and 5% sodium fluoride varnish is effective for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth; that high-fluoride (5000 ppm or 1.1% sodium fluoride) toothpastes or gels are effective for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth; that 5% sodium fluoride varnish is effective in arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth; and that 1.23% acidulated phosphate fluoride gel is effective on facial/lingual lesions, but only at longer follow-up times (12 months). In the second of the two reviews, there is inadequate evidence upon which to

draw firm conclusions about the effectiveness of combined non-surgical caries prevention methods, such as sealants and non-fluoride antibacterials or chemicals.

Late or restorative caries treatment in adults

Procedures and techniques for restorative treatment of caries in adults

We identified nine systematic reviews of restorative techniques and procedures to aid dental restorations in adults (Table 15). Regarding the use of dental cavity liners to aid the placement of dental restorations, there is inadequate evidence upon which to judge the performance of dental cavity liners regarding any difference in post-operative sensitivity, measured using either cold response or patient-reported response. There is also inadequate evidence upon which to judge the performance of different liners for their antibacterial effects, and the evidence is inconclusive – when dental cavity liners were compared with using no liners – regarding the longevity of composite resin restorations in permanent teeth. In one review, there is adequate evidence against using flowable composite liners to reduce microleakage from composite restorations. The evidence is inconclusive regarding whether etch and rinse or self-etch is the preferred adhesive technique to aid the placement of posterior resin composite restorations.

Regarding procedures and techniques for removing caries from adult teeth, there is adequate evidence to demonstrate the clinical advantage of using selective caries removal, compared with the complete removal of caries in both primary and permanent teeth. However, there is inadequate evidence upon which to compare the performance of laser therapy with mechanical methods, and there is inadequate evidence upon which to compare the performance of atraumatic restorative treatment versus the conventional technique when placing restorations in the permanent teeth of adults. In addition, there is inadequate evidence upon which to compare the procedure of pulp capping versus root canal treatment in young permanent teeth with pulp exposure. Finally, there is inadequate evidence upon which to judge the performance of coronal pulpotomy treatment, by comparison with amalgam or composite restoration, as an intervention to manage carious vital pulp exposure in permanent posterior teeth.

Restorative materials used in the treatment of cavitated caries in adults

We located nine systematic reviews of restorative materials for treatment of dental caries in adults (Table 16). In the five reviews that evaluated different aspects of composite resin restorations, the evidence is weak or insufficient, and there is therefore inadequate evidence upon which to judge the performance of the intervention being evaluated. For example, there is inadequate evidence upon which to judge the performance of composite resins, by comparison with amalgam, on restoration failure rates and the risk of secondary caries. There is no evidence upon which to compare replacing versus repairing defective resin composite dental restorations in permanent molar and premolar teeth. Similarly, there is inadequate evidence upon which to compare the performance of composite restorations containing antibacterial agents with composite restorations containing no antibacterial agents for the prevention of secondary dental caries. There is also inadequate evidence upon which to compare the performance of composite inlays and onlays with ceramic inlays and onlays. In addition, we judged the evidence in the fifth review to be inadequate regarding which is better relative to amalgam: resin composites placed without enamel/dentine conditioning, or resin composites placed with self-etching adhesive systems. Although composites appeared to fare better for colour match and fractures, there is no difference between composites and amalgam on the longevity of restorations, and there are notable limitations regarding the quality of the included studies.

In the two reviews that evaluated glass-ionomer cements, there is inadequate evidence upon which to judge the performance of high-viscosity glass-ionomer cement combined with a resinous coating, by comparison with amalgam or resin composite or other glass-ionomer cements in Class I restorations of posterior primary or permanent teeth. In addition, there is inadequate evidence upon which to judge the performance of resin-modified glass-ionomer cement restorations when compared with conventional glass-ionomer restorations to prevent secondary caries lesions at the margins of restorations in adult permanent teeth.

In the two remaining reviews that evaluated different materials, there is inadequate evidence with which to assess the effects of crowns compared with conventional fillings for the restoration of root-filled teeth, and there is inadequate evidence upon which to judge the performance of any material for retrograde filling.

Longitudinal survival of dental restorations in adults

We identified nine systematic reviews on the survival of direct and indirect dental restorations in adults (Table 17).

There is adequate evidence from two reviews that ceramic onlays acting as an indirect dental restorative material provide acceptable survival rates over both the medium and long term in posterior teeth, regardless of the ceramic material used, study design, or study setting. In addition, there is adequate evidence in a 2016 review that ceramic inlays and overlays produce acceptable high restoration survival rates of more than 90%. In two reviews, there is inadequate evidence upon which to draw comparisons in survival rates between indirect and direct methods of restoration.

In three reviews, there is inadequate evidence upon which to assess the clinical performance of composite restorations in posterior teeth. The clinical performance includes the survival rate of restorations and the potential influence of complicating factors (e.g. patient characteristics) on the survival rates. In a 2015 review, there is adequate evidence to suggest that amalgam posterior restorations in permanent teeth last longer when compared with composite resin restorations, and are associated with the presence of fewer secondary caries. In the only review from this section that examined the survival of restorations in permanent anterior teeth, there is inadequate evidence upon which to judge the performance of Class III and Class IV composite resin restorations. Finally, there is inadequate evidence with which to determine the influence of patient-related factors on restoration survival in posterior permanent teeth.

Conclusions

Where comparable, our findings from Question 3 are similar to those from the 2018 Scottish Dental Clinical Effectiveness Programme evidence review titled *Prevention and Management of Dental Caries in Children*. The findings are also comparable to Mejàre *et al.*, who appraised and summarised the evidence and evidence gaps for practice-relevant questions in paediatric dentistry. Finally, our findings on the quality of research focusing on children and adolescents are similar to those of Smaïl-Faugeron *et al.*, who assessed the methodological quality of Cochrane reviews of paediatric oral health. In addition, our findings pertaining to the quality of evidence for adult treatment evaluations reported in Question 4 are not that dissimilar to the quality assessment review by Sarkis-Onofre *et al.* However, the reports differ in that Sarkis-Onofre et al. appraised the quality of the systematic reviews while we assessed the level of evidence reported in the reviews. Our findings from Question 4 resonate with the conclusions drawn by the Scottish Dental Clinical Effectiveness Programme, and also with the work of Faggion in 2012. The examples we use from the work of Conway *et al.* and Fleming *et al.* illustrate the variation in the quality of evidence provided in systematic reviews.

The evidence available indicates that prevention and early treatment of caries is a more successful long-term strategy than restoring cavitated cavities for children, adolescents and adults. If prevention and early treatment was introduced on a large scale, then the requirement for alternatives to amalgam would be reduced. A summary of evidence base for caries is presented by dentition type in the table below:

Summary table: Current best evidence from systematic reviews for dental caries

Teeth type	What works
Primary teeth	
Prevention Fluoride ppm does not take account of water fluoridation	Brushing teeth with fluoride toothpaste is effective in preventing dental caries in preschool children aged 7 years and under (1 review, adequate evidence). Fluoride concentrations of 1500 ppm and 1450 ppm in toothpaste prevent dental caries in primary teeth (1 review, adequate evidence).
Early treatment	38% silver diamine fluoride was effective at arresting caries lesions when applied every six months to any coronal surface of primary teeth (4 reviews, adequate evidence) The combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary teeth (1 review, adequate evidence) Fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth (2 reviews, adequate evidence). Brushing teeth with highly concentrated fluoride toothpaste is effective in slowing the progression of early caries in pre-school children (1 review, adequate evidence).
Late treatment	Atraumatic restorative treatment technique and the conventional technique are equally effective when applying glass-ionomer cement to single-surface occlusal restorations in primary teeth. (1 review, inconclusive evidence as to which is better) The conventional technique is adequate when applying glass-ionomer cements to restore approximal or multi-surface cavities in primary teeth. (1 review, adequate evidence) Glass-ionomer cements are equal to other restorative materials for restorations in primary teeth, for preventing adjacent caries in occlusal surfaces, or for preventing or arresting secondary caries lesions in approximal surface in contact with occlusoproximal restorations in children. (4 reviews, inconclusive evidence as to which is better)
Mixed teeth	
Prevention Fluoride ppm does not take account of water fluoridation	Brushing teeth with fluoride toothpaste is effective in preventing dental caries in children and adolescents aged 5–16 years (1 review, adequate evidence). Fluoride concentrations of 1500 ppm and 1450 ppm in toothpaste prevent dental caries in primary and permanent teeth (1 review, adequate evidence). Fluoride technologies in the form of toothpastes, mouth rinses, gels, or varnishes are effective interventions to prevent dental caries in the primary and permanent teeth of children and adolescents aged 5–16 years (1 review, adequate evidence). The evidence regarding the superiority of one topical fluoride technology over another in primary and permanent teeth indicates that

	the products are equally effective (1 review, inconclusive evidence as to which is better). Fluoride varnishes are effective in preventing dental caries in the primary and permanent teeth of children and adolescents. (1 review, adequate evidence). Glass-ionomer-based sealants and resin-based sealants were equally effective in preventing dental caries in the permanent teeth of children and adolescents (2 reviews, inconclusive evidence as to which is better). Sealants and fluoride varnish are equally effective in preventing dental caries in the permanent teeth of young children (1 review, inconclusive evidence as to which is better).
Early treatment	The combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in permanent teeth (1 review, adequate evidence) 5% sodium fluoride varnish was the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth (1 review, adequate evidence). The application of 1.23% acidulated phosphate fluoride gel to facial/lingual lesions every 12 months is effective (1 review, adequate evidence). For early caries treatment, either sealing or infiltration, used separately, are superior to non-invasive treatment (1 review, adequate evidence). Sealing or infiltration are equally effective in treating early caries (2 reviews, inconclusive evidence as to which is better). Sealants or fluoride varnish are equally effective in treating early caries (1 review, inconclusive evidence as to which is better).
Late treatment	Atraumatic restorative treatment technique and the conventional technique are equally effective when applying glass-ionomer cement to single-surface occlusal restorations in permanent and primary teeth, (1 review, inconclusive evidence as to which is better) Regarding procedures and techniques for removing caries from teeth, there is adequate evidence to demonstrate the clinical advantage of using selective caries removal, compared with the complete removal of caries in both primary and permanent teeth (1 review, adequate evidence).
Premanent teeth	
Prevention	Two reviews evaluated fluoride technologies reported there is adequate evidence that brushing teeth with 1000 or 1100 ppm fluoride toothpaste reduces caries increment in decayed, missing, and filled permanent surfaces when compared with non-fluoride toothpaste in adults of all ages (2 reviews, adequate evidence). There is adequate evidence that fluoride gel is effective in preventing crown caries and reversing root caries in adults and older people (1 review, adequate evidence). One review contained adequate evidence that conventional resin-based sealants have a superior retention capacity when compared with glass-ionomer cement-based sealants (1 review, adequate evidence). One review reported that flowable composite sealants and conventional resin-based sealants have equal effectiveness on retention rates (1 review, adequate evidence). Two reviews reported that conventional resin-based sealants or glass-ionomer cement-based sealants are equally effective, and that resin-

	modified glass-ionomer cements and resin-based fissure sealants are equally effectivey in preventing caries in adult permanent teeth (1 review, adequate evidence)
Early treatment	There is adequate evidence in four reviews evaluating microinvasive strategies that resin infiltration and sealants are effective interventions for the early treatment of caries in adult teeth. In the two reviews that evaluated dental restorative materials, there is adequate evidence that glass-ionomer cement restorations showed superior retention levels when compared with resin-based composite restorations in follow-ups after between one and five years, and the evidence is adequate to support the claim that resin composite viscosity does not influence retention rates up to three years follow-up. One review included evaluations of interventions with elements of both remineralising agents and microinvasive strategies, and reported that there is adequate evidence that: • high-fluoride (5000 ppm or 1.1% sodium fluoride) toothpastes or gels are effective for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth; • 5% sodium fluoride varnish is effective in arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth; • 1.23% acidulated phosphate fluoride gel is effective on facial/lingual lesions, but only at longer follow-up times (12 months) (1 review, adequate evidence).
Late treatment	In one review, there is adequate evidence against using flowable composite liners to reduce microleakage from composite restorations (1 review, adequate evidence). Regarding procedures and techniques for removing caries from adult teeth, there is adequate evidence to demonstrate the clinical advantage of using selective caries removal, compared with the complete removal of caries in permanent teeth (1 review, adequate evidence).

1 Introduction

1.1 Mercury regulation

The European Union (EU) has introduced Regulation (EU) 2017/852[1] to implement the 2013 United Nations Minamata Convention on Mercury[2], which aims to protect human health and the environment from mercury pollution. This 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).[1] The use of mercury in dental amalgam is a key component of this agreement and has a fundamental impact on the delivery of dental restoration treatments in Ireland. This EU Regulation is binding in its entirety and is directly applicable in all Member States. The Department of Communications, Climate Action and Environment published Statutory Instrument No. 533 of 2018[3] to implement Regulation (EU) 2017/852[1] and the United Nations Minamata Convention on Mercury.[2] Since July 2018, the EU Regulation has introduced a ban on amalgam use in children under 15 years of age, and in pregnant or breastfeeding women, except where deemed strictly necessary by the dental practitioner based on the specific medical needs of the patient.[1]

1.2 National plan for mercury

By July 2019, the Irish Government must submit a plan to the EU[1] detailing Ireland*'s* approaches to the phase-down of amalgam up to 2030.[4] In general, the advice and guidance in Ireland to support the public and dental professionals in choosing dental restoration instead of amalgam is not sufficiently clear for either dental professionals or members of the public. Of note, the type of restoration will differ according to tooth type (permanent or deciduous, function, and position), age cohort (child, adolescent, adult, or older person), and for pregnant and breastfeeding women. Evidence for alternative approaches to amalgam restorations and root canal treatments is crucial, while clarity on the advantages and disadvantages of alternative materials is not easily available. This evidence base will be used to inform the negotiation of National Oral Health Policy 'packages of care'. The emphasis in the Policy is on prevention, minimal intervention, and, where possible, the use of a non-amalgam material for restoration (fillings). The preferred option in both children and adults will always be to select an alternative to amalgam for environmental reasons. In order to enable this, a variety of other choices needs to be available. Currently, the discussion substantially focuses on a binary decision between resin composite and amalgam, which may encourage excessive use of amalgam intervention because of its cheap cost and ease of use and longevity, by comparison with resin composites. Exploration of a variety of options is essential in order to ensure that this excessive use of amalgam does not inadvertently occur, and to give both dental professionals and the public greater choice.

1.3 Ireland's oral health policy

Smile agus Sláinte: National Oral Health Policy[4] was published in April 2019 and takes into account Regulation (EU) 2017/852[1] on mercury by providing for the phase-down of dental amalgam, in line with international policy on reducing mercury use. Two population cohorts – children under 15 years of age and pregnant and breastfeeding women – are initial target groups for the phase-down of amalgam use. The reduction in the use of traditional filling materials requires an overt change in the delivery of oral healthcare services, which to date have emphasised amalgam restoration as a central

intervention; this will have a fundamental impact on oral healthcare service provision. However, reduction in the use of amalgam does not involve only the substitution of amalgam fillings with an alternative restorative material in the future; prevention, non-intervention, and minimal intervention will be the preferred actions. Both prevention and intervention in children and younger age groups are based on packages of oral healthcare which include prevention and some intervention. This is to encourage minimal intervention, but the danger is that when intervention is required, the cheapest type of filling material may be used inappropriately. Keeping the younger age groups amalgam-free will be especially important, since once amalgam is used, it means that mercury will be released into the environment every time that filling is replaced over the course of a lifetime. The concern is that without clear guidance, the exceptions will be more common than should be expected. Adults will also have packages of care for preventive items (including one filling per year) through the new National Oral Health Policy. For adults who need more than one filling, additional dental restorations will be paid for through a fee-per-item system.

Smile agus Sláinte: the National Oral Health Policy supports the phase-down of amalgam through its emphasis on health promotion, prevention, and expansion of primary oral healthcare services for the public, for all ages.[4] In parallel, it supports education and broadening skills for dental professionals. The services proposed in the Policy will support the preferred use of alternative materials and restorations, rather than amalgam, throughout the life course. In the new system of service provision, amalgam will only be used in exceptional cases. Other means of enabling mercury reduction in dentistry will also be considered, such as supporting appropriate waste disposal mechanisms in dental practices.

1.4 Dental Council code of practice on amalgam

The Dental Council, established under the provisions of the Dentists Act, 1985[5], promotes high standards of professional education and professional conduct among dentists practising in Ireland. With respect to Regulation (EU) 2017/852[1] and amalgam, the Dental Council has drawn up a code of practice booklet for the dentistry profession.[6] It quotes Article 10 of the regulations and outlines that dentists must comply with this article.

"Article 10 of the regulations sets out the parameters for the use of dental amalgam:

1. From 1 January 2019, dental amalgam shall only be used in pre-dosed encapsulated form. The use of mercury in bulk form by dental practitioners shall be prohibited.
2. From 1 July 2018, dental amalgam shall not be used for dental treatment of deciduous teeth, of children under 15 years, and of pregnant or breastfeeding women, except when deemed strictly necessary by the dental practitioner based on the specific medical needs of the patient.
3. By 1 July 2019, each Member State shall set out a national plan concerning the measures it intends to implement to phase down the use of dental amalgam. Member States shall make their national plans publicly available on the internet and shall transmit them to the Commission within one month of their adoption.
4. From 1 January 2019, operators of dental facilities in which dental amalgam is used or dental amalgam fillings or teeth containing such fillings are removed shall ensure that their facilities are equipped with amalgam separators for the retention and collection of amalgam particles, including those contained in used water.
5. Capsules and amalgam separators complying with European standards, or with other national or international standards that provide an equivalent level of quality and retention, shall be presumed to satisfy the requirements set out in paragraphs 1 and 4.
6. Dental practitioners shall ensure that their amalgam waste, including amalgam residues, particles and fillings, and teeth, or parts thereof, contaminated by dental amalgam, is handled and collected by an authorised waste management establishment or undertaking." p2-3[6]

The code of practice goes on to state that dentists "have an ethical as well as a legal obligation to comply with these regulations". The dentists will "ensure that valid and explicit consent has been obtained to treat a patient using dental amalgam if it is being used for the treatment of deciduous teeth, in children under the age of 15 or of pregnant or breastfeeding women". In the cases where it is clinically necessary to use dental amalgam, the dentist is required to "record the specific clinical reasons why". p3[6]

1.5 Caries

Walsh *et al.*[7] summarised existing literature and 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 demineralisation of tooth structure by organic acids formed from the interactions between cariogenic bacteria in dental plaque and fermentable carbohydrates (mainly sugars). The dental caries process is influenced by the susceptibility of the tooth surface, the bacterial profile, the quantity and certainty of saliva, and the presence of fluoride, which promotes remineralisation and inhibits demineralisation of the tooth structure.

Caries in permanent teeth was the most prevalent condition among all those evaluated in the Global Burden of Disease Study 2016, affecting 2.4 billion people; the estimated prevalence of caries in deciduous teeth was 486 million children worldwide.[8]

1.6 Alternatives to amalgam

Due to time limitations, this section of the introduction relies heavily on the background presented in high-quality peer-reviewed systematic reviews, such as Cochrane reviews.

1.6.1 Amalgam

Dental amalgams are metallic alloys.[9] They have been predictable and inexpensive restorative materials for permanent damage caused by caries for more than 150 years.[9] Amalgams have been used for posterior coronal restorations[9] and root canal fillings.[10] Their use and success rate have been documented, and amalgams are available, inexpensive, and easy to handle in posterior teeth restorations.[9 10] However, amalgams are declining in use in dentistry, mainly due to their unaesthetic appearance and concerns about their mercury content,[9] despite the fact that amalgam restorations reduce the possibility of secondary caries over time by forming oxides in the margin of the cavities as a result of the natural corrosion of the material, mainly in alloys with high copper content.[11] Of note, and in line with current conservative practices, the need for more dental preparation, which is necessary to promote greater restoration retention, makes amalgam questionable for conservative dentistry.[11] In recent years, the efficacy of amalgam has been questioned, due to initial marginal leakage, corrosion, moisture sensitivity, mercury contamination of periapical tissue, and the potential hazards associated with mercury-containing materials.[10]

1.6.2 Resin composites

Dental resin composites are considered the most likely substitutes or alternatives to amalgam for posterior coronal restorations and were developed in response to people's demands for tooth-coloured restorations.[9] Dental resin composites are particle-reinforced resins.[9] The indications for the use of resin composites have expanded from the anterior restoration of tooth crowns to posterior restorations, and even to stress-bearing posterior restorations, as amalgam substitutes or amalgam alternatives.[9] Early composite restorations in posterior teeth were more likely to fail compared with amalgam restorations.[9] This was due to shrinkage, rapid loss of anatomic form, poor wear, and poor colour stability.[12] They also lacked stiffness and adhesion to tooth structures.[12] The higher sensitivity in the manufacturing technique, in addition to limitations such as contraction during polymerisation and the possibility of forming marginal gaps, can be critical factors for the durability of composites.[11] More recently, improved resin composites, techniques, and instruments have been developed in order to address these limitations.[12] The field of composite dental restoratives has also continued to advance resin formulation, filler loading and modification, and curing methodologies and mechanisms in recent years.[9] A systematic review by Downer, published in 1999, examined literature on the longevity of routine dental restorations in permanent teeth[13]. This review found that the most frequently reported median survival time (between 6 and 10 years) of resin composite restorations was comparable with that for amalgam restorations. Studies have also shown a low annual failure average for composite resins in occlusal and occlusoproximal restorations, varying from 1% to 3%.[11] The principal reasons for failure of restorations placed using contemporaneously available direct resin composites were secondary caries, fractures, marginal deterioration, discolouration, and wear.[12] Factors that influence clinical outcomes of resin composite restorations are the type of resin composite itself, the number of composite layers, the type of enamel or dentine conditioning, the operative technique used to bevel the enamel, and absolute versus relative isolation.[14]

1.6.3 Glass-ionomer cements

A glass-ionomer cement is a dental restorative material used in dentistry as a filling material and luting cement, including for orthodontic bracket attachment. Glass-ionomer cement is primarily used in the prevention of dental caries. This dental material has good adhesive bond properties to tooth structures, allowing it to form a tight seal between the internal structures of the tooth and the surrounding environment. Glass-ionomer cements act as sealants when pits and fissures in the tooth occur, and they release fluoride in order to prevent further enamel demineralisation and to promote remineralisation. Fluoride can also hinder bacterial growth by inhibiting their metabolisation of ingested sugars in the diet. It does this by inhibiting various metabolic enzymes within the bacteria. This leads to a reduction in the acid produced by the bacteria.

The attention to glass-ionomer cement restorative materials for primary dentition has increased;[15] for example, in Sweden, glass-ionomer cement restoration using hand tools is the first choice for primary dentition.[16] Its advantages are the greater maintenance of the intact tooth structure and good adhesion to the remaining tooth structure. These characteristics allow the use of more conservative restorative techniques, limiting the cavity preparation mainly to the removal of decayed tissue, thereby preserving the intact tooth structures.[15] Dias *et al*.[15] conclude that the materials analysed (glass-ionomer cement and composite resin) presented similar clinical performance as each other in terms of the percentage of failures, marginal adaptation, marginal discolouration, and anatomical form in Class II restorations in primary teeth. However, regarding the occurrence of secondary carious lesions, glass-ionomer cement presented superior clinical performance, and this effect was more evident for the resin-modified glass-ionomer cement used with rubber dam isolation.

1.6.4 Compomers

Dental compomers are materials which are used in dentistry as restorative materials. They were introduced in the early 1990s as a hybrid of two other dental materials: dental composites and glass-ionomer cement. They are also known as polyacid-modified resin composites. They are used for restorations in low-stress-bearing areas.

1.6.5 Indirect restoration methods

In dentistry, inlays, onlays, and overlays are a form of indirect restoration. This means that they are made outside of the mouth by a dental technician as a single, solid piece that fits the specific size and shape of the cavity. They are usually fabricated using gold or porcelain. Due to its tooth-like colour, porcelain provides better aesthetic value for the patient. In more recent years, inlays and onlays have increasingly been made out of ceramic materials. The restoration is then cemented in place in the mouth. This is an alternative to a direct restoration. New chairside devices allow for inlays and onlays to be created and fitted within a single appointment.

Inlays, onlays, and overlays are used in molars or premolars when the tooth has experienced too much damage to support a basic filling, but not so much damage that a crown is necessary. The key comparison between them is the amount and part of the tooth that they cover. An inlay will incorporate the pits and fissures of a tooth, mainly encompassing the chewing surface between the cusps. An onlay will involve one or more cusps being covered. If all cusps and the entire surface of the tooth are covered, this is then known as a crown.

There is adequate evidence that ceramic onlays on posterior teeth, acting as an indirect dental restorative material, provide acceptable survival rates over both the medium and long term, and all

ceramic materials tested performed well.[17 18] There is adequate evidence that ceramic inlays and overlays produce acceptable high restoration survival rates of more than 90%,[18] and there is adequate evidence that amalgam posterior restorations in permanent teeth last longer than composite resin restorations and are associated with a lower incidence of secondary caries.[11]

1.6.6 Amalgam compared with resin composites

1.6.6.1 Rationale, use, and adverse effects

Dental amalgam and resin composites are the most commonly used products for restoring permanent molar and premolar cavities.[9] Amalgam has been gradually replaced by resin composite as the preferred material to restore posterior teeth. This is thought to have been due to concerns relating to amalgam's lack of adhesive properties, its aesthetics, and its potential health effects.[12] Composite materials have been increasingly used for the restoration of posterior teeth since the early 1990s as a tooth-coloured alternative to amalgam.[12] These may be placed using either direct or indirect techniques.[12] Surveys and retrospective studies developed by groups of practice-based researchers differ in their conclusions about which is the material most commonly used in restorative dentistry in 2010.[9] Some indicate that the usage of composite resins has surpassed the usage of amalgam over the last 10 years, but amalgam is still widely used in many countries.[14] Based on the market volume and materials sold, it is estimated that more than 520 million direct dental restorations are placed around the world each year.[14] Of these, about 261 million are estimated to be direct composite resin restorations, followed by 236 million amalgam restorations and about 26 million compomer restorations.[14] However, the geographical distribution of these types of restorations demonstrates strong regional differences. Almost no amalgam restorations are placed in Scandinavian countries, whereas in central Europe and the United States of America (USA), more teeth are restored with composite than with amalgam, and in southern and eastern European countries, more teeth are restored with amalgam than with composite.[14] Amalgam use has been found to be decreasing in Australia, the United Kingdom (UK), and the USA.[12]

1.6.6.2 Outcomes

A 2015 meta-analysis based on the results of eight studies demonstrated greater longevity of amalgam restorations compared with composite resin restorations.[11] The main causes of failures reported in the studies assessed were the occurrence of secondary caries and fractures of the restorations or teeth, which had already been previously reported in previously published studies.[11] The presence of secondary caries was significantly higher in composite resin restorations than in amalgam restorations.[11] The oxides formed in the tooth against the amalgam interface help seal the margins, which may explain their lower incidence of caries.[11] In contrast, factors such as the adhesive technique, adhesive system, polymerisation shrinkage, type of dental substrate (enamel/dentine), and quality of the hybrid layer can act to increase adhesive failure in composites, thus increasing the risk of recurrent caries. With regard to fractures, there was no statistically significant difference between amalgam and composite resins.[11]

The cost of placing dental amalgams (USD 12.40) is only slightly lower than the cost of placing composite fillings (USD 15.90) for a single restoration provided in one dental session.[9] However, when the costs are considered in the long term, taking into consideration the differences in longevity of the two materials, it was calculated that the estimated cost over 10 years for a Class II restoration was USD 189.80 for an amalgam filling, compared with USD 363.70 for a composite filling.[9] Due to the high

cost of dental mercury pollution, however, amalgam is now recognised as possibly more expensive than other fillings when considering environmental costs.[19]

1.6.7 Retrograde treatment

1.6.7.1 Retrograde filling treatment

Root filling, or endodontic treatment, is a fairly routine dental procedure in which the dental pulp (nerve) is removed and replaced by a root canal filling.[20] It is usually indicated when there has been irreversible inflammation or necrosis (death) of the pulp as a consequence of caries or trauma.[20] For many years, amalgam was accepted as the material of choice for root-end filling, and the clinical application of amalgam was documented in several clinical studies with a reported success rate of 50% to 80%.[10]

Two methods of root canal treatment, direct and indirect, can be used for the functional and aesthetic restoration of root-filled teeth.[20] The direct method is performed through conventional techniques, in which the dentist places a restorative material – such as amalgam or another filling material – directly into the tooth. Conventional fillings usually need a single clinical appointment, are generally simpler to achieve than the indirect method, and have good survival characteristics. Indirect restorations (i.e. crowns) are fabricated with materials such as cast metal or ceramics (porcelain). According to their classical indication, single crowns can restore proportionately larger amounts of missing dentine and enamel than other approaches.[20] However, the need for impressions and associated laboratory work to complete the final restoration may add considerably to the overall costs.

Since the 1990s, amalgam has slowly given way to zinc oxide eugenol-containing materials, such as intermediate restorative material, which has 20% polymethacrylate added (by weight) to the base zinc oxide powder and super ethoxybenzoic acid for direct restoration.[10] In vitro leakage studies, animal studies, and retrospective in vivo studies indicate that these zinc oxide eugenol-containing materials are superior to amalgam in terms of sealability and biocompatibility. Shortcomings of the currently available zinc oxide eugenol-containing cements are their mild to moderate toxicity when freshly mixed, and their radiopacity.

Since 2015, a promising new root-end filling material – mineral trioxide aggregate, developed at Loma Linda University, California, USA – has received widespread attention.[10] Its major components are similar to Portland cement, which is a mixture of dicalcium silicate, tricalcium silicate, tricalcium aluminate, gypsum, and tetracalcium aluminoferrite. Although it is an expensive material and requires additional skill and equipment to use satisfactorily, a clinician can skillfully handle it after suitable training. Mineral trioxide aggregate has major advantages, including excellent biocompatibility, ideal adherence to cavity walls, low solubility, and the ability to induce cementogenesis at the root surface, with deposition of new cementum onto the exposed dentine and mineral trioxide aggregate surfaces. Mineral trioxide aggregate is an excellent bioactive material. When it is placed in direct contact with human tissues, it will form calcium hydroxide that releases calcium ions for cell attachment and proliferation; it also modulates cytokine production and encourages proliferation and migration of progenitors followed by their differentiation into odontoblast-like cells. However, the mean setting time of mineral trioxide aggregate is 165 ± 5 minutes, which is longer than amalgam, super ethoxybenzoic acid, and intermediate restorative material, and is potentially problematic in endodontic surgery.

In addition to polymers, glass-ionomer cements, polycarboxylate cements, zinc phosphate cements, calciumphosphate cements, and composite resins have all been employed as retrograde fillings.[10] Biodentine, which is reported to have reparative dentine synthesis properties, is awaiting clinical evaluation as a possible retrograde filling material.[10] All of these materials have different characteristics and are potential alternatives to traditional materials, although potential harm should be carefully considered before widespread use is considered.[10]

1.6.7.2 Coronal pulpotomy treatment

An alternative to root canal treatment is coronal pulpotomy treatment, which "involves removing the entire coronal pulp tissue and keeping the remaining pulp vital in the canals".P1[21] In one study, the authors concluded that coronal pulpotomy treatment "could increase tooth retention by providing a potential option particularly for low-income patients or in under-served areas worldwide [there is low-quality evidence to support this]. However, more studies having longer follow-up, larger sample size, and including a control group are needed to validate the possibility of performing coronal pulpotomy treatment as an alternative to root canal treatment."p7[21]

1.6.7.3 Outcomes

Ma *et al.* examined the outcomes of different materials used for retrograde filling in children and adults for whom retrograde filling is necessary in order to save the tooth, and concluded that "the limited evidence is insufficient to draw any conclusion as to the benefits of any one material over another, so the authors are not able to recommend which material is best to use in retrograde filling at present."p27[10]

Sequeira-Byron *et al.* assessed the effects of restoration of endodontically treated teeth (with or without post and core) by crowns versus conventional filling materials and concluded that "there is insufficient evidence to assess the effects of crowns compared to conventional fillings for the restoration of root-filled teeth."p15[20]

1.6.8 Atraumatic restorative treatment

Atraumatic restorative treatment, according to Dorri *et al.*, "is a minimally invasive approach, which involves removal of decayed tissue using hand instruments alone, usually without use of anesthesia and electrically-driven equipment, and restoration of the dental cavity with an adhesive material such as glass-ionomer cement, composite resins, resin-modified glass-ionomer cement or compomers".p6[22] Atraumatic restorative treatment is used in the Netherlands, Sweden, the UK, and the USA.[16]

1.6.9 Interventions to prevent cavitated caries

Interventions to prevent caries cavities are also legitimate alternatives to phase down or phase out the use of amalgam under Ireland's recently published *Smile agus Sláinte: National Oral Health Policy*.[4] Such interventions fall under two main groups: first, the prevention of caries cavities (fluoride technologies and pit and fissure sealants), and second, the early treatment of conditions that signal early dental caries (such as demineralisation, white spot lesions, and non-cavitated carious lesions).

1.6.9.1 Prevention

Walsh *et al.* state that "fluoride remains one of dentistry's key strategies to prevent dental caries", p9[7] and there is a broad consensus that fluoride prevents caries in children and adults of all ages.[23]

There are several modes of fluoride delivery, such as toothpaste, fluoridated water, milk, mouth rinses, gels, and varnish. Evidence regarding the effectiveness of such topical fluoride interventions has been synthesised in a series of Cochrane reviews.[7]

1.6.9.1.1 Fluoride products

Tooth brushing with fluoride toothpaste is by far the most common form of caries control, and fluoride toothpaste use is commonly linked with the decline in caries prevalence in many countries.[7] The usual concentration of fluoride in toothpaste ranges from 1000 to 1500 parts per million (ppm); however, toothpastes with higher and lower than conventional fluoride levels are available in many countries.[7] Regular use of fluoride toothpaste or mouth rinses (topical fluoride vehicles of relatively low concentration) results in sustained elevated fluoride concentrations in oral fluids during the demineralisation-remineralisation cycle, as small amounts are maintained constantly in the mouth.[7] Fluoride mouth rinses are typically based on neutral sodium fluoride solutions ranging from 0.05% to 0.2% (225–1000 ppm) and are intended for use by those six years of age and older. Systematic reviews have limited or low-quality evidence of a caries-preventive fraction of 24% to 29% when fluoride mouth rinses are compared with placebos in permanent teeth in schoolchildren and adolescents, as well as for root caries reversal/arrest in older adults.[23]

Concern has been expressed that dental fluorosis – enamel defects caused by young children chronically ingesting excessive amounts of fluoride during the period of tooth formation – is increasing in both fluoridated and non-fluoridated communities, and the early use of fluoride toothpaste by young children (under six years of age) may be an important risk factor for dental fluorosis (hypomineralization of tooth enamel).[7] It is generally recommended that children six years of age and under should be supervised when brushing their teeth with fluoride toothpaste and that only a pea-sized amount of toothpaste be used. The frequency of toothpaste use along with the method of rinsing after tooth brushing are other factors influencing the effectiveness and safety of fluoride toothpaste.[7]

Acidulated phosphate fluoride (APF) gels have high fluoride levels and are applied much less frequently, usually by a professional.[7 23] APF foam has the same fluoride concentration (12300 ppm) and pH as APF gels.[23] With high-concentration topical fluoride vehicles such as varnishes, foams, or gels, calcium fluoride is precipitated on the enamel surface and in the plaque.[7] This calcium fluoride acts as a fluoride reservoir, which is released when the oral pH falls.[7] The amount of fluoride deposited in the subsurface lesion is greater after topical application with high-concentration fluoride vehicles.[7] Fluoride gels and foams are professionally applied, and the gels display a preventive fraction of 21% compared with placebos, but the quality of the evidence is low.[23] It also seems that professional applications of fluoride foam may have a caries-preventive potential of the same magnitude as fluoride gel, but the quality of the evidence is very low.[23]

Many reviews support fluoride varnish as a caries-inhibitory agent. Evidence from six Cochrane systematic reviews involving 200 trials and more than 80,000 participants further confirms the effectiveness of fluoride varnish, applied professionally two to four times per year, in preventing dental caries in both primary and permanent teeth. The relative benefit of fluoride varnish application seems to occur irrespective of baseline caries risk, baseline caries severity, background exposure to fluorides, use of fluoride toothpaste, and application features such as prior prophylaxis, concentration of fluoride, or frequency of application.[24]

1.6.9.1.2 Pit and fissure sealants

Pit and fissure sealant therapy was introduced in the 1960s to protect pits and fissures on the occlusal tooth surfaces from dental caries.[25] The sealing material acts as an effective mechanical barrier to plaque retention, thereby minimising the harmful effect of cariogenic microorganisms on the enamel surface.[25] Many types of sealing materials are used, such as conventional resin-based fissure sealants (the most common material), glass-ionomer cements, compomers, and, more recently, flowable composites.[25] In a recent review, Alirezaei *et al.*[26] reported that conventional resin-based sealants exhibited the same caries prevention effect as glass-ionomer cement-based sealants, but that resin-based sealants had a significant positive effect on retention rates. Bagherian and Shiraz[25] found that flowable composites with adhesives added can slightly increase the retention rate of sealants compared with conventional resin-based sealants with no adhesive added; the caries effect was not reported.

1.6.9.2 Early treatment (secondary prevention)

Dental research has led to the development of a number of secondary prevention strategies that are based on the prompt treatment of disease at an early stage and include measures which arrest and/or reverse the caries process after initiation of clinical signs.[27] Various treatment options are available to treat pit and fissure early caries lesions in permanent teeth, and these include:[28]

- Non-invasive treatments to avoid any dental hard tissue removal (such as fluoride application [toothpaste, gel, varnish, mouth rinse, or a combination of these], antibacterial treatments [chlorhexidine], and/or oral hygiene advice),[28] and casein phosphopeptide-amorphous calcium phosphate alone or in combination with calcium fluoride phosphate[27]
- Microinvasive treatments (such as sealants), which remove only a few micrometers of hard tissues by etching,[28] and
- Minimally invasive methods (such as resin/sealant restoration), which remove carious dentine but avoid sacrificing sound tissues.[28]

Urquhart *et al.*[29] examined non-restorative treatments for caries and found that the combination of sealants and 5% sodium fluoride varnish was the most effective treatment for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth (moderate certainty). They also found that the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective treatment for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth (low certainty). Similarly, 5000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective treatment for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth (low certainty). Study-level data show that when compared with no intervention, 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth (low to moderate certainty). Study-level data also compared the use of 1.23% APF gel on facial/lingual lesions along with oral health education, although this treatment was effective only at 12 months (moderate certainty). For arresting advanced cavitated carious lesions, study-level data suggest that 38% silver diamine fluoride solution applied biannually was more effective on any coronal surface of primary teeth when compared with both 12% silver diamine fluoride solution applied biannually and 38% silver diamine fluoride solution applied annually (moderate to high certainty).

Most review authors conclude that studies using xylitol, chlorhexidine, and casein phosphopeptide-amorphous calcium phosphate vehicles alone or in combination with fluoride therapy are very limited

in number and, in the majority of cases, did not show a statistically significant reduction in the size of the carious lesion, nor did they arrest the lesion's progression.[27 30 31]

1.7 Research questions

The research questions are:

1. What are the medical or clinical grounds for exemption from the ban on amalgam across European jurisdictions?
2. What measures have other high-income (in particular European) countries reported to support the phasing out of dental amalgam?
3. What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for young people aged 16 and under?
4. What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for adults aged 16 and older?

2 Methods

2.1 The Health Research Board's chosen approach and rationale

This review employs a systematic rapid evidence assessment (SREA) approach. The SREA approach assembles evidence in a short time frame for the purpose of assisting policy-makers, and the approach has been documented by other reviewers.[32-35] The SREA is a focused and limited search review which seeks to use the same methods and principles as a systematic review, but reduces the scope of evidence considered in order to deliver the report more quickly. Thus, the SREA may not be as comprehensive and detailed as a full systematic review. However, the processes involved are carried out systematically, hence the use of the term 'SREA', as opposed to 'rapid evidence assessment'. The authors of the current review have sought to elaborate our decision-making processes and our chosen methods in an attempt to be transparent and accountable to our stakeholders. This is an important principle in undertaking SREAs, as, according to Haby *et al.,* "producers of rapid reviews should give greater consideration to the 'write up' or presentation of their reviews to make their review methods more transparent and to enable a fair quality assessment". p9[36]

Our decision to choose the SREA approach for this review was based on the relatively quick turnaround (14 weeks) that the policy-makers required for the draft of the completed report and the limited staff resources we had at our disposal to undertake this work. Rapid reviews of various iterations are a recognised approach to synthesising evidence in a timely manner while seeking to reduce the level of work involved in a full systematic review, due to time and resource constraints. According to Tricco *et al.,* "rapid reviews are a form of knowledge synthesis in which components of the systematic review process are simplified or omitted to produce information in a timely manner". p1[37]

There is much discussion in the literature about what qualifies as 'rapid' in this review type; is it the short time frame in which a review is completed, or is it the acceleratation strategies used by reviewers that contrast with the detailed steps taken in a full systematic review? According to Langlois *et al.,* "there is no consensus on the timeline that would qualify a review as being 'rapid', but it has been suggested that most rapid reviews are conducted in 12 weeks". p1[38]

Some authors have argued that the streamlined and acceleration strategies adopted in reviews of this type do not intrinsically qualify the review to be referred to as a rapid review. Plüddemann *et al.* argue for a redefinition of reviews of this type. According to Plüddemann *et al.,* "systematic reviews that have been called 'rapid reviews' have been misnamed, rapidity is not their cardinal feature, they would be better called 'restricted systematic reviews'. This is because when they are performed, certain elements that are required in full systematic reviews are simplified or omitted". p201[39] However, it is equally important to acknowledge that all review types, be they full systematic reviews or SREAs, contain some degree of trade-offs in their decision-taking and the methods chosen. According to Thomas *et al.*, "even reviews that are not branded as 'rapid' make trade-offs between sensitivity and precision in their searches; they do not guarantee to find every single relevant paper; they do not contact every author and insist on obtaining the primary data of every study they contain to ensure that nothing is missed or misinterpreted; and they are all compromises between what is desirable and what is possible". p24[40]

In the following sections, we will endeavour to describe the decisions we took and the methods we adopted in order to undertake this work on behalf of our stakeholders. First, we will outline our decision-making processes and methods chosen for Questions 3 and 4, and later in Chapter 2 we will

deal with Questions 1 and 2. We undertook the work for Questions 3 and 4 in two phases: a mapping phase and an in-depth phase.

2.2 Mapping phase

We commenced discussions with the Department of Health (DOH) in early February 2019 regarding its information needs. Following in-depth discussion with the DOH, it became apparent that it needed to have access to an evidence base to help inform its deliberations with, and guidance to, the dental profession on appropriate dental restorative measures to substitute for amalgam during its phasing out and ultimate replacement. However, at this early stage, there was some uncertainty in the DOH regarding the precise scope of its information needs. In addition, we speculated that the existing literature on dental restorative materials was likely to be vast and we needed to adopt an approach that would facilitate the DOH to move towards more focused, in-depth questions.

To progress our work, we agreed with the DOH to undertake a rapid descriptive mapping exercise to identify the nature and extent of the literature that examined alternatives to amalgam as a restorative solution. We agreed that the mapping exercise would document the main characteristics of peer-reviewed research undertaken to 2018 that compared dental restorative materials with amalgam and that focused on children and adolescents. This process would need to be repeated at a later stage for adults. The objective of this work was to produce a product to facilitate the DOH in prioritising a focused research question or inquiry that could be addressed through a subsequent in-depth review. According to Gough *et al.* "[Research] maps have three main purposes of: (i) describing the nature of a research field; (ii) to inform the conduct of a synthesis; and (iii) to interpret the findings of a synthesis."p5[41]

Research maps, which are sometimes called systematic maps, can vary in purpose, volume, and scope depending on the rationale as well as the time and resources available; they can also be called different things in the literature.[42] Mapping the research literature in order to fulfil the objectives outlined by Gough *et al.*[41] is increasingly being promoted and used by international teams who work with policy-makers to develop evidence syntheses for informing policy development.[33 43-45]

Due to the tight time frame within which the DOH was operating, it required that we report back in four weeks with the preliminary findings from our mapping exercise on children and adolescents. To facilitate this deadline, we ran a simplified search on limited sources, mainly electronic databases. The keywords used did not cover all possible relevant terms. Similar acceleration strategies have been used by Newman *et al.*, working within a similar tight time frame as the Health Research Board (HRB) reviewers.[34]

2.2.1 Search process for mapping phase

2.2.1.1 Bibliographic database searches

Taking into consideration the short time frame available, searches in bibliographic databases for Questions 3 and 4 were limited to four databases covering different ranges of journals. In addition, non-English databases were not included for this reason, nor were supplemental databases or websites such as Epistemonikos, OpenGrey, or CORE.

Initial database literature searches were designed and carried out by an experienced information specialist (CL) to search the published literature, including primary papers and systematic reviews on the topic of alternatives to amalgam for caries in children and adolescents. The concepts combined in the searches were: 1) alternatives to amalgam (alloys, cements, ionomers, sealants, resins, bonding, crowns, porcelain, etc.); 2) caries (cavities, caries, fissures, decay, etc.); 3) systematic reviews

(systematic reviews, meta-analyses, meta-regression, syntheses, etc.); 4) randomised controlled trial terms; and 5) age terms (paediatric and adult terms). The search findings indicated that there were a large number of primary papers and systematic reviews. After discussion with the DOH, it was decided to limit the same search to systematic reviews of the prevention and treatment of caries in children and adolescents. Search terms for these searches can be seen in the search strategies in Appendix 1.

The search filter for systematic reviews, health technology assessments, and meta-analyses designed by the Canadian Agency for Drugs and Technologies in Health (CADTH) was used in Ovid MEDLINE to limit the search to articles most likely to be systematic reviews.[46] The age filter used for searching for adult subjects was the one outlined in Kastner *et al*.[47] Details of a complete Ovid MEDLINE search strategy for systematic reviews on alternatives to amalgam for caries in children and in adults are available in Appendix 1. A subsequent supplemental database search was also carried out later which sought reviews on topical fluoride use for caries.

The initial search strategy was designed and tested in Ovid MEDLINE. The terms and syntax were then translated for use with Embase, EBSCO CINAHL, and the Cochrane Library, all of which use different search interfaces, search syntax, and field tags. Database searches were carried out from 23 to 26 February 2019.

Separate searches were conducted using the same process in each of the four databases for adult literature.

Once database searches were carried out, results were saved in RIS file format. These files were imported into EndNote X7.7, in which deduplication was carried out. Initial screening, using EndNote, was carried out by two researchers (MK, JL) and an information specialist (CL).

2.2.1.2 Database search results

Our search returned 519 systematic reviews and 3,867 randomised controlled trials which appeared to include a focus on children and adolescents (Appendix 2). To complete our mapping exercise in the short time available, we agreed with the DOH to focus exclusively on mapping the characteristics of the systematic reviews on children and adolescents, and then present our findings to the DOH. We based this decision on two grounds: 1) we estimated that it would take us approximately 48 working days to map the 3,867 randomised controlled trials, and this time frame exceeded the time available to us to meet our deadline; and 2) we reasoned that systematic reviews occupy the apex of the hierarchy of evidence and are widely regarded as the highest level of evidence upon which to consider and base clinical and policy decisions. Given that our search had yielded 810 systematic reviews in total, we decided that it was appropriate to focus on these as candidate data sources to potentially answer a future, more in-depth review question on children and adolescents.

Once we had agreed with the DOH to focus on mapping systematic reviews for children and adolescents (Question 3), we applied the same logic to Question 4, which examined alternatives to amalgam as a restorative solution for adults. Our search yielded 3,742 primary studies and 291 systematic reviews (Appendix 2).

2.2.1.3 Inclusion and exclusion

We were only interested in retaining systematic reviews that focused on cariology, and therefore we excluded reviews that were focused on other specialties such as endodontics, implantology, periodontics, orthodontics, dental prosthesis, and oral and maxillofacial surgery. This reduced the volume of reviews substantially. We also excluded reviews published before 2010 and we only retained the most recent versions of reviews that had updated earlier iterations. We excluded reviews that did not report comparing an intervention(s) with a control intervention.

We included systematic reviews that:

- Covered the populations children and adolescents (usually 16 years or under), or adults (usually 16 years or over)
- Covered interventions such as caries prevention, early treatment for non-cavitated carious lesions, direct and indirect restorations for cavitated caries, and other techniques, products, and processes associated with restoration
- Compared an intervention group with a control intervention
- Measured outcomes of primary caries prevention(such as prevention of caries in teeth), early caries treatment (such as arresting caries), and caries restorative treatment (such as survival or failure of restoration)
- Reviews that followed a documented systematic search and analysis process.

2.2.1.4 Data extraction

We (MK and JL) created two bespoke data extraction sheets: one for children and adolescents, and the other for adults and the data extraction was piloted on a subset of the systematic reviews for Question 3. Each extraction sheet had four sections: prevention, early treatment, late treatment, and restoration survival. We extracted data from the included review full texts on the following characteristics: author, year published, review question, description of the intervention and comparator, number and type of studies included, outcomes measured, sample size, age of participants, type of teeth treated, risk of bias of included studies and instrument used to assess bias, and authors' conclusions. MK extracted the pilot data for Question 3 and this data was checked by JL.

2.2.1.5 Level of evidence

We piloted and adapted Faggion's level of evidence[48] and assessed each primary outcome reported in each included review (see section 2.3.4).

2.2.1.6 Presentation of map to policy-maker

Towards the end of March 2019, we presented a simplified draft descriptive map of the characteristics of 37 systematic reviews for Question 3 to the DOH via PowerPoint presentation and face-to-face discussion; the purpose was to aid decisions on finalising the scope for the planned in-depth review.

Arising from the discussion with the DOH, we were able to agree the scope for an in-depth review, which we will present in Section 2.3, along with our decision-making process and our methods for undertaking the in-depth phase of this work. Again, it is important to state that this in-depth phase of our work relates to Questions 3 and 4.

2.3 In-depth phase

We agreed with the DOH that the in-depth review would exclusively focus on using data from systematic reviews to address the following two questions:

- What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for young people aged 16 and under?
- What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for adults aged 16 and older?

The DOH emphasised that it would require us to provide an evidence base that contained adequate descriptions of all interventions included, the precise age of participants, the type of teeth the intervention was treating, and an assessment of evidence upon which to judge the effectiveness of the interventions. We agreed that to meet the timeline set by the DOH, we would complete this in-depth phase of the work within two months for Questions 3 and 4. This meant that we needed to decide on a number of accelerating strategies that would help expedite our work while seeking to remain systematic and transparent regarding our decision-making and the methods chosen.

2.3.1 Abstract screening

As we had identified a total of 810 systematic reviews from our search in the mapping phase, we decided not to repeat or extend this search to other databases but rather to screen all abstracts and titles again to ensure that we were not missing any relevant material that came within the scope of this in-depth phase. We acknowledge that our search was comprehensive rather than exhaustive, but it is necessary given the short time (14 weeks) we had to complete this review. All citations (titles and abstracts) were uploaded into EPPI-Reviewer Version 4.9.2.1 (specialist systematic review software) for the management of publication retrieval, screening, and further decision-making. Two reviewers (MK and JL) and an information specialist (CL) screened all titles and abstracts and reached a consensus on inclusions and exclusions. We included reviews that focused on either children and adolescents or on adults; that compared dental restorative procedures and materials with controls; and that covered caries prevention, early treatment, and late treatment.

2.3.2 Additional literature

We supplemented the search from our mapping phase with a focused search for reviews that evaluated fluoride toothpaste and other fluoride technologies, as good prevention reduces the need for amalgam. In addition, we extended the number of relevant reviews identified from our search of the four bibliographic databases with reviews we identified from references lists in the published reviews we retrieved.

After abstract and full-text screening, we had 48 systematic reviews on children and adolescents and 52 systematic reviews on adults.

2.3.3 Data extraction

For the purposes of the in-depth review, we extracted data from the included reviews using the full text of each paper. A standardised framework, developed specifically for this review, was used to extract and record information from each review. Two reviewers (MK and JL) extracted data from the included reviews on the following characteristics: author, year published, review question, description of the intervention, outline of the controls, number and type of studies included, sample size, age of participants, type of teeth treated, risk of bias of included studies and instrument used to assess bias, main summary findings, primary outcomes measured, and authors' conclusions including their

assigned level of evidence. MK extracted the data for Question 3 and this data was checked by JL. JL extracted the data for Question 4 and this data was checked by MK.

2.3.4 Assigning a level of evidence

Due to our short time frame, we needed to select a method for assessing the level of evidence that we could apply quickly across a large number of reviews, but which would have some degree of consistency regarding our judgements. We chose an approach developed by Faggion[48] and we amended this approach to suit our conditions. We decided against a critical appraisal of the reviews using AMSTAR or an alternative instrument, as our stakeholders were more interested in the level of evidence from combining the primary studies than in an appraisal of the methods used to undertake the systematic reviews. Faggion had used a binary judgement of the level of evidence on a sample of Cochrane reviews in order to assess it as either adequate or inadequate based on the authors' conclusions.[48] We amended this approach to include an 'inconclusive' assessment category where it was not possible to determine which intervention was better based on the evidence available. The following describes the categories assigned to describe the level of evidence:

- Adequate evidence (unlikely to change)
    - When authors stated their confidence using words such as 'sound', 'high', or 'good quality' (which was rarely the case in the reviews examined), or when authors did not explicitly state that the evidence was weak, and reported some (moderate) evidence for effectiveness, the evidence was considered adequate which was more commonly the case in the reviews we examined.
- Inadequate evidence (likely to change)
    - When authors described weak or insufficient evidence (low or very low quality), or when no studies were included in the review (an empty review), the quality of evidence was considered inadequate.
- As stated above, we added: Inconclusive evidence
    - The evidence was considered inconclusive when it was not possible to determine which intervention was better or best.

MK and JL assessed the level of evidence presented in the systematic reviews included in Question 3 and Question 4.

2.3.5 Analysis and synthesis

We have grouped the findings from the reviews by intervention domain and intervention category. For Question 3, which focuses on interventions for children and adolescents, we have grouped the findings by intervention domain, which in this review comprises prevention, early treatment, and late treatment. In the section discussing prevention, we have further categorised the findings by fluoride technologies and non-fluoride technologies. In the section regarding treatment of early caries lesions, we have grouped the findings by remineralising agents and microinvasive strategies. In the section regarding late treatment of caries in children and adolescents, we have grouped the findings by restorative procedures and techniques and restorative materials. There is also a section examining the survival of restorations in children and adolescents. A summary extraction sheet has been provided in Appendix 4.

For Question 4, which focuses on interventions for adults, we have grouped the findings by intervention domain, which in this review also comprises prevention, early treatment, and late treatment. In the prevention section, we have grouped the findings by fluoride technologies and sealants. In the section on early caries treatment for adults, we have grouped the findings by

remineralising agents, microinvasive interventions, dental adhesives and retention aids, restoration materials, and the combination of remineralising agents and microinvasive strategies. In the section regarding late treatment of dental caries in adults, we have grouped the findings by restorative procedures and techniques, and restorative materials. In the section examining restoration survival and complications, we have grouped the findings by survival and complications of indirect restorations, survival and complications of composite resin restorations in posterior teeth, complicating factors for composite resin restorations in anterior teeth, and patient-related factors on restoration survival. A summary extraction sheet has been provided in Appendix 5.

We present our findings in narrative format, including a description of the population (including participants and teeth), intervention(s), comparator(s), and primary outcomes included in each review. We also describe the risk of bias of primary studies included in the review and the instrument used to assess bias for each review based on the reports by the review authors. In addition, we have provided a judgement on the level of evidence for the main findings evaluated in each review based on our adapted criteria of adequate, inadequate, or inconclusive evidence. The level of evidence assigned to each review considered the review authors' conclusions, the results of the risk of bias or quality assessment of the primary trials, and the review authors' stated limitations.

2.4 Methods for collecting data to address Questions 1 and 2

The answers to Questions 1 and 2 are a descriptive narrative summary of policy and technical reports. To answer Questions 1 and 2, we drew on an eclectic mix of both peer-reviewed and grey literature (such as technical reports) in order to document the reported exemptions allowed by other countries (Q1) and the reported measures taken by other EU member states, or by States closely aligned to the EU, to support the phasing out of dental amalgam, as well as the lessons learned from these countries (Q2).

We retrieved most of these data resources during the initial scoping stages of our work. For example, Our information specialist (CL) ran general searches in the search engine Google to gain an initial idea of terminology and likely key terms. Initial search terms used included combinations of mercury, dental amalgam, filling and caries. Further searches were carried out using the websites of national and international dental organisations, including national and international regulatory bodies, such as the World Health Organization, the United Nations Environment Programme, the Scottish Dental Clinical Effectiveness Programme, and the European Parliament and the Council of the European Union.

Some national governmental and organisational sites were also searched, focusing on countries which were known to have taken action on dental amalgam, or which planned to take action. Language was a barrier for many of these websites. While we had planned to follow up on citations from some key documents,[49 50] the extremely short time frame permitted for this review did not allow for these measures. A more detailed list of relevant websites we searched is included in Appendix 3.

The clear majority of data sources we used to answer Questions 1 and 2 were unpublished or difficult to locate technical reports: documents that had been prepared for a specific purpose, contained country-level data, and were primarily descriptive in nature. We drew on only a very small number of papers published in peer-reviewed journals, which mainly provided background and contextual data. The data we retrieved from these documents were nested within a wider exploration of a range of issues and discussions relating to the phase-out of dental amalgam.

We (MK and JL) extracted fragments of data from these papers when we judged the data relevant to answering our questions: clinical or medical justifications and measures named in the Minamata Convention on Mercury to phase down amalgam. From these fragments, we built a response to our

questions using a descriptive format. For Question 2, we organised the findings using the nine actions outlined in the Minamata Convention on Mercury.

Our answers to Questions 1 and 2 are limited to the number of papers or reports we located through our searches and to the data we selected for extraction from these descriptive sources. We acknowledge that we have only drawn on a limited number of data sources to answer Questions 1 and 2, and that a longer and more detailed search plus citation chasing may have yielded a more comprehensive set of data resources upon which to build a response to our questions. However, within the short time frame we had, we believe that we have adequate coverage to provide key insights into the questions posed.

2.5 Strengths and limitations of our methods

This review is a SREA that was completed in 14 weeks by a very small team (1.75 FTE). This means that the work contains some limitations that may interfere with the level of confidence placed in both the methods employed and our ultimate findings and conclusions. For example, the limited time scale of the project and the large body of literature covered required that the scope was curtailed in the following ways: the evidence for Questions 3 and 4 was restricted to systematic reviews accessed from four databases, and the information collected for Questions 1 and 2 was derived from a selection of data resources opportunistically retrieved following general Internet searches. Our search strategies were specific, as opposed to sensitive; we followed a comprehensive rather than an exhaustive search approach. Search sources for Questions 3 and 4 were limited to bibliographic databases and reference lists of key papers, and for Questions 1 and 2 were primarily limited to repositories of grey literature. We acknowledge the likelihood that we have missed reviews that could potentially speak to Questions 3 and 4 that a more targeted question comparing a specific intervention or family of interventions with controls could have yielded. In addition, we acknowledge that we could have missed relevant documents that speak to Questions 1 and 2 and which may have added important insights to what we found and reported. We did not assess the quality of the systematic reviews we included, and this may impair some confidence in our findings and conclusions. However, we did abstract the results of risk of bias assessments, GRADE (Grading of Recommendations, Assessment, Development and Evaluations) conclusions where available, and study limitations.

Some of the strong points of this work are that we have sought to be transparent in reporting our decisions and methods, and we have sought to be systematic by following, as closely as possible, the steps and principles employed in a full systematic review. In addition, we have included reviews which provide some of the most up-to-date assessments of evidence on a broad range of restoration procedures and materials. In addition, we did not quality assess the included reviews before extraction, which means that we included reviews of varying methodological quality; we believe this provides a more comprehensive picture of the nature of the evidence that exists around dental restorative procedures and materials. Finally, we have provided an assessment of the level of evidence for a broad range of procedures and materials, which may assist policy-makers and practitioners in their deliberations regarding policy and clinical choices for using alternatives to amalgam. The level of evidence assigned to each review considered the review authors' conclusions, the risk of bias in the primary trials, and the review authors' stated limitations.

3 Technical findings

Chapter 3 presents our technical findings for Questions 3 and 4.

3.1 Question 3

We retrieved 519 records from searches of Ovid MEDLINE (n=196), CINAHL (n=80), Embase (n=288), and the Cochrane Library (n=18). After deduplication, we had 465 records remaining. We screened the titles and abstracts of the 465 remaining records and excluded 335, as they did not meet our inclusion criteria (Figure 1). We were only interested in retaining records that focused on dental cariology, so we excluded reviews that were focused on other dental specialties such as endodontics, implantology, periodontics, orthodontics, dental prosthesis, and oral and maxillofacial surgery. This reduced the volume of records substantially.

We obtained the full-text versions of the remaining 130 records, and two reviewers and one information specialist screened these and made consensual decisions regarding their potential candidacy for the in-depth phase of the review. Following discussion, we then excluded a further 70 records which left us with 60 candidate papers, and we retrieved an additional 18 papers through supplemental searching, drawing on items identified in reference lists. Most of the 70 records excluded were not full systematic reviews, were primary studies, or were viewpoint papers.

Two reviewers and one information specialist then screened the full-text versions of the remaining 78 candidate papers and we rejected 41, as they did not meet our inclusion criteria. Most of these records were excluded as they did not explicitly compare an intervention with controls. We were then left with 37 papers, and we added a further 11 through additional supplemental searches for papers identified in reference lists from the retrieved papers. We included all of the remaining 48 papers in the in-depth phase of the review, all of which were systematic reviews.

We then categorised the 48 reviews according to the following terms: dental caries prevention (n=21), early treatment of dental caries (n=11), late treatment of dental caries (n=13), and longitudinal studies covering dental restoration survival rates (n=3). We further subcategorised these 48 papers to reflect the nature of the intervention being evaluated. Our subcategorisation is as follows: under late treatment responses to cavitated caries in children and adolescents, we grouped restorative procedures and techniques (n=7) and restorative materials (n=6); under early treatment responses to non-cavitated lesions in children and adolescents, we grouped remineralising agents (n=7) and microinvasive strategies (n=4); and under prevention of caries in children and adolescents, we grouped fluoride-based technologies (n=11) and non-fluoride-based technologies (n=10). We included three reviews that exclusively examined dental restoration survival rates, and we reported on these separately. Most of the reviews included in Question 3 exclusively included trials with children and adolescents, a small number included both children and adolescents and adults. A summary of the main characteristics of the all the reviews included in the in-depth phase of question 3 is provided in Appendix 4.

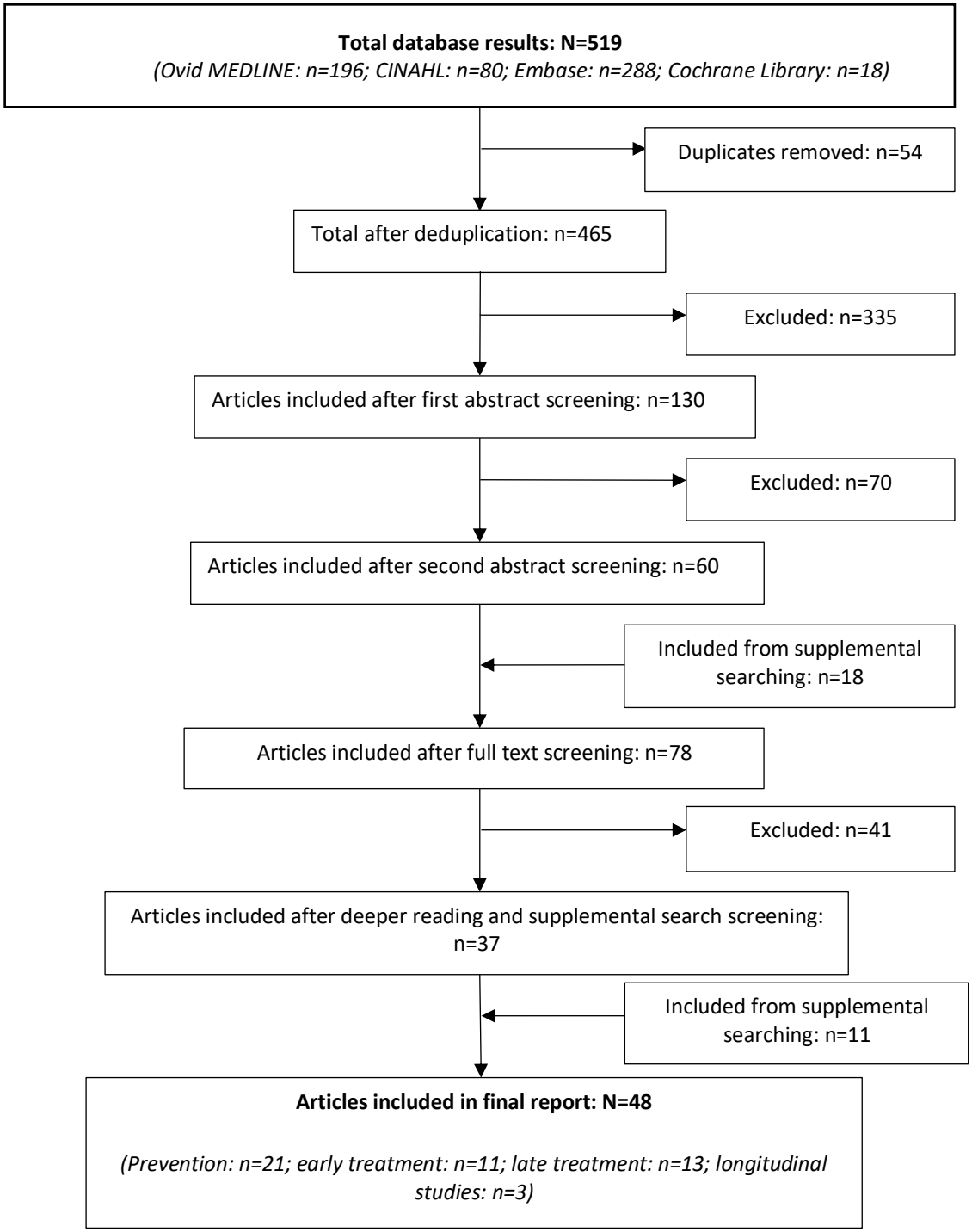

Figure 1 PRISMA flow chart for Question 3

3.2 Question 4

We retrieved 291 records from searches of Ovid MEDLINE (n=133), CINAHL (n=96), Embase (n=31), and the Cochrane Library (n=31). After deduplication, we had 247 records remaining. We screened the titles and abstracts of the 247 remaining records and, when screening was completed, we excluded 191 articles that did not meet our inclusion criteria (Figure 2). Most of the excluded records focused on dental specialties other than cariology, which was our exclusive focus, and some did not explicitly compare an intervention with controls. Two additional papers were added from supplemental searching of key references. We obtained the full-text versions of the remaining 53 records, and two reviewers (MK, JL) and one information specialist (CL) screened all 53 papers and determined that they met all our inclusion criteria, so we included them in the in-depth phase of the review. All 53 papers were systematic reviews.

We then categorised the 53 reviews as follows: prevention of dental caries (n=5), early treatment of dental caries (n=21), late treatment of dental caries (n=18), and longitudinal studies covering dental restoration survival rates (n=9). We further subcategorised the 53 reviews to reflect the nature of the intervention being evaluated. Our subcategorisation is as follows: under the late treatment of dental caries in adults, we grouped restorative procedures and techniques (n=9) and restorative materials (n=9); under the early treatment of dental caries in adults, we grouped remineralising agents (n=6), microinvasive strategies (n=5), sealant retention aids (n=6), restorations (n=2), and combining microinvasive elements with remineralising elements (n=2). For the prevention of dental caries in adults we grouped the interventions as follows; fluoride technologies (n=2) and different types of sealants (n=3). We included nine reviews that exclusively examined dental restoration survival rates and associated complications, and we reported on these separately.

All included reviews explicitly compared either a dental restorative technique or restorative material with controls, or examined the survival rates of restorations and any associated complications. The vast majority of the reviews we included exclusively relied on trials. Most of the reviews – both Cochrane and non-Cochrane – used the Cochrane risk of bias assessment to evaluate the included trials. A summary of the main characteristics of the all the reviews included in the in-depth phase of Question 4 is provided in Appendix 5.

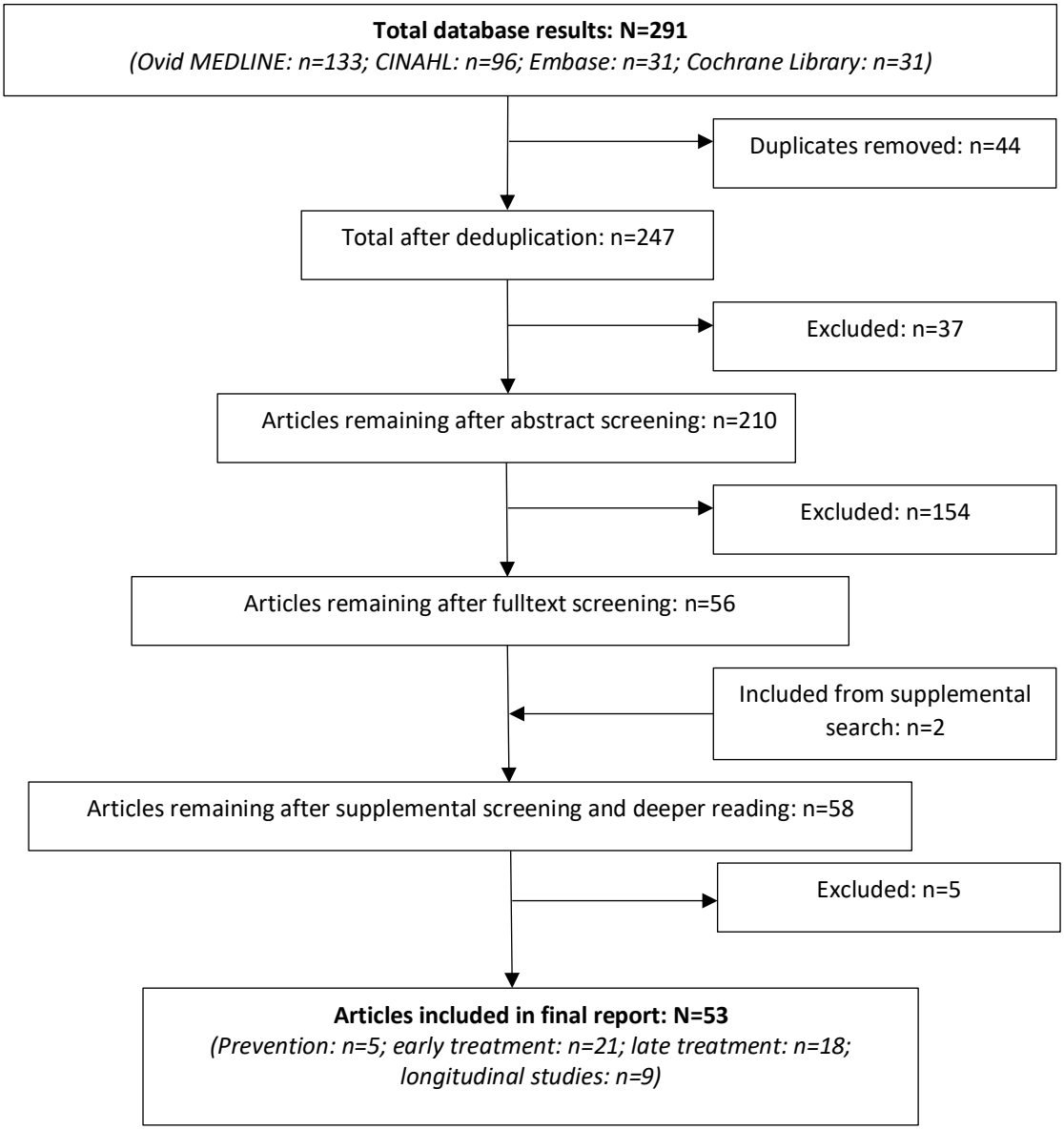

Figure 2 PRISMA flow chart for Question 4

4 Findings

4.1 Question 1: What are the medical or clinical grounds for exemption from the ban on amalgam across European jurisdictions?

To answer Question 1, we reviewed the peer-reviewed and grey literature to document the reported exemptions allowed by other countries, the rationale for these exemptions, and any limitations to the exemptions. We concentrated on the experience of EU Member States and those States closely aligned to the EU. Due to time limitations, we relied heavily on recent international and national review documents.

4.1.1 Minamata Convention on Mercury

The Minamata Convention on Mercury states that "measures to be taken by a Party to phase down the use of dental amalgam shall take into account the Party's domestic circumstances and relevant international guidance and shall include two or more of the measures from the following list:

1. Setting national objectives aiming at dental caries prevention and health promotion, thereby minimizing the need for dental restoration.
2. Setting national objectives aiming at minimizing its use.
3. Promoting the use of cost-effective and clinically effective mercury-free alternatives for dental restoration.
4. Promoting research and development of quality mercury-free materials for dental restoration.
5. Encouraging representative professional organizations and dental schools to educate and train dental professionals and students on the use of mercury-free dental restoration alternatives and on promoting best management practices.
6. Discouraging insurance policies and programmes that favor dental amalgam use over mercury-free dental restoration.
7. Encouraging insurance policies and programs that favor the use of quality alternatives to dental amalgam for dental restoration.
8. Restricting the use of dental amalgam to its encapsulated form.
9. Promoting the use of best environmental practices in dental facilities to reduce releases of mercury and mercury compounds to water and land." Annex 2[2]

4.1.2 Regulation (EU) 2017/852

On 4 July 2016, the European Environmental Bureau stated that "the use of mercury in dentistry should be phased out; mercury-free dental restorations are available, affordable, effective, and preferred by most EU citizens. Phase out is the most cost-effective way to prevent dental mercury pollution." p1[51]

The phasing down of dental amalgam use in specified patient groups is a legal requirement in all EU Member States from 1 July 2018 in compliance with EU and global agreements to reduce the use of mercury and mercury-containing products on environmental grounds.

Article 10 of Regulation (EU) 2017/852 contains the following provisions relating to dental amalgam:[1]

- Article 10(1): from 1 January 2019, dental amalgam shall only be used in pre-dosed encapsulated form.
- Article 10(2): from 1 July 2018, dental amalgam shall not be used for dental treatment of any deciduous teeth (primary teeth) of children under 15 years of age or of pregnant or breastfeeding women, except when deemed strictly necessary by the dental practitioner based on the specific medical needs of the patient.
- Article 10(3): by 1 July 2019, Ireland is required to submit a national plan on measures to phase down the use of amalgam to the EU.
- Article 10(4): from 1 January 2019 dental facilities are required to be equipped with an amalgam separator.

As a member of the EU, Ireland is required to implement Regulation (EU) 2017/852; therefore, the HRB limited its findings to the documented actions of other Member States. The current use of amalgam in the EU is presented in Figure 3.

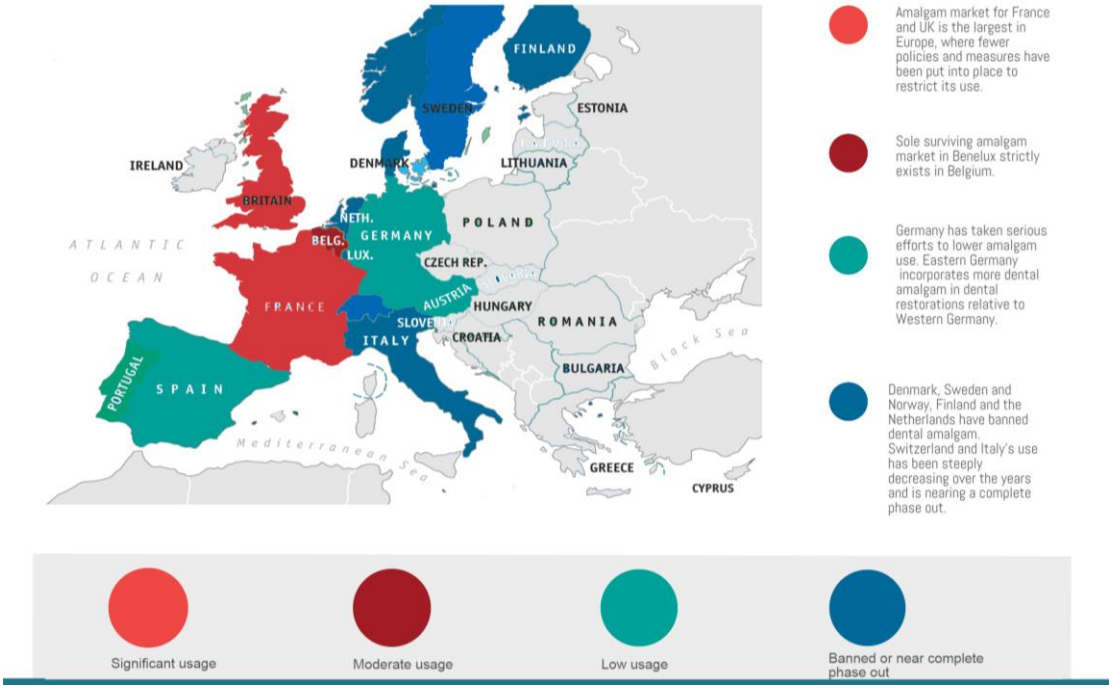

Figure 3 Proportion of amalgam usage in Europe

Source: iData Research[52]

4.1.3 Reasons for using or not using amalgam

According to Alexander *et al.,* "there is little research examining why (as opposed to when) dentists chose amalgam as a restorative material". p411[53]

Some potential reasons why a dentist may choose not to use dental amalgam were suggested by Alexander *et al.*[53] The first factor in dentist decisions includes tooth type, with amalgam restoration rarely placed in premolars and more likley to be used in a posterior restoration. In addition, amalgam restoration is avoided in areas of the mouth that are more visible when there is a preference to restore visible teeth using a tooth-coloured material. Females are less likely to receive an amalgam restoration than males, suggesting that aesthetics is more of a concern to females, or that dentists regard aesthetics as more important for females. Alexander *et al.*'s review of the literature also suggests that patients will choose aesthetics over longevity. Dentists are more likely to use amalgam if the patient exhibits a high caries risk, or if the extent of caries is high. Non-clinical factors have also been identified, such as socioeconomic status of the patient (that is, poorer patients are more likely to receive amalgam), years since the dentist has graduated (older dentists are more likely to use amalgam), size of the practice (fewer dentists more likely to use amalgam), gender (males are more likely to receive amalgam), race (marker for poverty and poorer people more likely to receive amalgam), older age more likely to use amalgam, and insurance status of the patient (non-insured or publicly funded more likely to use amalgam). Tooth type and tooth size are also factors in deciding to use amalgam. Dentists think that amalgam has benefits compared with tooth-coloured alternatives, such as a reduced risk of subsequent secondary caries and greater durability, and dentists have experienced difficulties with tooth-coloured restorations, such as sensitivity, but dentists also need to develop their own skills so as to enable use of alternatives to amalgam. The mix of factors that seems to influence dentists' decisions on whether or not to use amalgam, according to Alexander *et al.*, "raises questions as to whether dentists are making restorative decisions based on the available evidence, and if not, are they aware of the evidence?" p411[53] It is implied in Alexander *et al.* that dentists' decisions can overlap with patient preferences, so decisions may not be made solely based on clinical grounds. Also, the dentist's skills and experience influence the type of restorations provided.

4.1.4 Exemptions and justifications in other EU Member States

4.1.4.1 Denmark

The general sale of mercury has been forbidden in Denmark since 1994, but an exemption was initially granted for mercury in dental amalgam.[50] A subsequent recommendation of the Danish health authority stipulated that from 1999, amalgam fillings should not be placed in front teeth or milk teeth,[16 50] nor should amalgam be generally used for dental care of children.[50]

According to the United Nations Environment Programme, "The health authority [in Denmark] recommended that mercury-free alternatives should be the first choice for new fillings [of permanent teeth], except where: 1) it is not possible to keep the area dry; 2) it is difficult to access the cavity; 3) there is a particularly large cavity; or 4) the distance to the proximate tooth is too great. By 2013 amalgam was used in only 5% of restorations." p12[50]

4.1.4.2 Finland

After consultation with an expert group in 1993, Finland issued the recommendations that the use of amalgam should be reduced for environmental reasons, and that amalgam should be used only when other dental filling materials cannot be used.[50] Since 1994, Finland's national guidelines have stipulated that amalgam should not be used in restorations.[50] The use of amalgam has declined significantly, recently accounting for no more than 3% of dental restorations performed in Finland.[50] We did not find any list of exceptions.

4.1.4.3 Germany

In 1994, Germany required amalgam suppliers to amend their instructions to include a precaution against amalgam use in children and women of childbearing age. According to a more recent 2010 report prepared for the European Commission, Germany recommends not using dental amalgam on children (<16 years); on pregnant and nursing women; on people with kidney problems; when it would come in contact with other metals, such as braces; or in people with mercury sensitivity. [16 54]

4.1.4.4 The Netherlands

In the Netherlands, a major shift away from amalgam use took place in the 1990s after consultation with the dental sector, which eventually embraced the use of mercury-free dental restoration materials.[50 54] Consequently, the average use of amalgam in the 2000s was around 7% of all dental restorative fillings, dropping to less than 1% by 2011.[50] We could not identify a list of amalgam exemptions in the Netherlands.

4.1.4.5 Norway

In 1991, Norway issued guidelines that the use of amalgam should be limited due to environmental impacts.[50] Stronger guidelines were issued in 2003, requiring materials other than amalgams to be considered as the first choice in tooth fillings.[50] Since 2008, Norway has had a general ban on mercury products. This included a ban on dental amalgam, with an exemption period.[50]

In Norway, a temporary exemption was applied from 2008 to 2010 that allowed dental amalgam in special cases, for restorations carried out under general anaesthetic, and for those with allergies to mercury-free materials.[50] Since 2011, however, there has been a complete ban on dental amalgam in Norway.[50]

Prior to phasing out the use of dental amalgam in Norway, consultation with stakeholders documented the need for some time-limited exceptions to allow the use of amalgam for some patient groups. According to the 2012 document, *Review of Norwegian experiences with the phase-out of dental amalgam use*,[55] "the comments from the consultations of the proposed ban led to a 3-year exemption on the use of dental amalgam for two patient groups. One exemption was for patients that needed dental treatment under general anaesthesia. General anaesthesia in itself poses a certain risk and the time spent for a patient should be as limited as possible. Dental amalgam was considered to take less time to use than other restorative materials. It was also difficult to keep the filling area sufficiently dry (moisture control) when treating a patient who is under general anaesthesia, which is necessary when using composites. The second exemption was for patients that are allergic to components in mercury-free fillings. From 1 January 2011 these exemptions expired and the ban on the use of dental amalgam now is total. However, it is possible to apply for an exemption from the

Norwegian Climate and Pollution Agency (Klif) for the use of dental amalgam for a single patient. Very few applications for such use have been received by Klif." p19 [55]

Lynch and Wilson's findings support those reported by Klif: "in 2008 a general ban on the use of mercury in dental products was imposed in Norway. This ban provided a three-year exemption for the placement of amalgam while operating under general anesthesia and in the provision of care for patients found to be allergic to one or more components of alternate materials. A complete ban on the use of amalgam was introduced on 1 January 2011, with opportunity for dentists to apply for exemptions. Very few applications have been made, let alone approved. As a consequence the clinical practice of dentistry in Norway has essentially been 'amalgam free'". p159[56]

4.1.4.6 Scotland and the rest of the United Kingdom

Guidance for dentists regarding restrictions on mercury use that are set out in Regulation (EU) 2017/852 (specifically, the use of amalgam in pre-dosed encapsulated form only, the use of amalgam in vulnerable patients, and the requirement for an amalgam separator) will be made available through healthcare regulators. The Scottish Dental Clinical Effectiveness provided advice on the implementation of the regulation in its publication, *Restricting the Use of Dental Amalgam in Specific Patient Groups: Implementation Advice*.[57]

The advice aims to support dental professionals across the United Kingdom (UK) in interpreting and implementing these environmentally driven restrictions on dental amalgam use.[57] Information is provided on caries prevention, alternative caries management approaches, and restorative materials to inform practitioners' clinical decision-making.[57]

This implementation advice has been endorsed by the Faculties of Dental Surgery of the Royal College of Surgeons of Edinburgh and the Royal College of Physicians and Surgeons of Glasgow, and by the Faculty of General Dental Practice (UK).[57] More recently and in light of the UK leaving the EU, the Chief Dental Officers of Scotland, England, Northern Ireland, and Wales have decided to phase down rather than phase out amalgam.[58]

The scope of implementation advice in the Scottish document is limited to providing advice relating to Article 10(2) of Regulation (EU) 2017/852, which deals with specific groups, and indicates that amalgam should not be used in the "deciduous teeth (primary teeth) of children under 15 years, and of pregnant or breastfeeding women." p2[57] The Chief Dental Officers of Scotland, England, Northern Ireland, and Wales support Article 10(2) of Regulation (EU) 2017/852.[58]

The current clinical advice being promulgated in Scotland suggests that dentists may use amalgam when they consider its use to be in the "best interests of the patient based on the patient's specific dental needs; but the dentist must justify their decision and be accountable to external review." p7[57] The Chief Dental Officers of Scotland, England, Northern Ireland, and Wales make clear that they will continue to use amalgam in their adult population until practical clinical, and cost-effective alternative materials are available.[58]

4.1.4.7 Sweden

In Sweden "in 1991, the National Board of Health and Welfare investigated the preconditions for eliminating the use of dental amalgam. In 1995 there was a voluntary agreement between the state and county councils to put an end to amalgam use in dental restorations for children and young people. However, by 1997 the voluntary measures had not achieved the objective that had been

established. In 1999 the Swedish Parliament decided that patients should no longer be reimbursed for the cost of amalgam fillings under the national healthcare system. As a result, the cost to patients for amalgam became comparable to the cost for composites. There was a dramatic decrease in the use of dental amalgam between 1999 and 2010. Since 2009 there has been a general ban on mercury in Sweden that includes dental amalgam." p11[50]

The *Review of Norwegian experiences with the phase-out of dental amalgam use* also states that "In Sweden, since 1 June 2009 dental amalgam could only be used in special medical circumstances rather similar to those in Norway before end 2010. In June 2010, only three of a total of 68 hospital dental clinics that could still use dental amalgam had actually done so." p19[55]

The special medical circumstances where exemptions applied in Sweden up to 2012 were for use in adult patients in hospital dental clinics if the following criteria applied:[54]

1. The patient's specific medical condition makes use of alternative materials unsuitable
2. Alternative techniques do not provide adequate restoration, or
3. The clinic has adequate facilities to manage and dispose of amalgam waste, for example, amalgam separators.

The data suggest that in Sweden, only 16 cases out of 3.3 million restorations were carried out under this exemption, and the exemption was removed in 2012.[16 54]

4.1.5 Summary: clinical or medical justifications where dental amalgam is the only appropriate option

The only grounds for exemption from the amalgam ban were for the restoration of permanent teeth, and we found five European jurisdictions (Denmark, Finland, Norway, and Sweden), that have, or had in the past, an exemption policy. The exemptions are (or were): inability to keep the operating area dry (Denmark, Norway); too difficult to access the cavity (Denmark); a very large dental cavity (Denmark); too great a distance between the affected tooth and the proximate tooth (Denmark); restoration requires general anaesthesia (Denmark and Norway); allergy to components of mercury-free fillings (Norway); and the patient having a specific medical condition (Sweden). Finland and Sweden state that amalgam can be used when other dental filling materials cannot be used or do not provide an adequate restoration. The four chief dental officers in the United Kingdom (UK) state that amalgam can be used to address the specific needs of the adult population until practical clinical, and cost-effective alternative materials are available. A three-year time limit was placed on exemptions in Norway, which expired on 1 January 2011. At the end of December 2011, Sweden ceased its policy of exemptions.

4.2 Question 2: What measures have other high-income (in particular European) countries reported to support the phasing out of dental amalgam?

In order to answer Question 2, we reviewed the peer-reviewed and grey literature (technical reports) to document the reported measures taken by other EU member states, or by States closely aligned to the EU, to support the phasing out of dental amalgam and the lessons learned from these countries. Due to time limitations, we relied heavily on recent international and national reviews.

4.2.1 Introduction

The non-governmental organisation World Alliance for Mercury-Free Dentistry presented five steps in its 2014 publication titled *Toward mercury-free dentistry: how to successfully implement the dental amalgam phase-down measures of the Minamata Convention* that policy-makers should follow to introduce mercury-free dentistry:

1. "Set national objectives for minimizing amalgam use;
2. Promote mercury-free dental restorations, including raising public awareness of amalgam's mercury content;
3. Update dental school curricula to promote mercury-free dentistry;
4. Modify insurance and government programs to favour mercury-free dentistry;
5. End amalgam use in children and women." p6[49]

The World Health Organization and the United Nations Environment Programme developed a similar set of priorities or steps for phasing down dental amalgam in Kenya, Tanzania, and Uganda. These were:

1. "Focus on strengthening oral health promotion and disease prevention;
2. Phasing down, instead of phasing out;
3. Research and development of quality alternative materials;
4. Environmentally sound management of waste in dental clinics;
5. Promotion of measures to reduce releases during trade and supply as well as from dental clinics;
6. Strengthening the awareness of the general public to dental amalgam alternatives;
7. Training dental professionals in the use of alternatives". p10[59]

The World Health Organization and the United Nations Environment Programme used a logical framework-type approach to decide project components and activities, objectives, and targets.[59]

The United Nations Environment Programme's 2016 report, entitled *Lessons from Countries Phasing Down Dental Amalgam Use*, is a combination of literature and survey data from countries that have phased down their use of dental amalgam.[50] It is the most recent and comprehensive report that we identified. The United Nations Environment Programme advised countries to implement the actions recommended in the Minamata Convention on Mercury to phase down amalgam:

1. Setting national objectives aiming at dental caries prevention and health promotion, thereby minimizing the need for dental restoration.
2. Setting national objectives aiming at minimizing its use.
3. Promoting the use of cost-effective and clinically effective mercury-free alternatives for dental restoration.
4. Promoting research and development of quality mercury-free materials for dental restoration.
5. Encouraging representative professional organizations and dental schools to educate and train dental professionals and students on the use of mercury-free dental restoration alternatives and on promoting best management practices.
6. Discouraging insurance policies and programmes that favor dental amalgam use over mercury-free dental restoration.
7. Encouraging insurance policies and programs that favor the use of quality alternatives to dental amalgam for dental restoration.
8. Restricting the use of dental amalgam to its encapsulated form.
9. Promoting the use of best environmental practices in dental facilities to reduce releases of mercury and mercury compounds to water and land." p25[50]

We used this set of actions to organise the measures taken by other countries to progress the phase-down (or phase-out) of amalgam, although we have combined actions 6 and 7 into one section.

4.2.2 National objectives for dental caries prevention and health promotion

In 2011, Petersen *et al.* reported that "a caries decline has been observed in most high income countries over the past 20 years." p1[60] The authors explained that the caries decline is a result of a number of public health measures, including effective use of fluoride, coupled with changing living conditions, lifestyles, and improved self-care practices, and the establishment of school oral health programmes.[60] However, Petersen *et al.* have concluded that "despite much effort in health promotion and disease prevention, dental restorations are still needed". p58[60]

In a more recent paper, Fisher *et al.*stated that "making progress towards universal [oral] health coverage requires governments to have mechanisms to effectively manage oral health workforce planning, and to commit to mobilize and sustain adequate public funding for oral health, including budgetary resources for phasing down dental amalgam." p438[61]

The United Nations Environment Programme states that "in parallel with minimally invasive mercury-free dental fillings, health promotion and disease prevention programs should be an integral part of responsible oral health care." p24[50]

According to the Scottish Dental Clinical Effectiveness Programme, "While it is understood that the extent of dental disease varies in countries across Europe, several key factors are likely to have contributed to the successful reduction in dental amalgam use in the countries discussed. These include public and practitioner awareness of the environmental impact of dental amalgam, changes

to the balance of financial provision for amalgam versus mercury-free restorations, dental education focussing on alternative approaches and restorative materials and an emphasis on preventive policies. These facilitators are reflected in the Minamata Convention which advocates dental caries prevention and oral health promotion, the promotion of mercury-free alternatives, research and development of these, and education and training on their use, as some of the provisions to be selected for adoption by participating countries." p4[57]

The Government of Canada reported that "with respect to dental amalgam, the Canadian Oral Health Framework 2013-2018, produced by dental directors and dental consultants, which builds on the Canadian Oral Health Strategy 2005–2010, sets out national objectives for oral health and serves as a guide to improve oral health care in Canada, thereby minimizing the need for dental restoration. Also, Health Canada, through its community-based Children's Oral Health Initiative for First Nations and Inuit, focuses on the prevention of dental disease and the promotion of good oral health practices among children, their parents/caregivers, and pregnant women." p2[62]

Ireland's Smile agus Sláinte: the National Oral Health Policy supports the phase-down of amalgam, with its emphasis on health promotion, prevention, and expansion of primary oral healthcare services for the public, for all ages.[4]

4.2.3 National objectives and approaches for minimising the use of dental amalgam

The United Nations Environment Programme report states that "Norway and Sweden introduced step-by-step legislation that allowed time for the industry and for dentists to adapt to the new restrictions or guidelines. The process started with a recommendation against the use of amalgam for vulnerable populations such as children and pregnant women." p21[50]

Norway was the first EU country to implement a ban on the use of dental amalgam. According to the United Nations Environment Programme, "Interest in reducing amalgam use in Norway emerged during the 1980s as part of a broader policy to limit all releases of mercury, and also due to health concerns raised in the media by a patient association. In 1991, Norway issued guidelines that the use of amalgam should be limited due to environmental impacts. Stronger guidelines were issued in 2003, requiring materials other than amalgam to be considered as the first choice in tooth fillings." p12[50]

An important contextual feature of the Norway situation is that the country gradually progressed towards a total ban on the use of all mercury-containing products in January 2008. "Norway introduced step-by-step legislation that allowed time for the industry and for dentists to adapt to the new restrictions or guidelines. The process started with a recommendation against the use of amalgam for vulnerable populations such as children and pregnant women… In Norway amalgam use in children was reduced by 90% between 1995 and 2002". p21[50]

The United Nations Environment Programme report goes on to say that "following the lead of Norway and Sweden, some other European countries (Denmark, France, Germany) are following a similar precautionary approach by strictly limiting the use of amalgam in pregnant women and in the milk teeth of children". p21[50] In later text, the author adds Finland, Hungary, and the Netherlands as countries that have taken serious steps to phase down amalgam use for children and/or adults.[50] Italy and Catalonia (Spain) have also taken serious steps to phase down amalgam.[16]

The United Nations Environment Programme states that "dentists and, in particular, their dental associations will also need to be consulted at an early stage and throughout the phase down process.

It is important to understand their concerns regarding a phase down of amalgam use as well as to explain to them their country's obligations under the Minamata Convention [or, in this case, under Regulation (EU) 2017/852]." p18[50]

The United Nations Environment Programme reported that "when planning the amalgam phase down, Nordic countries experienced some resistance from the dental industry sector as dentists at that time:

- Were not aware of the environmental impacts of mercury from amalgam, and the social benefits of reducing mercury emissions.
- Were initially reluctant to invest in new equipment required to reduce mercury pollution or to support mercury-free fillings.
- Were not initially convinced of the durability of alternative filling materials.
- Demonstrated varying levels of skill in applying mercury-free techniques." p18[50]

The United Nations Environment Programme also reported that "The survey questionnaires returned by countries showed that during the phase down of amalgam use the committed involvement of the dental sector is necessary in order to achieve an efficient transition to alternatives.

- In Denmark, there were some initial objections from dentists. Subsequently, dental associations were directly consulted and then actively participated in the development of the health authority's 1999 policy to allow amalgam only in special cases…
- In Sweden, dentists' attitudes changed gradually as government agencies held a variety of consultations with different stakeholders, including circulating a questionnaire on the impact of amalgam reduction, meetings with the affected parties to discuss specific problem areas, two study visits concerning amalgam, and the opportunity to comment on a draft report.
- In Finland, the authorities worked with an expert group in the 1990s to prepare recommendations to reduce amalgam use, which declined significantly after the recommendations were introduced.
- In the Netherlands, a stepwise approach for eliminating the use of amalgam was employed after involving as many stakeholders as possible." p19[50]

An opinion piece written by two academic dentists, Lynch and Wilson,[56] draws on a report of the ban of dental amalgam in Norway to make suggestions about how dental policy and practice in the UK may learn from the Norwegian experience and adapt and prepare for the phasing down and the ultimate phasing out of dental amalgam. Lynch and Wilson[56] highlight the importance of strong leadership together with collaborative working by all relevant stakeholders for the successful phasing down and ultimate phasing out of dental amalgam. According to Lynch and Wilson, "It is clear in the experience of Norway that of the many factors that influenced the success of the Norway experience, strong leadership from the Directorate of Health, acceptance of the need to change by the profession, and effective collaborative working, involving all relevant stakeholders, including patients, was of paramount importance." p161[56]

Lynch and Wilson[56] suggest that the creation of a special task group with wide stakeholder representation, charged with planning, directing, and overseeing the necessary transition to phasing down and ultimately phasing out dental amalgam, could deliver similar leadership, vision, and clarity of purpose in other jurisdictions.

The United Nations Environment Programme suggests that "raising public awareness is an important factor that countries should consider because many people are not aware of the pros and cons of different dental restorations". p20[50] For example, "in Denmark, dentists were required to inform patients about the different dental restoration materials" so as to ensure informed choice." p20[50] "In Sweden, the government attributes high awareness of the environmental and health risks of mercury among patients as one of the most important explanations for that country's ability to virtually eliminate amalgam use." p20[50]

Lynch and Wilson[63] put forward what would appear to be some reasonable suggestions to enable the field of dentistry to adapt to the phase-down and ultimate phase-out of dental amalgam. However, they also acknowledge the challenges ahead and the need for a sustained shift in the allocation of resources away from amalgam and towards embracing alternatives. According to Lynch and Wilson, "The field of posterior composites is extensive and expanding at an ever-increasing rate that even experts in the area find challenging to keep pace with. A significant commitment in terms of resource and personnel will be required to seamlessly move from dental amalgam to composite as the predominant material in the restoration of posterior teeth." p112[63] In a recent statement of position on the use of amalgam in dentistry in the UK, the four chief dental officers support phasing down the use of amalgam rather than phasing it out.[58] They propose the continued use of encapsulated amalgam for older adults until a practical, clinical, and cost-effective alternative is available which they estimate may take another 10 years.[58] As already mentioned, they will contine to support the ban on amalgam in primary teeth and in the teeth of pregnant and breast feeding mothers.[58]

Fisher *et al.* also suggest that "a national coordination committee would facilitate efforts to phase down the use of dental amalgam. Such a committee could raise public awareness and support country-level communication strategies." p437[61]

4.2.4 Effective mercury-free alternatives for dental restoration

All stakeholders note that effective mercury-free alternatives for dental restoration are required.

"In Norway, the government adopted measures to present information on alternative dental restorative materials in a balanced manner. As a result, the move away from amalgam started even before the general ban on mercury in products was introduced." p20[50]

In respect of patients that use the services of dental practitioners, Lynch and Wilson suggest that "based on the experiences in Norway, patients may benefit considerably from a shift to the provision of preventatively orientated, patient-centred, minimally interventive operative dentistry that relies on, among other factors, the preservation of tooth tissues and the effective application of modern materials… its [minimally interventive operative dentistry] success is largely dependent on the level and sufficiency of oral healthcare maintenance practiced by the patient." p161[56]

Skjelvik reports on a Vista Analysis review of Norwegian experiences with the phase-out of dental amalgam use. [55]

"The general impression from the interviews completed for this report is that dentists are satisfied with the alternative materials. The most common material used now is resin-based composites, but various glass-ionomers and ceramic-based materials are also used to a lesser extent. These materials have been used for years, long before the ban on dental amalgam use entered into force. Thus, the necessary technical equipment and basic skills among the personnel have been established." p24[55]

Skjelvik also reports that "The main advantage from the dental treatment personnel's point of view is that they [amalgam alternatives] have good adhesive properties, implying that the dentist needs to remove less amounts of the fresh tooth compared to when using dental amalgam. This can offset some of the extra time needed for hardening of these materials especially for small fillings, and some dentists even claim that they use less time than when using amalgam… The dentists in the review for this study claim that they use 15–45 minutes more for large fillings, depending on the dentist experience and the complexity of the filling… [the dentists reported that] patients seem to like the alternative materials because of their tooth-like appearance". p24[55]

Skjelvik goes on to report that "The disadvantages are that the alternative materials could be challenging to use, especially for larger fillings. They need a completely dry environment to seal properly. Another disadvantage is that bacteria are more easily formed on the surface of the filling, thus requiring some more follow-up from both the patient and the dentist. Because of this and less 'chewing-strength' the composite fillings do not last as long as the amalgam fillings (some dentists say half the time of amalgam fillings), but the longevity is increasing and approaching the longevity of amalgam fillings. Since the alternative filling materials are sensitive to the techniques used, the skills and experiences of the dental treatment personnel are important to get a good result. Especially the sealing, i.e. the intensity of the light used for sealing and the wave length of the light are important in order to achieve a good filling". p24[55]

The review is a technical grey literature report prepared for the Norwegian Climate and Pollution Agency. The methods of data collection and data analysis are not reported in detail by Skjelvik. For example, Skjelvik reports doing telephone interviews among selected operating dentists and county dentists; Skjelvik does not report how the dentists were recruited, how many were interviewed, or how many refused to be interviewed.

Lynch and Wilson[56] draw attention to the 1993 establishment in Norway of the Dental Biomaterials Adverse Reaction Unit, initially as part of the Directorate of Health, to monitor adverse reactions to dental materials, in particular resin-based materials, the use of which was increasing at the time. The authors note that "while there has been an increase in the number of reports of adverse reactions to dental [composite] resins, the increase has not been in proportion to the increase in the placement of composite [resin] restorations, indicating causation other than a simple cause-and-effect relationship." p160[56]

The scientific effectiveness of dental restorative materials and techniques is reported in Section 4.3 for children and adolescents and in Section 4.4 for adults. The exemptions to allow the use of encapsulated dental amalgam are presented in Section 4.1.

4.2.5 Development and testing of mercury-free materials for dental restoration

In 2011, Petersen *et al.* reported that "in order to reduce the use of dental amalgam in the future, the meeting emphasizes that prevention is of paramount importance, including community interventions, proper use of fluorides, fissure sealants, and re-mineralization strategies. In the near term, alternative restorative materials including composites will need to be improved, as will the 'next generation' materials. In the longer term, tissue engineering approaches could be considered." p16[60]

Petersen *et al* went on to say that "the research into the development of improved and novel alternative restorative materials remains unsatisfactory since the 1997 WHO [World Health Organization] Consultation meeting [as] little progress has been observed. Further research is also

needed to assess the safety and adverse effects of restorative materials alternative to dental amalgam. Collaboration between material scientists, computer scientists, toxicologists, synthesis chemists and industry is critical." p16[60]

4.2.6 Education and training of dental professionals and students to prevent caries and use mercury-free alternatives and minimal invasive techniques

The United Nations Environment Programme indicated that "A Norwegian guideline was developed promoting minimally invasive dentistry on the basis of health care legislation, which took several years to complete. After reviewing the research, the Norwegian health authorities came to the following conclusions:

- When a dental filling is placed, the technique should involve the least possible amount of tooth tissue removal.
- While, on the basis of available information at the time, they considered amalgam to be the longest lasting, least expensive, and most durable filling material, it requires the removal of more healthy tooth tissue than mercury-free fillings.
- Every effort should be made to reduce the exposure of patients and dental health care personnel to chemical substances during dental treatment, both when placing and removing dental fillings". p24[50]

The United Nations Environment Programme reported "In Norway, the opinions of dentists changed over time. At first 'emotions were high', but dental practitioners accepted the principles developed through the consultative process of the Norwegian authorities. This included many consultations with stakeholders, a national hearing, and vetting the proposed regulation through the World Trade Organization and EU notifications". p19[50]

Lynch and Wilson[56] note how scepticism among dental practitioners regarding the use of posterior composites captured in a survey in 1998 had declined by 2002, when it was reported that a majority of dentists favoured the placement of composites instead of amalgam. By way of explaining this shift in attitudes, Lynch and Wilson note that "This change of opinion coincided with, among other developments, a marked increase in the teaching of posterior composites in Scandinavian dental schools, including the dental schools in Norway." p160[56]

The World Alliance for Mercury-Free Dentistry reported that by the "early 2000s, dental schools in Sweden provided instruction on mercury-free fillings first while amalgam instruction was only a small – and mostly theoretical – part of the training later", p9[49] while by 2014, "dental schools in the Netherlands were reportedly phasing out instruction on amalgam use." p9[49]

One of the papers by Lynch and Wilson, although set in the context of UK dentistry, raises issues and proposes suggestions that appear to apply to dentistry in a wider context.[63] The authors suggest that during the phase-down and ultimate phase-out of dental amalgam use, and in the likely absence of some 'gold standard' alternative restorative material being discovered, trialled, and implemented, the most reliable alternative for restoring posterior teeth in adults is composite resins. According to Lynch and Wilson, "for at least a decade or so following the implementation of the Minamata Treaty the public is going to look to the dental profession to successfully apply existing types of tooth coloured restorative systems, notably composites, in ways to meet patients' needs and expectations." p111[63]

Embedding the practice of teaching undergraduates in dental schools, as well as teaching practising dentists through continuous professional development, how to apply composite resins are two

specific measures suggested by Lynch and Wilson.[63] On the first point regarding dental schools, the authors note that teaching the application of composite resins has become established practice in international dental schools, including in Ireland. According to Lynch and Wilson, "the teaching of posterior composites is well established in dental school teaching, not only in the UK and Ireland, but in countries including the United States, Canada, Japan, Spain, Brazil and Iran… Nowadays, students in UK and Ireland dental schools gain more experience in the placement of posterior composites than amalgam, with a strong emphasis on minimally interventive dentistry (55% posterior composite versus 45% amalgam)". p111[63] One likely outcome of this established teaching practice in dental schools is that "the next generation of dentists and therapists to join the dental workforce will be more skilled and experienced in the application of composite systems and principles of minimally interventive dentistry than ever before". p111[63]

While it would appear that teaching the use of composite resins is becoming established in international dental schools, the procedure itself needs to be refined and improved so that undergraduate dentists are taught how to use composite resins as dental restorative material so as to maximise longevity. According to Lynch and Wilson, "A more immediate challenge for dental schools, as indicated in the various surveys on the teaching of posterior composites, is the need to work towards common approaches to certain aspects of posterior composite placement technique". p111-112[63] The authors suggest that "the teaching of dental amalgam replacement in dental schools should be discontinued with effect from no later than 2015 and the resources freed up from this change could be put towards work to reduce the uncertainty around finding the most reliable placement technique for posterior composite placement." p111[63] In addition, they suggest that "Existing and future students would also benefit from more instruction in the use of indirect ceramics systems in the restoration of teeth that are badly broken down, have suffered extensive wear or fracture, or are otherwise compromised in ways that may not be best managed by a direct restorative approach". p111[63]

Regarding the continuous professional development of practising dentists, Lynch and Wilson note that "Many dentists and dental therapists engaged in clinical practice in the UK graduated from dental school at a time when there was no teaching on posterior composite restorations and according to the findings of surveys on trends in general dental practice, many practitioners would appear not to have acted on whatever CPD [continuous professional development] they may have had on state-of-the-art posterior composite placement". p112[63]

While Lynch and Wilson specifically refer to the gap in knowledge and practice on posterior composite restorations in the UK, it may well be inferred that this is also a gap in other international jurisdictions, including Ireland.[63] To address this gap, the authors suggest that "With the dental amalgam phase-down clock ticking, postgraduate dental deans and other providers of CPD [continuous professional development] should give consideration to significantly increasing the provision of courses on posterior composites, while practitioners not familiar with the use of composites in the restoration of posterior teeth should seek opportunity to obtain the necessary skills, knowledge and understanding". p112[63]

Lynch and Wilson raise a number of important issues in this paper and put forward what would appear to be some reasonable suggestions to enable the field of dentistry to adapt to the phase-down and ultimate phase-out of dental amalgam.[63] However, they also acknowledge the challenges ahead and the need for a sustained shift in the allocation of resources away from amalgam and

towards embracing alternatives. According to Lynch and Wilson, "The field of posterior composites is extensive and expanding at an ever-increasing rate that even experts in the area find challenging to keep pace with. A significant commitment in terms of resources and personnel will be required to seamlessly move from dental amalgam to composite as the predominant material in the restoration of posterior teeth." p112[63]

One thing to note regarding the inclusion of the paper by Lynch and Wilson[63] is that although this paper does not document any reported measures taken by countries to support the phasing down of dental amalgam, it can be argued that the measures the authors do address – namely dental schools and dental professionals' continuous professional development – are important in helping dentists to adjust to the phase-down demands and the ultimate phase-out of amalgam.

4.2.7 Realignment of dental insurance policies and programmes to favour the use of quality alternatives to dental amalgam

The United Nations Environment Programme reported that some countries have found that addressing imbalances in insurance schemes can be a very important measure for phasing down amalgam use.[50]

Many national insurance schemes already fully or partially cover mercury-free fillings (including Belgium, Bulgaria, Finland, France, Hungary, Italy, and Slovenia). In Poland, mercury-free fillings are reimbursed for children and pregnant women. Similarly, in Estonia, fillings are free for children up to 19 years of age, regardless of which filling material is used.[16]

In Sweden, dental treatment for children is fully covered, and for adults 50% of the treatment cost is covered, although amalgam fillings are not covered.[50] "Sweden lists its decision to stop financial support for amalgam fillings from the national dental insurance service as among the most important explanations for ending the use of amalgam." p22[50] "The result was that the cost to the patient of an amalgam filling became as high as, or even higher than, the cost of a composite restoration. When insurance coverage for amalgam was eliminated, its use dropped substantially." p22[50]

In Norway, dental care is fully covered for children up to 18 years of age[50] and amalgam fillings are not permitted.[50]

The are no financial incentives in Denmark, Finland, or the Netherlands to discourage amalgam use.[50] "In Finland patients contribute 20% of costs on average of both amalgam and non-amalgam fillings so there is no financial incentive to restrict the use of amalgam." p22[50]

In order to support realignment of dental insurance policies and programmes to favour the use of quality alternatives to dental amalgam, Fisher *et al.* report that "evidence-based reviews could encourage and support insurance companies to examine policy and programme options that favour a shift to quality mercury-free materials for dental restoration, including materials that re-mineralize tooth substance." p348[61]

4.2.8 Restriction of the use of dental amalgam to its encapsulated form

The exemptions to allow the use of encapsulated dental amalgam are presented in Section 4.1.

4.2.9 Environmental practices in dental facilities that reduce releases of mercury

The United Nations Environment Programme report found that "some countries also adhere to a policy of substituting less hazardous chemical substances… For example, in Switzerland the 1989

Swiss Ordinance on Risk Reduction related to chemical products stated that amalgam may not be used if a mercury-free alternative can be applied in its place." p21[50]

The United Nations Environment Programme also reports that "there are a range of measures that countries may take to greatly limit dental mercury releases to the environment. First, an accurate inventory of amalgam use is very useful to estimate the quantity of mercury used by the dental sector". p14[50] "This data establishes a baseline from which to gauge the subsequent phase down progress of a country, it facilitates setting a reduction target, and it sheds light on any mechanisms at the national level that could present problems or opportunities." p15[50]

The United Nations Environment Programme report emphasises that "During the phase down, it is also important to limit any mercury releases to the environment, to the extent possible. This may be achieved with a waste management scheme that isolates amalgam scrap, capsules, or removed amalgam, and where possible…treats this solid waste in an appropriate manner. Best management practices for dental clinics also include the use of amalgam separators as the most effective method to minimize the amount of mercury released into wastewater. Depending on the size of the dental office and the number of separators required, the annual cost of amalgam separators (purchase, installation, maintenance) may vary between 60 USD and 270 USD per chair… More recent information indicates that the recovered mercury also needs proper handling and disposal, for which the additional cost could range between 95 USD and 750 USD per year, depending upon the size of the dental clinic and other local circumstances." p15[50]

A number of EU Member States have implemented legislation to ensure mandatory installation of amalgam separators in dental practices, including Austria, Belgium, the Czech Republic, Finland, France, Germany, Italy, Latvia, Malta, the Netherlands, Poland, Slovakia, Sweden, and the UK, and most recently, Portugal.[16 64] Most of the countries require proper maintence and disposal of amalgam. Denmark – and, more recently, Ireland – provides guidance that dental practices should install amalgam separators.[16 64] Periodic inspection of dental clinics with respect to compliance with Regulation (EU) 2017/852 is another activity that is required.[16]

The Government of Canada's "2010 Notice Requiring the Preparation and Implementation of Pollution Prevention Plans in Respect of Mercury Releases from Dental Amalgam Waste requires dental facilities to prepare and implement a pollution prevention plan if they have not already implemented best management practices for dental amalgam waste." p2[62]

4.2.10 Summary of measures by other countries to support the phasing out of dental amalgam

The United Nations Environment Programme (2016) in its report titled *Lessons from countries phasing down dental amalgam use* advised countries to take the actions outlined in the Minamata Convention on Mercury to phase down amalgam. These actions are based mainly on the experience of other countries, in particular Norway and Sweden, and include:

1. Setting national objectives to reduce the need for dental restoration by increasing primary and secondary prevention activities, as done by the World Health Organization and in Canada, Scotland, and, more recently, Ireland. Of note, the four chief dental officers in the UK support phasing down the use of amalgam rather than phasing it out.
2. Setting national objectives and approaches for minimising the use of dental amalgam by using a step-by-step approach to phasing down the use of amalgam, as done in Denmark, Finland, France, Germany, Hungary, the Netherlands, Norway, and Sweden. The first steps were raising awareness of the potential environmental hazards of mercury among the dental professions, the public, and other stakeholders, followed by forming a representative working group, and then identifying vulnerable populations (such as children and pregnant or breastfeeding women) and banning the use of amalgam in these populations. The last step was to allow the use of amalgam in exceptional (but justifiable) circumstances while ensuring patient consent.
3. In addition to a prevention and early treatment approach, ensuring access to reliable alternative dental restorative materials and techniques for amalgam restorations was essential. In Norway, there is a policy of minimally interventive operative dentistry which supports the use of resin composite for permanent teeth, and the use of other compounds for temporary and primary teeth restorations. Norway also introduced a Dental Biomaterials Adverse Reaction Unit to monitor adverse events from dental products.
4. Developing and testing new mercury-free materials for dental restoration is an action promoted by the World Health Organization and the United Nations Environment Programme. This action is less progressed by the countries that have progressed the implementation of mercury-free dentistry. The World Health Organization states that additional research is needed to assess the safety and adverse effects of alternative restorative materials to dental amalgam and, therefore, collaboration between material scientists, computer scientists, toxicologists, synthesis chemists, and industry is critical.
5. Educating and training dental professionals and students to use evidence-informed practice. The first step of this action is to work with the dental professions and dental schools in order to ensure an undergraduate curriculum and continuous professional development programme that is based on preventing caries, using mercury-free alternatives, and using minimally invasive techniques. In addition, resource allocation needs to be directed away from amalgam and towards embracing alternatives. The undergraduate curriculum has included training on posterior composite resin restorations using minimally invasive techniques in a number of countries, including Brazil, Canada, Iran, Ireland, Japan, Norway, Spain, Sweden, the UK, and the United States of America (USA). However, more needs to be done in some countries including Ireland to promote posterior composite resin restorations using minimally invasive techniques.
6. Realigning dental insurance policies and programmes to favour the use of quality alternatives to dental amalgam is an action taken by a number of European countries. In Sweden, dental treatment for children is fully covered, and 50% of the treatment cost is covered for adults. Amalgam fillings are not covered. In Norway, dental care is fully covered for children up to 18

years of age, and amalgam fillings are not permitted. Many other national insurance schemes already fully or partially cover mercury-free fillings (Belgium, Bulgaria, Finland, France, Hungary, Italy, and Slovenia).

7. Exemptions to the amalgam ban were permitted only for permanent tooth restoration, and we found four European jurisdictions (Denmark, Finland, Norway, and Sweden) that have (or had) an exemption policy.
8. Introducing environmental practices in dental facilities that reduce releases of mercury. Switzerland adheres to a policy of substituting less hazardous chemical substances, and mercury is included in this policy. In addition, the United Nations Environment Programme reports that there are a number of other measures that countries may take to limit dental mercury releases to the environment, such as an accurate inventory of amalgam use or the implementation of a waste management scheme that isolates amalgam scrap, capsules, or removed amalgam and disposes of it appropriately. Canada requires all dental practices to implement a best practice waste management scheme for dental amalgam.
9. A number of EU Member States have implemented legislation to ensure mandatory installation of amalgam separators in dental practices (Austria, Belgium, the Czech Republic, France, Finland, Germany, Italy, Latvia, Malta, the Netherlands, Poland, Portugal, Slovakia, Sweden, and the UK).

4.3 Question 3: What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for young people aged 16 and under?

4.3.1 Introduction to caries interventions for children and adolescents

We developed two secondary questions to help us answer our primary review question:

1. What types of dental restorative interventions have been evaluated in systematic reviews for the treatment and prevention of dental caries in young people aged 16 and under?
2. What is the level of evidence (adequate, inadequate, or inconclusive) for the effectiveness of dental restorative interventions for the treatment and prevention of dental caries in young people aged 16 and under?

Two reviewers (MK, JL) assigned a level of evidence based on an (adapted) version of Faggion:[48]

- Adequate evidence (unlikely to change)
    - When authors stated their confidence using words such as 'sound', 'high', or 'good quality' (which was rarely the case in the reviews examined)

  or

    - When authors did not explicitly state that the evidence was weak, and reported some (moderate) evidence for effectiveness, the evidence was considered adequate (which was more commonly the case in the reviews examined).
- Inadequate evidence (likely to change)
    - When authors described weak or insufficient evidence (low or very low quality), or when no studies were included in the review (an empty review), the evidence was considered inadequate
- Inconclusive evidence
    - The evidence was considered inconclusive when it was not possible to determine which intervention was better or best.

We identified two intervention categories that have been evaluated in systematic reviews as late treatment responses to cavitated caries in children and adolescents: restorative procedures and techniques, and restorative materials. We found two early treatment intervention categories for the treatment of early non-carious lesions in children and adolescents' teeth: remineralising agents and microinvasive strategies. We identified two categories of interventions that evaluated prevention of caries in children and adolescents: fluoride-based technologies and non-fluoride-based technologies (such as antibacterials, minerals, and sealants). The categorisation of interventions allowed us to capture the similarities between the interventions and to reflect the diversity of the different techniques and materials evaluated.

We have provided an assessment of the level of evidence (adequate, inadequate, or inconclusive) for each intervention evaluated. In some reviews there is more than one level of evidence reported to reflect the evaluation of more than one outcome. For each review we included, we have provided data to describe the age of the participants, the intervention under evaluation, the comparators, and the primary outcomes being assessed. In addition, we have provided a summary of the risk of bias for the primary trials or studies included in each review based on the systematic review authors' assessments and theauthors' conclusions including where available their assigned level of evidence.

It is important to note that when we say that the evidence for an intervention is inadequate, it generally means that the research base with which to evaluate the intervention is inadequate, rather than that the intervention itself is inadequate. Overall, there were few interventions that systematic review authors judged as not useful (specifically, dental liners and silver-reinforced glass-ionomer cement).

4.3.2 Prevention of dental caries in children and adolescents

Interventions to prevent caries fall under two categories: fluoride technologies (Category 1), and non-fluoride technologies such as antibacterial agents, non-fluoride mineral applications, and pit and fissure sealants (Category 2).

Category 1 included 11 reviews that compared fluoride toothpastes and other fluoride technologies with controls in preventing dental caries in children and adolescents.

Two reviews (Marinho *et al.*, 2003a;[65] and dos Santos *et al.*, 2013[66]) evaluated the effectiveness of fluoride toothpaste, and two reviews (Singh and Purohit, 2018;[67] and Walsh *et al.*, 2019[7]) examined the use of fluoride toothpaste in different concentrations.

The remaining seven reviews (Marinho *et al.*, 2003b;[68] Marinho *et al.*, 2004a;[69] Marinho *et al.*, 2004b;[70] Tubert-Jeannin *et al.*, 2011;[71] Marinho *et al.*, 2013;[72] Marinho *et al.*, 2015;[73] and Marinho *et al.*, 2016[74]) evaluated the use of fluoride technologies other than toothpastes. The fluoride technologies examined in these seven reviews typically included fluoride varnishes, gels, mouth rinses, and tooth mousse, and one review (Tubert-Jeannin *et al.*, 2011)[71] examined fluoride supplements (tablets, drops, lozenges), which we have also included as a technology.

Category 2 included 10 reviews that compared a range of non-fluoride technologies with controls in preventing dental caries in children and adolescents, such as antibacterial agents, non-fluoride mineral applications, and pit and fissure sealants.

Three reviews (Ahovuo-Saloranta *et al.*, 2017;[75] Ahovuo-Saloranta *et al.*, 2016;[76] and Hou *et al.* 2017[77]) evaluated sealants only, and one review (Yengopal and Mickenautsch, 2010)[78] evaluated both glass-ionomer cement and sealants. Two reviews (Marghalani *et al.*, 2017;[79] and Riley *et al.*, 2015[80]) evaluated xylitol, and one review (Wang *et al.*, 2017)[81] evaluated a range of different non-fluoride remineralising agents. Two reviews (Walsh *et al.*, 2015;[82] and James *et al.*, 2010)[83] evaluated chlorhexidine-based preparations, and one review (Botton *et al.*, 2016)[84] compared self-etch adhesive systems with prior-acid etching systems.

4.3.2.1 Fluoride technologies to prevent caries in children and adolescents

4.3.2.1.1 Topical fluoride therapy: toothpaste only

In one of the first Cochrane reviews to focus on the use of fluoride toothpaste as a preventive intervention for dental caries in children and adolescents, **Marinho *et al.*** (2003a)[65] compared fluoride toothpaste with placebo or with a non-fluoride toothpaste for preventing dental caries in children and adolescents. According to Marinho *et al.*, the intervention is described as "topical fluoride in the form of toothpastes only, using any of the following fluoride agents alone or in combination: sodium fluoride, sodium monofluorophosphate (SMFP), stannous fluoride (SnF_2), acidulated phosphate fluoride (APF), amine fluoride (AmF)". p6[65]

Seventy-four randomised controlled trials comprising 45,073 children and adolescents aged 5-16 years were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, 11 of the trials were judged to be at a low risk of bias, seven trials at a high risk of bias, and for the remaining 56 trials, the risk of bias was unclear.

Based on the findings of this review, there is adequate evidence to suggest that children and adolescents aged 5–16 years who brushed their teeth with fluoridated toothpaste had fewer decayed, missing, and filled permanent teeth after three years (regardless of whether their drinking water was fluoridated or not). Brushing their teeth with fluoride toothpaste twice a day increased the benefit. According to Marinho *et al.*, "taken together, the trials are of relatively high quality, and provide clear evidence that fluoride toothpastes are efficacious in preventing caries." p2[65]

In a more recent review, **dos Santos *et al.*** (2013)[66] compared the effectiveness of fluoride toothpaste with a placebo or with no intervention in preventing dental caries in the primary dentition of preschool children. The intervention in six of the trials included in this review comprised standard fluoride concentration toothpaste (1000–1500 ppm) and oral health education, and three trials comprised low fluoride concentration toothpaste (<600 ppm) and oral health education. One trial included both standard and low fluoride concentrations.

In total, ten randomised controlled trials were included in the review by dos Santos *et al*'[66], which evaluated children who were aged 7 years or under; the total number of children in the sample included in the analysis was not reported. The Cochrane Collaboration's risk of bias instrument was used to assess bias in the included trials. All eight trials included were judged to have a high risk of bias.

The main finding in this review suggests that there is adequate evidence that preschool children who brush their teeth with standard fluoride toothpaste had fewer caries than children in the control group. When tooth brushing with standard fluoride toothpaste (1000–1500 ppm) was compared with the placebo or with no intervention, significant caries reduction at surface (31%), tooth (16%), and individual (relative risk = 0.86) levels were observed. According to dos Santos *et al.,* "preschool children who brushed their teeth with standard fluoride toothpaste (1,000-1,500 ppm) experienced a significant reduction in the mean number of primary decayed, missing owing to caries, and filled dental surfaces and teeth. They also had a significantlt lower risk of developing dental caries than those who received no intervention." p7[66] The evidence for the effectiveness of using low-fluoride toothpastes (<600 ppm) is uncertain (or inconclusive).

Singh and Purohit (2018)[67] compared the effectiveness of high-fluoride toothpastes (≥2500 ppm) with standard fluoride toothpastes (≤1500 ppm) in preventing dental caries in children and adults.

Eight randomised controlled trials were included in this review. The age range of participants was 6–16 years in six trials and 27–103 years in two trials. The authors did not perform an age-related analysis of the data. The Cochrane Collaboration's risk of bias instrument was used to assess the quality of the included trials. Allocation sequence was judged to be adequate in all eight trials. However, allocation concealment was not declared explicitly in any of the eight trials. Apart from two studies with single blinding, knowledge of the allocated interventions was adequately prevented by double blinding in the remaining six trials.

The results of the review suggest that there is adequate evidence that brushing teeth with high-concentration fluoride toothpaste (≥2500 ppm) was significantly associated with lower caries increment compared with standard fluoride toothpaste use (≤1500 ppm). In addition, high-fluoride toothpastes were also associated with a greater preventive effect when compared with low-fluoride toothpastes. According to Singh and Purohit, "this meta-analysis suggests that high-fluoride toothpastes are superior to low-fluoride toothpastes in terms of reducing caries. When used judiciously, the results of this work should encourage the use of high-fluoride toothpaste, specifically among vulnerable populations, to maximize preventive benefits." p314[67]

In a very recent Cochrane review which again focused on the concentrations of fluoride toothpaste, **Walsh *et al.*** (2019)[7] compared the effectiveness of toothpastes of different fluoride concentrations with controls in preventing dental caries in children and adolescents. According to Walsh *et al.*, "the formulation and fluoride concentration of toothpaste is diverse, with a variety of fluoride compounds used singly and in combination including sodium fluoride, sodium mono-fluorophosphates, amine fluoride and stannous fluoride, and, according to each manufacturer's specifications, these must be compatible with other basic ingredients, especially abrasive systems (which account for almost half of the entire toothpaste formulation)." p9[7]

Ninety-six randomised controlled trials were included in this review, with children and adolescents up to 18 years of age. Based on the Cochrane Collaboration's risk of bias instrument, one trial was judged to have a low risk of bias, 14 trials were judged to have a high risk of bias, and for the remaining 81 trials, the risk of bias was unclear.

There is adequate evidence that brushing teeth with toothpaste containing 1500 ppm fluoride reduced the amount of new decay in the primary teeth of young children when compared with non-fluoride toothpaste (moderate-certainty evidence). The amount of new decay was similar among those who used 1055 ppm compared with 550 ppm fluoride toothpaste (moderate-certainty evidence), so the evidence is inconclusive for this finding. There was a slight reduction in the amount of new decay when using 1450 ppm toothpaste compared with 440 ppm fluoride toothpaste (moderate-certainty evidence), which renders the evidence adequate for this finding.

There is adequate evidence that brushing with toothpaste containing 1000–1250 ppm fluoride compared with non-fluoride toothpaste results in less new tooth decay in the permanent teeth of children and adolescents (high-certainty evidence), and that brushing with 1450–1500 ppm fluoride toothpaste compared with non-fluoride toothpaste results in less new tooth decay in the permanent teeth of children and adolescents (moderate-certainty evidence). There is adequate evidence that brushing with 1450–1500 ppm fluoride toothpaste reduces the amount of new decay more than

brushing with 1000–1250 ppm toothpaste does (moderate-certainty evidence). There was a similar amount of new decay when children and adolescents used toothpaste containing 1,700–2,200 ppm or 2400–2800 ppm fluoride compared with toothpaste containing 1,450–1,500 ppm fluoride (moderate-certainty evidence), so the evidence for this finding is adequate, as we can say that both concentrations are equally effective in preventing caries.

According to Walsh *et al.*, "There is high-certainty evidence that toothpaste containing 1,000 to 1,250 ppm fluoride is more effective than non-fluoride toothpaste [on permanent teeth in children and adolescents]. There is moderate-certainty evidence for the other findings reported… The stronger the fluoride concentration, the more decay is prevented." p3[7]

4.3.2.1.2 Topical fluoride therapy: varnishes, gels, mouth rinses, and toothpastes

We now present the findings from three Cochrane reviews that evaluated a range of different fluoride technologies as part of the same review.

Marinho *et al.* (2003b)[68] compared the effectiveness of fluoride varnishes, gels, mouth rinses, and toothpastes (known as topical fluoride therapy) with a placebo or with a no topical fluoride therapy group in preventing caries in children and adolescents. Marinho *et al.* describe the intervention as follows: "topical fluoride therapy in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration of fluoride, amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year." p4[68]

One hundred forty-four randomised controlled trials were included in this review, and 133 of the trials contributed data for the meta-analysis involving 65,169 children aged 5–16 years. Based on the Cochrane Collaboration's risk of bias instrument, 14 of the trials were judged to be at a low risk of bias, 21 trials were at a high risk of bias, and the risk of bias in the remaining 109 trials was unclear. Approximately two-thirds of the children used fluoride toothpaste, with fewer participants using a fluoride mouth rinse, fluoride gel, or fluoride varnish.

The findings of this review suggest that there is adequate evidence that children aged 5–16 years who applied fluoride in the form of toothpastes, mouth rinses, gels, or varnishes had fewer decayed, missing, and filled teeth in both their primary and permanent teeth, regardless of whether their drinking water was fluoridated. According to Marinho *et al.*, "there is strong evidence of a generalizable beneficial effect of topical fluoride therapy." p16[68]

Marinho *et al.* (2004a)[69] compared the effectiveness of using a combination of two topical fluoride therapies (toothpastes, mouth rinses, gels, or varnishes) with using one topical fluoride alone (mainly toothpaste) in preventing dental caries in children and adolescents. According to Marinho *et al.*, the intervention was described as follows: "topical fluoride therapy in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration of fluoride, amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year." p4[69]

Twelve randomised controlled trials were included in this Cochrane review, involving 4,026 children aged 14 or under. Based on the Cochrane Collaboration's risk of bias instrument, two of the trials were judged to be at a high risk of bias and the remaining 10 trials had an unclear risk of bias.

Based on the findings from this review, there appears to be weak and inadequate evidence to suggest that combining two fluoride technologies is better than using only fluoride toothpaste. Children and adolescents who used another form of topical fluoride (usually mouth rinses) in addition to fluoride toothpaste experienced a modest (10%) additional reduction in tooth decay compared with children who only used fluoride toothpaste. Despite the observed improvement in tooth decay in children and adolescents who combined the use of fluoride technologies, Marinho *et al.* signal the need for some caution: "although there is a suggestion of a modest caries inhibiting effect with the combined use of topical fluorides in the permanent dentition for most of the comparisons, a general lack of statistical significance is apparent. Further, in a few comparisons, the confidence intervals are relatively wide and the variation among the results of the studies can be substantial. This calls for a cautious interpretation of the data." p13-14[69]

Marinho *et al.* (2004b)[70] compared the effectiveness of one form of topical fluoride intervention with another in preventing dental caries in children and adolescents. According to Marinho *et al.*, the intervention comprises "topical fluoride therapy in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration of fluoride, amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year." p4[70]

Seventeen randomised controlled trials were included in this review, with participants aged 14 or under; data on 3,243 participants were analysed out of 4,423 initially randomised participants. Based on the Cochrane Collaboration's risk of bias instrument, one of the trials was judged to have a low risk of bias, two trials to have a high risk of bias, and the remaining 14 trials to have an unclear risk of bias.

Based on the findings from this review, the evidence appears to be inconclusive regarding the superiority of one topical fluoride technology over another. According to Marinho *et al.*, "compared with each other, fluoride toothpaste and mouthrinse, and toothpaste and gel appear to be effective to a similar degree in the prevention of dental caries in children; the benefits in terms of caries reduction from fluoride mouthrinse compared with gel, fluoride varnish compared with gel, and varnish compared with toothpaste (deciduous teeth only) are unclear." p14[70]

A further three Cochrane reviews undertaken by Marinho *et al.* compared three different types of fluoride technologies separately with controls: fluoride varnishes, gels, and mouth rinses.

Marinho *et al.* (2013)[72] compared the effectiveness of fluoride varnishes with a placebo (a treatment without fluoride) or with no treatment in preventing dental caries in children and adolescents. According to Marinho *et al.*, "there are two main preparations of fluoride varnish commercially known as Duraphat and Fluor Protector. Duraphat contains 5% sodium fluoride, in a natural resin carrier with some alcohol included as a solvent. Fluor Protector contains 0.9% difluorosilane by weight (1,000 ppm of fluoride) in polyurethane-based varnish and sets to a thin transparent film." p6[72]

Twenty-two randomised controlled trials with 12,455 participants within the age range of 1–15 years were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, most of the trials (15) were judged to be at a high risk of bias in at least one domain, and the remaining seven trials had an unclear risk of bias in at least one domain.

The main finding in this review suggests that there is adequate evidence that fluoride varnish is an effective intervention in the prevention of dental caries in both the primary and permanent teeth of children and adolescents. In the 13 trials that investigated permanent teeth of children and adolescents, the review found that the young people treated with fluoride varnish experienced on average a 43% reduction in decayed, missing, and filled tooth surfaces. In the 10 trials examining the effect of fluoride varnish on first or baby teeth, the evidence suggests a 37% reduction in decayed, missing, and filled tooth surfaces. According to Marinho *et al.*, "the application of fluoride varnishes two to four times a year, either in the permanent or primary dentition, is associated with a substantial reduction in caries increment." p21[72]

Marinho *et al.* (2015),[73] in an updated Cochrane review, compared the effectiveness of fluoride gels with a placebo or with no treatment in preventing dental caries in children and adolescents. According to Marinho *et al.*'s description of the intervention, "the 'classical' fluoride gels do not contain abrasives, their fluoride concentration is usually much higher than that of fluoride toothpaste and they are applied at relatively infrequent intervals." p6[73]

Twenty-eight randomised controlled trials (including three new trials since the original review) were included in this updated review. All trials involved a total of 9,140 children and adolescents aged 2–15 years. Based on the Cochrane Collaboration's risk of bias instrument, 20 trials were at high risk of bias and eight trials had an unclear risk of bias.

The main finding from this review suggests that there is adequate evidence that fluoride gels are an effective intervention to prevent dental caries in the permanent teeth of children and adolescents. The evidence is not as strong regarding the effectiveness of fluoride gels in primary teeth, and therefore we judge it to be weak and inadequate. According to Marinho *et al.*, "the application of fluoride gels, either by professionals or self-applied, is associated with a large reduction in caries increment in permanent teeth in children (the quality of evidence is moderate GRADE). There is less certainty of the large reduction observed in the first or baby teeth (low quality evidence: 3 trials)." p27[73]

Marinho *et al.* (2016)[74] compared the effectiveness of fluoride mouth rinses with a placebo (a mouth rinse without the active ingredient fluoride) or with no treatment in preventing dental caries in children and adolescents. According to Marinho *et al.*, "the fluoride compound most commonly used in mouthrinse is sodium fluoride." p6[74]

Thirty-seven randomised controlled trials involving 15,813 children and adolescents aged 6–14 were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, most of the trials (28) were at high risk of bias, and the remaining nine had an unclear risk of bias. Almost all participating children received a fluoride rinse formulated with sodium fluoride on either a daily, weekly, or fortnightly basis, and at two main strengths: 230 or 900 ppm fluoride.

The main finding from this review suggests that there is adequate evidence that fluoride mouth rinse is an effective intervention to prevent dental caries in the permanent teeth of children and adolescents. According to Marinho *et al.*, "supervised regular use of fluoride mouthrinse by children and adolescents is associated with a large (27%) reduction in tooth decay in children's permanent teeth." p28[74]

4.3.2.1.3 Fluoride supplements

Finally, in this section covering fluoride toothpaste and other fluoride technologies, we include a review by **Tubert-Jeannin *et al.*** (2011)[71] which compared the effectiveness of fluoride supplements (tablets, drops, lozenges) with no fluoride supplement or with other preventive measures, such as topical fluorides, in preventing dental caries in children under 16 years of age. According to Tubert-Jeannin *et al.*, the following types of fluoride supplements were considered in this review: "fluoride supplements in the form of tablets, drops, lozenges (or chewing gums): with or without the use of vitamins; using any fluoride agent, at any concentration, amount, frequency of use, duration of application, and with any technique of application (sucked or not, chewed or not); with or without the use of topical fluorides (fluoride rinse, topical fluoride application, fluoride varnish or fluoride toothpaste) or non-fluoride-based measures (chlorhexidine, xylitol, sealants, oral hygiene interventions." p 6-7[71]

Eleven randomised controlled trials with 7,196 children were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, 10 trials had an unclear risk of bias and one had a high risk of bias.

Based on the main findings from this review, we have judged the evidence overall to be weak, and determined that there is inadequate evidence upon which to judge the effectiveness of using fluoride supplements to prevent dental caries in primary or permanent teeth in children and adolescents. When fluoride supplements were compared with no fluoride supplement (three studies), the use of fluoride supplements was associated with a 24% reduction in decayed, missing, and filled surfaces in permanent teeth in children aged 5–12 years. For children aged 5 years and under, there was weak evidence that the use of fluoride supplements prevents dental caries in primary teeth. The effect of fluoride supplements was unclear on deciduous or primary teeth. When fluoride supplements were compared with topical fluorides or with other preventive measures, there was no differential effect on permanent or deciduous teeth. According to Tubert-Jeannin *et al.*, "We rated 10 trials as being at unclear risk of bias and one at high risk of bias, and therefore the trials provide weak evidence about the efficacy of fluoride supplements." p2[71]

4.3.2.2 Summary: fluoride technologies to prevent caries in children and adolescents

Table 1 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on 11 reviews of the use of fluoride technologies to prevent dental caries in children and adolescents. The primary research investment in this area is adequate.

There is adequate evidence from the reviews by Marinho *et al.* (2003a) and dos Santos *et al.* that brushing teeth with fluoride toothpaste is effective in preventing dental caries in children and adolescents aged 5–16 years, and in preschool children aged 7 years and under, respectively. Regarding the concentrations of fluoride toothpaste, there is adequate evidence in the review by Walsh *et al.* that fluoride toothpastes with fluoride concentrations of 1,500 ppm and 1,450 ppm prevent dental caries in primary teeth; however, the 1,450 ppm concentration only showed a slight reduction. There is also adequate evidence in the same review by Walsh *et al.* that toothpastes with fluoride concentrations of 1,000–1250 ppm and 1,450–1,500 ppm reduce caries in the permanent teeth of children and adolescents. There is inconclusive evidence regarding the effectiveness of the application of a fluoride concentration of 1,055 ppm versus 550 ppm on primary teeth in the review by Walsh *et al.*, so we cannot tell which is more effective. In addition, Walsh *et al.* found that brushing

teeth with the higher concentrations of fluoride toothpaste – 1,700–2,200 ppm or 2,400–2,800 ppm – is comparable with brushing with 1,450–1,500 ppm for preventing caries in the permanent teeth of children and adolescents, which may suggest that the effect of fluoride toothpaste plateaus at some point between 1500 ppm and 1700 ppm when applied to permanent teeth in children and adolescents. There is adequate evidence in the review by Singh and Purohit to suggest that brushing with a high concentration of fluoride toothpaste (>2,500 ppm) is more effective than the standard concentration (≤1,500 ppm). However, two of the eight trials included in the review by Singh and Purohit comprised adults aged 27 years and over, and this may have skewed the results.

There is adequate evidence in the review by Marinho *et al.* (2003b) that fluoride technologies in the form of toothpastes, mouth rinses, gels, or varnishes are effective interventions to prevent dental caries in the primary and permanent teeth of children and adolescents aged 5–16 years. In the review by Marinho *et al.* (2004a), the evidence is insufficient (and therefore inadequate) to suggest that combining two fluoride technologies is superior to using fluoride toothpaste on its own in preventing dental caries, and in Marinho *et al.* (2004b), the evidence is inconclusive regarding the superiority of one topical fluoride technology over another in preventing dental caries.

There is adequate evidence in the review by Marinho *et al.* (2013) that fluoride varnishes are effective in preventing dental caries in the primary and permanent teeth of children and adolescents. There is adequate evidence that fluoride gels are effective in permanent teeth, but inadequate evidence that they are effective in primary teeth, in the review by Marinho *et al.* (2015). There is adequate evidence that fluoride mouth rinses are effective in permanent teeth in the review by Marinho *et al.* (2016). Finally, based on the work of Tubert-Jeannin *et al.*, the evidence overall is weak; and there is therefore inadequate evidence upon which to judge the effectiveness of using fluoride supplements to prevent dental caries in primary or permanent teeth in children and adolescents.

Table 1 Eleven reviews of fluoride technologies for prevention of dental caries in children and adolescents

Lead author and year	Level of evidence
	Toothpaste
Marinho *et al.* (2003a)[65]	Adequate evidence that brushing teeth with fluoride toothpaste is effective in preventing dental caries in children and adolescents aged 5–16 years
dos Santos *et al.* (2013)[66]	Adequate evidence that brushing teeth with fluoride toothpaste is effective in preventing dental caries in preschool children aged 7 years and under
Walsh *et al.* (2019)[7]	Adequate evidence that fluoride concentrations of 1500 ppm and 1450 ppm in toothpaste prevent dental caries in primary teeth; however, the 1450 ppm concentration only showed a slight reduction in the increment of dental caries Adequate evidence that toothpastes with fluoride concentrations of 1000–1250 ppm and 1450–1500 ppm reduce caries in the permanent teeth of children and adolescents Inconclusive evidence regarding the application of a fluoride concentration of 1055 ppm versus 550 ppm on primary teeth, so we cannot tell which is more effective Evidence is equal (inconclusive) for brushing with the higher concentrations of fluoride toothpaste (1700–2200 ppm or 2400–2800 ppm) when compared with lower concentrations of 1450–1500 ppm for preventing dental caries in the permanent teeth of children and adolescents, which may suggest that the effect of fluoride toothpaste plateaus past the standard concentration of 1450–1500 ppm when applied to permanent teeth in children and adolescents
Singh and Purohit (2018) [67]	Adequate evidence that brushing with a high concentration of fluoride toothpaste (>2500 ppm) is more effective than using the standard concentration (≤1500 ppm) in preventing dental caries; however, two of the eight trials comprised adults aged 27 years and over, and this may have skewed the results
	Varnishes
Marinho *et al.* (2013)[72]	Adequate evidence that fluoride varnishes are effective in preventing dental caries in the primary and permanent teeth of children and adolescents
	Gels
Marinho *et al.* (2015)[73]	Adequate evidence that fluoride gels are effective in preventing caries in permanent teeth Inadequate evidence that fluoride gels are effective in preventing caries in primary teeth
	Mouth rinses
Marinho *et al.* (2016)[74]	Adequate evidence that fluoride mouth rinses are effective in preventing caries in permanent teeth
	Supplements
Tubert-Jeannin *et al.* (2011)[71]	Inadequate evidence upon which to judge the effectiveness of using fluoride supplements to prevent dental caries in primary or permanent teeth in children and adolescents
	Combined technologies
Marinho *et al.* (2003b)[68]	Adequate evidence that fluoride technologies in the form of toothpastes, mouth rinses, gels, or varnishes are effective interventions to prevent dental caries in the primary and permanent teeth of children and adolescents aged 5–16 years
Marinho *et al.* (2004a)[69]	Inadequate evidence to suggest that combining two fluoride technologies is superior to using fluoride toothpaste on its own
Marinho *et al.* (2004b)[70]	Inconclusive evidence regarding the superiority of one topical fluoride technology over another

4.3.2.3 Non-fluoride technologies to prevent caries in children and adolescents

Three reviews (Ahovuo-Saloranta *et al.*, 2017;[75] Ahovuo-Saloranta *et al.*, 2016;[76] and Hou *et al.*, 2017[77]) evaluated sealants and adhesives, and one review (Yengopal and Mickenautsch, 2010)[78] evaluated glass-ionomer cement and other sealants. Botton *et al.* (2016)[84] compared self-etch adhesive systems with prior-acid etching systems. Four reviews (Marghalani *et al.*, 2017;[79] Riley *et al.*, 2015;[80] Walsh *et al.*, 2015;[82] and James *et al.*, 2010[83]) evaluated xylitol and chlorhexidine-based preparations. Wang *et al.* (2017)[81] evaluated a range of different non-fluoride antibacterial and mineralising agents.

4.3.2.3.1 Sealants and adhesives

We begin by presenting the evidence regarding the effectiveness of sealants in preventing dental caries in children and adolescents.

Ahovuo-Saloranta *et al.* (2017)[75] updated earlier Cochrane reviews published in 2004, 2008, and 2013 to compare the effects of different types of fissure sealants in preventing caries in occlusal surfaces of permanent teeth in children and adolescents. Ahovuo-Saloranta *et al.* describe how sealants are applied: "dental sealant (resin-based and glass-ionomer) is applied to a tooth surface to provide a physical barrier that prevents growth of biofilm by blocking nutrition. Although sealants were introduced for preventing caries on occlusal surfaces, they are now considered active agents in controlling and managing initial caries lesions on occlusal surfaces and, recently, on approximal surfaces as well." p6[75]

Thirty-eight randomised controlled trials that involved a total of 7,924 children aged 5–16 years were included in this review; seven of the trials were new additions to this updated review and included a total of 1,693 participants. Based on the Cochrane Collaboration's risk of bias instrument, all the studies included were judged as having a high risk of bias because the dental professionals who were measuring the outcomes could see whether sealant had been used and could discriminate between materials after follow-up.

The main finding of this review suggests that there is adequate evidence that resin-based sealants are an effective intervention to prevent dental caries on the occlusal surfaces of permanent teeth in children and adolescents. Resin-based sealants applied on occlusal surfaces of permanent molars reduce dental caries by between 11% and 51% more than in children without sealant, when measured two years after application (moderate-quality evidence based on GRADE). According to Ahovuo-Saloranta *et al.*, "resin-based sealants applied on occlusal surfaces of permanent molars are effective for preventing caries in children and adolescents". p2[75] Evidence was inconclusive when a glass-ionomer-based sealant was compared with no sealant, and inconclusive when one type of sealant material was compared with another.

To update a Cochrane review published in 2010, **Ahovuo-Saloranta *et al.*** (2016)[76] compared fissure sealants with fluoride varnishes, and compared fissure sealants used in combination with fluoride varnishes with fluoride varnishes alone, to prevent dental caries in the occlusal surfaces of permanent teeth in children and adolescents. Ahovuo-Saloranta *et al.* describe the typical type of fissure sealants that are available for use as follows: "along with resin-based sealants, other sealant materials [include] glass-ionomer cements (combination of silicate and polyacrylate cement system). Glass-ionomer cements contain fluoride and are thought to prevent caries through fluoride release over a prolonged period… Novel materials called compomers, which were introduced in the 1990s to

combine benefits of resins and those of glass-ionomer cements have also been applied as sealants." p6[76]

Ahovuo-Saloranta *et al.* also describe the function of fluoride varnish: "the aim of topical fluoride varnish application is to treat hard tooth surfaces in such a way that caries is arrested or reversed. Fluoride acts to prevent caries in three ways: (1) by inhibiting the demineralisation and (2) promoting the remineralisation of dental enamel and (3) by inhibiting acid formation by plaque bacteria." p6[76]

Eight randomised controlled trials with 1,746 children aged 5–10 years were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, one trial was assessed as having a low risk of bias, and the remaining seven were either assessed as having a high risk or an unclear risk of bias.

The main overall finding from this review suggests that the evidence is inconclusive regarding the superiority of either sealants or fluoride varnishes in preventing dental caries in the occlusal surfaces of permanent teeth in children and adolescents aged 5–10 years. When resin-based fissure sealants were compared with fluoride varnishes, resin-based sealants prevented more caries than fluoride varnishes did in first permanent molars at two-year follow-up. However, the evidence is low quality using GRADE.

Three trials evaluated fluoride varnishes compared with glass-ionomer-based sealants: one trial with chemically cured glass-ionomer sealants, and two with resin-modified glass-ionomer sealants. There was a similar caries incidence observed between study groups regardless of which glass-ionomer material was used. Study designs were clinically diverse, and meta-analysis could not be conducted. The evidence is very low quality or inadequate.

When the use of resin-based sealants in combination with fluoride varnish was compared with the use of fluoride varnish alone in one trial analysing 92 children, there was a significant difference at two-year follow-up in favour of using resin-based fissure sealants in combination with fluoride varnish compared with using fluoride varnish only. However, the evidence was assessed as low quality and inconclusive.

According to Ahovuo-Saloranta *et al.*, "Although we found evidence suggesting the superiority of resin-based fissure sealants over fluoride varnishes applied to prevent occlusal caries in permanent molars, and some evidence for benefit of resin-based sealant together with fluoride varnish over fluoride varnish alone, this evidence is of low quality. We conclude that current scarce data mean that it is not possible to reach conclusions about whether to apply sealants or fluoride varnishes on occlusal surfaces of permanent molars." p25-26[76]

Hou *et al.* (2017)[77] compared pit and fissure sealants with no intervention for the prevention of dental caries in permanent first molars in children in China. According to Hou *et al.*, "pit and fissure sealants is where an adhesive resin material is placed at the pits and fissures of molar teeth without removing the tooth structure. Pit and fissure sealants can block these surfaces, stopping food and bacteria from accumulating, thereby protecting enamel from bacteria and metabolite erosion." p1[77]

Twenty randomised controlled trials were included in this review, with participants aged 6–20 years. The authors state that they used the Cochrane Collaboration's risk of bias instrument to assess bias in the trials, but they do not provide an overall assessment of their conclusions on the trials' risk of bias. They do state that limitations in the included trials include poor description of randomisation,

allocation concealment, and blinding, suggesting some degree of selection bias and measurement bias. The authors did not assess the quality of the evidence for their findings using GRADE.

The main finding of this review suggests that there is adequate evidence that resin-based sealants are an effective intervention to prevent dental caries in the permanent teeth of children and adolescents. The results demonstrate a significant association between pit and fissure sealants and the prevention of dental caries at six-month follow-up when sealants are compared with no intervention. According to Hou *et al.*, "pit and fissure [resin] sealants are an effective caries-preventive intervention… [however,] considering the quality of included studies, further research with larger sample sizes and rigorously designed clinical trials are required to confirm the conclusions." p6[77]

Yengopal and Mickenautsch (2010)[78] compared resin-modified glass-ionomer cement fissure sealants with resin-based fissure sealants in terms of the absence of caries in permanent teeth. According to Yengopal and Mickenautsch, "resin-based fissure sealant materials rely on the sealing of pits and fissures through micro-retention, created through tags after acid etching of enamel… resin-modified glass-ionomer cements contain approximately 10% of resin, usually hydroxyethyl-methacrylate." p18[78]

Six randomised controlled trials were included in this review; five trials involved participants with an age range of 5–27 years, and although the age of participants in the sixth trial is unclear, the trial involved paediatric patients. It is reported in the review that first molar, second molar, and premolar teeth were examined in the included trials. The Cochrane Collaboration's risk of bias instrument was used to assess the quality of the included trials. According to Yengopal and Mickenautsch, "the results of the quality assessment warrants that the data be treated with caution, owing to an increased risk of bias [in the included trials]." p22[78]

The main finding from this review suggests that the evidence is inconclusive regarding whether resin-modified glass-ionomer cements or resin-based fissure sealants are more effective in preventing dental caries in permanent teeth. The meta-analysis of homogeneous datasets at three-time intervals showed no statistical difference between resin-modified glass-ionomer cements and resin-based fissure sealants. The results of seven additional heterogeneous datasets were in line with the finding from the meta-analysis.

According to Yengopal and Mickenautsch, "this systematic review with meta-analysis found no evidence that either material was superior to the other in preventing dental caries. Therefore, both materials appear to be equally suitable for clinical application as fissure sealant for a period of up to 2 years." p24[78]

Botton *et al.* (2016)[84] compared self-etch adhesive systems with prior-acid etching systems in the retention of occlusal pit and fissure sealants in primary and permanent teeth. According to Botton *et al.*, "self-etch adhesive systems eliminate the prior acid etching and rinsing steps, reducing not only the technique sensitivity, but also the time of application and, consequently, decreasing the chair time." p403[84] The types of sealants included in the studies are unclear in the reporting in the review, although the authors do provide a description of the comparator prior-acid etching systems.

Five randomised controlled trials were included in this review, and participants in the trials were aged 4–21 years. Regarding the nature of the dentition under study, permanent teeth were the focus in four trials and primary teeth were the focus in one trial. The authors did not assess risk of bias using the Cochrane Collaboration's risk of bias instrument; they used a quality appraisal scoring system for

each included study, which included some elements of a risk of bias nature. The quality appraisal scoring system scored studies along the following parameters: strong evidence: 10–11, good evidence: 6–9, and reasonable evidence: 0–5. Four of the trials included in the review scored between 6 and 9 (good evidence) and one study scored 11 (strong evidence).

The main finding from this review suggests that there is inconclusive evidence upon which to judge whether prior-acid etching is a better technique than the self-etch system in sealing occlusal surfaces in primary and permanent teeth. According to Botton *et al.*, "sealants applied in the conventional manner, with prior acid etching, present superior retention throughout time compared to the occlusal sealants combined with the self-etch system." p410[84]

However, despite the evidence suggesting that prior-acid etching is superior to self-etch adhesive systems in the retention of sealants applied to the occlusal surfaces in primary and permanent teeth, the authors also issue a note of caution regarding the interpretation of this finding. According to Botton *et al.*, "considering that few studies were retrieved in this review, the results obtained should be carefully considered, because some trials used a small sample or showed a high dropout." p409[84]

4.3.2.3.2 Non-fluoride antibacterial and mineralising agents to prevent caries

Marghalani *et al.* (2017)[79] compared the effectiveness of xylitol with no treatment, a placebo, or other preventive strategies in reducing dental caries in children and adolescents aged 0–18 years. According to Marghalani *et al.*, "xylitol is a five-carbon sugar alcohol derived primarily from birch trees." p103[79]

Five randomised and five non-randomised controlled trials were included in this review and, based on the Cochrane Collaboration's risk of bias instrument, all 10 trials were judged to have a high risk of bias. The primary outcome assessed was decayed, missing, and filled primary and permanent surfaces/teeth.

The main finding from this review suggests that there is weak and inadequate evidence upon which to judge the effectiveness of xylitol as an intervention to prevent dental caries in children and adolescents. The analysis showed a small effect size from the five randomised controlled trials, with a very low quality of evidence rating based on GRADE and high heterogeneity that renders the preventive action of xylitol uncertain based on the current evidence. According to Marghalani *et al.*, this uncertainty is grounded in the observation "that the GRADE quality of evidence for all categories was determined to be very low due to the high risk of bias and inconsistency (heterogeneity) seen in the studies." p106[79]

Riley *et al.* (2015)[80] compared the effectiveness of different xylitol-containing products with that of a placebo (a substitute without xylitol) or no treatment for the prevention of dental caries in children and adults. According to Riley *et al.*, "xylitol is a 5-carbon sugar alcohol of crystalline structure, found in many fruits and plants. It achieves equal sweetness to sucrose without resulting in a physiological requirement for insulin production as it is not absorbed in the small intestine… xylitol has been produced in a variety of preparations including chewing gum, syrup, lozenges, sprays, mouthwashes, gels, toothpaste, candies, and varnishes." p6[80]

Ten randomised controlled trials involving 7,969 participants (5,903 of whom were included in the analyses) were included in this Cochrane review. One trial involved adults, and the others involved children aged 1 month to 13 years. Based on the Cochrane Collaboration's risk of bias instrument, one

trial was assessed as being at low risk of bias, two were assessed as being at unclear risk of bias, and the remaining seven were assessed as being at high risk of bias.

The main finding of this review is that the evidence is weak and inadequate for the effectiveness of xylitol-containing products as an intervention to prevent dental caries in the permanent teeth of children. The analysis revealed that, over 2.5–3 years of use, a fluoride toothpaste containing 10% xylitol may reduce caries in children by 13% when compared with a fluoride-only toothpaste (low-quality evidence using GRADE). The remaining evidence on children, from small single studies with high risk of bias, was insufficient to determine a benefit from other products containing xylitol.

According to Riley *et al.*, "There is low quality evidence to suggest that fluoride toothpaste containing xylitol may be more effective than fluoride-only toothpaste for preventing caries in the permanent teeth of children…the effect estimate should be interpreted with caution due to high risk of bias…the remaining evidence is low to very low quality and is insufficient to determine whether any other xylitol-containing products can prevent caries in infants, older children, or adults." p19-20[80]

Walsh *et al.* (2015)[82] compared a range of chlorhexidine-containing oral products – including gels, toothpastes, varnishes, mouth rinses, chewing gums, and sprays – with each other, with a placebo, or with no intervention in terms of their effectiveness in preventing caries in children and adolescents. According to Walsh *et al.*, "chlorhexidine gluconate is a cationic bis-biguanide with a broad spectrum of antibacterial activity…chlorhexidine-based preparations in a variety of formulations and a range of strengths [include] toothpastes (0.4%); mouthrinses in either alcohol-based (ethanol) or non-alcoholic formulations (0.12% and 0.2%); gels (1%); thymol-containing varnishes (1%, 10%, 20% and 35%); chewing gums; and sprays (0.2%)." p6[82]

Eight randomised controlled trials with a total of 2,876 participants aged 0–15 years, of whom 2,276 (79%) were included, were evaluated in this Cochrane review's analysis. The focus of the trials was on both primary and permanent teeth. Based on the Cochrane Collaboration's risk of bias instrument, six of the trials were judged to be at high risk of bias and two trials at unclear risk of bias.

Six of the studies compared dental professionals applying different strengths of chlorhexidine varnishes on the baby teeth, permanent teeth, or both types of teeth in children and adolescens with a control group receiving a placebo. The other two studies examined the effects of parents applying chlorhexidine gel to their children's baby teeth.

The main finding in this review is that there is insufficient and inadequate evidence upon which to judge the effectiveness of chlorhexidine-containing oral products (varnish or gel). Overall, the results did not provide enough evidence that chlorhexidine varnish or gel reduces tooth decay or reduces the bacteria that encourage tooth decay (very low-quality evidence using GRADE). According to Walsh *et al.*, "there is little evidence from the eight studies included in this review to either support or refute the assertion that chlorhexidine is more effective than placebo or no treatment in the prevention of caries in children and adolescents." p22[82]

James *et al.* (2010)[83] compared the effectiveness of chlorhexidine varnish with that of fluoride varnish, a placebo, or no treatment in preventing caries incidence in children and adolescents. According to James *et al.*, "chlorhexidine varnish is an antimicrobial agent that is particularly effective in reducing the levels of mutans streptococci in saliva and dental plaque. Its effectiveness is attributed to...its ability to maintain therapeutic activity for a prolonged period, which is facilitated by its adsorption onto tooth surfaces, pellicle, plaque and mucous membranes." p334[83]

Twelve randomised controlled trials with participants aged 4–18 years were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, four trials were judged to have a high risk of bias, four trials to have a low risk of bias, and the remaining four trials to have an unclear risk of bias. The authors do not report an overall quality of the evidence using GRADE. The tooth type/surface treated varied across the trials: in five trials, all teeth/surfaces were treated, and in the remaining seven trials, first permanent molars and second permanent molars, occlusal surfaces, and approximal surfaces were treated.

The main finding from this review suggests the evidence is inconclusive regarding whether chlorhexidine varnish or comparator is superior, as the results of the trials are conflicting. Six trials reported no statistically significant difference in caries incidence in permanent teeth with the application of chlorhexidine varnish compared with a placebo or no treatment. The results of four trials were conflicting: two trials found no significant difference in caries incidene between chlorhexidine varnish and controls, and two trials reported statistically significant results in favour of chlorhexidine varnish. One trial demonstrated a statistically significant reduction in caries incidence in primary teeth, while another trial comparing chlorhexidine varnish with fluoride varnish for preventing caries in adolescents was equivocal.

According to James *et al.*, "The results of the trials included in this review are conflicting, but in general, the evidence does not support the use of chlorhexidine varnish for preventing caries in children and adolescents." p338[83]

Wang *et al.* (2017)[81] compared the effectiveness of non-fluoride agents with that of controls for the prevention of dental caries in the primary dentition of children. According to Wang *et al.*, "five non-fluoride agents were used in the included studies: arginine, chlorhexidine, casein phosphopeptide amorphous calcium phosphate, triclosan and xylitol." p6[81]

Fourteen randomised controlled trials were included in this review, with a total of 4,269 participants aged 0–11 years. Based on the Cochrane Collaboration's risk of bias instrument, only one study had a low risk of bias, three studies had an unclear risk of bias, and the remaining 10 were judged to have a high risk of bias.

The main finding from this review is that the evidence is insufficient and inadequate to promote the use of these non-fluoride agents for preventing caries in the primary teeth of young children. The analysis shows that a study at low risk of bias indicated that daily use of xylitol wipes may be a useful adjunct for caries control in young children; however, this study included a small sample, so the authors suggest interpreting this finding with caution. Chlorhexidine and casein phosphopeptide-amorphous calcium phosphate may be more effective than placebos in managing caries in primary dentition, but their effectiveness remains unclear when compared with the use of fluoride. Arginine-containing mint confection and 0.3% triclosan varnish were found to reduce caries development in primary teeth, but the evidence was judged to be at a high risk of bias. In conclusion, Wang *et al.* point out that "the current research evidence is not sufficient to confirm that the use of these non-fluoride agents is more effective than placebo or fluoride for preventing dental caries in primary dentition." p6[81]

4.3.2.4 Summary: non-fluoride technologies to prevent caries in children and adolescents

Table 2 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on 10 reviews of non-fluoride technologies in preventing dental caries in children and adolescents. The primary research investment in this area is less than adequate.

There is adequate evidence in one Cochrane review by Ahovuo-Saloranta *et al.* (2017) that resin-based sealants are an effective intervention to prevent dental caries in permanent teeth in children and adolescents when compared with children who did not receive sealants. The results were inconclusive when glass-ionomer-based sealants were compared with no sealant, and inconclusive when one type of sealant material was compared with another. The review by Hou *et al.* also reports adequate evidence that resin-based sealants are an effective intervention to prevent dental caries in the permanent teeth of children and adolescents. However, the data analysed in the review by Hou *et al.* derives exclusively from trials undertaken with children in China and the likelihood of the trials being affected by bias is high, which means that they may have overestimated the effects observed, but this point is not adequately addressed by the authors.

An updated Cochrane review by Ahovuo-Saloranta *et al.* (2016) concludes that the evidence remains inconclusive regarding whether sealants or fluoride varnish is better in preventing dental caries in the permanent teeth of young children. In addition, a non-Cochrane review by Yengopal and Mickenautsch reports the evidence to be inconclusive regarding whether either resin-modified glass-ionomer cements or resin-based fissure sealants are superior in preventing dental caries in permanent teeth of children and adolescents; the authors suggest that both materials appear to be equally suitable for clinical application as a fissure sealant for a period of up to two years.

In the review by Botton *et al.*, there is inconclusive evidence upon which to judge whether prior-acid etching is a better technique than using the self-etch system to seal occlusal surfaces in primary and permanent teeth, as only five trials were included in this review and some used a small sample size or showed a high dropout, which may impair the confidence in the evidence.

In two reviews, by Marghalani *et al.* and Riley *et al.*, there is inadequate evidence upon which to judge the effectiveness of xylitol as an intervention to prevent dental caries in children and adolescents. In the review by Wang *et al.*, there is inadequate evidence to promote the use of non-fluoride agents (arginine, chlorhexidine, casein phosphopeptide-amorphous calcium phosphate, triclosan, and xylitol) for preventing caries in the primary teeth of young children.

In terms of the effectiveness of chlorhexidine-containing oral products (varnish or gel) compared with that of controls in preventing caries in children and adolescents, one review by Walsh *et al.* contains inadequate evidence, while an earlier review by James *et al.* contains conflicting and inconclusive evidence, upon which to judge this outcome.

Table 2 Ten reviews of non-fluoride technologies for prevention of dental caries in children and adolescents

Lead author and year	Level of evidence
	Sealants
Ahovuo-Saloranta *et al.* (2017)[75]	Adequate evidence that resin-based sealants are an effective intervention to prevent dental caries in permanent teeth in children and adolescents when compared with children without sealants Inconclusive evidence regarding whether glass-ionomer-based sealants are better than no sealant Inconclusive evidence regarding which glass-ionomer-based sealant is better
Ahovuo-Saloranta *et al.* (2016)[76]	Inconclusive evidence regarding whether sealants or fluoride varnish is better in preventing dental caries in the permanent teeth of young children Inadequate evidence upon which to compare glass-ionomer-based sealants with fluoride varnishes Inconclusive evidence regarding whether using a resin-based sealant in combination with fluoride varnish or using fluoride varnish alone is superior
Hou *et al.* (2017)[77]	Adequate evidence that resin-based sealants are an effective intervention to prevent dental caries in the permanent teeth of children, adolescents, and teenagers
Yengopal and Mickenautsch (2010)[78]	Inconclusive evidence regarding whether resin-modified glass-ionomer cements or resin-based fissure sealants are superior in preventing dental caries in the permanent teeth of children and adolescents
	Prior-acid etching
Botton *et al.* (2016)[84]	Inconclusive evidence upon which to judge whether prior-acid etching is a better technique than using the self-etch system to seal occlusal surfaces in primary and permanent teeth
	Non-fluoride agents
Marghalani *et al.* (2017)[79]	Inadequate evidence upon which to judge the effectiveness of xylitol as an intervention to prevent dental caries in children and adolescents
Riley *et al.* (2015)[80]	Inadequate evidence upon which to judge the effectiveness of xylitol as an intervention to prevent dental caries in children and adolescents
Walsh *et al.* (2015)[82]	Inadequate evidence upon which to judge the effectiveness of chlorhexidine-containing oral products (varnish or gel)
James *et al.* (2010)[83]	Inconclusive evidence upon which to judge whether chlorhexidine-containing oral products (varnish or gel) are more effective or less effective than controls
Wang *et al.* (2017)[81]	Inadequate evidence to promote the use of non-fluoride agents (arginine, chlorhexidine, casein phosphopeptide-amorphous calcium phosphate, triclosan, and xylitol) for preventing caries in the primary teeth of young children

4.3.3 Interventions to treat caries in children and adolescents

4.3.3.1 Interventions for the early treatment of non-cavitated and early stage cavitated caries in children and adolescents

In this second section covering interventions used in early caries treatment, we have included 11 reviews that evaluated interventions to manage and treat early caries lesions in the primary and permanent teeth of children and adolescents; these interventions address the treatment of demineralisation, white spot lesions, non-cavitated carious lesions and the arrestment of early-stage cavitated lesions. A working definition is provided by Young *et al.*, drawing on the American Dental Association Caries Classification System: "Non-cavitated caries lesions refers to initial caries lesion development, before cavitation occurs. Non-cavitated lesions are characterized by a change in colour, glossiness or surface structure because of demineralization before there is macroscopic breakdown in surface tooth structure. These lesions represent areas with net mineral loss due to an imbalance between demineralization and remineralization. Re-establishing a balance between demineralization and remineralization may stop the caries disease process while leaving a visible clinical sign of past disease." p80[85]

We have grouped the interventions used in early treatment into two categories:

- Category 1 includes what we have called remineralising agents or non-invasive treatments to avoid any dental hard tissue removal (such as fluoride application, antibacterial treatments [chlorhexidine and xylitol], and/or oral hygiene advice,[28] as well as casein phosphopeptide-amorphous calcium phosphate alone or in combination with calcium fluoride phosphate),[27] which primarily aim to promote tooth remineralisation in the area of carious lesions. Category 1 includes seven reviews which compare remineralising agents both with controls and with each other (Urquhart *et al.*, 2019;[29] Oliveira *et al.*, 2019;[86] Meyer *et al.*, 2018;[87] Ancira-González *et al.*, 2018;[88] Gao *et al.*, 2016;[89] Duangthip *et al.*, 2015;[90] and Benson *et al.*, 2013[91]).
- Category 2 includes what we have called microinvasive strategies, which seal and/or infiltrate early carious lesions. Sealants remove only a few micrometers of hard tissues through etching.[28] Resin sealant restoration removes carious dentine but avoids sacrificing sound tissues.[28] In Category 2, we have included four reviews that compare different microinvasive strategies with controls (Krois *et al.*, 2018;[92] Wright *et al.*, 2016;[93 94] Dorri *et al.*, 2015;[95] and Doméjean *et al.*, 2015[96]). Wright et al. published two papers covering the same study question.

4.3.3.1.1 Remineralisation agents for the treatment of early caries lesions in children and adolescents

Urquhart *et al.* (2019)[29] compared non-restorative treatments with other active intervention(s), or with no treatment or a placebo, for the arrest or reversal of non-cavitated and cavitated carious lesions on primary and permanent teeth in children and adults. According to Urquhart *et al.,* non-restorative treatments include "sodium fluoride (NaF), stannous fluoride toothpaste or gel, acidulated phosphate fluoride (APF), difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, amorphous calcium phosphate (ACP), casein phosphopeptide-amorphous calcium phosphate, nano hydroxyapatite, tricalcium phosphate, prebiotics and/or 1.5% arginine, probiotics, silver diamine fluoride (SDF), silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, and carbamide peroxide". p15[29]

Forty-four randomised controlled trials based on 48 reports, which involved 7,378 participants and assessed the effect of 22 interventions, were included in this review. The precise age range of the participants is not reported in the review. Twelve trials involved participants with primary dentition,

22 with permanent dentition, and 10 with mixed dentition. The risk of bias in the included trials was assessed using the Cochrane Collaboration's risk of bias instrument. The authors note that "information to judge most risk of bias domains was often incomplete or missing. The domain of allocation concealment was judged to be the most serious methodological issue, and overall most studies had serious issues of risk of bias". p17[29]

The results of this systematic review support a range of interventions that are effective in arresting and/or reversing non-cavitated and cavitated carious lesions. Results from the network meta-analysis suggest that there is adequate evidence that the combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth (moderate certainty based on GRADE). There is inadequate evidence that the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective treatment for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth (low certainty based on GRADE). The evidence is inadequate to suggest that 5,000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective treatment for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth (low certainty based on GRADE).

Results from the study-level data show that when compared with no intervention, there is adequate evidence that 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth (low to moderate certainty based on GRADE). There is adequate evidence that the use of 1.23% acidulated phosphate fluoride gel on facial/lingual lesions, compared with oral health education, was effective only at longer follow-up times (12 months) (moderate certainty based on GRADE). For arresting advanced cavitated carious lesions, there is adequate evidence to suggest that 38% silver diamine fluoride applied every six months was more effective on any coronal surface of primary teeth when compared with both 12% silver diamine fluoride solution applied biannually and 38% silver diamine fluoride solution applied every 12 months (moderate to high certainty based on GRADE). According to Urquhart *et al.,* "the certainty in the evidence ranged from very low to high for the outcome of arrest or reversal across all surfaces, types of lesions, and dentition. We predominantly downgraded the certainty due to serious issues of risk of bias and imprecision". p23[29]

Oliveira *et al.* (2019)[86] compared silver diamine fluoride against no treatment, a placebo, or alternative active treatments in preventing new caries lesions in primary teeth in children and adolescents. According to Oliveira *et al.,* "silver diamine fluoride derives from the conjunction of silver nitrate and fluoride. It reduces the growth of cariogenic bacteria, hampers degradation of collagen in dentine, inhibits demineralisation, and promotes remineralisation of both enamel and dentine". p25[86]

Oliveira *et al.*[86] included data from six reports of four randomised controlled trials that involved 1,118 children and analysed data on 915 of the participants. The children were aged 3–6 years in three of the trials and were aged 6 years or older in one trial. Two trials compared silver diamine fluoride with no treatment, one trial compared silver diamine fluoride with both a water placebo and with 5% sodium fluoride varnish, and one trial compared silver diamine fluoride with high-viscosity glass-ionomer cement. All four trials were judged to have at least one domain with an unclear or high risk of bias.

There is adequate evidence to suggest that silver diamine fluoride is more effective than controls in arresting caries lesions in primary teeth and in providing anti-caries benefits for the entire dentition.

When silver diamine fluoride was compared with a placebo or with no treatment when followed up after 24 months, silver diamine fluoride significantly reduced the development of dentine caries lesions in both treated and untreated primary teeth. In addition, the use of silver diamine fluoride also showed a wider preventive effect. According to Oliveira *et al.,* "when SDF [silver diamine fluoride] is used to arrest caries lesions in primary teeth it also provides an anti-caries benefit for the entire dentition; that is, 38% of silver diamine fluoride applications decrease by 77% the development of new caries in treated children compared to non-treated children… [However] this estimate of effect, although large, is based on two trials whose potential limitations may lower confidence in their findings". p29[86]

When comparing silver diamine fluoride with other active treatments in this review, the evidence comes from only two trials and is inconclusive overall. Silver diamine fluoride performed significantly better than fluoride varnish at 18 and 30 months follow-up in one trial, while in a different trial glass-ionomer cement outperformed silver diamine fluoride, but the difference was not statistically significant.

Meyer *et al.* (2018)[87] compared remineralising agents – such as calcium phosphates, used to manage early caries lesions in children and adolescents – with controls. The controls possibly received fluoride, but the precise description of the comparator is not clearly reported in the review. According to Meyer *et al.,* "calcium phosphates represent a group of common agents used in oral care that can be considered biomimetic due to the fact that the mineral phase of human teeth consists of the same basic compound found in calcium phosphates". p414[87]

Thirty-five studies derived from books, reviews, and original research papers, including both in vivo and in situ studies, were included in this review. The designs of the included studies or their data handling methods are not reported. It is not clear whether the quality of the studies included in the review was assessed, as quality appraisal is not reported. The age of the participants and the type of teeth under examination are not stated. According to Meyer *et al.,* "calcium phosphates represent a promising innovative approach for daily oral care that will broaden the range of future treatments in preventive dentistry". p417[87] Based on the reported findings of this review, we have judged the evidence for calcium phosphates as a remineralising agent to be inadequate, as the review does not document the methods used and does not report the precise nature of the evidence upon which it is claimed that calcium phosphates are a promising approach for oral care.

Calcium phosphate as part of a group of remineralising agents came into the spotlight again in another review we identified. **Ancira-González *et al.*** (2018)[88] compared the effectiveness of fluoride varnishes, gels, casein phosphopeptide-amorphous calcium phosphate, and other remineralisation agents with each other in the management of white spot lesions in children's primary teeth. As the focus of this review was comparing the effectiveness of different remineralising agents, it is important to describe what precisely the process of remineralising enamel in the human tooth involves. According to Ancira-González *et al.,* "remineralisation is the process whereby calcium and phosphate ions are supplied from a source external to the tooth to promote ion deposition into crystal voids in demineralised enamel to produce net mineral gain". p392[88] This review also stated that "topical fluoride-containing varnishes consist of highly concentrated fluoride (around 22,000 ppm) with a resin or synthetic base and casein phosphopeptide-amorphous calcium phosphate can be delivered as a paste." p392[88]

Nine randomised controlled trials were included in this review, with the age of the participating children in the trials ranging from 1–8 years.[88] The authors used the Centre for Evidence-Based Medicine guidelines, along with additional bespoke evaluation criteria, to assess the risk of bias in the included trials. The authors reported an overall rating of low to moderate risk of bias for the included trials.

The findings of this review suggest that fluoride varnishes are better remineralising agents when compared with placebo, with no intervention, or with chlorhexidine and when applied on primary tooth enamel. However, fluoride varnish was not found to be superior to pit and fissure sealants or laser treatment. In addition, the combination of fluoride varnish with chlorhexidine or laser treatment performed better at remineralisation than fluoride varnish alone. Based on this analysis of limited evidence, which shows a slight preference for the performance of fluoride varnish used alone and in combination with other agents, we conclude that there is adequate evidence to support the use of fluoride varnish as a remineralising agent. According to Ancira-González *et al*., "there is limited evidence indicating an outstanding remineralising capacity among the most wide-spread topical therapies used currently on primary tooth enamel with white spot lesion. However, a difference among these therapies is evident, mainly in favour of fluoride varnish". p393[88]

Gao *et al.* (2016)[89] compared professionally applied fluoride therapy with other active treatments, with placebo, or no intervention in remineralising and arresting dental caries in primary and permanent teeth in children. According to Gao *et al*., "professionally applied fluoride therapy is a relatively low-cost and easily operated treatment and has been used to arrest active dental caries… Fluoride inhibits plaque metabolism, alters plaque composition, affects plaque formation, and reduces plaque bacteria's ability to produce a large amount of acid from carbohydrates". p2[89]

Seventeen randomised controlled trials were included in this review; 10 trials investigated the remineralising effect on early enamel caries using silicon tetrafluoride, fluoride gel, silver diamine fluoride, or sodium fluoride, and seven trials investigated an arresting effect on dentine caries using silver diamine fluoride. The age range of the children involved in the trials is not reported in the review. The risk of bias of each study was assessed using the Cochrane Collaboration's risk of bias instrument. The authors do not make an overall judgement on the risk of bias in the included studies. However, they do state that "blinding of outcome measurement and allocation concealment were either not achieved or not mentioned by the researchers. The sample size of some studies was small, while some studies didn't report the statistical procedure of sample size calculation or justified the sample size used in their studies". p6[89]

Meta-analyses performed on four papers show that using 5% sodium fluoride varnish is superior to controls in remineralising early enamel caries; the overall percentage of remineralised enamel caries was 63.6%. According to the authors, "Apart from NaF [sodium fluoride] varnish, there is limited evidence to support the benefits of using other professional-applied fluoride agents such as 0.9% silicon tetrafluoride, 0.42% sodium fluoride gel and 10% SDF [silver diamine fluoride] in remineralising early enamel caries". p7[89]

Meta-analyses performed on five papers show that using 38% silver diamine fluoride is superior to controls in arresting dentine caries in both the primary and permanent teeth of children; the overall proportion of arrested dentine caries was 65.9%. Based on the findings of this review, there is adequate evidence to suggest that 5% sodium fluoride varnish is an effective remineralising agent for early caries and that 38% silver diamine fluoride is effective in arresting the progression of active

caries. According to Gao *et al.*, "professionally applied 5% sodium fluoride varnish shows the capability to remineralise early enamel caries in children. Silver diamine fluoride solution at 38% is effective in arresting active dentine caries." p8[89]

Duangthip *et al.* (2015)[90] compared non-surgical methods with controls in arresting or slowing down the progression of active dentine caries in primary teeth in preschool children aged six years and under. According to Duangthip *et al.,* "various non-surgical intervention methods such as fluoride agents (toothpaste, mouthrinse, gel, varnish, solution), silver diamine fluoride (SDF), dental sealant, resin infiltrant, chlorhexidine, xylitol, CPP-APC [casein phosphopeptide-amorphous calcium phosphate], ozone, and oral health education were included in this review". p2[90]

Three randomised controlled trials and one longitudinal study were included in this review. All children involved in the studies were aged six years and under. Assessment of the risk of bias in the included studies was undertaken using the Cochrane Collaboration's risk of bias instrument. Two studies were judged to have a low risk of bias, one study had a moderate risk, and one study had a high risk.

The findings in this review suggest that there is adequate evidence that silver diamine fluoride is an effective intervention for arresting dental caries in preschool children. Three studies reported significantly higher success rates of silver diamine fluoride treatment (65–91%) compared with no treatment (34%), sodium fluoride varnish (38–44%), and interim glass-ionomer restorations (39–82%) in arresting dental caries in preschool children. There is adequate evidence to suggest that brushing with high-fluoride-concentration toothpaste is effective in slowing the progression of caries in preschool children. One study reported a superior effect of daily brushing with a 1100 ppm fluoride toothpaste, when compared with brushing with a 500 ppm fluoride toothpaste, on slowing the progression of dental caries in preschool children. According to Duangthip *et al.,* "there is limited evidence (4 studies) to support the effectiveness of silver diamine fluoride applications once/twice a year and daily tooth-brushing with fluoride toothpaste in arresting or slowing down the progression of active dentine caries in primary teeth in preschool children". p8[90]

Benson *et al.* (2013)[91] compared the effects of various forms of fluoride used during orthodontic treatment on the development of demineralised white lesions (both with each other and with a placebo). According to Benson *et al.,* "the different ways of applying fluoride that were assessed included: topical fluorides, for example, fluoride-containing varnish, mouthrinse, gel or toothpaste; fluoride-releasing devices attached to the braces; in the control group, individuals did not receive additional fluoride as described, or they received a placebo or a different form of fluoride". p3[91]

Three randomised controlled trials with 458 participants were included in this updated Cochrane review. One study was assessed to have a low risk of bias for all domains, in one study the risk of bias was unclear, and the remaining study had a high risk of bias. Participants had a mean age of 15.7 years in one trial and 14.3 years ±1.6 years in another trial, and no age was reported in the third trial. No particular type of teeth were specified by the authors.

One trial comparing fluoride varnish applied every six weeks at the time of orthodontic review with a placebo (with 253 participants and a low risk of bias) provided moderate-quality evidence of an almost 70% reduction in demineralised white lesions. Although this finding is based on only one trial, given that the trial was judged to be at low risk of bias, we have judged this to be adequate evidence to suggest that fluoride varnish can be an effective intervention to reduce the development of white

spot lesions in children undergoing orthodontic treatment. According to Benson *et al.,* "The quality of the evidence found is moderate in the case of one well-designed study and weak in the remaining studies". p3[91]

4.3.3.1.2 Summary: remineralisation agents for the treatment of early caries lesions in children and adolescents

Table 3 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on seven reviews of remineralisation agents for early treatment of dental caries in children and adolescents. The primary research investment in early treatment is adequate.

There is adequate evidence in four reviews that silver diamine fluoride is more effective than controls: in the review by Duangthip *et al.*, silver diamine fluoride was effective in arresting dental caries in preschool children; in the review by Gao *et al.*, silver diamine fluoride was effective in arresting the progression of active caries in both primary and permanent teeth in children and adolescents; and in the review by Urquhart *et al.,* 38% silver diamine fluoride was more effective than controls when applied every six months on any coronal surface of primary teeth, when compared with both 12% silver diamine fluoride solution applied biannually and 38% silver diamine fluoride solution applied annually. In the review by Oliveira *et al.*, silver diamine fluoride was more effective (adequate) than controls in arresting caries lesions in primary teeth and providing an anti-caries benefit for the entire dentition. When silver diamine fluoride was compared with other active treatments in the review by Oliveira *et al.*, the evidence was conflicting and inconclusive, and was based on only two trials with limitations.

The other evidence assessed in the review by Urquhart *et al.* suggests that there are a range of remineralising agents that are effective in arresting and/or reversing non-cavitated and cavitated carious lesions. Results from the network meta-analysis suggest that there is adequate evidence that the combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth. There is inadequate evidence that the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective treatment for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth. The evidence is inadequate to suggest that 5000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective treatment for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth. Results from the study-level data show that, when compared with no intervention, there is adequate evidence that 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth. There is adequate evidence that the use of 1.23% acidulated phosphate fluoride gel is better than relying on oral health education to treat facial/lingual lesions at 12 months follow-up.

There is adequate evidence in two reviews – by Ancira-González *et al.* and Gao *et al.* – that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth. Finally, there is adequate evidence in the review by Duangthip *et al.* to suggest that brushing teeth with highly concentrated fluoride toothpaste is effective in slowing the progression of early caries in preschool children.

We judged the evidence to be adequate in the review by Benson et al. to suggest that fluoride varnish can reduce the development of white spot lesions in children undergoing orthodontic treatment. According to Benson *et al.,* "The quality of the evidence found is moderate in the case of one well-

designed study and weak in the remaining studies". p3[91] Finally, there is inadequate evidence in the review by Meyer et al. upon which to judge the effectiveness of calcium phosphates as a remineralising agent.

Table 3 Seven reviews of remineralisation agents for early treatment of dental caries in children and adolescents

Lead and year	Level of evidence
	Fluoride
Urquhart *et al.* (2019)[29]	Adequate evidence that the combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth Adequate evidence that 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth Adequate evidence that the use of 1.23% acidulated phosphate fluoride gel is better than relying on oral health education to treat facial/lingual lesions at 12 months follow-up. Adequate evidence that 38% silver diamine fluoride applied twice per year was more effective than controls in arresting caries lesions in primary teeth and in providing an anti-caries benefit for the entire dentition Inadequate evidence that the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective treatment for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth Inadequate evidence to suggest that 5000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective treatment for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth
Oliveira *et al.* (2019)[86]	Adequate evidence that silver diamine fluoride was more effective than controls in arresting caries lesions in primary teeth and in providing an anti-caries benefit for the entire dentition Inconclusive evidence when silver diamine fluoride was compared with other active treatments
Ancira-González *et al.* (2018)[88]	Adequate evidence to suggest that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth
Gao *et al.* (2016)[89]	Adequate evidence to suggest that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth Adequate evidence that silver diamine fluoride was more effective than controls in arresting the progression of active caries in both primary and permanent teeth in children and adolescents
Duangthip *et al.* (2015)[90]	Adequate evidence to suggest that brushing teeth with highly concentrated fluoride toothpaste is effective in slowing the progression of early caries in preschool children Adequate evidence that silver diamine fluoride was more effective than controls in arresting caries lesions in primary teeth in preschool children
Benson *et al.* (2013)[91]	Adequate evidence to suggest that fluoride varnish can be an effective intervention to reduce the development of white spot lesions in children undergoing orthodontic treatment
	Calcium phosphates
Meyer *et al.* (2018)[87]	Inadequate evidence that calcium phosphates as a remineralising agent are a promising approach for oral care

4.3.3.1.3 Microinvasive strategies for early treatment of caries lesions in children and adolescents

Krois *et al.* (2018)[92] compared microinvasive treatments with non-invasive treatments or with placebos to arrest early non-cavitated proximal carious lesions in children and adolescents. According to Krois *et al.,* "micro-invasive strategies (sealing and infiltration) remove a few micrometers of tissue during application, usually when conditioning the tooth surface with acids, and install a diffusion barrier onto (lesion sealing) or within (lesion infiltration) the carious tissue. The barrier (of resins or glass-ionomer cements) impedes acid diffusion into the hard tissue and further mineral loss from it, thereby arresting the lesion… Non-invasive strategies remove no carious tissue at all and include dietary control, biofilm control, or control of de- and remineralisation (via fluorides etc.) often combined with each other." p15[92]

Fifteen reports of 13 randomised controlled trials with 486 participants were included in this review. Four trials assessed lesions in primary teeth and nine trials assessed lesions in permanent teeth. Participants comprised children and adolescents with a mean age of 15 years.

The Cochrane Collaboration's risk of bias instrument was used to assess bias in the included trials. All trials had a low risk of bias regarding blinding of the assessment, and there was also limited indication of selective reporting or issues of random sequence generation. In contrast, blinding of operators or participants was always rated as unclear or high risk, and allocation concealment was rated as having an unclear risk of bias in seven studies. Nearly all trials on infiltration were sponsored by the treatments' manufacturers, and two trials were conducted by the treatments' inventors.

According to Krois *et al.,* "sealing or infiltration instead of non-invasive (NI) treatment would avoid 278 per 1,000 treated lesions to progress (44% NI and 16% sealed or infiltrated lesions would progress). The certainty of the evidence was graded as moderate. Sealing instead of NI would avoid 282 per 1,000 treated lesions to progress. The certainty of the evidence was graded as moderate. Infiltration instead of NI would avoid 266 per 1,000 treated lesions to progress (as the control group event proportion was lower). The certainty of the evidence was graded as high… Based on this review and analysis, micro-invasive treatment should be chosen over NI treatment (strong recommendation) … we are hence confident in this conclusion". p18[92]

Based on the findings of this review, there is adequate evidence that sealing/infiltration is superior to non-invasive treatment. In addition, there is adequate evidence to suggest that either sealing or infiltration used separately is superior to non-invasive treatment. The evidence is inconclusive regarding the superiority of sealing versus infiltration.

Dorri *et al.* (2015)[95] compared microinvasive treatments with non-invasive measures, no intervention, or a placebo for managing proximal caries lesions in primary and permanent dentition in children and adults. According to Dorri *et al.,* "Micro-invasive treatments involve conditioning the tooth surface using organic acids prior to treating the caries lesion. The conditioning involves the loss of few micro-meters of tooth enamel. There are two types of micro-invasive treatments: sealing and resin infiltration". p6[95]

Eight randomised controlled trials with 365 participants were included in this review. The authors do not provide the specific age of the participants, but they report that the participants ranged in age from 4–39 years. Based on assessment using the Cochrane Collaboration's risk of bias instrument, the

authors judged seven of the eight trials to be at high risk of bias, primarily due to lack of blinding of participants and personnel.

The findings in this review suggest that there is adequate evidence that microinvasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions and is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss). This finding is based on moderate evidence according to the GRADE levels of evidence, and the authors are "moderately confident that further research is unlikely to substantially change the estimate of effect". p2[95] However, the evidence is inconclusive regarding which microinvasive technique offers the greatest benefit, due to the small number of studies available for analysis.

Doméjean *et al.* (2015)[96] compared resin infiltration with fluoride varnish, sealant micro-brush, or water application to arrest non-cavitated caries lesions. According to Doméjean *et al.,* "resin infiltration is a technique that involves infiltrating the porosities of an enamel lesion with a low viscosity resin…the potential caries-inhibiting effect of RI [resin infiltration] is dependent on the occlusion of the pores within the body of the caries lesion". p217[96]

Three randomised controlled trials, which were reported on in four papers, were included in this review.[96] The trials involved children, adolescents, and adults. All four papers reported on proximal caries lesions. One trial had been conducted on 48 high-caries-risk children with a mean age of 7 years; one trial on 39 adolescents and young adults (mean age: 21), 46% had a low riskf of caries; 28% had a moderate risk and 26% were at high risk. The remaining trial included 22 young adults with a moderate risk of caries and a mean age of 25. The quality of the studies was assessed by the authors to be high with respect to randomisation, split-mouth design, and blinding; however, they reported using CONSORT (Consolidated Standards of Reporting Trials) as the instrument of assessment. It must be noted that CONSORT is primarily used for assessing the reporting quality of trials, and it does not evaluate the risk of bias.

The analysis of the data from all four papers based on the three trials showed significant differences in arresting the progression of caries in favour of resin infiltration compared with the control/placebo groups; however, the sample sizes were very small, so this suggests that there is inconclusive evidence that resin infiltration is effective in arresting the progression of caries. According to Doméjean *et al.,* "the use of RI [resin infiltration] to arrest the progression of non-cavitated caries lesions is encouraging. This suggests that RI is a promising noninvasive approach and might be considered as an additional option to non-operative and operative treatment approaches". p220[96]

Wright *et al.* (2016)[93 94] compared dental sealants with a control without sealants, with fluoride varnishes, and with other head-to-head comparisons for the prevention and management of pit and fissure occlusal carious lesions in primary and permanent teeth. For the purposes of the review, four categories of sealant materials were defined: resin-based sealants; glass-ionomer cements or glass-ionomer sealants; resin-modified glass-ionomer sealants; and polyacid-modified resin sealants, also known as compomers. According to Wright *et al.,* "sealants are dental materials that dentists apply to the pit and fissure surface of teeth. The sealant material penetrates and hardens, acting as a physical barrier to inhibit the ingress of bacteria". p283[94] For the purposes of the review, the comparators were defined as any type of sealant material irrespective of the application technique, the non-placement of sealants, and the use of fluoride varnish.

Twenty-three randomised controlled trials comprising children and adolescents aged 6–16 years were included in this review. The quality of the 23 trials was assessed using the Cochrane Collaboration's risk of bias instrument. Most of the trials were judged as having an unclear risk of bias due to inadequate reporting in the original papers.

The main finding from this review suggests that there is adequate evidence that sealants, when compared with no sealant or with fluoride varnish, are better in preventing carious lesions and arresting the progression of non-cavitated carious lesions. According to Wright *et al.,* "children and adolescents who receive sealants in sound occlusal surfaces or non-cavitated pit-and-fissure carious lesions in their primary or permanent teeth experienced a 76% reduction in the risk of developing new carious lesions after 2 years of follow-up compared to a control group who did not receive sealants. After 7 or more years of follow-up, children and adolescents with sealants had a caries incidence of 29% compared to those without sealants who had a caries incidence of 74%." p292[94] The quality of evidence is rated as moderate based on GRADE.

Sealants applied to the pits and fissures of primary and permanent teeth appeared to be more beneficial when compared with fluoride varnish, but the evidence was judged to be of low quality or inconclusive due to the risk of bias and inconsistency in the reporting of the trials. In addition, the evidence is inconclusive regarding the superiority of one sealant over another. According to Wright *et al.,* "although our analysis failed to find a hierarchy of effectiveness…about the relative merits of each sealant material, sealants compared to no sealants or fluoride varnishes prove superior in preventing carious lesions and arresting the progression of non-cavitated carious lesions." p292[94]

4.3.3.1.4 Summary: microinvasive strategies for early treatment of caries lesions in children and adolescents

Table 4 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on four reviews of microinvasive strategies for early treatment of dental caries in children and adolescents. The primary research investment in early treatment is adequate.

There is adequate evidence in two reviews – by Krois *et al.* and Dorri *et al.* – that microinvasive treatment (sealing and resin infiltration) is superior to non-invasive treatment; in the review by Krois *et al.*, there is adequate evidence to suggest that either sealing or infiltration used separately is superior to non-invasive treatment, although in the same review the evidence is inconclusive regarding the superiority of sealing or infiltration. In the review by Doméjean *et al.*, there is inconclusive evidence that resin infiltration, when compared with controls, is effective in arresting the progression of caries. Finally, there is adequate evidence in the review by Wright *et al.* that sealants, when compared with no sealant, are better in preventing carious lesions and arresting the progression of non-cavitated carious lesions. However, the evidence in this review for sealants versus fluoride varnish is inconclusive. The evidence in this review is also inconclusive regarding the superiority of one sealant over another.

Table 4 Four reviews of microinvasive strategies for early treatment of dental caries in children and adolescents

Lead author and year	Level of evidence
	Microinvasive treatment (sealing and resin infiltration)
Krois *et al.* (2018)[92]	Adequate evidence that microinvasive treatment (sealing and resin infiltration) is superior to non-invasive treatment Inconclusive evidence whether sealing or infiltration is superior
Dorri *et al.* (2015)[95]	Adequate evidence that microinvasive treatment (sealing and resin infiltration) is superior to non-invasive treatment in primary and permanent molars
Wright *et al.* (2016)[93 94]	Adequate evidence that sealants, when compared with no sealant, are better in preventing carious lesions and arresting the progression of non-cavitated carious lesions in primary and permanent molars Inconclusive evidence whether sealants or fluoride varnish is superior Inconclusive evidence regarding the superiority of one sealant over another
Doméjean *et al.* (2015)[96]	Inconclusive evidence that resin infiltration, when compared with controls, is effective in arresting the progression of caries

4.3.3.2 Late or restorative treatment of cavitated caries in children and adolescents

We have grouped the interventions used in late treatment of cavitated caries into two categories: 1) restorative procedures and techniques, and 2) restorative materials. The distinguishing feature of the interventions included in Category 1 is that the primary unit of investigation was either a technique or procedure to aid either the placement of restorative materials or the removal of caries. In contrast, the distinguishing feature of Category 2 is that the primary unit of investigation is the dental restorative material(s) used to fill the cavities in primary or permanent teeth.

In Category 1, restorative procedures and techniques, we have included interventions evaluated in seven reviews:

- Four reviews compare atraumatic restorative treatment with the conventional approach (Tedesco *et al.*, 2018;[97] Ruengrungsom *et al.*, 2018;[98] Dorri *et al.*, 2017;[22] and Tedesco *et al.*, 2016[99]).
- One review (Schenkel *et al.*, 2019)[100] compares the effectiveness of using dental cavity liners to aid the placement of restorations.
- One review (Montedori *et al.*, 2016)[101] compares laser and conventional treatment techniques for removing caries.
- One review (Ricketts *et al.*, 2013)[102] compares different procedures for removing caries.

In Category 2, restorative materials, we have included interventions evaluated in six reviews:

- Four reviews compare glass-ionomer cements with other restorative materials (Tedesco *et al.*, 2016;[99] Santos *et al.*, 2016;[103] Raggio *et al.*, 2016;[104] and Dias *et al.*, 2018[15]).
- One review (Innes *et al.*, 2015)[105] compares preformed crowns (using the Hall technique) with other restorative materials.
- One review (Ma *et al.*, 2016)[10] examines the effectiveness of different materials used for retrograde filling (root canal therapy) in children.

4.3.3.2.1 Procedures and techniques for restorative treatment of cavitated caries in children and adolescents

In this first section covering interventions used in late treatment of cavitated caries, we have included four reviews comparing atraumatic restorative treatment with the conventional approach (Tedesco *et al.*, 2018 [97]; Ruengrungsom *et al.*, 2018;[98] Dorri *et al.*, 2017;[22] and Tedesco *et al.*, 2016[99]) to placing different restorative materials to treat caries lesions in the primary and permanent teeth of children and adolescents. We have also included three reviews that examine different techniques to aid the placement of restorations in primary and permanent teeth in children and adolescents: Schenkel *et al.* (2019)[100] examine dental cavity liners; Montedori *et al.* (2016)[101] examine the laser extraction approach; and Ricketts *et al.* (2013)[102] compare different procedures for removing caries. We have presented a structured account of the focus, methods, and main findings for each review and we have provided an overall assessment of the quality of the evidence adduced in each review based on our revised framework adapted from the work of Faggion (2012).[48] In our conclusion to this section, we have sought to draw out the main overall points from the systematic reviews that we have considered.

Atraumatic restorative treatment

Tedesco *et al.* (2018)[97] undertook a review to determine the best treatment for caries lesion arrestment and the success rate of different treatments of the dentine caries lesions of primary teeth. The purpose of the review was to bridge a gap in the evidence by considering whether lesions of different depths and the number of surfaces involved affect treatment outcomes. According to Tedesco *et al.,* the absence of this evidence "makes recommending the best treatment for dentine caries lesions with different levels of progression challenging". p2[97]

Two different types of restorative procedures were considered in this review. According to Tedesco *et al.,* "Atraumatic restorative treatment (ART) was considered as a restorative procedure that included caries removal using only hand instruments and restoration with high-viscous glass-ionomer cement without the use of a rubber dam. Alternatively, conventional restorative technique was considered as including caries removal using rotary instruments and restoration with any restorative material, including the use of a rubber dam. Thus, studies reporting treatment procedures that differed from those definitions were not included in the present review". p3-4[97]

The actual types of restorative materials and restorative treatments that were studied in the trials in Tedesco *et al.'s* review included: stainless steel crown; non-restorative caries treatment; ultraconservative treatment; the Hall technique; interim restorative treatment; silver diamine fluoride; sodium fluoride; resin sealant; low-viscosity glass-ionomer cement; high-viscosity glass-ionomer cement; resin-modified glass-ionomer cement; resin composite; and amalgam.

Fourteen randomised controlled trials and one non-randomised observational study were included in this review. Participants in the trials were aged 2–10 years. The risk of bias in the included primary studies was evaluated using the Cochrane Collaboration's Risk of Bias instrument on the 14 randomised trials and the Risk of Bias in Non-randomized Studies – of Interventions (ROBIN-I) instrument on the non-randomised observational study. Most of the studies were scored as having weak evidence because they did not provide most of the information required. According to Tedesco *et al.,* "The risk of bias analysis performed on the clinical trials showed that all studies received more unclear scores because of the uncertainty regarding potential bias in the studies, especially those

related to allocation concealment, incomplete outcome data, and baseline imbalances given that we were unable to identify this information". p16[97]

The main findings from this review suggest that for occlusal surfaces, conventional restorative treatment using composite resin showed better results; however, this finding is based on data from only two studies. Conventional restorative treatment with compomers showed better results regarding the depth of caries lesions progression, and this finding is based on data from five studies. The Hall technique showed the best success rate for occlusoproximal surfaces, and this finding is based on data from seven studies. In addition, two annual applications of silver diamine fluoride showed the best non-restorative approach to arresting caries lesions on occlusal and smooth surfaces.

According to Tedesco *et al*. "there is low confidence in the results from most of the analyses done in the network meta-analysis due to the risk of bias in the included primary studies". p16 The low quality of the evidence coupled with the relatively small number of studies included suggest that the current evidence as adduced in this review is weak and inadequate and cannot be relied upon. According to Tedesco *et al.,* "the treatment of dentine caries lesions in primary teeth depends on the progression depth and surface involved. However, few studies exist, and most have a high risk of bias to provide enough evidence to strongly recommend the best treatment option". p16[97]

Ruengrungsom *et al.* (2018)[98] compared the performance of using atraumatic restorative treatment techniques with conventional restoration techniques when applying different types of glass-ionomer cements (original, resin-modified, and high-viscosity) as restorations to single- and multiple-surface restorations in occlusal and approximal cavities in primary and permanent teeth.

Sixty-seven primary studies – including longitudinal non-controlled prospective studies, retrospective studies, and randomised controlled trials – were included in this review. Twenty-one randomised controlled trials, eight longitudinal studies, and two retrospective studies examined restorations in permanent teeth. Thirty-two randomised controlled trials, five longitudinal studies, and three retrospective studies examined restorations in primary teeth. Four of the 67 studies examined restorations in both permanent and primary teeth. The clear majority of the studies involved children and adolescents, but their age range cannot be ascertained from the review. The risk of bias in the included studies was assessed using the ROBINS-I instrument, which was chosen as it allows for an assessment of the risk of bias in both randomised and non-randomised controlled trials. Five of the studies had all seven scores that the ROBINS-I instrument measures rated as having a low risk of bias, whereas six studies had one or two scores rated as having a serious risk of bias. The remaining 55 studies had one or more scores rated as having a moderate risk of bias. According to Ruengrungsom *et al.,* "no critical risk of bias was found in any domain of each study". p6[98]

For single-surface occlusal glass-ionomer cement restorations in both permanent and primary teeth, the conventional technique showed better survival rates when compared with the atraumatic restorative treatment technique. However, according to Ruengrungsom *et al.,* "the clinical performance of the ART [atraumatic restorative treatment] technique was satisfactory and likely to give comparable outcomes to the conventional technique if ART is performed by experienced trained operatives using newer strength-improved materials." p19[98] This assessment renders the evidence inconclusive regarding the superiority of the atraumatic restorative treatment technique or the conventional technique when applying glass-ionomer cement to single-surface occlusal restorations in permanent and primary teeth.

When using glass-ionomer cements to restore approximal or multi-surface cavities in primary and permanent teeth, "the conventional technique is preferred to the ART [atraumatic restorative treatment] technique, especially in primary teeth due to the lower annual failure rates". p19[98] This assessment renders the evidence adequate for using the conventional technique when applying glass-ionomer cements to restore approximal or multi-surface cavities in primary teeth.

Regarding the use of different types of glass-ionomer cements to restore approximal cavities in primary teeth, Ruengrungsom *et al.* suggest that the "resin-modified glass-ionomer cement using the conventional technique seems to be promising for restoring approximal cavities of primary teeth compared to other restorative materials". p19[98] This assessment suggests that there is adequate evidence to prefer resin-modified glass-ionomer cement applied using the conventional technique when restoring approximal cavities in primary teeth. The conventional restorative technique is not described in the paper; however, we infer that the technique is likely to be the traditional 'drill and fill'.

Dorri *et al.* (2017)[22] compared atraumatic restorative treatment with conventional treatment (the drill and fill approach) for managing dental caries lesions in the primary and permanent teeth of children and adults. Atraumatic restorative treatment, according to Dorri *et al.*, "is a minimally invasive approach, which involves removal of decayed tissue using hand instruments alone, usually without use of anesthesia and electrically driven equipment, and restoration of the dental cavity with an adhesive material such as glass-ionomer cement, composite resins, resin-modified glass-ionomer cement or compomers." p6[22] Conventional methods (drill and fill) involve the use of electric drills to clear away decayed areas of the tooth before filling. A local anaesthetic (painkiller) is normally injected to prevent pain during the procedure.

Fifteen randomised controlled trials with 3,760 participants were included in this Cochrane review. The mean age of the participants was 25.4 years (ranging from 3 to 101 years). Eleven studies evaluated the effects of atraumatic restorative treatment on primary teeth only, and four on permanent teeth. All 15 trials were judged to be at high risk of bias due to performance, attrition, and selective reporting bias based on the Cochrane Collaboration's risk of bias instrument. Two of the 15 trials had declared industry backing.

The main findings from this review suggest that the conventional technique using high-viscosity glass-ionomer cement may be less likely to result in the failure of restorations in primary teeth when compared with atraumatic restorative treatment using the same material. However, the evidence is weak and inadequate and cannot be relied upon. According to Dorri *et al*., "The available evidence suggests that atraumatic restorative treatment using high-viscosity glass-ionomer [cement] may have a higher risk of restoration failure than conventional treatment for caries lesions in primary teeth, but the evidence is of low quality and we cannot rely on the findings." p24[22]

The evidence is therefore inadequate regarding the effects of atraumatic restorative treatment versus conventional treatment when using resin-modified glass-ionomer cement or composite resin; this is mainly due to the very low quality of the evidence.

Tedesco *et al.* (2016)[99] compared the atraumatic restorative treatment approach with the conventional approach in the survival rate of occlusoproximal restorations in primary teeth in children. According to Tedesco *et al.,* "ART [atraumatic restorative treatment] is a treatment based on

the minimal intervention philosophy…it presents similar longevity to other treatments for the management of single-surface cavities in primary and permanent teeth". p201[99]

Four randomised controlled trials with 1,771 participants aged 2–9 years were included in this review. The Cochrane Collaboration's risk of bias instrument was used to assess bias in all four trials. All four trials had a low risk of bias for random sequence generation and incomplete outcome data; all four trials were unclear for allocation concealment; one trial had a low risk of bias and three were unclear for blinding of participants and personnel; three trials had a high risk of bias and one trial had a low risk for blinding of outcome assessment; and two trials had a low risk and two were unclear for free from baseline imbalance.

The main finding from this review suggest that the evidence is inconclusive regarding the superiority of atraumatic restorative treatment restorations compared with conventional treatment restorations for the survival rates of occlusoproximal cavity restorations in primary teeth. According to Tedesco *et al.,* "ART [atraumatic restorative treatment] restorations have similar survival rates compared to conventional treatment and are a viable option to restore occlusoproximal cavities in primary teeth". p208[99]

Dental liners

Schenkel *et al.* (2019)[100] compared the effects of using dental cavity liners with not using liners in the placement of Class I and Class II resin-based composite posterior restorations in permanent teeth in children and adults. According to Schenkel *et al.,* "Dental cavity liners are designed to protect the pulp from the toxic effects of dental restorative materials and to prevent the pain of thermal conductivity by placing an insulating layer between restorative material and the remaining tooth structure… The liners most commonly used in restorative dentistry include calcium hydroxide and glass-ionomer cements, both of which are available in either chemical or light-cured formulations". p7[100]

Eight randomised controlled trials comprising more than 700 participants were included in this review; the participants included children aged 15 years and older, but the authors did not specify the precise number of children involved in the trials. As this was a Cochrane review, the Cochrane Collaboration's risk of bias instrument was used to assess bias in the included trials. The risk of bias was judged to be high in five trials and unclear in the remaining three trials. The primary outcomes measured were the longevity of restorations and post-operative hypersensitivity.

When the use of dental cavity liners was compared with using no liners under the placement of composite resin restorations in permanent teeth, the evidence was judged to be inconsistent and low quality, and therefore inadequate, regarding any difference in post-operative sensitivity, measured using either cold response or patient-reported response. There was also no difference between using dental cavity liners, compared with using no liners, on the longevity of composite resin restorations in permanent teeth, which renders the evidence for this outcome inconclusive. In conclusion, based on the current evidence, Schenkel *et al*. see no reason why the use of liners would add any benefit to the routine resin-based restorations in permanent posterior teeth in adults. According to Schenkel *et al.* "the evidence does not currently support including the unnecessary step of placing any lining material underneath routine composite-based restorations in adult posterior teeth". p19[100]

Schenkel *et al*. do not offer a judgement regarding the use of liners in permanent teeth in children aged 15 years or older. However, the authors did note that "None of the trials evaluated the effects

of using a dental cavity liner in the permanent teeth of children under the age of 15. Thus, it may not be appropriate to apply this evidence to permanent teeth in younger children." p18[100]

Laser-based extraction method

Montedori *et al.* (2016)[101] compared laser-based methods with conventional mechanical methods for removing dental caries in deciduous and permanent teeth. According to Montedori *et al.,* "Laser is an acronym standing for light amplification by stimulated emission of radiation. Laser is a device emitting a high coherence light beam with waves at single frequency (very narrow spectrum)". p7[101] The conventional mechanical methods for removing dental caries are: a handpiece with a bur, the chemomechanical system, the sono-abrasion system, and the air-abrasion system.

Nine randomised controlled trials involving 662 participants with an age range of 3.5–84 years were included in this review. Four trials involved both children and adolescents; four trials involved adults only; and one trial involved children, adolescents, and adults. Overall, the individual trials had small sample sizes, and the majority were judged to have an unclear or high risk of bias based on using the Cochrane Collaboration's risk of bias instrument.

Regarding the primary outcome examined, which was the removal of caries from deciduous and permanent teeth, the quality of the evidence was insufficient to determine whether either lasers or mechanical drilling methods were superior for removing caries; only two included trials evaluated this outcome. Some studies seemed to favour laser therapy over the mechanical methods for pain control, the need for anaesthesia, and patient discomfort, but the evidence was rated as low quality based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) assessment and therefore inadequate. According to Montedori *et al.,* "despite some encouraging results, the applicability of lasers in current clinical practice is uncertain." p24[101]

Ricketts *et al.* (2013)[102] compared stepwise, partial, or no caries removal with complete caries removal in previously unrestored primary and permanent teeth in children and adults. According to Ricketts *et al.,* "Stepwise caries removal removes caries in stages over two visits some months apart, allowing the dental pulp time to repair itself and lay down dentine. Partial caries removal removes part of the caries and seals what is left into the tooth permanently. No dentinal caries removal does not remove any caries before sealing or restoring." p3[102] Traditional caries extraction treatment removes all the dental decay in one session.

Eight randomised controlled trials with 934 participants were included in this review; six of the trials involved only children and adolescents with an age range of 3–16 years. In this Cochrane review, all the eight included trials were judged to have a high risk of bias.

The main finding of this review suggests that stepwise and partial caries removal reduced the incidence of pulp exposure in primary and permanent teeth. This finding suggests that, although the primary studies have a high risk of bias, there is adequate evidence to demonstrate the clinical advantage of using selective caries removal over the complete removal of caries in both primary and permanent teeth. According to Ricketts *et al.,* "no evidence was found to suggest that incomplete caries removal is harmful. In fact, the reverse is true as complete caries removal is more likely to result in carious exposure of the pulp". p23[102] The evidence is inconclusive regarding the superiority of no caries removal compared with complete caries removal.

4.3.3.2.2 Summary: procedures and techniques for restorative treatment of cavitated caries in children and adolescents

Table 5 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on seven reviews of restorative procedures and techniques to enable restorative treatment of dental caries in children and adolescents. The primary research investment in restorative caries treatment is low and, in some cases, industry-led rather than public health-led.

Despite some signals in the data that the conventional restorative technique may be better than the atraumatic restorative treatment technique for placing restorative materials to treat caries lesions in primary and permanent teeth, the evidence provided by Tedesco *et al.* 2018 and Dorri *et al.* is weak and inadequate and cannot be relied upon to support this finding.

In the reviews by Ruengrungsom *et al.* and Tedesco *et al.* 2016 the evidence provided is inconclusive regarding the superiority of the atraumatic restorative treatment technique over the conventional technique; both techniques were compared when applying glass-ionomer cement to single-surface occlusal restorations in permanent and primary teeth in Ruengrungsom *et al.*, and for the survival rates of restorations of occlusoproximal cavities in primary teeth in Tedesco *et al.* 2016. However, it must be emphasized that in both reviews (Ruengrungsom *et al.* and Tedesco *et al.* 2016) the authors signal that ART is a suitable treatment for single surface occlusal restorations.

There is adequate evidence in Ruengrungsom *et al.* for using the conventional technique when applying glass-ionomer cements to restore approximal or multi-surface cavities in primary teeth, and in the same review there is adequate evidence to prefer resin-modified glass-ionomer cement applied using the conventional technique when restoring approximal cavities in primary teeth.

In the review by Schenkel *et al.*, the evidence provided is inadequate and cannot be relied upon regarding any difference in post-operative sensitivity arising from the use of dental cavity liners under the placement of composite resin restorations in permanent teeth. In the same review, the evidence provided is inconclusive regarding the superiority of either using or not using dental cavity liners to affect the longevity of composite resin restorations in permanent teeth. Schenkel *et al.* suggest that there is little benefit to be gained in considering the use of dental cavity liners.

Despite some signals in the data favouring laser therapy over mechanical methods for removing dental caries in the review by Montedori *et al.*, the evidence provided was low quality and inadequate, and cannot be relied upon. There is adequate evidence provided in the review by Ricketts *et al.* to suggest a clinical advantage in choosing selective caries removal over the complete removal of caries in both primary and permanent teeth.

Table 5 Seven reviews of procedures and techniques for restorative treatment of dental caries in children and adolescents

Lead author and year	Level of evidence
	Atraumatic restorative treatment
Tedesco *et al.* (2018)[97]	Inadequate evidence to determine whether the conventional restorative technique is better than the atraumatic restorative treatment technique for placing restorative materials to treat caries lesions in primary and permanent teeth
Dorri *et al.* (2017)[22]	Inadequate evidence to determine whether the conventional restorative technique is better than the atraumatic restorative treatment technique for placing restorative materials to treat caries lesions in primary and permanent teeth
Tedesco *et al.* (2016)[99]	Inconclusive evidence regarding the superiority of the atraumatic restorative treatment technique over the conventional technique for the survival rates of glass-ionomer cement restorations of occlusoproximal cavities in primary teeth
Ruengrungsom *et al.* (2018)[98]	Adequate evidence for using the conventional technique when applying glass-ionomer cements to restore approximal or multi-surface cavities in primary teeth Adequate evidence to prefer resin-modified glass-ionomer cement applied using the conventional technique when restoring approximal cavities in primary teeth Inconclusive evidence regarding the superiority of the atraumatic restorative treatment technique over the conventional technique when applying glass-ionomer cement to single-surface occlusal restorations in permanent and primary teeth
	Dental cavity liners
Schenkel *et al.* (2019)[100]	Inadequate evidence to promote the use of dental cavity liners under the placement of composite resin restorations in permanent teeth to prevent post-operative sensitivity Inconclusive evidence that dental cavity liners increase the longevity of composite resin restorations in permanent teeth
	Laser therapy
Montedori *et al.* (2016)[101]	Inadequate evidence to determine whether laser therapy is better than mechanical methods for extractions
	Selective caries removal
Ricketts *et al.* (2013)[102]	Adequate evidence to suggest a clinical advantage in choosing selective caries removal over the complete removal of caries in both primary and permanent teeth

4.3.3.2.3 Restorative materials for the treatment of cavitated caries in children and adolescents

In this second section covering late treatment interventions, we have included six reviews that compared various restorative materials with controls. Four of the reviews (Dias *et al.*, 2018;[15] Santos *et al.*, 2016;[103] Raggio *et al.*, 2016;[104] and Tedesco *et al.*, 2016[99]) compare glass-ionomer cements with controls. In the remaining two reviews, Ma *et al.* (2016)[10] examine different materials used for retrograde filling (root canal therapy) in children and adults, and Innes *et al.* (2015)[105] compare preformed crowns (using the Hall technique) with conventional fillings. We have provided a structured account for each review, with an assessment of the evidence.

Glass-ionomer cements compared with other restoration materials

Dias *et al.* (2018)[15] compared glass-ionomer cement with composite resin in Class II restorations in primary teeth. According to Dias *et al.,* "GICs [glass-ionomer cements] are adhesive materials that release fluoride to the oral environment, and their insertion technique is faster compared to composite resin, making this material an important resource for the treatment of children." p3[15]

Ten randomised controlled trials were included in this review. The children participating in the 10 trials were aged 3–11 years. The Cochrane Collaboration's risk of bias instrument was used to assess

bias in the 10 trials. Six trials were classified as having a low risk of bias and four as having an unclear risk of bias.

When glass-ionomer cement was compared with composite resin on marginal discolouration, marginal adaptation, retention of restoration, and wear of the restorative material in Class II restorations in primary teeth, the results were similar for both interventions. This assessment renders the evidence from this review inconclusive regarding whether glass-ionomer cement or composite resin is better for this finding.

However, there is adequate evidence that glass-ionomer cements were significantly better than composite resins at preventing the occurrence of secondary carious lesions in primary teeth. According to Dias *et al*., "regarding the occurrence of secondary carious lesions, GIC [glass-ionomer cements] presented superior clinical performance, and this effect was more evident for the resin-modified GIC used with rubber dam isolation". p12[15]

Raggio *et al.* (2016)[104] compared glass-ionomer cements with other restorative materials to prevent adjacent (secondary) caries lesions in the margins of occlusal and occlusoproximal restorations in primary teeth. The intervention group received either resin-modified glass-ionomer cement or high-viscosity glass-ionomer cement, and these were compared with amalgam, resin composite, or polyacid-modified resin composite.

Eight randomised controlled trials with 1,644 children aged 5–8 years were included in this review. All eight trials were assessed using the Cochrane Collaboration's risk of bias instrument and all eight trials had two or more unclear risk of bias scores.

The main finding from this review suggests that all restorative materials examined in this review performed similarly on preventing adjacent caries in occlusal surfaces. This assessment renders the evidence inconclusive for this finding.

Regarding the prevention of adjacent caries lesions in the margins of occlusoproximal surfaces in primary teeth, there is adequate evidence to suggest that glass-ionomer cements are superior when compared with other restorative materials. According to Raggio *et al.,* "there is moderate strength of evidence for a positive association between GIC [glass-ionomer cements] and the prevention of caries lesions only in the margins of occlusoproximal restorations of primary teeth". p184[104]

Santos *et al.* (2016)[103] compared glass-ionomer cements, composite resins, and compomers to determine which is superior in terms of restoration survival in the primary teeth of children. Glass-ionomer cements included conventional glass-ionomer cements, resin-modified glass-ionomer cement, and silver-reinforced glass-ionomer cement.

Eleven clinical trials, including randomised and non-randomised trials with 483 children aged 3–10 years, were included in this review. A modified version of the Jadad scale for reporting controlled trials was used to assess the risk of bias in the included trials. Most of the trials were judged to be at a high risk of bias.

There is weak or inadequate evidence that adhesive materials with a resin component (composite resin, compomers, and resin-modified glass-ionomer cement) have similar survival rates for 24 months and for up to 48 months.

There was no evidence (inadequate) that adhesive materials with a resin component have a greater survival rate when compared with glass-ionomer cement.

Among the glass-ionomer cements, silver-reinforced glass-ionomer cement seemed to have the worst survival rate and is not recommended for restoring primary teeth.

The overall conclusion is that the evidence is inadequate regarding the superiority of any of the adhesive-based materials for restoring primary teeth in children, excluding silver-reinforced glass-ionomer cement, which is not recommended for use in primary teeth. According to Santos *et al.,* "composite resin, compomers, resin-modified glass-ionomer cement and glass-ionomer cement are suitable for the restoration of primary teeth in children". p377[103]

Tedesco *et al.* (2016)[99] compared glass-ionomer cements with other dental restorative materials used to prevent or arrest secondary caries lesions in approximal surfaces in contact with occlusoproximal restorations in children.

Four longitudinal randomised controlled trials with 815 participants aged 2–16 years, as well as six laboratory trials, were included in this review.[99] The four trials comprising children examined both primary and permanent teeth, whereas the six in vitro studies all examined permanent teeth only. The risk of bias in the four trials comprising children was assessed using the Cochrane Collaboration's risk of bias instrument. The risk of bias in the six laboratory trials was evaluated using a bespoke instrument. Three of the 10 trials had a high risk of bias for one outcome, and all 10 trials had an unclear risk of bias for at least two outcomes. In all four trials comprising children, amalgam was the restorative material compared with glass-ionomer cements, and in the six in vitro studies, resin composite was the material most used by the control group, by comparison with glass-ionomer cements.

The results from this review suggest that the evidence is inconclusive regarding the superiority of either glass-ionomer cements or other restorative materials (amalgam and resin composite). On the one hand, the longitudinal trials with children and adolescents show no benefit for glass-ionomer cements compared with other restorative materials (amalgam). On the other hand, the laboratory studies show benefits for glass-ionomer cements compared with other restorative materials (composite resin) in arresting caries lesions in adjacent surfaces. According to Tedesco *et al.,* "in laboratory studies, GIC [glass-ionomer cements] shows better ability than other restorative materials to arrest caries lesions in adjacent surfaces, but this ability was not confirmed in longitudinal clinical trials." p170[99]

Retrograde filling

Ma *et al.* (2016)[10] examined the effectiveness of different materials used for retrograde filling (root canal therapy) in children and adults for whom retrograde filling is necessary in order to save the tooth. The different types of filling material mentioned in the review comprised mineral trioxide aggregate, intermediate restorative material, super ethoxybenzoic acid, dentine-bonded resin composite, glass-ionomer cement, and amalgam.

Six randomised controlled trials with 916 participants were included in this review; the reporting of the age of the children included in the trials was unclear. In this Cochrane review, all six included trials were judged to have a high risk of bias. The main finding in this review is that there is insufficient evidence upon which to judge whether any of the materials are effective, which renders the evidence inadequate. According to Ma *et al.*, "based on the present limited evidence, we do not have sufficient evidence to determine the benefits of any one material over another." p27[10]

Crowns versus fillings

Innes *et al.* (2015)[105] compared the effectiveness and safety of all types of preformed crowns (using the Hall technique) with conventional filling materials for restoring primary teeth in children. Preformed crowns were fitted using the Hall Technique which is a simplified method where the crown is placed on the tooth without the need for local anaesthesia, carious lesion or tooth tissue removal. According to Innes *et al.,* "traditionally, preformed crowns have been made of metal and referred to as either preformed metal crowns or stainless steel crowns. They are silver in colour. More recently, aesthetic preformed crowns have been developed and used for primary teeth; these crowns are white in colour… Placement of a preformed crown is intended to provide a more durable restoration compared to a conventional filling." p6[105] All types of preformed crowns were considered in this Cochrane review. The comparator conventional filling materials included amalgam, composite resin, glass-ionomer cement, resin-modified glass-ionomer cement, compomers, non-restorative caries treatment and no treatment.

Five randomised controlled trials that included 438 children with an age range of 2.6–10 years were included in this review. As this was a Cochrane review, the Cochrane Collaboration's risk of bias instrument was used, and all five trials were judged to have a high risk of bias.

The main findings suggest that crowns placed on primary teeth with carious lesions, or where pulp treatment has been carried out, are likely to reduce the risk of major failure or pain in the primary tooth in the long term compared with using fillings. The evidence supporting this finding is judged to be of moderate quality based on the GRADE criteria and suggests that crowns are more effective than fillings in managing dental decay in primary teeth.

Crowns fitted using the Hall technique may reduce discomfort at the time of treatment compared with using other fillings. The evidence supporting this finding is judged to be of moderate quality based on the GRADE criteria and suggests that crowns fitted using the Hall technique are less likely to cause abscesses and pain. Both findings suggest that there is adequate evidence to support the view that preformed crowns (using the Hall technique) are superior to conventional fillings for managing tooth decay in primary teeth. In reflecting on the generalisability of these findings, Innes *et al.* point out that "crowns seemed to perform better than fillings, and the variability between the studies reinforces the applicability of this finding to different settings." p22[105]

The evidence comparing preformed crowns with non-restorative caries management, and comparing preformed metal crowns with preformed white crowns, is of very low quality, so it is not possible to determine which is better; this renders the evidence inadequate.

4.3.3.2.4 Summary: restorative materials for the treatment of cavitated caries in children and adolescents

Table 6 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on six reviews of restorative materials used in the restorative treatment of dental caries in children and adolescents. The primary research investment in restorative caries treatment is low and, in some cases, is industry-led rather than public health-led.

When glass-ionomer cements were compared with other restorative materials, the evidence provided in four reviews is inconclusive overall to determine which material is superior for restorations in primary teeth (Dias *et al.*; Santos *et al.*), for preventing adjacent caries in occlusal surfaces (Raggio *et*

al.), and for preventing or arresting secondary caries lesions in approximal surfaces in contact with occlusoproximal restorations in children (Tedesco *et al.*).

There is adequate evidence in the review by Dias *et al.* that glass-ionomer cements were better than composite resins at preventing the occurrence of secondary carious lesions in primary teeth, and there is adequate evidence reported by Raggio *et al.* that glass-ionomer cements are better than other restorative materials for preventing adjacent caries lesions in the margins of occlusoproximal surfaces in primary teeth.

In the review by Ma *et al.*, there is insufficient and inadequate evidence upon which to judge whether any of the materials studied are effective in retrograde filling (root canal therapy) in children and adults. In the review by Innes *et al.*, there is adequate evidence that preformed crowns (using the Hall technique) are superior to conventional fillings for managing tooth decay in primary teeth. However, the evidence in the same review is inadequate when comparing preformed crowns with non-restorative caries management and when comparing preformed metal crowns with preformed white crowns.

Table 6 Six reviews of restorative materials for late treatment of dental caries in children and adolescents

Lead author and year	Level of evidence
	Glass-ionomer cements
Dias *et al.* (2018)[15]	Inconclusive evidence to determine whether glass-ionomer cements were superior to other materials for restorations in primary teeth
Santos *et al.* (2016)[103]	Inconclusive evidence to determine whether glass-ionomer cements were superior to other materials for restorations in primary teeth
Raggio *et al.* (2016)[104]	Inconclusive evidence to determine whether glass-ionomer cements were superior to other materials in preventing adjacent caries in occlusal surfaces
Tedesco *et al. (*2016)[99]	Inconclusive evidence to determine whether glass-ionomer cements were superior to other materials in preventing or arresting secondary caries lesions in approximal surfaces in contact with occlusoproximal restorations in children
	Root canal materials
Ma *et al.* (2016)[10]	Inadequate evidence to judge whether any of the materials are effective in retrograde filling (root canal therapy) in children and adults
	Crowns
Innes *et al.* (2015)[105]	Adequate evidence that preformed crowns (using the Hall technique) are superior to fillings for managing tooth decay in primary teeth Inadequate evidence for comparing preformed crowns with non-restorative caries management in primary teeth Inadequate evidence for comparing preformed metal crowns with preformed white crowns in primary teeth

4.3.3.3 Longitudinal survival of dental restorations in children and adolescents

We identified three reviews that employed a longitudinal cohort approach to examine the survival of restorative interventions rather than the comparative effectiveness of the interventions. Two of the three reviews – those by Chisini *et al.* (2018)[106] and de Amorim *et al.* (2018)[107] – investigated the longevity of restorations in primary and permanent teeth, and the review by Papageorgiou *et al.* (2017)[108] investigated whether the characteristics of different individual teeth affected the clinical performance of pit and fissure sealants.

Chisini *et al.* (2018)[106] investigated the longevity of primary teeth restorations and the reasons for failure. According to Chisini *et al.*, "the included studies evaluated the clinical performance of Class 1, Class II, and/or crown restorations due to caries with seven different materials: amalgam (6 studies), compomers (9 studies), composite resin (6 studies), conventional glass-ionomer cement (5 studies), modified resin glass-ionomer cement (4 studies) resin-modified glass-ionomer cement (10 studies) and steel crowns (3 studies)". p125-126[106]

Twenty-one randomised controlled trials and 10 observational studies evaluating 12,047 posterior restorations in primary teeth in children with an age range of 1–13 years were included in this review. The risk of bias in the included studies was assessed using the Cochrane Collaboration's risk of bias instrument. According to Chisini *et al.,* "in general the included studies presented high risk of bias, mainly selection, performance, and detection bias". p126[106]

The main finding in this review suggests that the evidence is inconclusive regarding the best material for posterior restorations in primary teeth, due to a wide range of timepoints for data collection and different year endpoints for individual studies.

The restoration success rates for each type of material were as follows: amalgam: 82% at three years; composite resin: 79% at four years; glass-ionomer cement: 89% at four years; compomers: 91% at three years; resin-modified glass-ionomer cement: 94% at four years; modified resin glass-ionomer cement: 57% at three years; and steel crowns: 96% at three years. The highest success rate was for steel crowns, followed by resin-modified glass-ionomer cement, and the highest failure rate was for modified resin glass-ionomer cement.

The overall annual failure rate ranges for each type of restorative material were as follows: composite resin: 1.7–12.9% over four years; amalgam: 1–28% over three years; glass-ionomer cement: 0.8–16.6% over four years; compomers: 1.7–15.4% over three years; resin-modified glass-ionomer cement: 0.9–16.9% over four years; steel crowns: 1.4–19% over three years; and modified resin glass-ionomer cement: 10–29% over three years.[106] Modified resin glass-ionomer cement restorations had the highest annual failure rate, and composite resin had the lowest upper range for annual failure.

The main reasons for failure over three or four years were secondary caries, restoration loss, marginal adaptation, and fractured teeth.[106]

According to Chisini *et al.,* "there is a large variation in longevity of posterior restorations in primary teeth. Composite resin exhibited the lowest annual failure rates, whereas modified resin glass-ionomer cement exhibited the highest annual failure rate. The steel crowns had the highest rate of success." p136[106]

de Amorim *et al.* (2018)[107] investigated the survival rate of atraumatic restorative treatment glass-ionomer restorations and atraumatic restorative treatment sealants in primary and permanent

posterior teeth. Atraumatic restorative treatment is done using hand tools, not the drill and fill method. Its restorative component is based on the selective removal of carious tissues down to the soft dentine in deep or very deep lesions, and to firm dentine in shallow lesions. According to de Amorim *et al.,* "the rationale for the widespread use of ART [atraumatic restorative treatment] lies in the fact that principles of ART are in accordance with the contemporary philosophy of dental caries management, which is minimal intervention dentistry." p2704[107]

Forty-two publications examining 34 clinical trials from 22 countries were included in the review; it is not clear from the reporting in the review how many randomised controlled trials were included. Twenty-eight trials were exclusively focused on children, three focused on both children and adults, and three focused on adults. Only two trials scored low for risk of bias across all parameters, while the remaining 32 trials scored high for risk of bias for one or more parameters.

Based on the analysis provided, there is adequate evidence to suggest that restorations placed using the atraumatic restorative treatment approach with high-viscosity glass-ionomer cements produce high levels of restoration survival for both single-surface restorations in primary posterior teeth and single-surface restorations in permanent posterior teeth, and that they produce medium levels of restoration survival for multiple-surface restorations in primary posterior teeth. The evidence is inconclusive for multiple-surface restorations in permanent posterior teeth. In addition, there is adequate evidence that high-viscosity glass-ionomer cement sealants placed using the atraumatic restorative treatment approach are effective in preventing caries lesions.

The survival rates of single-surface and multiple-surface atraumatic restorative treatment restorations in primary posterior teeth over the first two years were 94.3% (± 1.5%; high survival rate) and 65.4% (± 3.9%; medium survival rate), respectively.

Single-surface atraumatic restorative treatment restorations in permanent posterior teeth over the first three years had a survival rate of 87.1% (± 3.2%; high), and multiple-surface atraumatic restorative treatment restorations in permanent posterior teeth over the first five years had a survival rate of 77% (± 9.0%; medium survival rate).

Mean annual dentine-carious-lesion failure percentages in previously sealed pits and fissures using atraumatic restorative treatment sealants in permanent posterior teeth were 0.9% at three years and 1.9% at five years (high failure rate).

According to de Amorim *et al.,* "Twelve years after the publication of the first meta-analysis, the atraumatic restorative treatment approach has been consistently shown as an effective evidence-based option for managing carious lesions. The time has come to consider atraumatic restorative treatment as no longer an alternative option, but, for some cases, the treatment of first choice." p2720[107]

Papageorgiou *et al.* (2017)[108] compared pit and fissure sealants with other active interventions, no treatment, or a placebo to prevent caries or manage the early signs of caries in both primary and permanent teeth. According to Papageorgiou *et al.,* "the procedure of 'sealing' the pits and fissures of teeth includes the placement of a liquid material onto the occlusal surface (i.e. pits and fissures) of posterior teeth, thereby forming a layer that is bonded micromechanically and acts mainly as a barrier against acids and the subsequent mineral loss from within the tooth. Pit-and-fissure sealants can be placed on either caries-free posterior teeth to prevent pit-and-fissure caries or on teeth with incipient caries lesions to prevent their progression to definitive caries." p3[108]

Sixteen randomised clinical trials with 2,778 patients (males: 49.1%; females: 50.9%) and an average age of 8.4 years were included. The specific age range of participants in primary studies is unclear, although indicators are that participants were between 5 and 15 years. The risk of bias for all included trials was assessed using the Cochrane Collaboration's risk of bias instrument. According to Papageorgiou *et al.*, "a high risk of bias was found in 9 (56%) of the trials for at least one bias domain, with the most problematic being complete blinding of outcome assessments (missing in 50% of the trials), randomization procedure (improper in 19% of the trials), and incomplete outcome data (in 6% of the trials)." p8[108]

The overall finding from this review suggests that the characteristics of individual teeth had little to no influence on the clinical performance of pit and fissure sealants, and there is inconclusive evidence that all deciduous or permanent posterior teeth could be effectively sealed. According to Papageorgiou *et al.*, "The performance of pit and fissure sealants in terms of caries of the sealed tooth or retention loss of the sealant do not seem to be negatively affected by mouth side, jaw, and tooth type. The only exception was the use of pit and fissure sealants on premolars, which was associated with lower sealant failure rate compared to the use of pit and fissure sealants on the first permanent molar, indicating favourable performance on the premolars. From the perspective of the sealant's clinical performance all deciduous or permanent posterior teeth could be effectively sealed". p14[108]

4.3.3.4 Summary: longitudinal survival of dental restorations in children and adolescents

Table 7 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on three reviews of longitudinal survival of dental caries treatments in children and adolescents. The primary research investment in this area requires continued investment in the survival of various dental caries treatment techniques.

In the review by Chisini *et al.*, composite resin exhibited the lowest annual failure rate for posterior restorations, and modified resin glass-ionomer cement exhibited the highest annual failure rate. Steel crowns had the highest success rate. However, the evidence is inconclusive regarding the best material for posterior restorations in primary teeth, due to wide ranges for failure or success and different endpoints. There is adequate evidence in the review by de Amorim *et al.* that using the atraumatic restorative treatment technique to place high-viscosity glass-ionomer cement sealants produce medium to high levels of survival and that using the atraumatic restorative treatment technique to place high-viscosity glass-ionomer cement sealants effectively prevent caries lesions in children and adolescents. In the review by Papageorgiou *et al.*, there is inconclusive evidence that the characteristics of individual teeth had any influence on the clinical performance of pit and fissure sealants, or on the sealing of deciduous or permanent posterior teeth.

Table 7 Three reviews of longitudinal survival of dental restorations in children and adolescents

Lead author and year	Level of evidence
	Materials for posterior restorations
Chisini *et al.* (2018)[106]	Inconclusive evidence regarding the best material for posterior restorations in primary teeth, due to wide ranges for failure or success, as well as different endpoints
	Atraumatic restorative treatment to place high-viscosity glass-ionomer cement sealants
de Amorim *et al.* (2018)[107]	Adequate evidence that the atraumatic restorative treatment technique to place high-viscosity glass-ionomer cement sealants produces medium to high levels of survival Adequate evidence that using the atraumatic restorative treatment technique to place high-viscosity glass-ionomer cement sealants effectively prevents caries lesions in children and adolescents
	Performance of pit and fissure sealants
Papageorgiou *et al.* (2017)[108]	Inconclusive evidence that the characteristics of individual teeth had any influence on the clinical performance of pit and fissure sealants

4.4 Question 4: What is the evidence from systematic reviews regarding alternatives to amalgam as a restorative solution for adults aged 16 and older?

4.4.1 Introduction to caries interventions for adults

We developed two secondary questions to help us answer our primary review question:

(1) What types of dental restorative interventions have been evaluated in systematic reviews for the treatment and prevention of dental caries in adults?
(2) What is the level of evidence (adequate, inadequate, or inconclusive) for the effectiveness of dental restorative interventions for the treatment and prevention of dental caries in adults?

Two reviewers (MK and JL

assigned a level of evidence based on an (adapted) version of Faggion:[48]

- Adequate evidence (unlikely to change)
    - When authors stated their confidence using words such as 'sound', 'high', or 'good quality' (which was rarely the case in the reviews examined)

  or

    - When authors did not explicitly state that the evidence was weak, and reported some (moderate) evidence for effectiveness, the evidence was considered adequate (which was more commonly the case in the reviews examined).
- Inadequate evidence (likely to change)
    - When authors described weak or insufficient evidence (low or very low quality), or when no studies were included in the review known as "(an empty review), the evidence was also considered inadequate.
- Inconclusive evidence
    - The evidence was considered inconclusive when it was not possible to determine which intervention was better or best.

We identified several studies that evaluated direct and indirect restoration treatment responses to repair cavitated caries in adults, a category we titled late treatment. Late treatment includes: restorative procedures and techniques, and restorative materials. We have also identified evaluations of early treatment interventions for the management of non-carious lesions in adult permanent teeth. For early treatment interventions, we identified five categories of interventions: remineralisation, microinvasive strategies, dental adhesives and other retention aids, restorative materials, and a combination of both remineralisation and microinvasive strategies. We also found systematic reviews that examined the survival of restorations in adults. Finally, we identified two categories of interventions that evaluated prevention of caries in adults: fluoride-based technologies, and sealants. The categorisation of interventions allowed us to capture the similarities between the interventions and to reflect the diversity of the different techniques and materials evaluated.

We have provided an assessment of the level of evidence (adequate, inadequate, or inconclusive) for each intervention evaluated. In some reviews there is more than one level of evidence reported to reflect the evaluation of more than one outcome. For each review we included, we have provided data to describe the age of the participants, the intervention under evaluation, the comparators, and the primary outcomes being assessed. In addition, we have provided a summary of the risk of bias for

the primary trials or studies included in each review based on the systematic review authors' assessments and theauthors' conclusions including where available their assigned level of evidence.

It is important to note that when we say that the evidence for an intervention is inadequate, it generally means that the research base upon which to evaluate the intervention is inadequate, rather than that the intervention itself is inadequate. There were few cases where the intervention was not useful (such as dental liners).

4.4.2 Prevention of dental caries in adults

4.4.2.1 Introduction

We identified five systematic reviews that evaluated interventions to prevent caries in adults. There are two reviews that evaluated the effectiveness of fluoride technologies in preventing dental caries in adults: Walsh *et al.* (2019)[7] compared the effects of toothpastes of different fluoride concentrations, and Twetman and Keller (2016)[23] compared fluoride mouth rinses, gels, or foams with no intervention or a placebo. We identified three reviews that evaluated the effectiveness of different types of sealants to prevent dental caries in adults. Bagherian and Shiraz (2018)[25] compared the effectiveness of flowable composite resins as pit and fissure sealants with that of conventional resin-based pit and fissure sealants; Alirezaei *et al.* (2018)[26] compared glass-ionomer cements and resin-based sealants on their retention and their ability to prevent the occurrence of caries; and Yengopal and Mickenautsch (2010)[78] compared resin-modified glass-ionomer cement fissure sealants with resin-based fissure sealants in terms of the absence of caries in permanent teeth.

4.4.2.2 Fluoride technologies to prevent caries in adults

Walsh *et al.* (2019)[7] compared the effects of toothpastes of different fluoride concentrations (ppm) in preventing dental caries in children, adolescents, and adults. According to Walsh *et al.* "the formulation and fluoride concentration of toothpaste is diverse, with a variety of fluoride compounds used singly and in combination including sodium fluoride, sodium mono-fluorophosphates, amine fluoride and stannous fluoride, and, according to each manufacturer's specifications, these must be compatible with other basic ingredients, especially abrasive systems (which account for almost half of the entire toothpaste formulation)." p9[7]

On the basis of fluoride concentrations of toothpastes in regular use, the authors proposed the following categories: "0 (parts per million (ppm)) fluoride (F) (non-fluoride or placebo toothpaste), 250 ppm F, 440 to 550 ppm F, 1000 to 1250 ppm F, 1450 to 1500 ppm F, 1700 to 2200 ppm F, 2400 to 2800 ppm F. There were no restrictions placed on the fluoride agents which could be used singly or in combination: sodium fluoride; sodium monofluorophosphate (SMFP); stannous fluoride (SnF2), acidulated phosphate fluoride (APF); amine fluoride (AmF)." p11[7]

Ninety-six randomised controlled trials were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, one trial was judged to have a low risk of bias, 14 trials were judged to have a high risk of bias, and for the remaining 81 trials, the risk of bias was unclear.

Based on the meta-analysis of three studies examining permanent teeth in 2,161 adults, there is adequate evidence that brushing with 1000 or 1100 ppm fluoride toothpaste reduces caries increment in decayed, missing, and filled permanent surfaces when compared with using non-fluoride toothpaste in adults of all ages. The evidence is inconclusive regarding the magnitude of the effect, due to considerable variability of effect across the included studies. According to Walsh *et al.*, "For the mature permanent dentition of adults, toothbrushing with 1000 or 1100 ppm fluoride toothpaste reduces DMFS [decayed, missing, and filled surfaces of teeth] when compared to non-fluoride

toothpaste in adults of all ages (moderate-certainty evidence). We are uncertain as to the magnitude of this benefit, as there was considerable variability of effect across studies." p37[7]

Twetman and Keller (2016)[23] compared fluoride mouth rinses, gels, or foams with no intervention or with a placebo for the prevention of dental caries among children and adults. According to Twetman and Keller, "fluoride mouth rinse has a long tradition as a school-based measure worldwide, but the procedure is also commonly recommended for domestic use for subjects at caries risk, e.g. patients with fixed orthodontic appliances and vulnerable elderly… Fluoride gels are professionally applied in trays and display a preventive fraction of 21% compared to placebo… Neutral or acidulated fluoride foam is a professional option to gel but less studied in clinical trials." p38-39[23]

Sixteen randomised controlled trials, two non-randomised trials, and one cohort study were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, 11 studies were judged to have a high risk of bias, two studies to have a medium risk of bias, and six to have a low risk of bias.

All fluoride measures appeared to be beneficial in preventing crown caries and reversing root caries, but the quality of evidence was graded as low for fluoride mouth rinse (inadequate), moderate for fluoride gel (adequate), and very low for acidulated fluoride foam (inadequate) based on GRADE and taking account of the bias detected in the majority of the included studies.

According to Twetman and Keller, "this preventive effect of fluoride mouth rinse, fluoride gel and foam has previously been established in systematic reviews. The quality of evidence according to GRADE could, however, not be altered. The lack of clinical trials free from bias is still a concern, especially for fluoride mouth rinses and fluoride foam. There is also a scientific knowledge gap on the benefit and optimal use of these fluoride supplements in combination with daily tooth brushing in adults and the elderly." p43[23]

4.4.2.3 Summary: fluoride technologies to prevent caries in adults

Table 8 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on two reviews of fluoride technologies to prevent dental caries in adults. The primary research investment in this area is fairly adequate.

Regarding the two reviews that evaluated fluoride technologies, there is adequate evidence (Walsh *et al.*) that brushing teeth with 1000 or 1100 ppm fluoride toothpaste reduces caries increment in decayed, missing, and filled permanent surfaces when compared with using non-fluoride toothpaste in adults of all ages. However, the evidence is inconclusive (Walsh *et al.*) regarding the magnitude of the effect, due to considerable variability of effect across the included studies. In the review by Twetman and Keller, there is adequate evidence that fluoride gel is effective in preventing crown caries and reversing root caries in adults and older people, but there is inadequate evidence from the same review upon which to judge the performance of fluoride mouth rinse and fluoride foam.

Table 8 Two reviews of fluoride technologies for prevention of dental caries in adults

Lead author and year	Level of evidence
Walsh *et al.* (2019)[7]	Adequate evidence that brushing with 1000 or 1100 ppm fluoride toothpaste reduces caries increment in decayed, missing, and filled permanent surfaces when compared with using non-fluoride toothpaste in adults of all ages Inconclusive evidence regarding the magnitude of the effect, due to considerable variability of effect across the included studies
Twetman and Keller (2016)[23]	Inadequate evidence for the use of fluoride mouth rinse to prevent caries in adults Adequate evidence for the use of fluoride gel to prevent caries in adults Inadequate evidence for the use of fluoride foam to prevent caries in adults

4.4.2.4 Sealants to prevent caries in adults

Bagherian and Shiraz (2018)[25] compared flowable composite resins as pit and fissure sealants with conventional resin-based pit and fissure sealants. According to Bagherian and Shiraz, "Flowable resin composite was first introduced in 1972 for use in restoring cervical erosion and has found many applications in dentistry, such as stress-relieving gingival increments in Class II and V restorations. Over the past 15 years, these materials have been further developed, and the applicability of flowable composites as pit and fissure sealants has expanded because of their desirable properties, such as low viscosity, low modulus of elasticity, and ease of handling. It has been proposed that a greater quantity of filler particles may lower the porosity and cause less polymerisation shrinkage with better wear resistance, which is particularly important when the material used is of low thickness relative to conventional resin-based pit and fissure sealants." p92[25]

Eleven randomised controlled trials were included in this review; the age and number of participants involved in the trials or the type of teeth sealed are not reported. The risk of bias of the included trials was assessed using a modified version of the JADAD scale; four trials were judged to have a low risk of bias, and seven trials were judged to have a medium risk of bias.

The main finding from this review is that using flowable composite resins as fissure sealants had a slightly significant positive effect on retention rates compared with the use of conventional resin-based sealants. However, we judge the current evidence from this review to be inconclusive, as the borderline significance and bias in the primary studies means that we cannot conclude that either flowable composite resin sealants or conventional resin-based sealants are superior to the other.

According to Bagherian and Shiraz, "it seems that using flowable composite as a fissure sealing material in clinical practice can be a good alternative in fissure sealant treatment, specifically when it is combined with an adhesive system; although, the findings of this study points to the need for further clinical research to achieve a more reliable clinical implication." p96[25]

Alirezaei *et al.* (2018)[26] compared glass-ionomer cements with resin-based sealants with respect to retention and their ability to prevent the occurrence of caries. According to Alirezaei *et al.*, "the conventional fissure resin-based sealants are based on bisphenol A-glycidyl methacrylate resins or urethane-based hydrophobic products that are easy to apply, have proper flow, allow for unlimited working time, and require no mixing, but their effectiveness may be jeopardized by the difficulty in obtaining ideal isolation during application. Alternatively, glass-ionomer cement-based sealants are moisture-friendly materials that clinicians have used as an alternative fissure sealing material because they are less technique sensitive, have a chemical bond to dental tissue, and have anticariogenic properties that result from the production of an acid-resistant surface of fluoride-modified hydroxyapatite because of the fluoride reservoir. Glass-ionomer cement-based sealants reduce chair time because, unlike the resin-based sealants, they do not require intermediate steps, such as etching." p640[26]

Thirty-one randomised controlled trials were included in this review; the age and number of the participants in the trials are not reported, and the type of teeth under investigation is not identified. The Jadad scale was used to assess the risk of bias for the included studies; 16 trials were judged to have a low risk of bias, and the remaining 15 trials were judged to have a medium risk of bias.

The main findings from this review suggest that there is adequate evidence that conventional resin-based sealants have a superior retention capacity compared with glass-ionomer cement-based sealants. There is no difference between these materials for preventing caries, so the evidence is inconclusive for this finding. According to Alirezaei *et al.*, "there was no difference between the percentage of caries development with use of GICs [glass-ionomer cements] as fissure sealing

material and that for conventional RBSs [resin-based sealants]. However, the retention rate of the conventional RBSs was much higher than that of the GICs." p648[26]

Yengopal and Mickenautsch (2010)[78] compared the effect of resin-modified glass-ionomer cement fissure sealants with resin-based fissure sealants on the absence of caries in permanent teeth. According to Yengopal and Mickenautsch, the use of "resin-based fissure sealant materials relies on the sealing of pits and fissures through micro-retention, created through tags after acid etching of enamel…resin-modified glass-ionomer cements contain approximately 10% of resin, usually hydroxyethyl-methacrylate." p18[78]

Six randomised controlled trials were included in this review. Five trials involved participants with an age range of 5–27 years; the age of participants in the sixth trial is unclear, but the trial involved paediatric patients. It is reported in the review that first molar, second molar, and premolar teeth were examined in the included trials. The Cochrane Collaboration's risk of bias instrument was used to assess the quality of the included trials. All trials were rated as having an unclear risk of selection bias; having a high risk for detection bias, as it was not possible to blind in the trials; and having a moderate risk of attrition bias, as drop-outs were less than 30%. According to Yengopal and Mickenautsch, "the results of the quality assessment warrants that the data be treated with caution, owing to an increased risk of bias [in the included trials]." p22[78]

The main finding from this review suggests that the evidence is inconclusive regarding whether resin-modified glass-ionomer cements or resin-based fissure sealants are more effective in preventing dental caries in permanent teeth. The meta-analysis of homogeneous datasets at three-time intervals showed no statistical difference between resin-modified glass-ionomer cements and resin-based fissure sealants. The results of seven additional heterogeneous datasets were in line with the finding from the meta-analysis.

According to Yengopal and Mickenautsch, "this systematic review with meta-analysis found no evidence that either material was superior to the other in preventing dental caries. Therefore, both materials appear to be equally suitable for clinical application as fissure sealant for a period of up to 2 years." p24[78]

4.4.2.5 Summary: sealants to prevent caries in adults

Table 9 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on three reviews of sealants to prevent dental caries in adults. The primary research investment in this area requires more investment.

From the three reviews that evaluated sealants, there is adequate evidence from one review (Alirezaei *et al.*) that conventional resin-based sealants have a superior retention capacity compared with glass-ionomer cement-based sealants. In the review by Bagherian and Shiraz, the evidence is inconclusive regarding whether flowable composite sealants or conventional resin-based sealants have superior retention rates. Finally, in the two reviews by Alirezaei *et al.* and Yengopal and Mickenautsch, the evidence is inconclusive regarding whether conventional resin-based sealants or glass-ionomer cement-based sealants, and resin-modified glass-ionomer cements or resin-based fissure sealants, respectively, perform better in terms of preventing caries in adult permanent teeth.

Table 9 Three reviews of sealants to prevent caries in adults

Lead author and year	Level of evidence
Bagherian and Shiraz (2018)[25]	Inconclusive evidence comparing flowable composite sealants with conventional resin-based sealants for retention rates
Alirezaei *et al.* (2018)[26]	Adequate evidence that conventional resin-based sealants have superior retention capacity compared with glass-ionomer cement-based sealants Inconclusive evidence comparing conventional resin-based sealants with glass-ionomer cement-based sealants for preventing caries
Yengopal and Mickenautsch (2010)[78]	Inconclusive evidence regarding whether resin-modified glass-ionomer cements or resin-based fissure sealants perform better in terms of preventing caries in permanent teeth

4.4.3 Treatment of dental caries in adults

4.4.3.1 Early treatment for non-cavitated caries in adults

4.4.3.1.1 Introduction

In total, we included 20 reviews that evaluate interventions for early treatment of caries in adults. We have grouped the interventions covered in the 20 reviews into five categories:

- Category 1 includes remineralising agents; for example, casein phosphopeptide-amorphous calcium phosphate and fluoride therapies
- Category 2 includes microinvasive strategies; for example, sealing and infiltration
- Category includes dental adhesives and other retention aids; for example, self-etch, etch and rinse, and enamel bevelling
- Category 4 includes restorations; for example, glass-ionomer cements and composite resins, and
- Category 5 contains interventions that combine elements of microinvasive strategies with elements of remineralising agents.

4.4.3.1.2 Remineralising agents for the treatment of early caries lesions in adults

We have included six reviews that compare remineralising agents with each other, with a placebo, or with no intervention. Tao *et al.* (2018)[30] and Li *et al.* (2014)[109] compared casein phosphopeptide-amorphous calcium phosphate used in combination with fluorides with the use of fluoride therapies alone; Indrapriyadharshini *et al.* (2018)[31] compared casein phosphopeptide-amorphous calcium phosphate in paste form with fluoride varnishes and with a placebo; Paula *et al.* (2017)[110] compared fluoride therapies, casein phosphopeptide-amorphous calcium phosphate, and ICON resins with each other; Raphael and Blinkhorn (2015)[111] compared casein phosphopeptide-amorphous calcium phosphate technologies with routine oral care; and Yengopal and Mickenautsch (2010)[78] compared resin-modified glass-ionomer cement with fluoride-containing composite resin and with composite resin without fluoride for reducing demineralisation in hard tooth tissues.

Tao *et al.* (2018)[30] compared the use of casein phosphopeptide-amorphous calcium phosphate in combination with fluorides with the use of fluorides monotherapy in patients with early caries lesions in permanent teeth. According to Tao *et al.*, "casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) is a nanocomplex derived from milk. It can stabilise higher concentrations of calcium and phosphate in an amorphous state to enhance remineralisation… Fluoride can facilitate calcium and phosphate diffusion into the demineralised lesions to remineralise the crystalline structures. The rebuilt crystalline structures, composed of fluoridated hydroxyapatite and fluorapatite, are much

more resistant to acid attack than the original ones. Furthermore, fluoride can also affect cariogenic bacterial metabolism through several complex mechanisms." p2[30]

Ten randomised controlled trials involving 559 patients were included in this review. The Cochrane Collaboration's risk of bias instrument was used to assess the quality of the included trials. One trial was scored as having a high risk of bias, six as having an unclear risk of bias, and three as having a low risk of bias. The age of study participants in the trials is unclear, but young adults appear to have been included.

The analysis showed that the combination of casein phosphopeptide-amorphous calcium phosphate and fluorides treatment was better than fluorides monotherapy for occlusal early caries lesions. In addition, fluorides combined with casein phosphopeptide-amorphous calcium phosphate achieved the same results for early caries lesions on smooth surfaces.

However, the main finding from this review suggests that there is insufficient, incomplete, and inadequate evidence upon which to judge the effectiveness of the combination of casein phosphopeptide-amorphous calcium phosphate and fluorides when compared with fluorides monotherapy. According to Tao *et al.*, "the limited number of studies resulted in tiny subgroups, which suggests that the evidence is incomplete and is not generalizable." p8[30]

Li *et al.* (2014)[109] compared the use of casein phosphopeptide-amorphous calcium phosphate in any modality with the use of fluoride toothpastes or mouthwashes, placebos, topical creams, and chewing gum in order to assess their long-term (>3 months) remineralising effect on early caries lesions.

The review included 2,340 participants in eight randomised or quasi-randomised clinical trials in which casein phosphopeptide-amorphous calcium phosphate was delivered by any method. The findings were presented in a narrative analysis. There were no age limits; some participants were adults, but nearly all participants were adolescents. Five studies had a high risk of bias, two had an unclear risk of bias, and one had a low risk of bias.

Casein phosphopeptide-amorphous calcium phosphate has a long-term remineralising effect on early caries lesions, by comparison with a placebo, although this does not appear to be significantly different from that of fluorides. There appears to be no significant advantage to using casein phosphopeptide-amorphous calcium phosphate as a supplement to fluoride-containing products in biased studies; therefore, the evidence for this intervention is inadequate.

Indrapriyadharshini *et al.* (2018)[31] compared casein phosphopeptide-amorphous calcium phosphate in paste form with fluoride varnish or with a placebo in both naturally occurring and post-orthodontic white spot lesions in vivo in any age or type of teeth. According to Indrapriyadharshini *et al.*, "a new calcium phosphate remineralization technology has been developed based on CPP-ACP [casein phosphopeptide-amorphous calcium phosphate], where CPP stabilizes high concentrations of calcium and phosphate ions, together with fluoride ions, at the tooth surface by binding to pellicle and plaque. The calcium phosphate-based remineralization technology has been shown as a promising adjunctive treatment to fluoride therapy in the management of early caries lesions… Since CPP-ACP can stabilize calcium and phosphate in the solution, it can also help in the buffering of plaque pH and so calcium and phosphate level in plaque is increased. Therefore, calcium and phosphate concentration within the subsurface lesions is kept high which results in remineralization." p488[31]

Eleven randomised controlled trials and one non-randomised controlled trial with a total of 1,118 participants of all ages were included in this review; the remineralising effect of the intervention compared with that of the controls was considered on either primary or permanent teeth. Based on

the Cochrane Collaboration's risk of bias instrument, seven trials were judged to have a low risk of bias, three trials to have a moderate risk of bias, and two trials to have a high risk of bias.

Four of the 12 studies evaluated the effect of casein phosphopeptide-amorphous calcium phosphate in paste form on naturally occurring early caries lesions compared with that of a placebo or with no treatment, out of which three studies reported a significant reduction in caries increment after using the paste compared with a placebo. The remaining eight trials examined secondary caries as a result of orthodontic treatment, which is beyond the scope of this evidence review.

The main finding from this review suggests that there is inconclusive evidence to support the claim that casein phosphopeptide-amorphous calcium phosphate is potentially an effective remineralising agent for treating naturally occurring white spot lesions.

We base this judgement on the finding that casein phosphopeptide-amorphous calcium phosphate performed better than a placebo in three randomised controlled trials; however, these comparisons did not yield a statistically significant difference between intervention and comparator, and high levels of heterogeneity among the trials prevented a meta-analysis from being performed.

The judgement of Indrapriyadharshini *et al.* based on the present evidence for casein phosphopeptide-amorphous calcium phosphate, is that "within the limitation of this systematic review, a high level of evidence of remineralizing potential of CPP-ACP [casein phosphopeptide-amorphous calcium phosphate] on naturally occurring WSL [white spot lesions]…was found in comparison with placebo…without any statistically significant difference." p495[31]

Paula *et al.* (2017)[110] compared different remineralisation agents (fluoride products, casein phosphopeptide-amorphous calcium phosphate, and ICON resin) with each other for the treatment of white spot lesions in both permanent and primary teeth.

Thirteen randomised controlled trials with 1,187 participants were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, eight trials were judged to have a high risk of bias, four trials to have a medium risk of bias, and one trial to have an unclear risk of bias.

Most of the studies included in this review reported that therapy with remineralising agents reduces white spot lesions (in terms of their size or visual appearance). Three of four studies concluded that fluoride products were associated with the remineralisation of white spot lesions. Studies of the effects of casein phosphopeptide-amorphous calcium phosphate and ICON resin indicated an association with the regression of white spot lesions, either in size or in their clinical visual appearance.

Despite these signals in the data, the main finding from this review suggests that there is weak and inadequate evidence upon which to assess the effectiveness of the different remineralising agents included in the review, due to bias.

According to Paula *et al.*, "More studies are required for scientific evidence in order to reach a conclusion of the most suitable therapeutic method for the treatment of surface and subsurface demineralization of the enamel." p23[110]

Raphael and Blinkhorn (2015)[111] compared the effectiveness of Tooth Mousse® (MI Paste®) and Tooth Mousse Plus® (MI Paste Plus®), containing the active ingredient casein phosphopeptide-amorphous calcium phosphate, with that of a routine oral care regimen for the prevention and treatment of early dental caries. According to Raphael and Blinkhorn, "Tooth Mousse® (MI Paste®) contains 10% of the Recaldent® molecule by weight. Calcium phosphopeptide (CPP) is milk derived protein able to bind calcium and phosphate ions and stabilise them as amorphous calcium phosphate (ACP). Casein phosphopeptide-amorphous calcium phosphate adheres intra-orally to plaque pellicle, hydroxyapatite as well as soft tissues. It supplies bioavailable calcium and phosphate into saliva and

plaque fluid enabling it to drive remineralisation… Tooth Mousse Plus® (MI Paste Plus®) contains 900 parts per million fluoride in a molar ratio with the calcium and phosphate of 5 calcium, 3 phosphate and 1 fluoride which is reported as the ideal ratio for building fluorapatite." p2[111]

Ten randomised and two non-randomised controlled trials with 1,481 participants aged 0–31 years were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, one trial was judged to have a low risk of bias and three trials to have an unclear risk of bias, and the remaining eight were judged to have a high risk of bias. Three of the trials focused on preventing and nine on controlling dental caries.

The main finding from this review is that there is insufficient and inadequate evidence upon which to judge the effectiveness of the interventions under investigation. According to Raphael and Blinkhorn, "there is a lack of evidence to support the use of Tooth Mousse® (MI Paste®) over a routine preventive fluoride regimen for the prevention of early dental caries. With regard to the use of Tooth Mousse® (MI Paste®) and Tooth Mousse Plus® (MI Paste Plus®) for the regression of white spot lesions associated with orthodontic treatment there is a tendency towards a benefit for their use, but the quality of evidence is limited. Furthermore, at this time there is a lack of support for the use of the fluoride-containing formulation – Tooth Mousse Plus® (MI Paste Plus®) –over Tooth Mousse® (MI Paste®)…the lack of sufficient high-level clinical evidence for the efficacy of these specific casein phosphopeptide-amorphous calcium phosphate containing products remains a limitation." p11[111]

Yengopal and Mickenautsch (2010)[78] compared the effectiveness of resin-modified glass-ionomer cement with that of fluoride-containing composite resin and with that of composite resin without fluoride in reducing demineralisation in hard tooth tissues under caries challenge.

Nine two-arm laboratory trials, three randomised in situ trials, and one randomised controlled trial were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, the randomised in situ trials and the randomised controlled trial were judged to have an unclear risk of bias. The ages of the participants and the types of teeth under investigation are unclear in the review. No quality assessment was undertaken for the laboratory trials.

The main findings from this review suggest that there is some evidence that the use of resin-modified glass-ionomer cements is associated with a higher reduction of demineralisation in adjacent hard tooth tissue compared with the use of composite resin without fluoride. However, this evidence derives from only four small in situ trials with an unclear risk of bias and is therefore considered to be inadequate evidence upon which to judge the effectiveness of the interventions under investigation. As pointed out by Yengopal and Mickenautsch, "the in situ results favouring RM-GIC [resin-modified glass-ionomer cement] above composite resin may have been overestimated; not only because of the lack of adequate random sequence allocation and allocation concealment, but also because of the very small sample sizes of the in situ trials." p355[78]

No difference was found when resin-modified glass-ionomer cements were compared with fluoride-containing composite resin, so we judge the evidence for this comparison to be inconclusive, as it is not possible to know which intervention is better.

4.4.3.1.3 Summary: remineralisation agents for the treatment of early caries lesions in adults

Table 10 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on six reviews of remineralising agents to enable early treatment of dental caries in adults. The investment in, and quality of, primary research in this area appears to be inadequate.

In four of the six reviews that evaluated remineralising agents, there is inadequate evidence upon which to judge the performance of the intervention when compared with controls. For example,

there is inadequate evidence (Tao *et al.* and Li *et al.*) upon which to judge the effectiveness of the combination of casein phosphopeptide-amorphous calcium phosphate and fluorides when compared with fluorides monotherapy; inadequate evidence (Raphael and Blinkhorn) upon which to judge the effectiveness of casein phosphopeptide-amorphous calcium phosphate technologies compared with routine oral care; and, in the review by Paula *et al.,* there is inadequate evidence upon which to assess the effectiveness of casein phosphopeptide-amorphous calcium phosphate, fluoride products, and resins when compared with each other. We judged the evidence to be inconclusive (Indrapriyadharshini *et al.*) to support the claim that casein phosphopeptide-amorphous calcium phosphate is an effective remineralising agent with which to treat naturally occurring white spot lesions. In addition, we determined that there was inadequate evidence (Yengopal and Mickenautsch) upon which to judge the performance of resin-modified glass-ionomer cement when compared with fluoride-containing composite resin, and with composite resin without fluoride, in reducing demineralisation in hard tooth tissues.

Table 10 Six reviews of remineralisation agents for early treatment of dental caries in adults

Lead author and year	Level of evidence
Tao *et al.* (2018)[30]	Inadequate evidence upon which to judge the effectiveness of the use of casein phosphopeptide-amorphous calcium phosphate in combination with fluorides when compared with fluorides monotherapy
Indrapriyadharshini *et al.* (2018)[31]	Inconclusive evidence to support casein phosphopeptide-amorphous calcium phosphate as an effective remineralising agent to treat naturally occurring white spot lesions
Paula *et al.* (2017)[110]	Inadequate evidence upon which to assess the effectiveness of different remineralising agents
Raphael and Blinkhorn (2015)[111]	Inadequate evidence upon which to judge the effectiveness of Tooth Mousse® (MI Paste®) and Tooth Mousse Plus® (MI Paste Plus®), containing the active ingredient casein phosphopeptide-amorphous calcium phosphate, for preventing and treating early dental caries
Li *et al.* (2014)[109]	Inadequate evidence that casein phosphopeptide-amorphous calcium phosphate in any modality is better than fluoride toothpastes or mouthwashes, placebos, topical creams, or chewing gum in treating early caries lesions
Yengopal and Mickenautsch (2010) [78]	Inadequate evidence upon which to judge the performance of resin-modified glass-ionomer cement when compared with fluoride-containing composite resin, and with composite resin without fluoride, in reducing demineralisation in hard tooth tissues

4.4.3.1.4 Microinvasive strategies for early treatment in adults

We included five reviews that compare microinvasive interventions with less invasive interventions, a placebo, or no treatment. Liang *et al.* (2018)[112] compared microinvasive interventions with non-invasive measures (e.g. fluoride), a placebo, or no treatment; Krois *et al.* (2018)[92] compared microinvasive treatments with non-invasive treatments or with a placebo; Schwendicke *et al.* (2015a)[28] compared non-invasive, microinvasive, and minimally invasive treatments with each other, and with no active treatment, a placebo treatment, or with standard oral home care; Dorri *et al.* (2015)[95] compared microinvasive treatments with non-invasive measures, invasive measures, no intervention, or a placebo; and Doméjean *et al.* (2015)[96] compared resin infiltration with the use of a fluoride varnish, sealant micro-brush, or water application.

Liang *et al.* (2018)[112] compared the effectiveness of microinvasive interventions with non-invasive measures (e.g. fluoride), a placebo, or no treatment in arresting non-cavitated proximal caries lesions and analysed their effectiveness in acting on caries lesions of different depths. According to Liang *et*

al., microinvasive interventions primarily belong in two categories: sealants and resin infiltration. The authors go on to state that "the reported sealing materials were classified into three types: resin sealant (which included adhesives and pit and fissure sealant), glass-ionomer cement, and polyurethane tape… Resin infiltration, a low-viscosity resin, can fill the pores of demineralized enamel and create a barrier by capillary action after enamel pre-treatment to block further bacterial diffusion and lesion development." p2676[112]

Eight citations of seven trials (six randomised and one non-randomised) with follow-up periods from 12–36 months were included in the review. The trials involved 303 participants with an age range of 6.5–39 years. Of the seven trials assessed using the Cochrane Collaboration's risk of bias instrument, two trials were judged to have a low risk of bias, four had a high risk of bias, and one had an unclear risk of bias.

The main finding from this review suggests that there is adequate evidence that resin infiltration and resin sealants are effective microinvasive interventions in arresting the progression of non-cavitated proximal caries. There is inadequate evidence to judge the effectiveness of glass-ionomer cements as, according to Liang *et al.*, "it remains unclear whether GIC [glass-ionomer cement] is effective...more clinical studies are needed to further explore this issue." p2681[112]

Further analysis of the interventions for caries lesions of different depths indicated that there is adequate evidence that resin infiltration could arrest progression of enamel caries and caries around the enamel-dentine junction. However, when the outer third of the dentine was involved, resin infiltration did not yield significantly different results compared with the control group. In contrast, according to Liang *et al.*, "The subgroup analysis showed that resin sealant was ineffective for reducing the caries progression rate at different depths, even for enamel caries, which was contradictory to the overall effect. This contradiction may be associated with limited original studies that focused on different depths of non-cavitated proximal caries". p2682[112] For dentine caries as distinct from enamel caries, the therapeutic effectiveness of resin infiltration was not significantly different (inconclusive) from the control group. According to Liang *et al.*, "based on existing evidence, dentists should carefully select appropriate micro-invasive interventions according to the different depths of non-cavitated proximal caries." p2675[112]

Krois *et al.* (2018)[92] compared microinvasive treatments with non-invasive treatments or a placebo to arrest early non-cavitated proximal carious lesions in children and adolescents. According to Krois *et al.*, "micro-invasive strategies (sealing and infiltration) remove a few micro-meters of tissue during application, usually when conditioning the tooth surface with acids, and install a diffusion barrier onto (lesion sealing) or within (lesion infiltration) the carious tissue. The barrier (of resins or glass-ionomer cements) impedes acid diffusion into the hard tissue and further mineral loss from it, thereby arresting the lesion… Non-invasive strategies remove no carious tissue at all and include dietary control, biofilm control, or control of de- and re-mineralisation (via fluorides etc.) often combined with each other." p15[92]

Fifteen reports of 13 randomised controlled trials with 486 participants were included in this review. Four trials assessed lesions in primary teeth and nine trials assessed lesions in permanent teeth. Participants comprised children, adolescents, and young adults with a mean age of 15 years.

The Cochrane Collaboration's risk of bias instrument was used to assess bias in the included trials. All trials showed a low risk of bias with regard to blinding of the assessment, but there were limited indications of selective reporting or issues of random sequence generation. In contrast, blinding of operators or participants was always rated as having an unclear or high risk of bias, and allocation concealment was rated as having an unclear risk of bias in seven studies. Nearly all trials on

infiltration were sponsored by the the treatments' manufacturers, and two trials were conducted by the treatments' inventors.

Based on the findings of this review, there is adequate evidence that sealing/infiltration is superior to non-invasive treatment. In addition, there is adequate evidence to suggest that either sealing or infiltration used separately is superior to non-invasive treatment. The evidence is inconclusive regarding the superiority of sealing compared with infiltration.

According to Krois *et al.,* "sealing or infiltration instead of non-invasive (NI) treatment would avoid 278 per 1,000 treated lesions to progress (44% NI and 16% sealed or infiltrated lesions would progress). The certainty of the evidence was graded as moderate. Sealing instead of NI would avoid 282 per 1,000 treated lesions to progress. The certainty of the evidence was graded as moderate. Infiltration instead of NI would avoid 266 per 1,000 treated lesions to progress (as the control group event proportion was lower). The certainty of the evidence was graded as high… Based on this review and analysis, micro-invasive treatment should be chosen over NI treatment (strong recommendation) … we are hence confident in this conclusion".p18[92]

Schwendicke *et al.* (2015a)[28] compared non-invasive, microinvasive, and minimally invasive treatments with each other, with no active treatment or a placebo treatment, or with standard oral home care for treating pit and fissure lesions in permanent posterior teeth in adults. According to Schwendicke *et al.*, "non-invasive strategies e.g. fluoride avoid any removal of hard tissues and focus, for example, on influencing the equilibrium of demineralization and remineralization or removing/controlling the biofilm activity. Micro-invasive strategies, e.g. sealants, involve conditioning of dental hard tissues and are thus not completely non-invasive; however, only a few micrometers of enamel or dentine are removed. These strategies aim at establishing a diffusion barrier for acids, minerals, or carbohydrates via sealing the lesion…minimally invasive treatments include preventive resin restorations, sealant restorations, or enameloplasty and do not follow the principle of 'extension for prevention' but are guided by the extension of the caries lesion and aim at preserving hard tissues. Occlusally, they can be performed without greatly sacrificing sound tooth tissue (which is a difference to treatment of proximal lesions), while the effectiveness of the resulting restoration is largely independent from patients' compliance, with potentially long retention times of such minimally invasive restorations." p522-23[28]

Ten randomised and four non-randomised controlled trials involving 1,440 patients with 3,551 treated lesions in permanent posterior teeth were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, all 14 trials were judged to have a high risk of bias.

The analysis showed that microinvasive and minimally invasive treatments were potentially effective in avoiding invasive retreatments after treating pit and fissure lesions in permanent posterior teeth. In addition, there was some evidence that non-invasive treatments might also be effective in avoiding invasive retreatments after treating pit and fissure lesions in permanent posterior teeth. The need for any retreatment was significantly higher in microinvasively sealed lesions than in those that received non-invasive or minimally invasive treatments.

However, the main finding of this review suggests that the evidence is weak (due to the high risk of bias in all studies) and there is inadequate evidence upon which to judge the effectiveness of the interventions under evaluation. According to Schwendicke *et al.*, "the studies supporting these findings were mostly of limited quality; thus, the overall certainty of our findings [based on GRADE] is thus low or very low." p531[28]

Dorri *et al.* (2015)[95] compared microinvasive treatments with non-invasive measures, invasive measures, no intervention, or a placebo for managing proximal caries lesions in primary and

permanent dentition in children and adults. According to Dorri *et al.*, "micro-invasive treatments involve conditioning the tooth surface using organic acids prior to treating the caries lesion. The conditioning involves the loss of few micro-meters of tooth enamel. There are two types of micro-invasive treatments: sealing and resin infiltration." p6[95]

Eight randomised controlled trials with 365 participants were included in this review. The authors report that the participants ranged in age from 4–39 years. Based on assessment using the Cochrane Collaboration's risk of bias instrument, the authors judged seven of the eight trials to be at high risk of bias, primarily due to lack of blinding of participants and personnel.

The findings in this review suggest that there is adequate evidence that microinvasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions and is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss). This finding is based on moderate evidence according to the GRADE levels of evidence, and the authors are "moderately confident that further research is unlikely to substantially change the estimate of effect". p2[95] However, the evidence is inconclusive regarding which microinvasive technique offers the greatest benefit, due to the small number of studies available for analysis.

Doméjean *et al.* (2015)[96] compared the effectiveness of resin infiltration with the use of a fluoride varnish, sealant micro-brush, or water application in arresting non-cavitated caries lesions. According to Doméjean *et al.*, "resin infiltration is a technique that involves infiltrating the porosities of an enamel lesion with a low viscosity resin…the potential caries-inhibiting effect of RI [resin infiltration] is dependent on the occlusion of the pores within the body of the caries lesion." p217[96]

Three randomised controlled trials, which were reported in four articles, were included in this review. The trials involved children, adolescents, and adults. All four articles reported on proximal caries lesions. One article had 48 high-caries-risk children while the other three (n=22, 22, and 39, respectively) had moderate- and low-caries-risk adolescents and adults. The quality of the studies was assessed by the authors to be high with respect to randomisation, split-mouth design, and blinding; however, they reported using CONSORT (Consolidated Standards of Reporting Trials) as the instrument for quality assessment. It must be noted that CONSORT is primarily used for assessing the reporting quality of trials, and it does not evaluate the risk of bias, so it is the reporting quality of the included trials that is judged to be high.

All four papers analysed (based on three trials with small sample sizes) showed significant differences in caries progression in favour of resin infiltration compared with the control/placebo groups. However, the risk of bias was not assessed appropriately, and the overall sample (N=131) was small, which suggests that there is inconclusive evidence that resin infiltration is effective in arresting the progression of caries. According to Doméjean *et al.*, "the use of RI [resin infiltration] to arrest the progression of non-cavitated caries lesions is encouraging. This suggests that RI is a promising non-invasive approach and might be considered as an additional option to non-operative and operative treatment approaches". p220[96]

4.4.3.1.5 Summary: microinvasive strategies for early treatment in adults

Table 11 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on five reviews of microinvasive strategies to enable early treatment of dental caries in adults. The investment in, and quality of, primary research in this area appears to be adequate.

There is adequate evidence in three of the five reviews evaluating microinvasive strategies that resin infiltration and sealants are effective interventions for the early treatment of caries in adult teeth. For example, there is adequate evidence (Liang *et al.*) that resin infiltration and resin sealants are

effective microinvasive interventions to arrest the progression of non-cavitated proximal caries, and that resin infiltration could arrest the progression of enamel caries and caries around the enamel-dentine junction. There is inconclusive evidence for the therapeutic effectiveness of resin infiltration on dentine caries (Liang *et al.*). There is adequate evidence (Krois *et al.*,) that sealing/infiltration is superior to non-invasive treatment and that either sealing or infiltration used separately is superior to non-invasive treatment. Dorri *et al.* report adequate evidence that microinvasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions, and that this is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss). In the review by Doméjean *et al.*, there is inconclusive but positive evidence that resin infiltration may be effective in arresting the progression of dental caries in adults, although there is inconclusive evidence (Krois *et al.*; Dorri *et al.*) regarding which microinvasive technique offers the greatest benefit. There is inadequate evidence (Schwendicke *et al.* 2015a) upon which to judge the effectiveness of non-invasive, microinvasive, and minimally invasive treatments, as all included studies had a high risk of bias and the authors graded the evidence as being of low or very low quality. In addition, there is inadequate evidence (Liang *et al.*) upon which to judge the effectiveness of glass-ionomer cements.

Table 11 Five reviews of microinvasive strategies for early treatment of dental caries in adults

Lead author and year	Level of evidence
Liang *et al.* (2018)[112]	Adequate evidence that resin infiltration and resin sealants are effective microinvasive interventions to arrest the progression of non-cavitated proximal caries Inadequate evidence upon which to judge the effectiveness of glass-ionomer cements Adequate evidence that resin infiltration could arrest the progression of enamel caries and caries around the enamel-dentine junction Inconclusive evidence for the therapeutic effectiveness of resin infiltration on dentine caries
Krois *et al.* (2018)[92]	Adequate evidence that sealing/infiltration is superior to non-invasive treatment Adequate evidence that either sealing or infiltration used separately is superior to non-invasive treatment Inconclusive evidence regarding the superiority of sealing compared with infiltration
Schwendicke *et al.* (2015a)[28]	Inadequate evidence upon which to compare the effectiveness of non-invasive, microinvasive, and minimally invasive treatments
Dorri *et al.* (2015)[95]	Adequate evidence that microinvasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions, and is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss) Inconclusive evidence regarding which microinvasive technique offers the greatest benefit
Doméjean *et al.* (2015)[96]	Inconclusive evidence that resin infiltration is effective in arresting the progression of caries in adults

4.4.3.1.6 Dental adhesives and other retention aids for early caries treatment in adults

We included six reviews that compared dental adhesives and other retention aids with each other or with no treatment. The interventions were primarily evaluated on their potential to aid the preparation and retention of dental restorations in adult teeth. da Silva *et al.* (2018)[113] compared 2-hydroxyethyl methacrylate (HEMA)-free adhesive systems with HEMA-containing systems; Schroeder *et al.* (2017)[114] compared self-etch with etch-and-rinse adhesive strategies; Szesz *et al.* (2016)[115] compared selective etching of enamel margins with no etching as a method of improving retention

rates; Schroeder *et al.* (2015)[116] compared enamel bevelling with no enamel bevelling to improve retention rates; Peumans *et al.* (2014)[117] compared a range of contemporary adhesives with each other; and Chee *et al.* (2012)[118] compared simplified adhesives (two-step self-etch and one-step self-etch) with conventional adhesives (three-step etch and rinse and two-step etch and rinse).

da Silva *et al.* (2018)[113] compared HEMA-free adhesive systems with HEMA-containing systems to treat non-carious cervical lesions in permanent teeth in adults. According to da Silva *et al.*, "2-hydroxyethyl methacrylate (HEMA) seems to be the most commonly used [component in dental adhesives] and it is an important chemical component. This monomer was introduced in the adhesive composition during the 1970s with the aim of improving the wettability and diffusion into the demineralized collagen fibrils because of its high hydrophilicity. However, some long-term disadvantages have been reported, particularly with regard to its high hydrophilicity over time. The increased water uptake results in hydrolytic degradation of the adhesive interface. For this reason, manufacturers launched adhesive systems without this monomer, the so-called HEMA-free adhesives, into the market to avoid its negative effects." p1[113]

Twenty-two randomised controlled trials involving a total of 997 adults were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, 13 trials were judged to be at low risk of bias, and in the remaining nine trials, the risk of bias was judged to be unclear.

The main finding from this review is that when HEMA-free adhesive systems were compared with HEMA-containing adhesive systems, the evidence is inconclusive regarding which system is better, as performance is similar for both. According to da Silva *et al.*, "the results of the meta-analysis for RE [restoration effectiveness] showed no significant difference between the two groups compared (HEMA-free versus HEMA-containing systems). Therefore, both HEMA-free and HEMA-containing adhesive systems had a good behavior for RE in NCCL [non-carious cervical lesion] restorations within the reviewed studies. Thus, it can be stated that even monomers, or a blend of monomers, without HEMA, may interpenetrate, cure, and play their main initial role in the RE of the composite resin." p12[113]

Schroeder *et al.* (2017)[114] compared composite restorations bonded to self-etch adhesives with composite restorations bonded to etch-and-rinse adhesives for post-operative sensitivity, retention rates, and marginal discolouration in non-carious cervical lesions. In describing some of the functions of both adhesive strategies and the type of lesion under investigation in this review, Schroeder *et al.* point out that "for the good performance of etch and rinse systems, a preliminary etching of the dental substrate with phosphoric acid is needed prior to the application of the bonding solution. The aim of this procedure is to remove smear layer, which, in turn, increases the dentine permeability and hydraulic conductance of dentine…self-etch systems do not remove but incorporate the smear layer in the hybridized complex; this had led to widespread belief that self-etch systems produce composite restorations with less risk of post-operative sensitivity…cervical lesions are usually hypermineralised dentine lesions, characterised by the presence of dentine sclerotic casts within the dentine tubules." p36[114]

Fifty articles based on 42 randomised controlled trials were included in this review, and follow-ups of the same studies were merged for analysis. The authors report great variation in the age range of adult participants involved in the trials where age was reported. Based on the Cochrane Collaboration's risk of bias instrument, 13 of the 42 trials were judged to be at a high risk of bias. The remaining 29 trials were judged to be at low risk of bias, and only these 29 were included in the meta-analysis.

The results of this review suggest that there is adequate evidence that using etch-and-rinse adhesives with composite restorations can result in a better reduction of marginal discolouration when compared with using self-etch adhesives. In addition, there is adequate evidence that using either bonding strategy does not influence the risk of post-operative sensitivity, which, according to Schroeder *et al.*, "reinforces the fact that the adhesive strategy is not responsible for post-operative sensitivity". p49[114] When considering the loss of restoration, the evidence is inconclusive, as no significant differences between etch-and-rinse versus self-etch adhesives were observed in any of the follow-up periods. In conclusion, Schroeder *et al.* point out that "composite resin restorations placed with self-etch and etch and rinse adhesives produce restorations with a similar retention rate and post-operative sensitivity; however using etch and rinse adhesives can reduce marginal discoloration." p51[114]

Szesz *et al.* (2016)[115] compared selective etching of enamel margins with no etching to improve the retention rates and marginal discolouration of cervical composite restorations in non-carious cervical lesions of adult patients. The authors do not provide a detailed description of the intervention aside from pointing out that "selective etching of enamel margins with phosphoric acid has been recommended prior to the application of self-etch adhesives." p2[115]

Ten randomised controlled trials with 242 adult participants were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, three trials were at high risk of bias and seven trials were judged to be at low risk of bias.

The main finding from this review is that there is adequate evidence that the selective enamel etching technique is better than controls for improving the marginal adaptation, discolouration, and retention of composite restorations in non-carious cervical lesions in the adult population.

The meta-analysis undertaken in this review revealed that, except for at one-year follow-up, there was a significantly lower marginal discolouration and better marginal adaptation during all follow-up periods when selective enamel etching was performed. Significantly less loss of restorations at the three-year follow-up was also observed when the selective enamel etching technique was used.

Szesz *et al.* conclude that "the selective enamel etching prior to application of self-etch adhesive systems in non-carious cervical lesions can produce composite restorations with better esthetics (lower marginal discoloration rates and better marginal integrity) and higher longevity (higher retention rates)." p10[115]

Schroeder *et al.* (2015)[116] compared enamel bevelling with no enamel bevelling to improve the retention of composite restorations in non-carious cervical lesions of adult patients. According to Schroeder *et al.*, "considering the enamel substrate, the placement of an enamel bevel may be a good option, taking into consideration that laboratory studies have shown that this procedure can reduce marginal microleakage, reduce the risk of fracture in the marginal enamel, result in better adhesion and yield to improved aesthetics." p778[116]

Four randomised controlled trials with 164 adult participants were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, one trial had a low risk of bias, two trials were judged to have a high risk of bias, and one had an unclear risk of bias.

The main finding in this review suggests that the evidence is inconclusive, as there was no difference between bevelled and non-bevelled restorations at the short-term follow-up of 12–18 months. However, this finding is based on only two trials with noted limitations. According to Schroeder *et al.*, "the present study did not indicate any superiority of the restorations where enamel bevelling was performed, and the extrapolation of these conclusions to the overall practice should be done with caution." p786[116]

Peumans *et al.* (2014)[117] compared a range of contemporary adhesives with each other for the restoration of non-carious cervical lesions in permanent teeth in terms of restoration retention over time. According to Peumans *et al.*, "contemporary adhesives can be classified according to their mode of action into etch&rinse and self-etch adhesives. Materials with adhesive potential to tooth tissue can be categorized into 6 main classes: 3-step etch&rinse adhesives, 2-step etch&rinse adhesives, 2-step self-etch adhesives, 1-step self-etch adhesives, all four can bond restorative composite to tooth tissue, glass-ionomers and self-adhesive composites." P1090[117] Eighty-seven clinical trials, including both randomised and non-randomised trials, were included in this review. Neither the age nor the number of participants in the trials were reported in the review. The authors do not report undertaking a risk of bias assessment of the included studies.

The main findings reported in this review suggest that the lowest annual failure rate scores were recorded for glass-ionomers, closely followed by two-step etch-and-rinse adhesives, three-step etch-and-rinse adhesives, and one-step self-etch adhesives_mild. Significantly higher annual failure rate scores were recorded for one-step self-etch adhesives, two-step etch-and-rinse adhesives, and two-step self-etch adhesives. In addition, significant differences in annual failure rates were noticed between adhesives of the same class, except for glass-ionomer and two-step self-etch adhesives_mild. Finally, selective enamel etching (compared with non-etching) did not significantly influence the retention rates of self-etch adhesives. Based on the absence of a quality assessment of such a large number of included studies, we conclude that the current evidence is weak and insufficient, and that there is inadequate evidence upon which to judge the effectiveness of the interventions under investigation for restoring non-carious cervical lesions in permanent teeth.

Chee *et al.* (2012)[118] compared simplified adhesives (two-step self-etch and one-step self-etch) with conventional adhesives (three-step etch and rinse and two-step etch and rinse) for treatment of non-carious cervical lesions in the permanent teeth of adults. According to Chee *et al.*, "the 3-step etch-and-rinse approach conventionally involves etching the tooth with 30–40% phosphoric acid, followed by the application of a primer and subsequently an adhesive resin… Two-step etch-and rinse systems combine the primer and adhesive into one bottle but maintain a separate etching step to remove the smear layer and demineralise the surface layer of enamel and dentine. Self-etch systems penetrate through the smear layer and incorporate it into the hybrid layer to varying degrees dependent upon their acidity. They consist of either a self-etching primer accompanied by an adhesive resin applied as a subsequent step, or a self-etch adhesive which does not require a separate primer." p444[118]

Twenty-six randomised controlled trials involving 1,032 adults comparing at least two adhesives in non-carious cervical lesions in permanent teeth, with at least 18 months of follow-up, were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, 10 trials were judged to be at a high risk of bias, and the risk of bias was unclear in the remaining 16 trials.

The main finding from this review suggests that there is insufficient and inadequate evidence upon which to judge the effectiveness of the interventions under investigation. According to Chee *et al.*, "there was insufficient evidence to make firm recommendations for the use of one adhesive system or bonding strategy over another. The proportion of information obtained from studies with an unclear or high risk of bias was high. The null hypothesis of no difference could not be supported or rejected with the data currently available… There is not enough evidence to support one adhesive or bonding strategy over another for treatment of non-carious cervical lesions." p450[118]

4.4.3.1.7 Summary: dental adhesives and other retention aids for early caries treatment in adults

Table 12 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on six reviews of adhesives and other retention aids to enable early treatment of dental caries in adults. The investment in, and quality of, primary research in this area appears to be improving.

Regarding the six reviews that evaluated dental adhesives and other retention aids, there is adequate evidence (Szesz *et al.*) that the selective enamel etching technique is better than controls for improving the marginal adaptation, discolouration, and retention of composite restorations in non-carious cervical lesions in the adult population. When the HEMA-free adhesive system is compared with the HEMA-containing adhesive system, the evidence is inconclusive (da Silva *et al.*) regarding which system is better, as performances for both are similar. There is inconclusive evidence (Schroeder *et al.* 2015) regarding whether bevelled restorations or non-bevelled restorations are superior at short-term follow-up of 12–18 months.

In two reviews that evaluated adhesives, there is inadequate evidence (Peumans *et al.*; Chee *et al.*) upon which to judge the effectiveness of contemporary adhesives for the restoration of non-carious cervical lesions in permanent teeth. In contrast, Schroeder *et al.* (2017) compared restorations bonded using self-etch adhesives with restorations bonded using etch-and-rinse adhesives for post-operative sensitivity, retention rates, and marginal discolouration in non-carious cervical lesions, and found adequate evidence that using etch-and-rinse adhesives can result in a better reduction of marginal discolouration when compared with using self-etch adhesives. In addition, there is adequate evidence (Schroeder *et al.* 2017) that neither bonding strategy (etch and rinse or self-etch) influences the risk of post-operative sensitivity; regarding the retention of restorations, the evidence is inconclusive (Schroeder *et al.* 2017), as no significant differences between etch-and-rinse compared with self-etch adhesives were observed at any point during the follow-up period. It must be noted that although three reviews (Peumans *et al.*; Chee *et al.*; Schroeder *et al.* 2017) examined the trial evidence for the same types of adhesives and found similar outcomes, the conclusions we can draw from the earlier reviews by Peumans *et al.* and Chee *et al.* and those we can draw from the latest work by Schroeder *et al.* in 2017 are quite distinct, and can be explained by the variation in the quality of the evidence assessed in each review. For example, the review by Peumans *et al.* did not report assessing the risk of bias in the included trials, and in the review by Chee *et al.*, the risk of bias in the included trials was either high or unclear, whereas in the review by Schroeder *et al*. (2017), the 29 trials that were used in the meta-analysis were all judged to be at low risk of bias.

Table 12 Six reviews of early treatment of adhesives and other retention aids for early treatment of dental caries in adults

Lead author and year	Level of evidence
da Silva *et al.* (2018)[113]	Inconclusive evidence regarding whether HEMA-free adhesive systems or HEMA-containing adhesive systems are superior
Schroeder *et al.* (2017)[114]	Adequate evidence that using etch-and-rinse adhesives with composite restorations can result in a better reduction of marginal discolouration when compared with using self-etch adhesives Adequate evidence that neither bonding strategy (etch and rinse or self-etch) influences the risk of post-operative sensitivity in composite restorations Inconclusive evidence regarding which adhesive strategy is superior for retention of restoration, as no significant differences between etch-and-rinse and self-etch adhesives were observed at any point during the follow-up period
Szesz *et al.* (2016)[115]	Adequate evidence that the selective enamel etching technique is better than controls in improving the marginal adaptation, discolouration, and retention of composite restorations in non-carious cervical lesions in the adult population
Schroeder *et al.* (2015)[116]	Inconclusive evidence regarding whether bevelled or non-bevelled restorations are superior, as there is no difference between bevelled and non-bevelled restorations at short-term follow-up of 12–18 months
Peumans *et al.* (2014)[117]	Inadequate evidence upon which to judge the effectiveness of contemporary adhesives for the restoration of non-carious cervical lesions in permanent teeth
Chee *et al.* (2012)[118]	Inadequate evidence upon which to judge the effectiveness of simplified adhesives compared with conventional adhesives

4.4.3.1.8 Dental restorative materials for early treatment in adults

We included two reviews that compared different restorative materials with each other for the treatment of non-carious cervical lesions in the permanent teeth of adults. Boing *et al.* (2018)[119] compared retention and colour match of glass-ionomer cement restorations with resin-based composite restorations, and Szesz *et al.* (2017)[120] compared flowable resin composite restorations with regular resin composites for improving the marginal adaptation, marginal discolouration, and retention rates of restorations.

Boing *et al.* (2018)[119] compared retention and colour match of glass-ionomer cement restorations with resin-based composite restorations in non-carious cervical lesions in the permanent teeth of adults. According to Boing *et al.*, "out of the 15 studies analyzed in this systematic review, 10 used resin-modified glass-ionomer cement (RMGIC) and only 5 used glass-ionomer cement (GIC). RMGICs were developed to overcome some of the problems of early moisture sensitivity and reduced mechanical strength of the GIC… RMGIC/GIC are self-adhesive by forming ionic bonds between the carboxyl groups of polyalkenoic acid and hydroxyapatite and by producing micromechanical interlocking of the polymer with the dentine substrate." p444[119]

Nineteen articles examining 15 randomised controlled trials were included in this review. The Cochrane Collaboration's risk of bias instrument was used to assess the quality of the included trials, and all 15 trials were judged to have an unclear risk of bias.

The main findings in this review suggest that there is adequate evidence that glass-ionomer cement restorations showed superior retention rates compared with resin-based composite restorations in follow-ups of between one and five years. The quality of evidence was graded as moderate to low.

However, the authors do signal a note of caution: "this [finding in favour of resin-modified glass-ionomer cement] should be interpreted with caution, because the articles included are at 'unclear' risk of bias. Well-designed RCTs [randomised controlled trials] with a large sample size should be conducted to confirm the findings of this review and meta-analysis." p450[119]

Szesz *et al.* (2017)[120] compared flowable resin composite restorations with regular resin composites for improving the marginal adaptation, marginal discolouration, and retention rates of restorations placed in non-carious cervical lesions in permanent adult teeth. According to Szesz *et al.*, "flowable resin composites are low-viscosity restorative materials that differ from regular viscosity resin composites by having lower filler load and less viscous resin content. As a result, these materials are less rigid and have an elastic modulus 20% to 30% lower than that of regular viscosity composites. This reduced low elastic modulus can theoretically absorb the stresses generated during the polymerization shrinkage of composites and during mechanical loading in which the teeth are subjected during function." p12[120]

Eight randomised controlled trials with 262 adult participants were included in this review. The quality of the included trials was assessed using the Cochrane Collaboration's risk of bias instrument; two trials were judged to be at high risk of bias, and the remaining six trials had an unclear risk of bias.

The main findings from this review suggest that there is adequate evidence that resin composite viscosity does not influence retention rates at up to three years follow-up. The analysis showed that there was no significant difference in loss of retention between the intervention and comparator in any follow-up period (the quality of the evidence was moderate at three-year follow-up and low at two-year follow-up, based on GRADE). According to Szesz *et al.*, "data were not heterogeneous in any of the periods, which means that all studies included in the analysis share a common effect size." p16[120]

The evidence is weak and there is therefore inadequate evidence upon which to judge the effectiveness of either group of resin composites on marginal discolouration and marginal adaptation. The analysis showed that there was no significant difference between groups for marginal discolouration in any recall period (the quality of the evidence for marginal discolouration and marginal adaptation is low for all follow-up periods based on GRADE). Flowable composites showed better results for marginal adaptation at the one- and three-year follow-ups (the quality of the evidence is low to very low for both follow-up periods based on GRADE).

According to Szesz *et al.*, "the retention rates and marginal discoloration of resin composite restorations in non-carious cervical lesions are not affected by the resin viscosity, although flowable composites showed a better marginal adaptation. The quality of the evidence was graded as moderate for the retention rate at 3 years. All other outcomes were graded as low and very low quality." p20[120]

4.4.3.1.9 Summary: dental restorative materials for early treatment in adults

Table 13 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on two reviews of restorative materials for the early treatment of dental caries in adults. The investment in, and quality of, primary research in this area appears to be improving.

In the two reviews that evaluated dental restorative materials, there is adequate evidence (Boing *et al.*) that glass-ionomer cement restorations showed superior retention levels compared with resin-based composite restorations in follow-ups at between one and five years, and there is adequate evidence (Szesz *et al.*) to support the claim that resin composite viscosity does not influence retention rates at up to three years follow-up. The quality of this evidence was judged to be moderate in both

reviews based on GRADE. There is inadequate evidence (Szesz *et al.*) upon which to compare flowable resin composite restorations with regular resin composites in terms of marginal discolouration and marginal adaptation, as the quality of the evidence was judged to be low.

Table 13 Two reviews of dental restorative materials for early treatment in adults

Lead author and year	Level of evidence
Boing *et al.* (2018)[119]	Adequate evidence that glass-ionomer cement restorations showed superior retention rates compared with resin-based composite restorations in follow-ups at between one and five years (moderate evidence based on GRADE)
Szesz *et al.* (2017)[120]	Adequate evidence that resin composite viscosity does not influence retention rates at up to three years follow-up Inadequate evidence upon which to judge the effectiveness of either flowable resin composite restorations or regular resin composites on marginal discolouration and marginal adaptation

4.4.3.1.10 Remineralising agents and microinvasive strategies combined for early treatment in adults

We included two reviews that compared interventions which combined elements of microinvasive strategies and elements of remineralising agents with each other, with other active interventions, with a placebo, or with no treatment. Urquhart *et al.* (2019)[29] compared non-restorative treatments with other active intervention(s), no treatment, or a placebo, and Tellez *et al.* (2013)[27] compared non-surgical methods with each other, no treatment, a placebo, saline, professional oral hygiene, fluoride toothpaste or mouthwash, or fluoride gel.

Urquhart *et al.* (2019)[29] compared non-restorative treatments with other active intervention(s), or with no treatment or a placebo, for the arrest or reversal of non-cavitated and cavitated carious lesions on primary and permanent teeth in children and adults. According to Urquhart *et al.*, non-restorative treatments include "sodium fluoride, stannous fluoride toothpaste or gel, acidulated phosphate fluoride, difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, amorphous calcium phosphate (ACP), casein phosphopeptide–ACP (CPP-ACP), nano hydroxyapatite, tricalcium phosphate, prebiotics and/or 1.5% arginine, probiotics, silver diamine fluoride, silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, and carbamide peroxide". p15[29]

Forty-three randomised controlled trials based on 48 reports, which involved 7,378 participants and assessed the effectiveness of 22 interventions, were included in this review. The precise age range of the participants is not reported in the review. Twelve trials involved participants with primary dentition, 22 with permanent dentition, and 9 with mixed dentition. The risk of bias in the included trials was assessed using the Cochrane Collaboration's risk of bias instrument. The authors note that "information to judge most risk of bias domains was often incomplete or missing. The domain of allocation concealment was judged to be the most serious methodological issue, and overall most studies had serious issues of risk of bias". p17[29]

The results of this systematic review support a range of interventions that are effective in arresting and/or reversing non-cavitated and cavitated carious lesions. Results from the network meta-analysis suggest that there is adequate evidence that the combination of sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth (moderate certainty based on GRADE). There is inadequate evidence that the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective intervention for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth

(low certainty based on GRADE). Similarly, the evidence is inadequate to suggest that 5000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective intervention for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth (low certainty based on GRADE).

Results from the study-level data show that when compared with no intervention, there is adequate evidence that 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth (low to moderate certainty based on GRADE). There is adequate evidence that the use of 1.23% acidulated phosphate fluoride gel on facial/lingual lesions, compared with oral health education, was effective, although only at longer follow-up times (12 months) (moderate certainty based on GRADE). According to Urquhart *et al.*, "the certainty in the evidence ranged from very low to high for the outcome of arrest or reversal across all surfaces, types of lesions, and dentition. We predominantly downgraded the certainty due to serious issues of risk of bias and imprecision". p23[29]

Tellez *et al.* (2013)[27] compared the effectiveness of non-surgical caries prevention methods with each other, no treatment, a placebo, saline, professional oral hygiene, fluoride toothpaste or mouthwash, or fluoride gel in arresting or reversing the progression of non-cavitated carious lesions.

According to Tellez *et al.*, "this review evaluated the following therapies: fluorides in varying vehicles (toothpaste, gel, varnish, mouthrinse, and combination), chlorhexidine alone or in combination with F [fluoride], resin infiltration, sealants, xylitol in varying vehicles (lozenges, gum, or in combination with F and/or xylitol), casein phosphopeptide-amorphous calcium phosphate or in combination with calcium fluoride phosphate". p80[27]

Twenty-nine randomised controlled trials were included in this review, incorporating 5,771 participants aged 6–39 years at the start of the studies. The quality of the included trials was assessed initially using the criteria reported in the *American Dental Association Clinical Recommendations Handbook for randomised clinical trials*; in addition, the trials were assessed using the Cochrane Collaboration's risk of bias instrument, and ratings for the overall strength of the evidence (poor, fair, or good) were assigned by consensus among three of the authors. According to Tellez *et al.*, "no formal weighting scheme was employed in making these judgments, but authors considered all the parameters accounted for in the ADA's [American Dental Association's] quality assessment in addition to sample size and duration of the trial". p81[27] The great majority of the included trials (65.5%) did not use intention to treat analysis, 21% did not use any blinding techniques, and 41% reported concealment allocation procedures. Slightly more than half of the trials (55%) factored in background exposure to other fluoride sources, and only 41% properly adjusted for potential confounders.

The analysis suggests that fluoride interventions (varnishes, gels, and toothpastes) seem to have the most consistent benefit in decreasing the progression and incidence of non-carious cervical lesions. Studies using xylitol, chlorhexidine, and casein phosphopeptide-amorphous calcium phosphate vehicles alone or in combination with fluoride therapy are very limited in number, and in the majority of cases they did not show a statistically significant reduction in non-carious cervical lesions. Sealant and resin infiltration studies point to a potential consistent benefit in slowing the progression of or reversing non-carious cervical lesions.

Despite these tentative signals in the data that both fluoride- and non-fluoride-based prevention may yield some benefit in treating non-carious cervical lesions, we conclude that the current evidence is weak and there is therefore inadequate evidence upon which to draw firm conclusions about the effectiveness of the interventions under investigation. According to Tellez *et al.*, "more than half of the trials assessed had moderate to high risk of bias or may be categorized as 'poor'". p94[27]

4.4.3.1.11 Summary: early treatment for dental caries in adults using remineralising agents and microinvasive strategies combined

Table 14 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on two reviews of remineralising agents and microinvasive strategies used in combination to enable early treatment of dental caries in adults. The investment in, and quality of, primary research in this area appears to be improving.

In the review by Urquhart *et al.* evaluating combinations of remineralising agents and microinvasive strategies, there is adequate evidence that the combination of sealants and 5% sodium fluoride varnish is effective for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth; that 5% sodium fluoride varnish is effective in arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth; and that 1.23% acidulated phosphate fluoride gel is effective on facial/lingual lesions, but only at longer follow-up times (12 months). There is inadequate evidence that the combination of resin infiltration and 5% sodium fluoride varnish is effective for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth; that 5000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel is effective for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth;There is inadequate evidence (Tellez *et al.*) upon which to draw firm conclusions about the effectiveness of combined non-surgical caries prevention methods, such as sealants and non-fluoride antibacterials or chemicals.

Table 14 Two reviews of early treatment for dental caries in adults using remineralising agents and microinvasive strategies combined

Lead author and year	Level of evidence
Urquhart *et al.* (2019)[29]	Adequate evidence that the combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in permanent teeth Adequate evidence that 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on permanent teeth Adequate evidence that the use of 1.23% acidulated phosphate fluoride gel is better than relying on oral health education to treat facial/lingual lesions at 12 months follow-up. Adequate evidence that 38% silver diamine fluoride applied twice per year was more effective than controls in arresting caries lesions in primary teeth and in providing an anti-caries benefit for the entire dentition Inadequate evidence that the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective treatment for non-cavitated carious lesions on approximal surfaces in permanent teeth Inadequate evidence to suggest that 5000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective treatment for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth
Tellez *et al.* (2013)[27]	Inadequate evidence upon which to draw firm conclusions about the effectiveness of combined non-surgical caries prevention methods, such as sealants and non-fluoride antibacterials or chemicals

4.4.3.2 Late or restorative treatment of cavitated caries in adults

4.4.3.2.1 Introduction

In total, we have included 18 reviews that speak to the late treatment of caries in adults. We have grouped the interventions covered in these reviews into two categories: 1) restorative procedures and techniques, and 2) restorative materials. The distinguishing feature of the interventions included in Category 1 is that the primary unit of investigation was either a technique or procedure to aid either the placement of restorative materials or the removal of caries. In contrast, the distinguishing feature of interventions included in Category 2 is that the primary unit of investigation was the dental restorative material(s) used to restore cavities in adult teeth.

4.4.3.2.2 Restorative procedures and techniques used in the treatment of cavitated caries in adults

We included nine reviews that compared either techniques or procedures with each other, a placebo, or no intervention. Three reviews (Schenkel *et al.*, 2019;[100] Boruziniat *et al.*, 2016;[121] and Schwendicke *et al.*, 2015b [122]) compared different types of dental cavity liners with controls. Two reviews (Montedori *et al.*, 2016;[101] and Ricketts *et al.*, 2013[102]) compared different procedures for removing dental caries; one review (Reis *et al.*, 2015)[123] compared adhesive techniques for bonding restorations; and one review (Dorri *et al.*, 2017)[22] compared atraumatic restorative treatment with conventional drill and fill for placing restorations in adult teeth. Brodén *et al.* (2016)[124] compared pulp capping procedures with root canal treatments, and Alqaderi *et al.* (2016)[21] compared coronal pulpotomy treatment with amalgam or composite restoration to treat carious vital pulp exposure in permanent posterior teeth. Here, we present a structured account for each of the nine reviews in the order presented in this paragraph.

Schenkel *et al.* (2019)[100] compared the effects of using dental cavity liners with those of not using liners in the placement of Class I and Class II resin-based composite posterior restorations in permanent teeth in children and adults. According to Schenkel *et al.*, "dental cavity liners are designed to protect the pulp from the toxic effects of dental restorative materials and to prevent the pain of thermal conductivity by placing an insulating layer between restorative material and the remaining tooth structure… The liners most commonly used in restorative dentistry include calcium hydroxide and glass-ionomer cements, both of which are available in either chemical or light-cured formulations." p7[100]

Eight randomised controlled trials comprising more than 700 participants were included in this review; the participants included children aged 15 years and older, and adults. Based on the Cochrane Collaboration's risk of bias instrument, the risk of bias was judged to be high in five trials and unclear in the remaining three trials. The primary outcomes measured were the longevity of restorations and post-operative hypersensitivity.

When the use of dental cavity liners was compared with using no liners under the placement of composite resin restorations in permanent teeth, the evidence was judged to be inconsistent and low quality, and there is therefore inadequate evidence upon which to judge the performance of the intervention regarding any difference in post-operative sensitivity, measured using either cold response or patient-reported response. There was no difference between using dental cavity liners compared with using no liners on the longevity of composite resin restorations in permanent teeth, which renders the evidence for this outcome inconclusive. In conclusion, based on the current evidence, the authors see no reason why the use of liners would add any benefit to the routine resin-based restorations in permanent posterior teeth in adults. According to Schenkel *et al.*, "the evidence

does not currently support including the unnecessary step of placing any lining material underneath routine composite-based restorations in adult posterior teeth." p19[100]

Boruziniat *et al.* (2016)[121] compared an application of flowable composite as a liner with no liner being applied on the amount of microleakage in Class II composite restorations. According to Boruziniat *et al.*, "because of their lower filling loading, flowable composites exhibited lower modules of elasticity and more stress buffering capacity than hybrid composite resins, and this leads to the better marginal seal of flowable composites. On the other hand, some studies demonstrate that application of flowable composites has no effect on marginal adaption or microleakage and its low viscosity may lead to increased incidence of gingival overhangs." p94[121]

Twelve randomised controlled trials and six non-randomised trials were included in this review. There was no restriction on age or type of tooth being restored. The number of participants and types of teeth examined are not reported in this review. Although the authors do not report their methods of assessing the risk of bias for the included studies, they do mention that they assessed the methodological quality of the studies using a validated checklist, and they also mention that only high- and moderate-quality papers were selected for data extraction.

The main finding from this review is that there is adequate evidence in favour of not using flowable composite liners to reduce microleakage from composite restorations. We base this judgement on the absence of any mention of the current evidence being weak or insufficient; indeed, the authors signal that they relied on moderate- to high-quality studies. However, our confidence in the findings could have been improved if the quality of the methods used in this review were improved. According to Boruziniat *et al.*, "the results of the present study showed that the application of flowable composite as an intermediate layer has neither improved the performance of the composite restoration nor reduced its performance." p100[121]

Schwendicke *et al.* (2015b) [122] compared the antibacterial effects of different cavity liners with each other, a placebo, or no liner. According to Schwendicke *et al.*, "as liners are thought to induce the development of reactionary dentine, reduce post-operative pulpal inflammation, or isolate the pulp from chemical irritants like hydroxyethyl methacrylate, they are commonly used for pulp protection… A second reason why the use of liners has been advocated was their remineralizing effects, especially when selective (incomplete) or stepwise excavation was performed prior to restoration… Last, lining materials are used as they might reduce bacterial numbers, i.e. acting as cavity disinfection: This has been especially postulated for the most widely used material, calcium hydroxide, whose alkaline pH is supposed to exert strong antibacterial effects." p1298 [122]

Eleven randomised controlled trials and three non-randomised trials with a total of 457 participants were included in this review; two studies used the same control group and were combined for the analysis. The age of the patients ranged from 4–67 years. Based on the Cochrane Collaboration's risk of bias instrument, all included trials were assessed as being at high or unclear risk of bias.

Based on the analysis of the 11 trials included in the network meta-analysis, mineral trioxide lining yielded the greatest probability of achieving sterile cavities after a lining/sealing period (73%), followed by an antibiotic/disinfectant (8%) and zinc oxide eugenol (7%). Only six studies assessed bacterial reduction after lining/sealing, and zinc oxide eugenol was found to have the highest probability of achieving a bacterial reduction. In both analyses, not providing any lining was found to have low antibacterial effects.

However, we judge the evidence to be insufficient and weak, and we find that there is inadequate evidence upon which to judge the performance of different liners for their antibacterial effects. According to Schwendicke *et al.*, "the underlying data for these findings are sparse, the ranking

should thus be interpreted with caution, as indicated by the absence of statistically significant differences in both pairwise and network meta-analyses estimates." p1303 [122]

Montedori *et al.* (2016)[101] compared laser-based methods with conventional mechanical methods for removing dental caries in deciduous and permanent teeth. According to Montedori *et al.*, "laser is an acronym standing for light amplification by stimulated emission of radiation. Laser is a device emitting a high coherence light beam with waves at single frequency (very narrow spectrum)." p7[101] The conventional mechanical methods for removing dental caries are: handpiece with a bur, the chemomechanical system, the sono-abrasion system, and the air-abrasion system.

Nine randomised controlled trials involving 662 participants with an age range of 3.5–84 years were included in this review. Four trials involved children and adolescents; four trials involved only adults; and one trial involved children, adolescents, and adults. Overall, the individual trials had small sample sizes, and the majority were judged to have an unclear or high risk of bias based on the Cochrane Collaboration's risk of bias instrument.

Regarding the primary outcome examined, which was the removal of caries from deciduous and permanent teeth, the quality of the evidence was insufficient to determine whether either lasers or mechanical drill methods were superior for removing caries; only two included trials evaluated this outcome. Some studies seemed to favour laser therapy over the mechanical methods for pain control, the need for anaesthesia, and patient discomfort, but the evidence was rated as low quality based on the GRADE assessment and therefore inadequate. According to Montedori *et al.*, "despite some encouraging results, the applicability of lasers in current clinical practice is uncertain." p24[101]

Ricketts *et al.* (2013)[102] compared stepwise, partial, or no caries removal with complete caries removal in previously unrestored primary and permanent teeth in children and adults. According to Ricketts *et al.*, "stepwise caries removal removes caries in stages over two visits some months apart, allowing the dental pulp time to repair itself and lay down dentine. Partial caries removal removes part of the caries and seals what is left into the tooth permanently. No dentinal caries removal [does not remove any] caries before sealing or restoring." p3[102] What is referred to as the traditional treatment removes all the dental decay in one session.

Eight randomised controlled trials with 934 participants were included in this review. In this Cochrane review, all of the eight included trials were judged to have a high risk of bias.

The main finding of this review suggests that stepwise and partial caries removal reduced the incidence of pulp exposure in primary and permanent teeth that were symptomless, vital, and carious. This finding suggests that there is adequate evidence to demonstrate the clinical advantage of using selective caries removal over the complete removal of caries in both primary and permanent teeth. According to Ricketts *et al.*, "no evidence was found to suggest that selective caries removal is harmful. In fact, the reverse is true as complete caries removal is more likely to result in carious exposure of the pulp." p23[102] The evidence is inconclusive regarding the superiority of no caries removal compared with complete caries removal.

Reis *et al.* (2015)[123] compared the effects of posterior resin composite restorations that were bonded using self-etching with posterior resin composite restorations that were bonded using etch-and-rinse adhesives on the risk and intensity of post-operative sensitivity in permanent dentition (posterior restorations) of adult patients. According to Reis *et al.*, "etch-and-rinse systems employ a phosphoric acid to etch enamel and dentine prior to the application of the bonding solution. As a consequence, the smear layer is removed and the dentine tubules are opened, increasing the dentine permeability and hydraulic conductance of dentine…[in contrast,] self-etch systems are thought to lower the risk of

postoperative sensitivity (POS) as they do not remove, but incorporate the smear layer in the hybridized complex with the advantage of being less technique-sensitive." p1053[123]

Twenty-nine randomised clinical trials that compared self-etch with etch-and-rinse adhesives used for direct resin composite restorations in permanent posterior restorations in adult patients were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, five trials were at high risk of bias and 11 were considered to have an unclear risk of bias; the remaining 13 trials, with a total of 1,010 participants, were judged to be at low risk of bias and were used in the meta-analysis.

The main finding from this review suggests that the evidence is inconclusive regarding which type of adhesive strategy – etch and rinse or self-etch – is superior, as the use of either adhesive strategy did not affect the risk of post-operative sensitivity in posterior resin composite restorations.

According to Reis *et al.*, "one may conclude that the type of adhesive strategy (ER [etch and rinse] or SE [self-etch]) for posterior resin composite restoration does not seem to influence the risk and intensity of postoperative sensitivity. However further studies should be conducted to evaluate if this is still applied for large and deep posterior resin composite restorations." p1065[123]

Dorri *et al.* (2017)[22] compared atraumatic restorative treatment with conventional treatment (the drill and fill approach) for managing dental caries lesions in the primary and permanent teeth of children and adults. Atraumatic restorative treatment "is a minimally invasive approach, which involves removal of decayed tissue using hand instruments alone, usually without use of anesthesia and electrically driven equipment, and restoration of the dental cavity with an adhesive material such as glass-ionomer cement, composite resins, resin-modified glass-ionomer cement, or compomers." p6[22] Conventional methods (drill and fill) involve the use of electric drills to clear away decayed areas of the tooth before filling. A local anaesthetic (painkiller) is normally injected in order to prevent pain during the procedure.

Fifteen randomised controlled trials with 3,760 participants were included in this Cochrane review. The mean age of the participants was 25.4 years (ranging from 3–101 years). Eleven studies evaluated the effects of atraumatic restorative treatment on primary teeth only, and four on permanent teeth only. All 15 trials were judged to be at high risk of bias due to performance, attrition, and selective reporting bias based on the Cochrane Collaboration's risk of bias instrument. Two of the 15 trials had declared industry backing.

The main finding from this review suggests that there is weak and inadequate evidence upon which to compare the performance of atraumatic restorative treatment with that of the conventional technique when placing restorations in the permanent teeth of adults. According to Dorri *et al.*, "given the very low quality of the evidence from single studies, we are uncertain about the restoration failure of atraumatic restorative treatment compared with conventional treatment using composite over a 24-month follow-up period and atraumatic restorative treatment using resin-modified glass-ionomer cement in the permanent teeth of older adults with root caries lesions over a six-month follow-up period." p24[22]

Brodén *et al.* (2016)[124] compared pulp capping procedures with root canal treatments undertaken on young permanent teeth where the vital pulps had been exposed by caries. According to Brodén *et al.*, "the issue of pulp capping in the case of a cariously exposed vital pulp is controversial. It has been advocated that pulp capping should be reserved only for pulps exposed due to reasons other than caries. However, young teeth have a rich apical perfusion and the pulp has a high capacity to respond to insults; therefore, the success rate of pulp capping in young patients might be higher than in adult patients. Root canal treatments are invasive, resource intensive and technically difficult procedures.

In adults, the success rates of root canal treatments of teeth with vital pulps range from 92 to 93%." p201[124]

Two randomised controlled trials and eight trials without control groups were considered in this review. The quality of all 10 studies was rated as low. The search failed to disclose any study directly comparing pulp capping and root canal treatment.

The main finding from this review suggests that there is insufficient and inadequate evidence upon which to compare the performance of pulp capping with root canal treatment. According to Brodén *et al.*, "based on the included studies, the level of evidence on pulp capping procedures versus root canal treatment in young permanent teeth with pulp exposure due to caries, was assessed as very low." p205[124]

Alqaderi *et al.* (2016)[21] compared coronal pulpotomy treatment with amalgam restoration and with composite resin restoration to manage carious vital pulp exposure in permanent posterior teeth with closed root apices. According to Alqaderi *et al.*, "coronal pulpotomy treatment (CPT) involves removing the entire coronal pulp tissue and keeping the remaining pulp vital in the canals… CPT has been considered as a definitive treatment to manage carious pulp exposure for primary teeth, young immature permanent teeth as well as in treating traumatic pulp exposure in mature teeth. It has been shown that the cariously exposed vital pulp has the ability to repair and heal and remain vital after removing the inflamed pulp tissue." p1-2[21]

One randomised controlled trial and five cohort studies were included in this systematic review. The number of participants in the six studies was 265, with an age range of 7–70 years. The assessment of the single randomised trial using the Cochrane Collaboration's risk of bias instrument showed a low level of bias; the cohort studies were assessed using the Newcastle-Ottawa Scale, and the mean total score of the five studies was 4.6 (± 0.5) on a scale of 0–9.

The main finding from this review suggests that there is insufficient, weak, and therefore inadequate evidence upon which to judge the performance of coronal pulpotomy treatment as an intervention to manage carious vital pulp exposure in permanent posterior teeth. According to Alqaderi *et al.*, "coronal pulpotomy treatment could increase tooth retention by providing a potential option particularly for low-income patients or in underserved areas worldwide. However, more studies having longer follow-up, larger sample size, and including a control group are needed to validate the possibility of performing CPT as an alternative to root canal therapy." p6[21]

4.4.3.2.3 Summary: procedures and techniques for restorative treatment of dental caries in adults

Table 15 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on nine reviews of restorative techniques and procedures used to aid dental restorations in adults. The investment in, and quality of, primary research in this area appears to be somewhat inadequate.

Regarding the use of dental cavity liners to aid the placement of dental restorations, there is inadequate evidence (Schenkel *et al.*) upon which to judge their performance, as there is no difference in post-operative sensitivity, measured using either cold response or patient-reported response, between those with liners and those without. There is inadequate evidence (Schwendicke *et al.* 2015b) upon which to judge the performance of different liners for their antibacterial effects, and the evidence is inconclusive (Schenkel *et al.*) when the use of dental cavity liners was compared with not using liners on the longevity of composite resin restorations in permanent teeth. In the review by Boruziniat *et al.*, there is adequate evidence in favour of not using flowable composite liners to reduce microleakage from composite restorations.

Regarding procedures and techniques for removing caries from adult teeth, there is inadequate evidence (Montedori *et al.*) upon which to compare the performance of laser therapy with mechanical methods, and the review by Ricketts *et al.* presents adequate evidence to demonstrate the clinical advantage of using selective caries removal over the complete removal of caries in both primary and permanent teeth.

The evidence is inconclusive (Reis *et al.*) regarding whether etch and rinse or self-etching is the preferred adhesive technique to aid the placement of posterior resin composite restorations, and there is inadequate evidence (Dorri *et al.*) upon which to compare the performance of atraumatic restorative treatment versus the conventional technique when placing restorations in the permanent teeth of adults. In addition, there is inadequate evidence (Brodén *et al.*) upon which to compare the procedure of pulp capping with root canal treatment in young permanent teeth with pulp exposure, and there is inadequate evidence (Alqaderi *et al.*) upon which to judge the performance of coronal pulpotomy treatment when compared with amalgam or with composite resin restoration as an intervention to manage carious vital pulp exposure in permanent posterior teeth.

Table 15 Nine reviews of procedures and techniques for restorative treatment of dental caries in adults

Lead author and year	Level of evidence
	Liners
Schenkel *et al.* (2019)[100]	Inadequate evidence upon which to judge the performance of dental cavity liners regarding any difference in post-operative sensitivity, measured using either cold response or patient-reported response Inconclusive evidence comparing the use of dental cavity liners with not using liners on the longevity of composite resin restorations in permanent teeth
Boruziniat *et al.* (2016)[121]	Adequate evidence in favour of not using flowable composite liners to reduce microleakage from composite restorations
Schwendicke *et al.* (2015b) [122]	Inadequate evidence upon which to judge the performance of different liners for their antibacterial effects
	Laser therapy
Montedori *et al.* (2016)[101]	Inadequate evidence upon which to compare the performance of laser therapy with mechanical methods for removing caries
	Selective caries removal
Ricketts *et al.* (2013)[102]	Adequate evidence to demonstrate the clinical advantage of using selective caries removal over the complete removal of caries in both primary and permanent teeth
	Adhesives
Reis *et al.* (2015)[123]	Inconclusive evidence regarding whether the etch and rinse or the self-etching adhesive strategy is superior for posterior resin composite restorations
	Atraumatic restorative treatment
Dorri *et al.* (2017)[22]	Inadequate evidence upon which to compare the performance of atraumatic restorative treatment with the conventional technique when placing restorations in the permanent teeth of adults
	Pulp treatments
Brodén *et al.* (2016)[124]	Inadequate evidence upon which to compare the performance of pulp capping with root canal treatment in young permanent teeth with pulp exposure
Alqaderi *et al.* (2016)[21]	Inadequate evidence upon which to judge the performance of coronal pulpotomy treatment as an intervention to manage carious vital pulp exposure in permanent posterior teeth

4.4.3.2.4 Restorative materials used in the treatment of cavitated caries in adults

We included nine reviews that compared dental restorative material(s) used to restore cavities in adult teeth with each other, with another active intervention, with a placebo, or with no intervention. Five reviews (Rasines Alcaraz *et al.,* 2014;[9] Sharif *et al.,* 2014;[12] Pereira-Cenci *et al.,* 2013;[125] Fron-Chabouis *et al.*, 2013;[126] and Heintze and Rousson, 2012[14]) evaluated different aspects of composite resin restorations; two reviews (Kielbassa *et al.,* 2017;[127] and Mickenautsch *et al.,* 2010[128]) focused primarily on glass-ionomer cements; one review (Sequeira-Byron *et al.*, 2015[20]) compared single crowns with conventional dental filling materials; and one review (Ma *et al.*, 2016[10]) evaluated different materials used for retrograde filling. We have presented a structured account of each of the nine reviews in this order.

Rasines Alcaraz *et al.* (2014)[9] compared the restoration failure of direct composite resin fillings with amalgam fillings for permanent posterior teeth. According to Rasines Alcaraz *et al.*, "Dental resin composites were developed in response to people's demands for tooth-colored restorations. Dental resin composites are particle-reinforced resins. The indications of resin composites have expanded from anterior teeth to restricted posterior restorations and even to stress-bearing posterior

restorations as amalgam substitutes or amalgam alternatives. Other advantages of dental resin composite restorations include their conservative design and reparability." p6[9]

Seven randomised controlled trials, with data drawn from 10 articles on these trials, were included in this review. The exact age of participants was unclear in some studies; however, both children and adults with permanent teeth at the back of the mouth that required fillings were included. Based on the Cochrane Collaboration's risk of bias instrument, all seven trials were judged to be at high risk of bias.

There is low-quality evidence to suggest that resin composites lead to higher failure rates and risk of secondary caries than amalgam restorations do.

Based on an analysis of the five trials that did not report the participants to be exclusively adults, amalgam fillings had lower failure rates compared with tooth-coloured composite resin fillings used to fill holes caused by decay in permanent teeth at the back of the mouth. However, there is weak, inadequate, and insufficient evidence upon which to judge the performance of composite resins, when compared with amalgam, on restoration failure rates and the risk of secondary caries. According to Rasines Alcaraz *et al.,* "There is low-quality evidence to suggest that resin composites lead to higher failure rates and risk of secondary caries than amalgam restorations." p18[9] However, there is adequate evidence that restoration fracture is the same for both amalgam and resin composite fillings.

Sharif *et al.* (2014)[12] compared the effects of replacing resin composite with repairing it (with resin composite) in the management of defective resin composite dental restorations in permanent molar and premolar teeth. There is inadequate evidence upon which to judge the effectiveness of resin composite replacement versus repair, as no trials met the inclusion criteria. Another reviewer, Faggion *et al.,* also describe the evidence as inadequate. [48]

Pereira-Cenci *et al.* (2013)[125] compared antibacterial agents incorporated into composite restorations with composite restorations containing no antibacterial agents for the prevention of dental caries. Participants of interest included adults and adolescents in any age group with restorations in the permanent dentition, and children with restorations in the primary dentition. According to Pereira-Cenci *et al.,* "composite restorations consist of two major components: a resin composite for filling and the bonding systems to be applied to the cavity before the placement of filling materials. The incorporation of antibacterial substances in these two components would have different roles relating to the prevention of the harmful effects caused by bacteria within the biofilm covering the tooth/restoration interface. The antibacterial effects of composites for filling would be mainly relevant to inhibition of plaque accumulation on the surface of the materials and tooth around the restoration. In contrast, for bonding systems, their antibacterial effects are discussed in terms of disinfection of the cavity as well as inactivation of bacteria which could invade the adhesive interface due to microleakage." p3[125]

The main finding from this review is that there is insufficient and inadequate evidence upon which to compare the performance of antibacterial agents incorporated into composite restorations with composite restorations containing no antibacterial agents for the prevention of dental caries. According to Pereira-Cenci *et al.,* "No studies were included in this review, as we were unable to find any trials directly comparing antibacterial containing composites to other active interventions or controls." p6[125]

Fron-Chabouis *et al.* (2013)[126] compared composite inlays and onlays with ceramic inlays or onlays for restoring posterior teeth in adults. According to Fron-Chabouis *et al.,* "ceramic inlays and onlays are mainly composed of glass, with some crystals added to increase strength. Composite inlays and

onlays are made of a resinous matrix and fillers of different types. Ceramic materials are resistant to compressive forces than composite materials but are susceptible to tensile stresses and more prone to fracture. However, ceramics are harder than composites and more wear-resistant but can induce more wear than usual with the opposing tooth's surface. Furthermore, adhesive cement interfaces are made of composite material, so the wear of the interface and restoration material should be closer for composites and marginal integrity could be better. Another disadvantage of composites is their resinous matrix and the possible monomer release if it is incompletely polymerized." p1210[126]

Two randomised controlled trials involving 138 inlays (no onlays were evaluated) in 80 patients were included in this review. Based on the Cochrane Collaboration's risk of bias instrument, both trials were judged to be at high risk of bias.

There is some evidence that ceramics may perform better than composite materials for inlays in the short term. However, this evidence is insufficient and weak, and there is therefore inadequate evidence upon which to judge the performance of composite inlays and onlays with ceramic inlays and onlays. According to Fron-Chabouis *et al.,* "although we provide some evidence that ceramic inlays perform better than composite inlays in the short term, this review included only 2 randomized clinical studies and 138 restorations and the 3-year result may not remain in the long term." p1216[126]

Heintze and Rousson (2012)[14] compared both resin composites placed without enamel/dentine conditioning and resin composites placed with self-etching adhesive systems with amalgam restorations in permanent teeth. According to Heintze and Rousson, "in the 1980s, enamel etching became integrated into the operative procedure and it became common practice to use an unfilled, hydrophobic, low-viscosity bonding material between resin and dental tissue. The resins were at first light cured with UV [ultra violet] light units and later with halogen lamps. In addition to the macrofilled composites, microfilled composites appeared on the market. In the late 1980s, the first dentine bonding agents were developed, but these materials still required separate etching of enamel. This method was later replaced by an etch and rinse technique, which involves the simultaneous etching of both enamel and dentine. In 1999, the first self-etching enamel-dentine adhesive systems were released on the market. Since then, these systems – either one- or two-step – have gained popularity among dental practitioners because they shorten and simplify the operational procedures. Self-etching adhesive systems account for about 50% of the market share of all adhesive systems." p408[14]

The authors report that the inclusion criteria for this review meant that only prospective clinical trials with at least two years of observation were considered for inclusion. They note that 59 studies met the inclusion criteria, but they do not provide further information regarding the precise design of the included studies.

According to Heintze and Rousson, "The best overall performance (good color match, small amount of fractures) was achieved with restorations based on hybrid and microfilled composites; the overall longevity was similar to that of amalgam restorations." p417[14] The main finding from this review is that there does not appear to be a great deal of difference between the intervention and the comparator on the main outcome assessed. Thus, we judge the evidence to be inconclusive, as we cannot draw conclusions that one approach is better than the other. In addition, we note that the authors did not report undertaking a quality assessment of the included studies, which raises questions about the adequacy of the evidence. Therefore, we judge the evidence to be inadequate.

Kielbassa *et al.* (2017)[127] compared the use of high-viscosity glass-ionomer cement combined with a resinous coating with the use of amalgam (no studies), resin composite, or other glass-ionomer cements in Class I restorations of posterior primary or permanent teeth. According to Kielbassa *et al.*,

"recently, high-viscosity glass-ionomer cement (hvGIC) processed with a resinous coating (RC) has been introduced, and has been marketed as a restorative material in load-bearing Class I cavities (and in Class II cavities with limited size), thus serving as a possible alternative to amalgam filling." p9[127]

The reporting quality in this review is poor and excludes the search strategy and a risk of bias assessment of the included studies. Seven clinical trials were included, comprising both randomised and non-randomised trials, but it is not clear how many of each type were included in the review. Two of the included studies were industry funded, and the funding status of the other clinical trials remained unclear. It is possible that another two studies were industry sponsored. The authors say that the quality of the randomised controlled trials needs improvement, but they do not elaborate on this statement. The focus in the primary studies that were included appears to be posterior teeth, but it is unclear whether these are permanent or primary teeth.

According to Kielbassa *et al.*, "Within the respective indications and cavity geometries, the high-viscosity glass-ionomer cement with a resinous coating in Class I restorations of posterior primary or permanent teeth would seem possible; this could merge the phase-down of mercury and the objectives of minimally invasive treatment to some extent, and might be a restorative alternative for patients with Class I cavities suffering from allergies to or not willing to afford other sophisticated or expensive techniques, such as composite resin." p16[127]

However, the evidence from this review is weak and insufficient, and there is therefore inadequate evidence upon which to judge the performance of high-viscosity glass-ionomer cement-resin composites as a restorative intervention.

Mickenautsch *et al.* (2010)[128] compared the effectiveness of resin-modified glass-ionomer restorations with conventional glass-ionomer restorations in preventing secondary caries lesions at the margins of restorations. According to Mickenautsch *et al.*, "the original glass-ionomer cements, now referred to as conventional glass-ionomer cements hardened in the tooth cavity because of an acid-based reaction…they were sensitive to water uptake and loss in the first hours or days after setting and this led to the development of resin-modified glass-ionomer cements where approximately 10% of the set material is resin." p139[128]

Four randomised/quasi-randomised controlled trials were included in this review. Two trials involved children and two involved adults. Both primary and permanent teeth were included in the analysis. Based on the Cochrane Collaboration's risk of bias instrument, three trials were judged to be at high risk of bias and one trial had an unclear risk of bias.

According to Mickenautsch *et al.*, the analysis of the two trials examining permanent teeth in adults revealed that "there is no evidence from the two trials in permanent teeth that any difference exists in the incidence of secondary caries adjacent to conventional glass-ionomer cement or resin-modified glass-ionomer cement restorations." p144[128]

However, based on only two trials with weak evidence, we conclude that there is inadequate evidence upon which to judge the performance of resin-modified glass-ionomer restorations compared with conventional glass-ionomer restorations in preventing secondary caries lesions at the margins of restorations in adult permanent teeth. According to Mickenautsch *et al.*, "the review identified a lack of high-quality trials…and further high-quality trials are needed to confirm the observed results." p144[128]

Sequeira-Byron *et al.* (2015)[20] compared the effectiveness of single crowns with that of conventional dental filling materials in restoring endodontically treated permanent teeth (with or without a post and core). In describing both the intervention (indirect) and the comparator (direct), Sequeira-Byron *et al.* outline the following features of both: "indirect restorations (i.e. crowns) are fabricated with

materials such as cast metal or ceramics (porcelain). According to their classical indication, single crowns can restore proportionately larger amounts of missing dentine and enamel than other approaches. However, the need for impressions and associated laboratory work to complete the final restoration may add considerably to the overall costs… The direct approach is through conventional techniques, in which the dentist places a restorative material such as amalgam or composite directly into the tooth. Conventional fillings usually need a single clinical appointment, are generally simpler to achieve than the indirect method, and have good survival characteristics." p6[20]

One randomised controlled trial compared 117 randomised participants who had a root-filled, premolar tooth restored with a carbon fibre post with those who had either a full-coverage metal-ceramic crown or a direct adhesive composite restoration. Based on the Cochrane Collaboration's risk of bias instrument, the trial was judged to be at high risk of bias.

There was no clear difference between the crown and composite group and the composite-only group in terms of non-catastrophic failures of the restoration or in terms of failures of the post at three-year follow-up. However, the evidence is insufficient and weak, and there is therefore inadequate evidence upon which to judge the performance of the intervention under investigation. According to Sequeira-Byron *et al.*, "there is insufficient evidence to assess the effects of crowns compared to conventional fillings for the restoration of root-filled teeth. Until more evidence becomes available, clinicians should continue to base decisions about how to restore root-filled teeth on their own clinical experience, whilst taking into consideration the individual circumstances and preferences of their patients." p2[20]

Ma *et al.* (2016)[10] examined the effectiveness of different materials used for retrograde filling (root canal therapy) in children and adults for whom retrograde filling is necessary in order to save the tooth. The different types of filling materials mentioned in the review comprised mineral trioxide aggregate, intermediate restorative material, super ethoxybenzoic acid, dentine-bonded resin composite, glass-ionomer cement, and amalgam.

Six randomised controlled trials involving 916 participants and 988 permanent teeth were included in this review. In this Cochrane review, all six included trials were judged to have a high risk of bias. The main finding in this review is that there is insufficient evidence upon which to judge whether any of the materials are effective, which renders the evidence inadequate. According to Ma *et al.*, "based on the present limited evidence, we do not have sufficient evidence to determine the benefits of any one material over another." p27[10]

4.4.3.2.5 Summary: materials for caries restoration in adults

Table 16 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on nine reviews of restorative materials for the treatment of dental caries in adults. The investment in, and quality of, primary research in this area appears to be inadequate.

In the five reviews we include that evaluated different aspects of composite resin restorations, the evidence is weak and insufficient, and there is therefore inadequate evidence upon which to judge the performance of the intervention being evaluated. For example, there is inadequate evidence (Rasines Alcaraz *et al.*) upon which to judge the performance of composite resins when compared with amalgam on restoration failure rates and the risk of secondary caries. There is no evidence (Sharif *et al.*) upon which to compare replacing resin composite with repairing resin composite for defective resin composite dental restorations in permanent molar and premolar teeth. Similarly, the evidence is inadequate (Pereira-Cenci *et al.*) upon which to compare the performance of composite restorations containing antibacterial agents with composite restorations containing no antibacterial agents for the prevention of dental caries, and there is inadequate evidence (Fron-Chabouis *et al.*)

upon which to compare the performance of composite inlays and onlays with ceramic inlays and onlays. We judged the evidence to be inadequate in the fifth review (Heintze and Rousson) regarding which is better: resin composites placed without enamel/dentine conditioning or resin composites placed with self-etching adhesive systems, compared with amalgam. Although composites appeared to fare better for colour match and fractures, there was no difference between composites and amalgam on the longevity of restorations, and there are notable limitations regarding the quality of the included studies.

In the two reviews that evaluated glass-ionomer cements, there is inadequate evidence (Kielbassa *et al.*) upon which to judge the performance of high-viscosity glass-ionomer cement combined with a resinous coating when compared with amalgam, resin composite, or other glass-ionomer cements in Class I restorations of posterior primary or permanent teeth. In addition, there is inadequate evidence (Mickenautsch *et al.*) upon which to judge the performance of resin-modified glass-ionomer cement restorations when compared with conventional glass-ionomer restorations in preventing secondary caries lesions at the margins of restorations in adult permanent teeth.

In the two remaining reviews that evaluated different materials, there is inadequate evidence (Sequeira-Byron *et al.*) with which to assess the effects of crowns compared with conventional fillings for the restoration of root-filled teeth, and there is inadequate evidence (Ma *et al.*) upon which to judge the performance of any material for retrograde filling (root canal therapy).

Table 16 Nine reviews of restorative materials for late treatment of dental caries in adults

Lead author and year	Level of evidence
	Composite resin
Rasines Alcaraz *et al.* (2014)[9]	Inadequate evidence upon which to judge the performance of composite resins when compared with amalgam on restoration failure rates and the risk of secondary caries
Sharif *et al.* (2014)[12]	Inadequate evidence upon which to compare replacing (using resin composite) with repairing (using resin composite) defective resin composite restorations in permanent molar and premolar teeth
Heintze and Rousson (2012)[14]	Inadequate evidence regarding which is better: resin composites placed without enamel/dentine conditioning or resin composites placed with self-etching adhesive systems, compared with amalgam
Pereira-Cenci *et al.* (2013)[125]	Inadequate evidence upon which to compare the performance of antibacterial agents incorporated into composite restorations with composite restorations containing no antibacterial agents for the prevention of dental caries
	Glass-ionomer cement
Kielbassa *et al.* (2017)[127]	Inadequate evidence upon which to judge the performance of high-viscosity glass-ionomer cement combined with a resinous coating as a restorative intervention
Mickenautsch *et al.* (2010)[128]	Inadequate evidence upon which to judge the performance of resin-modified glass-ionomer restorations compared with conventional glass-ionomer restorations in preventing secondary caries lesions at the margins of restorations in adult permanent teeth
	Indirect restorations
Fron-Chabouis *et al.* (2013)[126]	Inadequate evidence upon which to compare the performance of composite inlays and onlays with ceramic inlays and onlays
	Crowns
Sequeira-Byron *et al.* (2015)[20]	Inadequate evidence upon which to assess the effects of crowns compared with conventional fillings for the restoration of root-filled teeth
	Root canal therapy
Ma *et al.* (2016)[10]	Inadequate evidence upon which to assess the effects of any material used for retrograde filling (root canal therapy)

4.4.3.3 Longitudinal survival of dental restorations in adults

4.4.3.3.1 Introduction

We included nine reviews that primarily investigate the survival rates of dental restorations and some of the factors that may complicate or impair the longevity of restorations. Three reviews (Vagropoulou *et al.*, 2018;[129] Abduo and Sambrook, 2018;[17] and Morimoto *et al.*, 2016[18]) investigated the survival rates and associated complications for different indirect dental restorations, and in the reviews by Vagropoulou *et al.*[129] and Morimoto *et al.*,[18] indirect methods were compared with direct restorative methods. Four reviews (Astvaldsdottir *et al.*, 2015;[130] Beck *et al.*, 2015;[131] Moraschini *et al.*, 2015;[11] and Opdam *et al.*, 2014[132]) investigated the survival of composite resin restorations in posterior permanent teeth, and some of these four reviews included an examination of associated complicating factors. Heintze *et al.* (2015)[133] examined factors that may complicate or impair composite resin restorations in anterior permanent teeth. The remaining review, by van de Sande *et al.* (2016),[134] investigated the influence of patient-related factors on restoration survival in posterior permanent teeth without isolating a specific restorative material for examination. We have presented a structured account of the relevant data we extracted, as well as our judgement on the level of evidence reported, for each review. We conclude this section with a summary on the levels of evidence for the interventions examined.

4.4.3.3.2 Survival rates and associated complications for different indirect dental restorations

Vagropoulou *et al.* (2018)[129] investigated whether different types of indirect restorations (inlay, onlay, both inlay and onlay, and crown) used for single permanent anterior, premolar, or molar teeth had different biological or technical complications, or different survival rates. According to Vagropoulou *et al.*, "complete coverage restorations are used extensively in everyday clinical practice, especially when tooth structure loss is more than 50%. Gold, metal ceramic, all ceramic and zirconia crowns have been used successfully and they all represent different restorative material options… Ceramic inlays and onlays present very high survival rates too… Failures in both complete and partial coverage restorations are related to fractures/chipping, endodontic complications, recurrent decay, retention loss and in cases of all-ceramic restorations severe marginal staining may result as well". p904[129]

Three prospective and six retrospective cohort studies were included in this review, as the authors state that no randomised controlled trials were identified from their search; the studies involved mainly adults (permanent anterior, premolar, or molar teeth). Based on a modified version of the Cochrane Collaboration's risk of bias instrument, seven of the studies were assessed as having a high risk of bias, and two as having an unclear risk of bias. The precise age of the participants in the included studies is unclear; however, in an attempt to fill in this information gap, Vagropoulou *et al.* point out that "the restorative treatments examined in the studies included in this systematic review were performed in both males and females and in a very wide range of ages, covering the whole spectrum of adulthood". p915[129]

Based on the analysis of the included studies, the mean survival rate of inlays was 90.89% at five years, while for onlays and crowns it was 93.50% and 95.38%, respectively. For the fourth study group, consisting of both inlays and onlays, the survival rate was found to be 99.43%. This means that both direct and indirect restorations show survival rates over 90%, which is judged to be very high by the authors.

In addition, the analysis demonstrated caries to be the main biological complication for all types of restorations, followed by root and/or tooth fracture incidence (11.34%) and endodontic incidence. Ceramic fractures represented the most common technical complication, followed by loss of retention, and porcelain chipping.

However, the evidence is derived from non-randomised studies with high or unclear risk of bias, and therefore we judge it to be weak and determine that there is inadequate evidence upon which to assess the performance of both direct and indirect restoration techniques. According to Vagropoulou *et al.*, "The overall quality of evidence of the 9 studies was low. Due to the heterogeneity of the included studies no meaningful comparison could be made between types or restoration of materials". p917[129]

Abduo and Sambrook (2018)[17] investigated the longevity of ceramic onlays in the permanent teeth of adults and adolescents and the factors that influence their survival. According to Abduo and Sambrook, "over the last 20 years, ceramic restorations have become very popular and are routinely used in clinical practice. This is further driven by the significant developments that have improved the mechanical and optical properties of ceramic materials available for dental restorations. In addition, the development of modern manufacturing techniques has reduced the risk of internal flaw development within the ceramic material, which can further enhance its performance. In parallel to ceramic improvements, there have been advances in adhesive and cementation agents that combine enhanced bonding between the tooth and the ceramic material and ease of use. Consequently, a new range of conservative, tooth-colored and durable restorative options are available. Contemporary ceramics have been used to restore teeth with inlays, onlays, crowns, or even fixed partial dentures". p193[17]

Twelve prospective and nine retrospective cohort studies were included in this review; the participants' ages ranged from 15–81 years. Critical Appraisal Skills Programme guidelines were used to evaluate the methodological quality of the included studies. According to the authors, "the CASP [Critical Appraisal Skills Programme guidelines] aim to ensure the study's trustworthiness, importance of the study's results and the study's relevance to the area of practice. This was achieved by asking 12 questions for every article." p194[17] The studies' quality scores ranged from 7 to 12, with 12 being the maximum score to be achieved. A total of 16 studies (76.2%) were rated as high quality, three studies (14.3%) had a quality rating of high to moderate, and two studies (9.5%) were rated as being of moderate quality.

The main findings from this review suggest that there is adequate evidence that ceramic onlays provide acceptable survival rates over both the medium and long term in posterior teeth. According to the 12 medium-term studies (two to five years), the survival rates ranged from 91–100%. The nine longer-term studies (more than five years) indicated a reduced survival rate (71–98.5%). According to Abduo and Sambrook, "the clinical performance of the ceramic onlay appears acceptable regardless of the follow-up duration." p211[17] In addition, the analysis revealed that fracturing of the ceramic onlay is the predominant cause of failure, and the most observed form of deterioration was associated with the restoration margin. Marginal integrity and discolouration were also issues.

Morimoto *et al.* (2016)[18] investigated the survival rate of ceramic and resin inlays, onlays, and overlays and the complication types associated with the main clinical outcomes. According to Morimoto *et al.*, "partial indirect restorations classified as inlays (without covering the cusps), onlays (covering at least 1 cusp), and overlays (covering all cusps), enable conservation of the remaining dental structure, promoting reinforcement of a tooth compromised by caries or fractures. Numerous resin or ceramic materials are currently available for fabricating indirect partial restorations and mechanical strength is important for their durability in posterior applications… Differences in the

mechanical properties of resin-based and ceramic materials raise the question as to which material can survive longer, especially in loadbearing posterior regions of the mouth." p985-86[18]

Eleven retrospective studies, two cohort studies, and one randomised controlled trial were included in this review, and the age of participants involved in the studies ranged from 12–79 years. The authors do not report the instrument they used to assess the quality of the studies; however, they do report that the percentage likelihood of bias in the individual studies ranged from 46.1% to 76.9%, but as they do not elaborate on this, it remains unclear what this rating means for the quality of the evidence.

The main findings from this review suggest that there is adequate evidence that ceramic inlays, onlays, and overlays produce acceptable high restoration survival rates of over 90% regardless of the ceramic material, study design, or study setting. According to Morimoto *et al.*, "the pooled estimated survival rate was 95% for 5 y of follow-up and the survival rate decreased to 91% after 10 y of follow-up (93% for glass-ceramics and 91% feldspathic porcelain), yet this was not a significant difference. One explanation for the similar performance of glass-ceramics and feldspathic porcelain could be the adhesive cementation that likely compensated for the mechanical differences between the 2 ceramic materials." p991[18] The authors also report that "fractures remain the most frequent type of failure. And the type of tooth does not seem to affect survival rates, but restorations survived longer on vital teeth." p993[18]

There is insufficient and inadequate evidence with which to draw comparisons between direct and indirect methods of restoration. According to Morimoto *et al.*, "no study with resin inlays, onlays, and overlays could be selected in this review. Therefore, it was not possible to perform a meta-analysis…[to test] whether resins survive longer than ceramics." p991[18]

4.4.3.3.3 Survival rates of composite resin restoration in posterior permanent teeth and associated complicating factors

Astvaldsdottir *et al.* (2015)[130] investigated the longevity of posterior resin composite restorations in permanent teeth in adults. According to Astvaldsdottir *et al.*, "the longevity of restorations is influenced by a number of factors, such as the considerable differences in mechanical, physical, adhesive and handling properties of the various resin composites and adhesive systems." p935[130]

Eight randomised controlled trials were included in this review, with a minimum follow-up time of four years. The methodological quality of the included studies was assessed using the Swedish Council on Health Technology Assessment standard checklist for determining the extent to which studies meet basic quality criteria. The criteria assess risk for selection bias, performance bias, detection bias, attrition bias, and reporting bias. The quality of the included studies (i.e. the risk of bias) was rated as high, moderate, or low. Only studies of high or moderate quality – i.e. those with moderate to low risk of bias – were considered for grading of scientific evidence and conclusions. Five of the included studies were judged to be of moderate quality and three of high quality. The authors do report that "all but one [of the eight included studies] was conducted by the same research group." p938[130] The research group in question was led by van Dijken, who is the author or co-author of seven of the included studies, and van Dijken is also an author to the Astvaldsdottir *et al.* (2015) review, which is expressed in the conflict of interest.

The analysis of the included studies revealed that "in an efficacy setting, the overall survival proportion of posterior resin composite restorations is high and the major reasons for failure are secondary caries and restoration fracture which supports the importance of adequate follow-up time." p953[130]

However, as the evidence adduced in this review derives exclusively from efficacy trials, we conclude that there is inadequate evidence upon which to assess the effectiveness and longevity of posterior resin composite restorations in permanent teeth in adults. According to Astvaldsdottir *et al.*, "all the included studies presented an efficacy setting and study design. Therefore, the results should be interpreted with caution and not be extrapolated to an effectiveness setting." p952[130]

Beck *et al.* (2015)[131] investigated the clinical performance of composite restorations in posterior teeth. According to Beck *et al.*, "initially, composite as a filling material for posterior restorations was reserved for small cavities, but as a decline of amalgam's popularity, it is also used for large (multi-surface) restorations." p959[131]

The authors report that 88 prospective clinical studies of direct composite restorations in permanent posterior teeth were included in this review; however, they fail to report on the design of the studies included, and there is no report of a quality assessment of the included studies provided. Both of these absences from the review raise considerable concerns regarding the quality and reliability of the evidence.

Some of the findings reported suggest that the failure rate of composite restorations in posterior teeth increases with longer observation periods (at between 3% and 27% at five years and between 3% and 32% at 10 years). In the study period of one to four years, the most common reasons for failure reported were fracture, followed by marginal defects, and then secondary caries. For longer study periods (five years or longer), secondary caries and fracture turned out to be the predominant reasons for failure and were similarly distributed. However, we would urge extreme caution when interpreting these findings, due to the absence of a quality assessment of the included studies and failure to report the design of the included studies; based on these limitations, we suggest that the evidence is weak, and there is therefore inadequate evidence upon which to assess the clinical performance of composite restorations in posterior teeth. Beck *et al.* do provide some explanation for the apparent unreliable quality of the included studies: "a categorization of all trials in regard to quality (e.g. influence of possible bias, calculation of sample size, randomization method) could not be conducted due to the large heterogeneity and the very low number of studies, which reported following the CONSORT statement." p982[131]

Moraschini *et al.* (2015)[11] compared the failure rates of amalgam and composite resin occlusal and occlusoproximal restorations in posterior permanent teeth. According to Moraschini *et al.*, "although amalgam restorations still have the highest functional durability, its use has been questioned in recent decades due to the incorporation of mercury to the metal alloy. In addition, the need for more dental preparation, necessary to promote greater restoration retention, makes amalgam questionable for conservative dentistry. For these reasons, the use of composite resins has been increasing throughout the world for direct posterior teeth restorations… The most frequent reason for failure [in composite resins] is recurrent or secondary marginal restoration caries, thus indicating possible failures in the adhesion process. On the other hand, amalgam restorations reduce the possibility of secondary caries over time by forming oxides in the margin of the cavities as a result of the natural corrosion of the material, mainly in alloys with high copper content." p1044[11]

Five prospective studies, one retrospective cohort study, and two randomised controlled trials were included in this review. The age range of participants was not reported in most of the included studies. Based on the Newcastle-Ottawa Scale, where the maximum score assigned to a study is nine stars/points (highest scientific evidence), all eight included studies had a score higher than six and were classified as high quality.

Based on the relative high quality of the included studies and with the exception of one paper, all of the included studies reported a greater longevity for amalgam restorations in posterior teeth; we therefore judge the evidence to be adequate that amalgam posterior restorations in permanent teeth last longer compared with composite resin restorations and are associated with the presence of fewer secondary caries. According to Moraschini *et al.*, "this systematic review revealed that occlusal and occlusoproximal amalgam posterior restorations have greater clinical longevity when compared to composite resin restorations… The results of this meta-analysis were expressed as relative risk (RR), a statistical analysis often used in binary results, which is defined as the probability of an event to occur. Regarding restoration failures, this meta-analysis indicated a RR of 0.46 (95% CI: 0.28–0.78), i.e. the composite resin restorations have a 54% higher probability of failure when compared to amalgam restorations… The presence of secondary caries was significantly higher in composite resin restorations." p1048-1049[11]

The evidence is inconclusive in comparing amalgam with composite restorations regarding fractures as, according to Moraschini *et al.*, "with regard to fractures, there was no statistically significant difference between the two materials…indicating a lower sensitivity of the posterior restorations to fracture when compared to recurrent caries." p1049[11]

Opdam *et al.* (2014)[132] investigated the influence of patient-, material-, and tooth-related variables on the survival of posterior resin composite restorations. According to Opdam *et al.*, "posterior resin composites are widely considered the first-choice material for posterior direct restorations. Their survival is good, since reviews have concluded that mean annual failure rates vary between 1% and 3%. Most clinical studies focused on comparing different brands and types of resin composites, and observation times seldom exceeded 5 years. In recent times, with growing evidence that the material properties in themselves are more than adequate, we focus more on other factors that may determine the survival of restorations, such as patient risk factors… The aim of the present meta-analysis was to include and combine raw data from long-term follow-up studies of at least 5 years' observation time on posterior resin composite restorations…to investigate failure rates, failure reasons, and the influence of patient, materials, and tooth-related variables on restoration survival." p943-44[132]

Nine prospective and three retrospective longitudinal cohort studies with at least five years follow-up were included in this review. The number of direct posterior resin composite restorations in permanent teeth included in the analysis totalled 2,816. The age of the participants is not reported, and the authors do not report undertaking a formal quality assessment of the included studies. However, they do discuss potential issues of bias relating to the studies. For example, they point to "differences in practice settings, survival criteria, number of included restorations per study, and the fact that 10 of the 12 studies were delivered by only 3 research groups lead to possible bias." p946[132]

The analysis of the data suggests that caries risk plays a major role in restoration survival. According to Opdam *et al.*, "with high or medium caries risk associated with a 2- to 3-times higher risk of restoration failure, this patient risk factor is probably more important than material factors for survival of dental restorations." p947[132] The analysis also suggested that larger restorations have a higher risk for failure, since every extra surface included in a restoration increases this risk by 30% to 40%.[132]

In conclusion, Opdam *et al.* summarise the findings "that caries risk and number of restored surfaces play a significant role in restoration survival, and that, on average, posterior resin composite restorations show a good survival, with annual failure rates of 1.8% at 5 years and 2.4% after 10 years of service." p948[132]

However, we judge the current evidence to be weak and there is therefore inadequate evidence upon which to assess the influence of patient-, material-, and tooth-related factors on the survival of posterior resin composite restorations. First of all, the authors do not report a formal quality assessment of the included studies, which prohibits an assessment of the quality of the evidence. Second, the authors draw attention to a number of potential biases that may weaken the reliability of the included studies, some of which we have already alluded to. These potential biases raise too many unanswered questions regarding the quality and conduct of the primary studies, and taken overall, these limitations impair our confidence in the findings reported. Indeed, the authors make a very interesting admission regarding the nature of the evidence produced in this review, which, to a large extent, supports the view that the evidence is weak and inadequate. Opdam *et al.* "want to make clear that this is not the ultimate degree of evidence for considering the longevity of posterior resin composites, which might be suggested from its meta-analytic design. In the authors' opinion, the relevance of the present study is that it might bring us a step further in clarifying the overall picture on how long posterior composites survive and what factors may influence their survival." p946[132]

4.4.3.3.4 Factors that complicate or impair composite resin restorations in anterior permanent teeth

Heintze *et al.* (2015)[133] investigated whether specific material classes, tooth conditioning methods, or operational procedures influence the result for Class III and Class IV composite resin restorations in anterior permanent teeth. According to Heintze *et al.*, "restorations that involve the proximal part of an anterior tooth but not the incisal edge are defined as Class III restorations… Restorations that involve a part of the incisal edge are defined as Class IV restorations… The restoration of fractured teeth (Class IV) with composite is usually the first treatment option." p482[133]

The authors report that prospective clinical trials with at least two years of observation were part of the inclusion criteria. They go on to report that 21 clinical trials met the inclusion criteria, 14 of them for Class III restorations, six for Class IV restorations, and one trial for closure of diastemata, which was included in the Class IV group; however, they do not report the design of the 21 trials included. In addition, they do not report undertaking a quality assessment of the included trials, which means that we do not have enough information upon which to assess the level of the evidence in this review.

Some of the findings reported in this review suggest that the failure rate of anterior restorations was relatively low. Class IV restorations showed more fractures than Class III restorations. However, we conclude that both the conduct and the reporting in this review by Heintze *et al.* warrants caution when interpreting any of the findings reported, and therefore we suggest that there is currently inadequate evidence upon which to judge the performance of Class III and Class IV composite resin restorations in anterior permanent teeth. First of all, the evidence is weak, as the design of the included studies is unknown, and the studies' quality is not reported in the review. Second, it appears that the included studies are outdated and contain evaluations of earlier iterations of types of resin materials which have subsequently been superseded by improved versions; there is therefore insufficient evidence upon which to make judgements on the contemporary status of resin materials for Class III and Class IV restorations in anterior teeth. According to the authors, "most of the included studies were carried out between 1980 and 2000 and there were only 6 studies on Class IV restorations. As this is the first systematic review or meta-analysis of that kind, also studies that evaluated resin materials that are no longer available on the market, such as macrofilled materials had been included. Likewise, studies that did not use enamel or dentine conditioning agent, had also been taken into consideration." p492[133]

4.4.3.3.5 Influence of patient-related factors on restoration survival in posterior permanent teeth

van de Sande *et al.* (2016)[134] investigated the influence of patient-related factors on restoration survival in posterior permanent teeth. According to van de Sande *et al.*, "patient-related factors such as caries risk and bruxism have been associated with the main reasons for failure for composite resin restorations in posterior teeth and were found to influence restoration survival in retrospective studies. Likewise, when examined, patient-related factors seem to negatively affect the survival of other restorative procedures, including ceramic and amalgam restorations. Thus, investigations on restoration survival should include patient factors in the analysis to assist with the process of basing clinical decision making on more predictable outcomes and also for patient awareness." pS8[134]

Fifty-one studies employing both prospective and retrospective designs were included in this review. Forty-five articles included the assessment of patient factors and were selected for the first part of the review, and 27 of these studies included an analysis of patient factors in the outcome and qualified for the second part of the review. The age range of participants in the included studies is reported to be 8–87 years. The authors do not report whether they undertook an evaluation of the quality of the included studies.

van de Sande *et al.* summarise the main findings as follows: "patient-related factors mentioned in the studies included age; gender; caries risk; caries activity/severity; decayed, missing, filled teeth; number of restorations; oral hygiene; and bruxism, among others. Sixteen studies included the patient age or age range in the analysis, which was found to be significant in 47% of the studies. Regarding gender, four of 17 reports found a significant effect on survival, showing more failures for men in three studies. The caries risk profile or related variables were included in the analysis of 15 studies, and a significant effect on survival was reported for high-caries-risk individuals (or related variables) in 67% of these studies. Bruxism was also found to influence restoration survival in three of six studies where this variable was investigated." pS7-S8[134]

However, due to the inconsistent methods of investigation reported in the included studies, we deem the current evidence to be inadequate to determine the influence of patient-related factors on restoration survival in posterior permanent teeth. According to van de Sande *et al.*, "there is a lack of standardized methods to assess patient-related factors. Even in studies in which these factors were investigated, there was no uniformity on clinical parameters used, and the description of cut-off points was frequently missing or vague. This is likely due to the difficulty of establishing the relationship between etiological factors and clinical signs and the diagnosis for several conditions in the dental field." pS15[134]

4.4.3.4 Summary: Longitudinal survival of dental restorations in adults

Table 17 presents a summary of the systematic review evidence on alternatives to, or replacements for, amalgam based on nine reviews of survival of direct and indirect dental restorations in adults. The investment in, and quality of, primary research in this topic area appears to be improving.

There is adequate evidence from two reviews (Abduo and Sambrook; Morimoto *et al.*) that a ceramic onlay acting as an indirect dental restorative material provides acceptable survival rates over both the medium and long term in posterior teeth (Abduo and Sambrook) and regardless of the ceramic material used, study design, and study setting (Morimoto *et al.*). In addition, there is adequate evidence in the review by Morimoto *et al.* that ceramic inlays, onlays, and overlays produce acceptable high restoration survival rates of over 90%. There is inadequate evidence from two reviews (Vagropoulou *et al.*; Morimoto *et al.*) upon which to draw comparisons between indirect and direct methods of restoration.

There is inadequate evidence in three reviews (Astvaldsdottir *et al.*; Beck *et al.*; Opdam *et al.*) upon which to assess the clinical performance of composite restorations in posterior teeth; clinical performance includes the survival rate of restorations and the potential influence of complicating factors, e.g. patient characteristics, on the survival rates. In the review by Moraschini *et al.,* there is adequate evidence to suggest that amalgam posterior restorations in permanent teeth last longer compared with composite resin restorations and are associated with the presence of fewer secondary caries. In the only review from this section that examined the survival of restorations in permanent anterior teeth (Heintze *et al.*), there is inadequate evidence upon which to judge the performance of Class III and Class IV composite resin restorations. Finally, in the review by van de Sande *et al.*, there is inadequate evidence with which to determine the influence of patient-related factors on restoration survival in posterior permanent teeth.

Table 17 Nine reviews of longitudinal survival of dental restorations in adults

Lead author and year	Level of evidence
	Indirect restorations
Vagropoulou *et al.* (2018)[129]	Inadequate evidence with which to compare direct and indirect restoration techniques
Abduo and Sambrook (2018)[17]	Adequate evidence that ceramic onlays provide acceptable survival rates over both the medium and long term in posterior teeth
Morimoto *et al.* (2016)[18]	Adequate evidence that ceramic inlays, onlays, and overlays produce acceptable high restoration survival rates of over 90% regardless of the ceramic material, study design, or study setting Inadequate evidence with which to draw comparisons between direct and indirect methods of restoration
	Direct restorations
Astvaldsdottir *et al.* (2015)[130]	Inadequate evidence upon which to assess the effectiveness and longevity of posterior resin composite restorations in permanent teeth in adults
Beck *et al.* (2015)[131]	Inadequate evidence upon which to assess the clinical performance of composite restorations in posterior teeth
Moraschini *et al.* (2015)[11]	Adequate evidence that amalgam posterior restorations in permanent teeth last longer compared with composite resin restorations, and are associated with the presence of fewer secondary caries Inconclusive evidence that the frequency of restoration fracture is the same for both amalgam and resin composite restorations
Opdam *et al.* (2014)[132]	Inadequate evidence upon which to assess the influence of patient-, material-, and tooth-related factors on the survival of posterior resin composite restorations
Heintze *et al.* (2015)[133]	Inadequate evidence upon which to judge the performance of Class III and Class IV composite resin restorations in anterior permanent teeth
van de Sande *et al.* (2016)[134]	Inadequate evidence with which to determine the influence of patient-related factors on restoration survival in posterior permanent teeth

5 Discussion and conclusions

5.1 Introduction

We found three papers with which we could compare and contrast our findings for Question 3. The first was the Scottish Dental Clinical Effectiveness Programme (2018) evidence review, which examined the prevention and treatment of dental caries in children and adolescents and made recommendations to the dental profession in the UK based on its findings.[135] In the second comparative document, Mejàre *et al.* (2015)[136] appraised and summarised the evidence and evidence gaps for practice-relevant questions in paediatric dentistry. The third review, by Smaïl-Faugeron *et al.* (2014),[137] assessed the methodological quality of Cochrane reviews of paediatric oral health. We have used the main conclusions from these three papers to compare, where feasible, our findings for interventions that prevent and treat dental caries in children and adolescents.

We found three papers with which we could compare and constrast our findings for Question 4. The review by the Scottish Dental Clinical Effectiveness Programme (2018a) examined the evidence from systematic reviews on interventions for the prevention and treatment of dental caries in adults.[135] The review by Faggion (2012)[48] provides a critique of the level of evidence in Cochrane reviews covering interventions in Oral Health and the review by Sarkis-Onofre *et al*. (2019)[138] critically examines systematic reviews in restorative dentisty. In addition, we include two papers, one by Conway *et al.* (2017)[139] and the other by Fleming *et al.* (2016)[140], which examine the quality of systematic reviews in fields other than dentistry; we believe the key messages from these two papers adds useful context to our own finding and highlights the variation in the quality of evidence produced in systematic reviews. Finally, we include two additional papers to our discussion, one by Innes *et al.* (2019)[141] and the other Levey *et al.* (2017)[142], that provide useful background information to some of the issues we wish to highlight in our discussion around the work we reviewed for Question 4.

5.2 Main findings and comparison with other research

5.2.1 Children and adolescents

5.2.1.1 What does the evidence tell us about the late restorative treatment of cavitated caries in children and adolescents?

In one of our Cochrane reviews, Ricketts *et al.*, which examined the extent of caries removal before restoration, there is adequate evidence, which the review assessed as moderate, that stepwise and selective/partial caries removal is preferred to complete caries removal in vital, symptom-free primary or permanent teeth.[102] According to the review by the Scottish Dental Clinical Effectiveness Programme, this finding in favour of selective caries removal over the complete removal of caries in both primary and permanent teeth is "consistent with two other systematic reviews." p128[135] We did not retrieve the two reviews (Schwendicke *et al.*, 2013[143]; Hoefler *et al.*, 2016[144]) referred to by the Scottish Dental Clinical Effectiveness Programme[135].

The Scottish Dental Clinical Effectiveness Programme suggests that "atraumatic restoration treatment (ART) is suitable for a primary tooth with a single surface". p93[135] In the reviews we examined, the evidence suggest that ART is not superior to the conventional technique but is likely to show comparable effectiveness for treating single surface lesions so is deemed a suitable treatment for this type of dental procedure. For example, in two reviews there is inadequate evidence upon which to compare the conventional restorative technique with the atraumatic restorative treatment technique for placing restorative materials to treat caries lesions in primary and permanent teeth.[22 97] In two

other reviews, the evidence is inconclusive regarding whether atraumatic restorative treatment is superior to the conventional technique overall, but ART is judged to provide comparable effectiveness for treating single surface lesions in both reviews.[98 99]

However, in a review published after the Scottish Dental Clinical Effectiveness Programme's work, there is adequate evidence for using the conventional technique when applying glass-ionomer cements to restore approximal or multi-surface cavities in primary teeth, and there is adequate evidence to prefer resin-modified glass-ionomer cement applied using the conventional technique when restoring approximal cavities in primary teeth.[98] In addition, there is inadequate evidence regarding any difference in post-operative sensitivity when using dental cavity liners under the placement of composite resin restorations in permanent teeth, and inconclusive evidence as to whether or not dental cavity liners affect the longevity of composite resin restorations in permanent teeth.[100] The comments of one peer review expert on the use of glass-ionomer cements to restore multi-surface caries should be noted as an indicative update to this review.

According to the Scottish Dental Clinical Effectiveness Programme, "in primary teeth, the evidence available does not indicate a preferred restorative material. However, there is moderate-quality evidence that [preformed] crowns [using the Hall technique] placed on primary molar teeth with carious lesions or following pulp treatment reduce the risk of pain or infection in the long-term compared to restoration." p125[135] Our findings regarding restorative materials for children and adolescents are in line with the assessment by the Scottish Dental Clinical Effectiveness Programme. For example, when glass-ionomer cements were compared with other restorative materials, the evidence provided in four reviews is inconclusive overall to determine which material is superior for restorations in primary teeth,[15 103] for preventing adjacent caries in occlusal surfaces,[104] and for preventing or arresting secondary caries lesions in approximal surfaces in contact with occlusoproximal restorations in children.[99]

In addition, our findings on the effectiveness of crowns are consistent with those of the Scottish Dental Clinical Effectiveness Programme. We found adequate evidence in the review by Innes *et al.* that preformed crowns (using the Hall technique) are superior to conventional fillings for managing tooth decay in primary teeth.[105] In addition, we found adequate evidence in the same review that crowns fitted using the Hall technique may reduce discomfort at the time of treatment compared with using conventional fillings. The evidence supporting this finding is judged to be of moderate quality based on the GRADE criteria, and suggests that crowns fitted using the Hall technique are less likely to cause abscesses and pain than conventional fillings.

However, we included two reviews – by Dias *et al.*[13] and Raggio *et al.*[67] – that were not included in the review by the Scottish Dental Clinical Effectiveness Programme,[135] one of which was published after the Scottish review. The evidence from both reviews suggests that there is adequate evidence that glass-ionomer cements are better than composite resins and other restorative materials in preventing the occurrence of secondary carious lesions in primary teeth.[15 104]

5.2.1.2 What does the evidence tell us about the early treatment of non-cavitated caries in children and adolescents?

The Scottish Dental Clinical Effectiveness Programme[135] cites the work of Gao *et al.*[89] and Lenzi *et al.* (2016)[145], which found in favour of professionally applied 5% fluoride varnish for remineralising early enamel caries in primary and permanent teeth. We did not retrieve the review by Lenzi *et al.* (2016)[145], and the Scottish Dental Clinical Effectiveness Programme suggests that the quality of the evidence in the reviews by Gao *et al.* and Lenzi *et al.* was low.[135] We found three reviews (Duangthip *et al.*, 2015[75]; Gao *et al.*, 2016[74]; and Urquhart *et al.*, 2019 [70]) indicating that there is adequate evidence that silver diamine fluoride is more effective than controls, and one review indicating that the evidence is inconclusive when comparing silver diamine fluoride with other active treatments.[86] In addition, Urquhart *et al.* found adequate evidence that using individual sealants in combination with 5% sodium fluoride varnish was effective for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth.[29]

We judged the evidence to be adequate in two reviews – by Ancira-González *et al.* 2018[73] and Gao *et al.* 2016[74] – that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth. Additionally, although we acknowledge some limitations in the trials included in the work by Gao *et al.* based on our level-of-evidence assessment, we contend that the evidence is adequate to support the claim that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth.

However, there is inadequate evidence upon which to assess the use of resin infiltration in combination with 5% sodium fluoride varnish in treating non-cavitated carious lesions on approximal surfaces in primary and permanent teeth, and there is inadequate evidence upon which to judge the performance of 5,000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel in treating non-cavitated and caitated carious lesions on root surfaces in permanent teeth".[29]

In the review by Wright *et al.*[93], there is adequate evidence that sealants, when compared with no sealant, are better in preventing carious lesions and arresting the progression of non-cavitated carious lesions in permanent teeth.[93 94] The American Dental Association has used the findings from this review by Wright *et al.* to make clinical recommendations for the use of pit and fissure sealants. According to the Scottish Dental Clinical Effectiveness Programme (2018), "the ADA [American Dental Association] recommends use of fissure sealants on non-cavitated occlusal lesions to prevent their progression in both children and adolescents." p128[135] However, the evidence from the same review by Wright *et al.* does not indicate which type of sealant is superior, and there is no discernible difference between sealants and fluoride varnish.[93 94]

There is adequate evidence in two reviews – by Krois *et al.*[77] and Dorri *et al.*[80]– that microinvasive treatment (lesion sealing and resin infiltration) is superior to non-invasive treatment for managing proximal enamel and initial dentinal caries lesions. In the Cochrane review by Dorri *et al.*, which involved both children and adults, the evidence is judged to be moderate for this effect. According to the Scottish Dental Clinical Effectiveness Programme, "this review [Dorri *et al.*] is supportive of the consideration of these emerging techniques when managing non-cavitated proximal lesions in permanent and primary teeth, taking into account clinical indications and the feasibility of different techniques." p128[135] The review by Krois *et al.* (2018) was published after the Scottish review, but it confirms that there is adequate evidence to suggest that using either sealing or infiltration separately is superior to non-invasive treatment;[92] however, once again, the evidence does not indicate whether sealing or infiltration is better in managing proximal lesions in primary and permanent teeth.

5.2.1.3 What does the evidence tell us about the prevention of caries in the primary and permanent teeth of children and adolescents?

According to the Scottish Dental Clinical Effectiveness Programme, "high quality evidence from systematic reviews indicates there is a dose-response relationship between toothpaste fluoride concentration and levels of caries reduction." p122[135] The review by the Scottish Dental Clinical Effectiveness Programme (2018) cites nine reviews to support this conclusion. In our review, we included three of these nine reviews, but we did not retrieve the remaining six reviews (Wong *et al.*[146], 2010; Twetman, 2009[147]; Twetman *et al.*, 2003[148]; Walsh *et al.*, 2010[149]; Steiner *et al.*, 2004[150]; and Twetman, 2007[151]). Our omission of these six reviews is explained as follows: we excluded Wong *et al.* (2010)[146] because the review primarily focused on fluoride as a potential cause of dental fluorosis in children, which was outside the remit of our review. The three reviews led by Twetman (2003, 2007, and 2009)[147 148 151], as well as the review by Steiner *et al.* (2004)[150], predated our publication inclusion threshold of 2010. We only made an exception for this threshold for Cochrane reviews which we deemed relevant. We included two updated iterations of the Walsh *et al.* (2010) review, so there was no need to extract this earlier review.[7 82] We included the other three reviews[65 66 68] cited by the Scottish Dental Clinical Effectiveness Programme.[135] Two of the four Cochrane reviews by Marinho *et al.* are examples of reviews that were included even though they predated our publication inclusion threshold of 2010.[65 68-70]

Our overall findings regarding the effectiveness of fluoride technologies in preventing dental caries in children and adolescents are in line with the conclusions in the Scottish Dental Clinical Effectiveness Programme review.[135] We found adequate evidence in the reviews by Marinho *et al.* (2003a) [85] and dos Santos *et al.* (2013)[86] that brushing teeth with fluoride toothpaste is effective in preventing dental caries in children and adolescents aged 5–16 years, and in preschool children aged 7 years and under, respectively. The Scottish Dental Clinical Effectiveness Programme review did not include the work of dos Santos *et al.* (2013).[135] The findings of the review by Mejàre *et al.*[136] concur with our findings and with those of the Scottish Dental Clinical Effectiveness Programme; according to Mejàre *et al.*, "the quality of the evidence is high for the caries-preventive effect of daily use of fluoride toothpaste and that supervised tooth-brushing is more effective than unsupervised." p5[136]

Regarding the concentrations of fluoride toothpaste, there is adequate evidence in the review by Walsh *et al.* that fluoride concentrations of 1500 ppm and 1450 ppm prevent dental caries in primary teeth; however, the 1450 ppm concentration only showed a slight reduction.[7] There is also adequate evidence in the same review by Walsh *et al.* that fluoride concentrations of 1000–1250 ppm and 1450–1500 ppm reduce caries in the permanent teeth of children and adolescents.[7] There is adequate evidence in the review by Singh and Purohit[67] to suggest that brushing teeth with a high concentration of fluoride toothpaste (>2500 ppm) is more effective than the standard concentration (≤1500 ppm). However, two of the eight trials included in the review by Singh and Purohit comprised adults aged 27 years and over, which may have skewed the results.[67] According to the Scottish Dental Clinical Effectiveness Programme, "for standard prevention, toothpastes in the range 1000 to 1500ppm fluoride are recommended for use by children up to 18 years. Higher dose toothpaste may be beneficial for older children at increased caries risk." p123[135]

In addition, we found adequate evidence in the review by Marinho *et al.* (2003b) that fluoride technologies in the form of toothpastes, mouth rinses, gels, or varnishes are effective interventions to prevent dental caries in the primary and permanent teeth of children and adolescents aged 5–16 years.[68] As part of the Cochrane Oral Health Group, Marinho *et al.* have updated the evidence on fluoride technologies since their review in 2003. We found adequate evidence that fluoride varnishes are effective at preventing dental caries in primary and permanent teeth of children and

adolescents;[72] adequate evidence that fluoride gels are effective in permanent teeth;[73] and adequate evidence that fluoride mouth rinses are effective in permanent teeth.[74] There is inadequate evidence upon which to assess the performance of fluoride gels for preventing dental caries in the primary teeth of children and adolescents.[73] The Scottish Dental Clinical Effectiveness Programme is in agreement with our findings regarding the evidence for varnish and mouth rinses.[135] According to the Scottish Dental Clinical Effectiveness Programme, "there is moderate quality evidence that fluoride varnish is the most effective additional topical fluoride agent and that it significantly reduces caries increment in both primary and permanent teeth…[and] fluoride mouthwash may be useful as an alternative to or in addition to varnish, for example for those who are at risk of an allergic reaction or for enhanced protection for those at increased caries risk." p125[135] The Scottish Dental Clinical Effectiveness Programme review did not include the review by Marinho *et al.* showing adequate evidence for fluoride gels as a caries-preventing agent in permanent teeth.[73] Mejàre *et al.* (2015), citing a review by Petersson *et al.* (2004) which was not included in either our review or the review by the Scottish Dental Clinical Effectiveness Programme, concur that "fluoride varnish is effective for preventing caries in permanent teeth." p9[136] In acknowledging the evidence base underpinning the effectiveness of fluoride varnish as a dental caries prevention strategy, the Scottish Dental Clinical Effectiveness Programme recommends that "all children (over 2 years of age) should receive fluoride varnish application at least twice a year as part of standard prevention. More frequent applications of fluoride varnish to children assessed at higher risk of caries is also recommended." p125[136]

We found that in the review by Tubert-Jeannin *et al.*, there was inadequate evidence upon which to judge the effectiveness of using fluoride supplements to prevent dental caries in primary or permanent teeth in children and adolescents.[71] The review by the Scottish Dental Clinical Effectiveness Programme concurs with our findings and suggests that "there is little evidence that other topical fluoride delivery systems (beads, drops, tablets, lozenges) are effective." p125[135]

In addition to the many fluoride-based technologies for preventing caries in children and adolescents reported in the literature, there are a number of non-fluoride technologies which have also been evaluated. For example, we found adequate evidence in one Cochrane review by Ahovuo-Saloranta *et al.* [95] and in one non-Cochrane review by Hou *et al.* [97] that resin-based sealants are an effective intervention to prevent dental caries in permanent teeth in children and adolescents when compared with children without sealants. Drawing on the evidence from the review by Ahovuo-Saloranta *et al.*, the Scottish Dental Clinical Effectiveness Programme agrees and states that "fissure sealants have been shown to reduce pit and fissure caries in primary and permanent teeth." p124[135] In addition, Mejàre *et al.* (2015), citing an earlier iteration of the Cochrane review by Ahovuo-Saloranta *et al.*, report that "there is a moderate quality of evidence of a caries-preventive effect of fissure sealing with resin-based materials." p15[136] These consistent signals in the evidence base regarding the effectiveness of resin-based sealants has led the Scottish Dental Clinical Effectiveness Programme to issue recommendations for the application of sealants to all children in Scotland to prevent dental caries. According to the Scottish Dental Clinical Effectiveness Programme (2018), "the evidence from two Cochrane reviews and one review by the American Dental Association supports the use of fissure sealants. Resin-based sealants may be preferred based on their superior retention. However, glass ionomer sealants are effective and may be particularly useful for application to newly erupted teeth. We recommend the application of fissure sealants to the permanent molars of all children in Scotland to prevent dental caries… Some children may also benefit from sealant applications to other teeth." p124[135] According to the Scottish Dental Clinical Effectiveness Programme (2018), "there is no clear evidence to suggest which sealant material is more effective at preventing caries but resin-based sealants have been shown to be better retained than glass-ionomer cements." p124[135] Based on the review by Ahovuo-Saloranta *et al.*, we also found the evidence to be inconclusive when one type of

sealant material was compared with another.[75] In addition, we found that the evidence in the same review is inconclusive when the use of a glass-ionomer-based sealant was compared with not using a sealant.[75]

In the earlier Cochrane review by Ahovuo-Saloranta *et al.*, we found that the evidence remains inconclusive regarding whether sealants or fluoride varnish is better in preventing dental caries in the permanent teeth of young children.[76] However, citing the same work by Ahovuo-Saloranta *et al.*, the review by the Scottish Dental Clinical Effectiveness Programme disagrees with this finding and suggests that "fissure sealants are more effective in reducing decay in occlusal surfaces than fluoride varnish." p124[135] We contend that, although there appear to be some signals in the data that sealants perform better than varnish, the evidence upon which to judge the superiority of either is low quality and it is not possible to conclude with confidence that either is superior. According to Ahovuo-Saloranta *et al.*, "although we found evidence suggesting the superiority of resin-based fissure sealants over fluoride varnishes applied to prevent occlusal caries in permanent molars, and some evidence for benefit of resin-based sealant together with fluoride varnish over fluoride varnish alone, this evidence is of low quality. We conclude that current scarce data mean that it is not possible to reach conclusions about whether to apply sealants or fluoride varnishes on occlusal surfaces of permanent molars." p25-26[76]

In addition, a non-Cochrane review by Yengopal and Mickenautsch [78] shows the evidence to be inconclusive regarding whether either resin-modified glass-ionomer cements or resin-based fissure sealants are superior in preventing dental caries in permanent teeth of children and adolescents; the authors suggest that both materials appear to be equally suitable for clinical application as fissure sealants for a period of up to two years.

In the review by Botton *et al.*, the evidence is inconclusive upon which to judge whether prior-acid etching is a better technique than using the self-etch system to seal occlusal surfaces in primary and permanent teeth, as only five trials were included in this review and some used a small sample size or showed a high dropout, which may impair the confidence in the evidence.[84] The Scottish Dental Clinical Effectiveness Programme did not make any recommendation on etching.

In two reviews – by Marghalani *et al.* [99] and Riley *et al.* [100]– there is inadequate evidence upon upon which to judge xylitol for preventing dental caries in children and adolescents. There is inadequate evidence in a review by Wang *et al.* [81] upon which to assess non-fluoride agents (arginine, chlorhexidine, casein phosphopeptide-amorphous calcium phosphate, triclosan, and xylitol) for preventing caries in the primary teeth of young children. Walsh *et al.* report inadequate evidence upon which to judge the value of chlorhexidine-containing oral products (varnish or gel).[82] The Scottish Dental Clinical Effectiveness Programme did not make any recommendation on xylitol, chlorhexidine, or casein phosphopeptide-amorphous calcium phosphate.

In our evidence review, we included both Cochrane and non-Cochrane reviews, as did the review by the Scottish Dental Clinical Effectiveness Programme.[135] Overall, both our findings and those of the Scottish Dental Clinical Effectiveness Programme are in broad agreement regarding the nature of the evidence supporting various interventions to prevent caries in the primary and permanent teeth of children and adolescents. In particular, we found that there is good (adequate) evidence to support the use of topical fluoride treatments (toothpaste, varnish, and gels) and the use of sealants to prevent caries and children and adolescents. We also found that there remains a great deal of uncertainty about the effectiveness of some of the other interventions which have been evaluated and which we have documented in this review. These findings are also supported by Smaïl-Faugeron *et al.*, who reviewed a large number of Cochrane reviews covering paediatric dentistry and oral health and concluded that "there is strong evidence that topical fluoride treatments and sealants are

effective for children and adolescents and should be implemented in practice. However, a substantial number of reviews yielded inconclusive findings." p6[137]

5.2.2 Adults

5.2.2.1 What does the evidence tell us about the late restorative treatment of cavitated caries in adult teeth?

Overall the evidence base for effective interventions to treat dental caries in adults is sporadic. For example, our findings pertaining to the evidence base for treating latter stage dental caries in adults are in some ways similar to Sarkis-Onofre *et al.*[138] Although Sarkis-Onofre *et al*. assessed the methodological quality of fifteen systematic reviews in the field of restorative dentistry, and in contrast, we judged the confidence of the evidence in a cohort of systematic reviews using the review authors' conclusions and elements of our own judgement, there is room for discussing some of the similarities that arise from both accounts.

For example, Sarkis-Onofre *et al.*[138] used the AMSTAR 2 instrument to rate the quality of 15 systematic reviews that evaluated the clinical performance of direct composite resin restoration in permanent posterior teeth or compared direct composite resin with other materials/techniques.[152] According to Sarkis-Onofre *et al*. "...ten of the systematic reviews (66.6%) presented more than one critical flaw and the overall confidence in the results were classified as critically low..." p8.[138] We included six of the fifteen reviews that were rated by Sarkis-Onofre *et al.*[138] The overall confidence in the results of five of these six reviews was rated by Sarkis-Onofre *et al.* as being critically low. We judged the evidence to be inadequate in four of the reviews rated by Sarkis-Onofre *et al.* as being critically low. We differ slightly with the judgement of Sarkis-Onofre *et al.* regarding the review by Moraschini *et al*.[11] which was rated critically low by Sarkis-Onofre *et al.* We judged the evidence to be adequate to support the finding that amalgam posterior restorations in permanent teeth last longer compared to composite resin restorations and is associated with the presence of less secondary caries. In addition, we judged the evidence to be inconclusive for a separate finding in the same review where both amalgam and resin composite seem to show similar results on restoration fracture. Regarding the review by Rasines Alcaraz *et al.*[9] which Sarkis-Onofre *et al.* rated with high confidence in the results, we judged the evidence to be of low quality and inadequate upon which to judge the performance of composite resins when compared to amalgam on restoration failure rates and the risk of secondary caries. Our assessment is primarily based on the conclusions by Rasines Alcaraz et al. who pointed out "…There is low-quality evidence to suggest that resin composites lead to higher failure rates and risk of secondary caries compared to amalgam restorations…" p18[9] Our assessment regarding the quality of the evidence being weak and inadequate is consistent with the assessment of Sarkis-Onofre *et al.*[138] who reported high confidence in the results of the review based on the rigor of the methods used. This means that our assessment of confidence in the evidence resonates with the methodological quality of five of the six reviews that were rated by Sarkis-Onofre *et al.*[138]

We included nine systematic reviews evaluating procedures and techniques for late treatment of dental caries in adults with ten primary outcomes. The evidence is adequate for two outcomes, inconclusive for two outcomes, and inadequate for six outcomes. The two outcomes with adequate evidence report that flowable composite liners are not any better than comparators to reduce micro-leakage from composite restorations;[121] and that removing minimal amount of caries in permanent teeth is better than extraction. [102] Regarding the latter finding, which emerged from the review by Ricketts *et al.*,[102] the Scottish Dental Clinical Effectiveness Programme concurs with our rating of the evidence. According to the Scottish Dental Clinical Effectiveness Programme "…this Cochrane

systematic review, which included studies assessed as of moderate quality, concluded that stepwise and selective/partial caries removal are preferred to complete caries removal in vital-symptom free primary or permanent teeth. This is consistent with other systematic reviews…" p11[135] The Scottish Dental Clinical Effectiveness Programme (2018a) cite three additional systematic reviews (Ferreira *et al.* 2012[153]; Schwendicke *et al*. 2013[143] and Hoefler *et al*. 2016[144]) that support the findings of the review by Ricketts *et al.*, however, as explained above, we did not retrieve these three reviews.

The two outcomes where the evidence is inconclusive are: whether dental cavity liners are better or worse than using no liners on the longevity of composite resin restorations in permanent teeth;[100] and whether etch and rinse or self-etch is the superior adhesive technique to aid the placement of posterior resin composite restorations.[123] The evidence to assess the remaining six outcomes was inadequate. It is important to note that when we say that the evidence for an outcome is inadequate, it generally means that the data collected and analysed are inadequate upon which to robustly evaluate the intervention; we do not infer that this means the intervention itself is inadequate. There were few cases where the intervention was not deemed useful by the review authors (such as dental liners).

There were nine systematic reviews measuring the survival of direct and indirect dental restorations in adults. Three estimated survival for indirect dental restorations and six measured survival for direct restorations. There is adequate evidence that ceramic onlays on posterior teeth, acting as an indirect dental restorative material, provide acceptable survival rates over both the medium and long term, and all ceramic materials tested performed adequately.[17 18] There is adequate evidence that ceramic inlays and overlays produce acceptable high restoration survival rates of over 90%,[18] and there is adequate evidence that amalgam posterior restorations in permanent teeth last longer than composite resin restorations and are associated with a lower incidence of secondary caries.[11] There is inconclusive evidence that restoration fracture rates are the same for both amalgam and resin composites.[11] There is inadequate evidence upon which to compare direct and indirect restoration techniques.[18 129]

5.2.2.2 What does the evidence tell us about the early treatment of non-cavitated caries in adult teeth?

The evidence for the early treatment of dental caries in adults is more extensive and the evidence seems more promising compared to that for late treatment. Most of this promise derives from the improvement in knowledge about the nature of caries and the evaluation of minimal invasive interventions to respond to dental caries. According to Innes *et al.* "…studies on sealing found and later carious tissue showed that sealants impede acid diffusion into-and mineral diffusion out of-the dental tissue and isolates sealed bacteria from their dietry carbohydrate source. These studies were initially carried out for enamel and later for noncavitated lesions with the use of sealant materials and then cavitated ones extending into dentin with the use of more mechanically robust materials. Sealing lesions is less mechanically destructive and more protective of the dental pulp than techniques involving the removal of all carious tissue…" p613[141]

Three reviews demonstrate adequate evidence for micro-invasive strategies in the form of resin infiltration and dental sealants as effective interventions in the early treatment of caries in adult teeth [92 95 112] and the evidence is inconclusive as to whether sealant or infiltration strategy offer the greatest advantage. [92 95] According to the Scottish Dental Clinical Effectiveness Programme "although there is insufficient evidence to favour a particular technique (sealing or infiltration), this review is supportive of the consideration of these emerging techniques when managing non-cavitated proximal lesions in permanent teeth, taking into account clinical indications and the feasibility of different techniques." p12[135]

There is adequate (or moderate) evidence that glass-ionomer cement restorations have better retention levels on non-carious cervical lesions compared to resin-based composite restorations as measured at time points between one and five years,[119] and adequate evidence that the viscosity of resin composite does not influence retention rates up to 3 years.[120]

There is adequate evidence that selective enamel etching technique is better than no etching; [115] that using etch and rinse adhesives can result in a better reduction of marginal discolouration when compared to using self-etch adhesives[114] and that using either bonding strategy (etch and rinse or self-etch) does not influence the risk of post-operative sensivity.[114] There is inconclusive evidence as to whether HEMA-free adhesives or HEMA-containing adhesives are better, [113] bevelled restoration or non-bevelled restorations are superior,[116] and etch and rinse adhesives are better than self-etch better.[114]

There is adequate evidence in one review that combining sealants and 5% sodium fluoride varnish is effective for non-cavitated carious lesions on occlusal surfaces in permanent teeth and combining other micro-invasive elements with remineralising agents can also yield good effects in permanent teeth.[29]

The evidence is inadequate in three reviews upon which to judge the performance of remineralising agents[30 78 110 111] and inconclusive in the remaning review.[31]

The evidence is inadequate for the remaining reviews that evaluated a range of interventions for the early treatment of caries in adult teeth.

5.2.2.3 What does the evidence tell us about the prevention of dental caries in adult teeth?

Regarding the prevention of caries in adults' teeth, we found only five reviews that evaluated prevention strategies. The evidence indicates that fluoride toothpaste demonstrates a clinical preventive caries effect for adults [7 23] and that conventional resin-based sealants have a superior retention capacity compared to glass-ionomer cement-based sealants but inconclusive evidence that sealants prevent adult caries. [25 26 78]

Overall, the evidence-base for making decisions on interventions to treat later stage caries in adults is weak, the evidence is slightly stronger for interventions to prevent and treat the early stages of dental caries in adult teeth. We base this judgement on our review of a comprehensive selection of both Cochrane and non-Cochrane systematic reviews whilst acknowledging that we have not assessed all candidate reviews. Our finding is consistent with the conclusions of Faggion[48] who exclusively undertook an analysis of Cochrane reviews in Oral Health including cariology and restorative dentistry. According to Faggion "assesment of Cochrane reviews in dentistry furnished disappointing results regarding the quality of evidence in the different fields of dentistry." p133[48]

Questions regarding the quality of the evidence from Cochrane reviews is not just confined to dentistry. For example, Conway *et al.* reviewed the quality of evidence in 159 Cochrane reviews based on the authors conclusions and the implications for practice section in the reviews.[139] According to Conway *et al.* "only one in ten of the Cochrane reviews published in Anaesthesia, Critical Care and Emergency Medicine that used the GRADE approach, graded the quality of evidence for a primary outcome as high" p811[139]

Similar findings regarding the quality of evidence reported in Cochrane reviews was observed by Fleming *et al* in a comprehensive assessment of a large body of work published via the Cochrane database.[140] According to Fleming *et al.* "Overall, 1,394 systematic reviews were identified. Of these, 608 (43.6%) incorporated GRADE. Within these reviews, only 13.5% (*n* = 82) reported a high quality

and 30.8% (*n* = 187) a moderate quality of evidence for the first listed primary outcome, whereas 31.7% (*n* = 193) had low level and 24% (*n* = 146) had very low level of evidence" p39[140]

Returning to the field of dentistry, Levey *et al.* have suggested some of the underlying reasons why the quality of evidence reported in systematic reviews remain sub-optimal upon which to robustly assess the effectiveness of an intervention.[142] According to Levey *et al.* "imperfections in the conduct and reporting of caries prevention and management trials has meant that systematic reviews have only been able to present poor or moderate quality evidence for even the most common preventive and management interventions. Inadequate number of participants recruited (sample size), clinical heterogeneity, high risk of bias, and inappropriate comparator or outcome choice within caries prevention and management trials have impacted negatively on the quality and strength of evidence" p2[142] This means that in most cases, clinicians do not have firm evidence to support the effectiveness of many interventions that remain ubiquteous in use in clinical practice.

5.3 Strengths and limitations of our methods and the primary papers

This review is a systematic rapid evidence assessment that was completed in 14 weeks by a very small team (1.75 FTE). This means that the work contains some limitations that may interfere with the level of confidence placed in both the methods employed and our ultimate findings and conclusions. For example, the limited time scale of the project and the large body of literature covered required that the scope was curtailed in the following ways: the evidence for Questions 3 and 4 was restricted to systematic reviews accessed from four databases, and the information collected for Questions 1 and 2 was derived from a selection of data resources opportunistically retrieved following general Internet searches. Our search strategies were specific, as opposed to sensitive; this involved employing a comprehensive rather than an exhaustive search approach. Search sources for Questions 3 and 4 were limited to bibliographic databases and reference lists of key papers, and for Questions 1 and 2 were primarily limited to repositories of grey literature. We acknowledge the likelihood that we have missed reviews that could potentially speak to Questions 3 and 4 that a more targeted question comparing a specific intervention or family of interventions with controls could have yielded. In addition, we acknowledge that we could have missed relevant documents that speak to Questions 1 and 2 and which may have added important insights to what we found and reported. We did not assess the quality of the systematic reviews we included, and this may impair some confidence in our findings and conclusions. However, we did abstract the results of risk of bias assessments, GRADE conclusions where available, and study limitations.

Some of the strong points of this work are that we have sought to be transparent in reporting our decisions and methods, and we have sought to be systematic by following, as closely as possible, the steps and principles employed in a full systematic review. In addition, we have included reviews which provide some of the most up-to-date assessments of the evidence on a broad range of restoration procedures and materials. This is an important point given that our primary review questions were to explore the nature of the systematic review literature that covered interventions for preventing and treating dental caries in children, adolescents, and adults. Our secondary questions were to identify the nature of the interventions evaluated via systematic reviews and to examine the nature of the evidence base underpinning the evaluated interventions. This means that we were not primarily seeking to undertake an effectiveness review on any specific intervention or family of interventions; hence we included a rich variety of reviews that covered different interventions and different levels of evidence which we believe illustrates the nature of the literature. Furthermore, we did not assess the quality of the included reviews before extraction, which means that we included reviews of varying methodological quality. We believe that this provides a more comprehensive picture of the nature of the evidence that exists around dental restorative procedures and materials. Finally, we have

provided an assessment of the level of evidence for a broad range of procedures and materials, which may assist policy-makers and practitioners in their deliberations regarding policy and clinical choices for using alternatives to amalgam. The level of evidence assigned to each review considered the review authors' conclusions, the risk of bias in the primary trials, and the review authors' stated limitations.

5.4 Conclusions

Where comparable, our findings from Question 3 are similar to those from the 2018 Scottish Dental Clinical Effectiveness Programme evidence review titled *Prevention and Management of Dental Caries in Children*. The findings are also comparable to Mejàre *et al.*, who appraised and summarised the evidence and evidence gaps for practice-relevant questions in paediatric dentistry. Finally, our findings on the quality of research focusing on children and adolescents are similar to those of Smaïl-Faugeron *et al.*, who assessed the methodological quality of Cochrane reviews of paediatric oral health. In addition, our findings pertaining to the quality of evidence for adult treatment evaluations reported in Question 4 are not that dissimilar to the quality assessment review by Sarkis-Onofre *et al.* However, the reports differ in that Sarkis-Onofre et al. appraised the quality of the systematic reviews while we assessed the level of evidence reported in the reviews. Our findings from Question 4 resonate with the conclusions drawn by the Scottish Dental Clinical Effectiveness Programme, and also with the work of Faggion in 2012. The examples we use from the work of Conway *et al.* and Fleming *et al.* illustrate the variation in the quality of evidence provided in systematic reviews.

The evidence available indicates that prevention and early treatment of caries is a more successful long-term strategy than restoring cavitated cavities for children, adolescents and adults. If prevention and early treatment was introduced on a large scale, then the requirement for alternatives to amalgam would be reduced. A summary of evidence base for caries is presented by dentition type in the table below:

Summary table: Current best evidence from systematic reviews for dental caries

Teeth type	What works
Primary teeth	
Prevention Fluoride ppm does not take account of water fluoridation	Brushing teeth with fluoride toothpaste is effective in preventing dental caries in preschool children aged 7 years and under (1 review, adequate evidence). Fluoride concentrations of 1500 ppm and 1450 ppm in toothpaste prevent dental caries in primary teeth (1 review, adequate evidence).
Early treatment	38% silver diamine fluoride was effective at arresting caries lesions when applied every six months to any coronal surface of primary teeth (4 reviews, adequate evidence) The combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary teeth (1 review, adequate evidence) Fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth (2 reviews, adequate evidence). Brushing teeth with highly concentrated fluoride toothpaste is effective in slowing the progression of early caries in pre-school children (1 review, adequate evidence).
Late treatment	Atraumatic restorative treatment technique and the conventional technique are equally effective when applying glass-ionomer cement to single-surface occlusal restorations in primary teeth. (1 review, inconclusive evidence as to which is better) The conventional technique is adequate when applying glass-ionomer cements to restore approximal or multi-surface cavities in primary teeth. (1 review, adequate evidence) Glass-ionomer cements are equal to other restorative materials for restorations in primary teeth, for preventing adjacent caries in occlusal surfaces, or for preventing or arresting secondary caries lesions in approximal surface in contact with occlusoproximal restorations in children. (4 reviews, inconclusive evidence as to which is better)
Mixed teeth	
Prevention Fluoride ppm does not take account of water fluoridation	Brushing teeth with fluoride toothpaste is effective in preventing dental caries in children and adolescents aged 5–16 years (1 review, adequate evidence). Fluoride concentrations of 1500 ppm and 1450 ppm in toothpaste prevent dental caries in primary and permanent teeth (1 review, adequate evidence). Fluoride technologies in the form of toothpastes, mouth rinses, gels, or varnishes are effective interventions to prevent dental caries in the primary and permanent teeth of children and adolescents aged 5–16 years (1 review, adequate evidence). The evidence regarding the superiority of one topical fluoride technology over another in primary and permanent teeth indicates that the products are equally effective (1 review, inconclusive evidence as to which is better). Fluoride varnishes are effective in preventing dental caries in the primary and permanent teeth of children and adolescents. (1 review, adequate evidence).

	Glass-ionomer-based sealants and resin-based sealants were equally effective in preventing dental caries in the permanent teeth of children and adolescents (2 reviews, inconclusive evidence as to which is better). Sealants and fluoride varnish are equally effective in preventing dental caries in the permanent teeth of young children (1 review, inconclusive evidence as to which is better).
Early treatment	The combination of individual sealants and 5% sodium fluoride varnish was the most effective intervention for non-cavitated carious lesions on occlusal surfaces in permanent teeth (1 review, adequate evidence) 5% sodium fluoride varnish was the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth (1 review, adequate evidence). The application of 1.23% acidulated phosphate fluoride gel to facial/lingual lesions every 12 months is effective (1 review, adequate evidence). For early caries treatment, either sealing or infiltration, used separately, are superior to non-invasive treatment (1 review, adequate evidence). Sealing or infiltration are equally effective in treating early caries (2 reviews, inconclusive evidence as to which is better). Sealants or fluoride varnish are equally effective in treating early caries (1 review, inconclusive evidence as to which is better).
Late treatment	Atraumatic restorative treatment technique and the conventional technique are equally effective when applying glass-ionomer cement to single-surface occlusal restorations in permanent and primary teeth, (1 review, inconclusive evidence as to which is better) Regarding procedures and techniques for removing caries from teeth, there is adequate evidence to demonstrate the clinical advantage of using selective caries removal, compared with the complete removal of caries in both primary and permanent teeth (1 review, adequate evidence).
Premanent teeth	
Prevention	Two reviews evaluated fluoride technologies reported there is adequate evidence that brushing teeth with 1000 or 1100 ppm fluoride toothpaste reduces caries increment in decayed, missing, and filled permanent surfaces when compared with non-fluoride toothpaste in adults of all ages (2 reviews, adequate evidence). There is adequate evidence that fluoride gel is effective in preventing crown caries and reversing root caries in adults and older people (1 review, adequate evidence). One review contained adequate evidence that conventional resin-based sealants have a superior retention capacity when compared with glass-ionomer cement-based sealants (1 review, adequate evidence). One review reported that flowable composite sealants and conventional resin-based sealants have equal effectiveness on retention rates (1 review, adequate evidence). Two reviews reported that conventional resin-based sealants or glass-ionomer cement-based sealants are equally effective, and that resin-modified glass-ionomer cements and resin-based fissure sealants are equally effectivey in preventing caries in adult permanent teeth (1 review, adequate evidence)

Early treatment	There is adequate evidence in four reviews evaluating microinvasive strategies that resin infiltration and sealants are effective interventions for the early treatment of caries in adult teeth. In the two reviews that evaluated dental restorative materials, there is adequate evidence that glass-ionomer cement restorations showed superior retention levels when compared with resin-based composite restorations in follow-ups after between one and five years, and the evidence is adequate to support the claim that resin composite viscosity does not influence retention rates up to three years follow-up. One review included evaluations of interventions with elements of both remineralising agents and microinvasive strategies, and reported that there is adequate evidence that: • high-fluoride (5000 ppm or 1.1% sodium fluoride) toothpastes or gels are effective for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth; • 5% sodium fluoride varnish is effective in arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth; • 1.23% acidulated phosphate fluoride gel is effective on facial/lingual lesions, but only at longer follow-up times (12 months) (1 review, adequate evidence).
Late treatment	In one review, there is adequate evidence against using flowable composite liners to reduce microleakage from composite restorations (1 review, adequate evidence). Regarding procedures and techniques for removing caries from adult teeth, there is adequate evidence to demonstrate the clinical advantage of using selective caries removal, compared with the complete removal of caries in permanent teeth (1 review, adequate evidence).

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Appendix 1 Literature search strategies for review of evidence Q3 and Q4

Bibliographic database information

Database	Platform/ Publisher	Coverage	Date of final search
MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to present (Wolters Kluwer)	Ovid	1946-present	23 February 2019
CINAHL	EBSCO	1946-present	26 February 2019
Embase	Elsevier	1947-present	26 February 2019
Cochrane Library	John Wiley & Sons, Inc.	1996-present	26 February 2019

Note: Complete search strategies for questions 3 and 4 (Alternatives to amalgam, caries, systematic reviews and paediatrics/adults) are here provided for Ovid Medline, EBSCO CINAHL, Elsevier's Embase and the Cochrane Library. Also presented are initial searches done for alternatives to amalgam, caries, paediatrics/adults and randomized controlled trials.

List of search strategies included here:

- Q3: Alternatives to amalgam, caries, children and systematic reviews. Ovid Medline
- Q4: Alternatives to amalgam, caries, adults, systematic reviews. Ovid Medline
- Q3: Alternatives to amalgam, caries, children and systematic reviews. EBSCO CINAHL
- Q4: Alternatives to amalgam, caries, adults and systematic reviews. EBSCO CINAHL
- Q3: Alternatives to amalgam, caries, children and systematic reviews. Embase
- Q4: Alternatives to amalgam, caries, adults and systematic reviews. Embase
- Q3. Alternatives to amalgam, caries, children, systematic reviews. Cochrane Library
- Q4. Alternatives to amalgam, caries, adults, systematic reviews. Cochrane Library
- Alternatives to amalgam, caries, children and RCTs. Ovid Medline
- Alternatives to amalgam, caries, adults and RCTs. Ovid Medline
- Alternatives to amalgam, caries, adult (not children) and RCTs. EBSCO CINAHL
- Alternatives to amalgam, caries, children and RCTs. EBSCO CINAHL
- Alternatives to amalgam, caries, children and RCTs. Elsevier Embase
- Alternatives to amalgam, caries, adult and RCTs. Elsevier Embase
- Alternatives to amalgam, caries, children and RCTs. Cochrane Library
- Alternatives to amalgam, caries, adults and RCTs. Cochrane Library

Q3: Alternatives to amalgam, caries, children and systematic reviews: Ovid Medline			
Alternatives to Amalgam	1	exp Dental Alloys/ or alloy$.mp.	50916
	2	exp Dental Cements/ or (cement$.mp. or Ionomer$ or Glass-ionomer$ or Glassionomer$ or RMGIC or Cermet or glass-polyalkenoate).mp.	70180
	3	(Polycarboxylat$ or polyalkenoat$ or silicat$).mp.	23784

	4	exp Resins, Synthetic/ or Photoinitiators, Dental/ or (Resin$ or Composite$ or nanocomposite$ or white filling$).mp.	259060
	5	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite).mp.	2516
	6	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic).mp.	7063
	7	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton).mp.	590
	8	"Pit and Fissure Sealants"/ or (Sealant$ or Orthodontic adhesive$).mp.	7718
	9	(bisphenol A Glycidyl methacrylate or Bis-GMA or BisGMA or TEGDMA or UEDMA).mp.	5206
	10	exp Dental Bonding/ or (Enamel bond$ or dentine bond$ or single bond$).mp.	27123
	11	(Bulk fill or nanofill or Microhybrid or nanohybrid).mp.	2081
	12	(compomer$ or Polymer$ or carbomer$ or ormocer$).mp.	926109
	13	exp Crowns/ or (crown$ or "Hall's technique" or Hall technique).mp.	45763
	14	exp Root Canal Filling Materials/ or root canal filling.mp.	7884
	15	Dental Porcelain/ or exp Ceramics/ or (porcelain$ or ceramic$ or nanoceramic$).mp.	36080
	16	Inlays/ or (Inlay$ or in-lay$ or onlay$ or on-lay$).mp.	20668
	17	Dental Pulp Capping/ or Pulpectomy/ or Pulpotomy/ or "Pulp Capping and Pulpectomy Agents"/ or (pulp cap$ or Pulp therap$ or pulpotom$ or pulpect$ or mineral trioxide aggregate or formocresol).ab,ti,kf.	6673
	18	Calcium Hydroxide/ or Calcium hydroxide.ab,ti,kf. or "Ca(OH)2".ab,ti,kf.	6093
	19	(Zinc oxide or eugenol or Nano-hydroxyapatite or casein phosphopeptide or amorphous calcium phosphate or CPP-ACP).ab,ti,kf.	11418
	20	or/1-19	1322060
Caries	21	exp Dental Caries/	43589
	22	Dental Cavity preparation/	7584
	23	(ICDAS or ICDAS-II).af.	391
	24	(Caries or carious or karie* or "cariës" or carie).af.	61312
	25	((decalcif* or demineral* or hypomineral* or decay or fissures or white spots or cavit$ or defect$) adj10 (dent$ or tooth or teeth)).af.	35388
	26	or/21-25	87960
Paediatrics	27	exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or child* or girl? or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.	4172157
	28	exp Tooth, Deciduous/ or ((deciduous or milk or primary or natal or baby or exfoliat$ or transitional) adj2 (tooth or teeth or dentition)).mp.	16102
	29	Pediatric Dentistry/ or Dental Care for Children/ or pedodontic$.mp.	8307
	30	exp Child Health/ or Child Health Services/ or exp Pediatrics/	74405
	31	or/27-30	4182916
Systematic reviews	32	meta-analysis.pt.	97387
	33	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	183003
	34	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	152510
	35	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	9431

	36	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	22370
	37	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	22773
	38	(handsearch* or hand search*).ti,ab,kf,kw.	8375
	39	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	23162
	40	(meta regression* or metaregression*).ti,ab,kf,kw.	7077
	41	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	254360
	42	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.	8346
	43	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	183631
	44	(cochrane or (health adj2 technology assessment) or evidence report).jw.	18401
	45	(meta-analysis or systematic review).mp.	236251
	46	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	11888
	47	(outcomes research or relative effectiveness).ti,ab,kf,kw.	8373
	48	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.	1880
	49	or/32-48	398627
Alternatives to amalgams + Caries + Paediatrics	50	20 and 26 and 31	5881
Alternatives to amalgams + Caries + Paediatrics + Systematic Reviews	**51**	**49 and 50**	**196**

Q4: Alternatives to amalgam, caries, adults, systematic reviews: Ovid Medline			
Alternatives to amalgam	1	exp Dental Alloys/ or alloy$.mp.	50916
	2	exp Dental Cements/ or (cement$.mp. or Ionomer$ or Glass-ionomer$ or Glassionomer$ or RMGIC or Cermet or glass-polyalkenoate).mp.	70180
	3	(Polycarboxylat$ or polyalkenoat$ or silicat$).mp.	23784
	4	exp Resins, Synthetic/ or Photoinitiators, Dental/ or (Resin$ or Composite$ or nanocomposite$ or white filling$).mp.	259060
	5	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite).mp.	2516
	6	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic).mp.	7063
	7	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton).mp.	590
	8	"Pit and Fissure Sealants"/ or (Sealant$ or Orthodontic adhesive$).mp.	7718

	9	(bisphenol A Glycidyl methacrylate or Bis-GMA or BisGMA or TEGDMA or UEDMA).mp.	5206
	10	exp Dental Bonding/ or (Enamel bond$ or dentine bond$ or single bond$).mp.	27123
	11	(Bulk fill or nanofill or Microhybrid or nanohybrid).mp.	2081
	12	(compomer$ or Polymer$ or carbomer$ or ormocer$).mp.	926109
	13	exp Crowns/ or (crown$ or "Hall's technique" or Hall technique).mp.	45763
	14	exp Root Canal Filling Materials/ or root canal filling.mp.	7884
	15	Dental Porcelain/ or exp Ceramics/ or (porcelain$ or ceramic$ or nanoceramic$).mp.	36080
	16	Inlays/ or (Inlay$ or in-lay$ or onlay$ or on-lay$).mp.	20668
	17	Dental Pulp Capping/ or Pulpectomy/ or Pulpotomy/ or "Pulp Capping and Pulpectomy Agents"/ or (pulp cap$ or Pulp therap$ or pulpotom$ or pulpect$ or mineral trioxide aggregate or formocresol).ab,ti,kf.	6673
	18	Calcium Hydroxide/ or Calcium hydroxide.ab,ti,kf. or "Ca(OH)2".ab,ti,kf.	6093
	19	(Zinc oxide or eugenol or Nano-hydroxyapatite or casein phosphopeptide or amorphous calcium phosphate or CPP-ACP).ab,ti,kf.	11418
	20	or/1-19	1322060
Caries	21	exp Dental Caries/	43589
	22	Dental Cavity preparation/	7584
	23	(ICDAS or ICDAS-II).af.	391
	24	(Caries or carious or karie* or "cariës" or carie).af.	61312
	25	((decalcif* or demineral* or hypomineral* or decay or fissures or white spots or cavit$ or defect$) adj10 (dent$ or tooth or teeth)).af.	35388
	26	or/21-25	87960
Adults	27	adult.mp. or middle aged.sh. or age:.tw.	8497790
Systematic reviews	28	meta-analysis.pt.	97387
	29	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	183003
	30	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	152510
	31	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	9431
	32	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	22370
	33	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	22773
	34	(handsearch* or hand search*).ti,ab,kf,kw.	8375
	35	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	23162
	36	(meta regression* or metaregression*).ti,ab,kf,kw.	7077
	37	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	254360

	38	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.	8346
	39	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	183631
	40	(cochrane or (health adj2 technology assessment) or evidence report).jw.	18401
	41	(meta-analysis or systematic review).mp.	236251
	42	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	11888
	43	(outcomes research or relative effectiveness).ti,ab,kf,kw.	8373
	44	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.	1880
	45	or/28-44	398627
Alternatives to amalgam AND caries	46	20 and 26	24802
Alternatives to amalgam AND caries AND adult	47	27 and 46	7084
Alternatives to amalgam AND caries AND adult AND systematic reviews	48	45 and 47	133

Q3: Alternatives to amalgam, caries, paediatrics and systematic reviews: EBSCO CINAHL		
S1	(MH "Dental Alloys+") OR (TX alloy*)	6364
S2	(MH "Dental Cements+") OR (TI (cement* OR Ionomer* OR Glass-ionomer* or Glassionomer* OR RMGIC or Cermet OR glass-polyalkenoate)) OR (AB (cement* OR Ionomer* OR Glass-ionomer* OR Glassionomer* OR RMGIC OR Cermet OR glass-polyalkenoate))	10,765
S3	(MH "Resins, Synthetic+") OR (TI (resin* OR composite* OR nanocomposite* OR “white filling” OR “white filings”)) OR (AB (resin* OR composite* OR nanocomposite* OR “white filling” OR “white filings”))	28,970
S4	(TI (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA)) OR (AB (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA))	85
S5	(MH “Dental Bonding”) OR (TI (Enamel Bond* OR Dentine Bond* OR Single Bond*)) OR (AB (Enamel Bond* OR Dentine Bond* OR Single Bond*))	2,501
S6	(TI (“bulk fill” OR “nano fill” OR nanofill OR microhybrid OR nanohybrid)) OR (AB (“bulk fill” OR “nano fill” OR nanofill OR microhybrid OR nanohybrid))	249
S7	(TI (Polymer* or compomer* or carbomer* or ormocer*)) OR (AB (Polymer* or compomer* or carbomer* or ormocer*))	24,390

S8	(MH “Crowns”) OR (TI (crown* OR “Hall’s technique” OR “Hall technique”)) OR (AB (crown* OR “Hall’s technique” OR “Hall technique”))	5,732
S9	(TI (“root canal filling”)) OR (AB (“root canal filling”)) OR (MH "Root Canal Filling Materials")	1,161
S10	(MH "Dental Porcelain") OR (TI (porcelain* OR ceramic* OR nanoceramic*)) OR (AB (porcelain* OR ceramic* OR nanoceramic*))	4,033
S11	(MH “Inlays”) OR (AB (inlay OR inlays OR in-lay OR in-lays OR onlay OR onlays OR on-lay OR on-lays))	6,997
S12	(MH "Pulpectomy") OR (MH "Pulpotomy") OR (TX pulp cap* OR pulp therap* OR pulpect* OR “mineral trioxide aggregate” OR formocresol)	1,026
S13	(MH "Pit and Fissure Sealants") OR (TI (sealant* OR Orthodontic adhesive*)) OR (AB (sealant* OR Orthodontic adhesive*))	1,840)
S14	(TI polycarboxylat* OR polyalkenoat* OR Silicate*)) OR (AB (polycarboxylat* OR polyalkenoat* OR Silicate*))	934
S15	(TI ("Calcium Hydroxide” OR “Ca(OH)2”)) OR (AB ("Calcium Hydroxide” OR “Ca(OH)2”))	429
S16	(TI (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP)) OR (AB (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP))	695
S17	(TI (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite)) OR (AB (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite))	180
S18	(TI (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic)) OR (AB (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic))	563
S19	(TI (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton)) OR (AB (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton))	57
S20	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	79,592
S21	(MH “Dental Caries”)	10,434
S22	(TX (ICDAS OR ICDAS-II))	325
S23	(TI (Caries OR carious OR karies* OR "cariës" OR carie)) OR (AB (Caries OR carious OR karies* OR "cariës" OR carie))	9,105
S24	(TX (decalcification or demineral?ation or hypomineral?ation or decay or fissures or white spots or cavit* or defect* or lesion*) N10 (dent* or tooth or teeth or enamel))	12,648
S25	S21 OR S22 OR S23 OR S24	22,868
S26	(S20 AND S25)	3,782
S27	(MH “Adolescence+”) OR (MH “Child+”) OR (MH “Infant+”) OR (MH “Minors”) OR (TI adolescen* or babies or baby or boy* or boyfriend or boyhood or child* or girl* or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler* or underage* or under-age* or youth*) OR (AB adolescen* or babies or baby or boy* or boyfriend or boyhood or child* o ...	1,166,284
S28	(MH "Tooth, Deciduous+") OR (MH "Dentition, Primary") OR (MH “Dentition, Mixed”)	2,491

S29	(TI (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*)) OR (AB (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*))	2,908
S30	(MH "Pediatric Dentistry") OR (MH "Pediatrics+") OR (MH "Dental Care for Children") OR (MH "Child Health") OR (MH "Child Health Services+") OR (TI pedodont*) OR (AB pedodont*)	52,344
S31	S27 OR S28 OR S29 OR S30	1,167,628
S32	S26 AND S31	1,435
S33	(MH "Meta Analysis") OR (MH "Meta Synthesis") OR (MH "Systematic Review")	86,978
S34	(TI ((systematic OR methologic*) N3 (review OR overview))) OR (AB ((systematic OR methologic*) N3 (review OR overview))) OR (MW ((systematic OR methologic*) N3 (review OR overview)))	106,659
S35	(TI ((quantitative N3 (review* or overview* or synthes*)) or (research N3 (integrati* or overview*)))) OR (AB ((quantitative N3 (review* or overview* or synthes*)) or (research N3 (integrati* or overview*))))	4,989
S36	(TI ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*))) OR (AB ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*)))	10,526
S37	TI (data synthes* or data extraction* or data abstraction*) OR AB (data synthes* or data extraction* or data abstraction*)	(8,140
S38	TI (handsearch* OR “hand search”) OR AB (handsearch* OR “hand search”)	1,535
S39	(TI (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*)) OR (AB (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*))	5,848
S40	(TI (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*)) OR (AB (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*))	3,273
S41	(TI (meta regression* or metaregression*)) OR (AB (meta regression* or metaregression*))	2,429
S42	(TI (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*)) OR (AB (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*))	101,201
S43	(TI (medline or cochrane or pubmed or medlars or embase or cinahl)) OR (AB (medline or cochrane or pubmed or medlars or embase or cinahl)) OR (MW (medline or cochrane or pubmed or medlars or embase or cinahl))	101,826
S44	(SO (cochrane or (health N2 technology assessment) or evidence report)))	7,039
S45	(TI (comparative N3 (efficacy or effectiveness))) OR (AB (comparative N3 (efficacy or effectiveness)))	4,383
S46	(TI (outcomes research or relative effectiveness)) OR (AB (outcomes research or relative effectiveness))	3,400
S47	(TI ((indirect or indirect treatment or mixed-treatment) N2 comparison*)) OR (AB ((indirect or indirect treatment or mixed-treatment) N2 comparison*))	879
S48	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	184,296
S49	S32 AND S48	80

	Q4: Alternatives to amalgam, caries, adults and systematic reviews: EBSCO CINAHL	
S1	(MH "Dental Alloys+") OR (TX alloy*)	6,364
S2	(MH "Dental Cements+") OR (TI (cement* OR Ionomer* OR Glass-ionomer* or Glassionomer* OR RMGIC or Cermet OR glass-polyalkenoate)) OR (AB (cement* OR Ionomer* OR Glass-ionomer* OR Glassionomer* OR RMGIC OR Cermet OR glass-polyalkenoate))	10,765
S3	(MH "Resins, Synthetic+") OR (TI (resin* OR composite* OR nanocomposite* OR "white filling" OR "white filings")) OR (AB (resin* OR composite* OR nanocomposite* OR "white filling" OR "white filings"))	28,970
S4	(TI (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA)) OR (AB (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA))	85
S5	(MH "Dental Bonding") OR (TI (Enamel Bond* OR Dentine Bond* OR Single Bond*)) OR (AB (Enamel Bond* OR Dentine Bond* OR Single Bond*))	2,501
S6	(TI ("bulk fill" OR "nano fill" OR nanofill OR microhybrid OR nanohybrid)) OR (AB ("bulk fill" OR "nano fill" OR nanofill OR microhybrid OR nanohybrid))	249
S7	(TI (Polymer* or compomer* or carbomer* or ormocer*)) OR (AB (Polymer* or compomer* or carbomer* or ormocer*))	24,390
S8	(MH "Crowns") OR (TI (crown* OR "Hall's technique" OR "Hall technique")) OR (AB (crown* OR "Hall's technique" OR "Hall technique"))	5,732
S9	(TI ("root canal filling")) OR (AB ("root canal filling")) OR (MH "Root Canal Filling Materials")	1,161
S10	(MH "Dental Porcelain") OR (TI (porcelain* OR ceramic* OR nanoceramic*)) OR (AB (porcelain* OR ceramic* OR nanoceramic*))	4,033
S11	(MH "Inlays") OR (AB (inlay OR inlays OR in-lay OR in-lays OR onlay OR onlays OR on-lay OR on-lays))	6,997
S12	(MH "Pulpectomy") OR (MH "Pulpotomy") OR (TX pulp cap* OR pulp therap* OR pulpect* OR "mineral trioxide aggregate" OR formocresol)	1,026
S13	(MH "Pit and Fissure Sealants") OR (TI (sealant* OR Orthodontic adhesive*)) OR (AB (sealant* OR Orthodontic adhesive*))	1,840
S14	(TI polycarboxylat* OR polyalkenoat* OR Silicate*)) OR (AB (polycarboxylat* OR polyalkenoat* OR Silicate*))	934
S15	(TI ("Calcium Hydroxide" OR "Ca(OH)2")) OR (AB ("Calcium Hydroxide" OR "Ca(OH)2"))	429
S16	(TI (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP)) OR (AB (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP))	695
S17	(TI (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite)) OR (AB (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite))	180
S18	(TI (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic)) OR (AB (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic))	563
S19	(TI (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton)) OR (AB (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton))	57
S20	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	79,592

S21	(MH “Dental Caries”)	10,434
S22	(TX (ICDAS OR ICDAS-II))	325
S23	(TI (Caries OR carious OR karies* OR "cariës" OR carie)) OR (AB (Caries OR carious OR karies* OR "cariës" OR carie))	9,105
S24	(TX (decalcification or demineralization or hypomineralization or decay or fissures or white spots or cavit* or defect* or lesion*) N10 (dent* or tooth or teeth or enamel))	12,648
S25	S21 OR S22 OR S23 OR S24	22,868
S26	(S20 AND S25)	3,782
S27	(MH "Meta Analysis") OR (MH "Meta Synthesis") OR (MH "Systematic Review")	86,978
S28	(TI ((systematic OR methologic*) N3 (review OR overview))) OR (AB ((systematic OR methologic*) N3 (review OR overview))) OR (MW ((systematic OR methologic*) N3 (review OR overview)))	106,659
S29	(TI ((quantitative N3 (review* or overview* or synthes*)) or (research N3 (integrati* or overview*)))) OR (AB ((quantitative N3 (review* or overview* or synthes*)) or (research N3 (integrati* or overview*))))	4,989
S30	(TI ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*))) OR (AB ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*)))	10,526
S31	TI (data synthes* or data extraction* or data abstraction*) OR AB (data synthes* or data extraction* or data abstraction*)	8,140
S32	TI (handsearch* OR “hand search”) OR AB (handsearch* OR “hand search”)	1,535
S33	(TI (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*)) OR (AB (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*))	5,848
S34	(TI (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*)) OR (AB (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*))	3,273
S35	(TI (meta regression* or metaregression*)) OR (AB (meta regression* or metaregression*))	2,429
S36	(TI (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*)) OR (AB (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*))	101,201
S37	(TI (medline or cochrane or pubmed or medlars or embase or cinahl)) OR (AB (medline or cochrane or pubmed or medlars or embase or cinahl)) OR (MW (medline or cochrane or pubmed or medlars or embase or cinahl))	101,826
S38	(SO (cochrane or (health N2 technology assessment) or evidence report)))	7,039
S39	(TI (comparative N3 (efficacy or effectiveness))) OR (AB (comparative N3 (efficacy or effectiveness)))	4,383
S40	(TI (outcomes research or relative effectiveness)) OR (AB (outcomes research or relative effectiveness))	3,400
S41	(TI ((indirect or indirect treatment or mixed-treatment) N2 comparison*)) OR (AB ((indirect or indirect treatment or mixed-treatment) N2 comparison*))	879
S42	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41	184,296
S43	S26 AND S42	176
S44	(MH “Adolescence+”) OR (MH “Child+”) OR (MH “Infant+”) OR (MH “Minors”) OR (TI adolescen* or babies or baby or boy* or boyfriend or boyhood or child* or girl* or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-	1,166,284

	born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler* or underage* or under-age* or youth*) OR (AB adolescen* or babies or baby or boy* or boyfriend or boyhood or child* o ...	
S45	(MH "Tooth, Deciduous+") OR (MH "Dentition, Primary") OR (MH "Dentition, Mixed")	2,491
S46	(TI (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*)) OR (AB (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*))	2,908
S47	(MH "Pediatric Dentistry") OR (MH "Pediatrics+") OR (MH "Dental Care for Children") OR (MH "Child Health") OR (MH "Child Health Services+") OR (TI pedodont*) OR (AB pedodont*)	52,344
S48	S44 OR S45 OR S46 OR S47	1,167,628
S49	S43 NOT S48	96

Q3: Alternatives to amalgam, caries, pediatrics and systematic reviews: Elsevier Embase		
#1	'dental alloys'/exp/mj OR 'dental alloys' OR alloy*:ti	17,947
#2	'dental cements'/exp/mj OR cement*:ti OR ionomer*:ti OR 'glass ionomer*':ti OR glassionomer*:ti OR rmgic:ti OR cermet:ti OR 'glass polyalkenoate':ti	27,147
#3	((polycarboxylat* OR polyalkenoat* OR silicat*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	310
#4	'resins, synthetic'/exp/mj OR resin*:ti OR composite*:ti OR nanocomposite*:ti OR 'white filling*':ti	79,877
#5	'fluor protector':ti OR 'nuva seal':ti OR panavia:ti OR 'rely x':ti OR retroplast:ti OR geristore:ti OR 'fleck s':ti OR epoxylite:ti	94
#6	'vertise flow':ti OR filtek:ti OR sonicfill:ti OR clearfil:ti OR smartcem2:ti OR scotchbond:ti OR sbmp:ti OR dyract:ti OR heliomolar:ti OR compoglass:ti OR adaptic:ti	145
#7	vidrion:ti OR meron:ti OR optiband:ti OR multicure:ti OR 'ultra band lok':ti OR helioseal:ti OR 'xeno iii':ti OR delton:ti	21
#8	'fissure sealant'/exp/mj OR sealant*:ti OR 'orthodontic adhesive*':ti	4,387
#9	'bisphenol a glycidyl methacrylate':ti OR 'bis gma':ti OR bisgma:ti OR tegdma:ti OR uedma:ti	270
#10	'dental bonding'/exp/mj OR 'enamel bond*':ti OR 'dentine bond*':ti OR 'single bond*':ti	13,604
#11	'bulk fill':ti OR nanofill:ti OR microhybrid:ti OR nanohybrid:ti	702
#12	((compomer* OR polymer* OR carbomer* OR ormocer*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	983
#13	'crowns'/exp/mj OR crown*:ti OR 'hall s technique':ti OR 'hall technique':ti	18,894
#14	'root canal filling materials'/exp/mj OR 'root canal filling':ti	3,978

#15	'dental ceramics'/exp/mj OR porcelain*:ti OR ceramic*:ti OR nanoceramic*:ti	16,486
#16	'dental inlay'/exp/mj OR inlay:ti OR inlays:ti OR 'in lay':ti OR 'in lays':ti OR onlay:ti OR onlays:ti OR 'on lay':ti OR 'on lays':ti	3,394
#17	'dental pulp capping'/exp/mj OR 'pulpectomy'/exp/mj OR 'pulpotomy'/exp/mj OR 'pulp cap*':ti OR 'pulp therap*':ti OR pulpotom*:ti OR pulpect*:ti OR 'mineral trioxide aggregate':ti OR formocresol:ti	2,490
#18	'calcium hydroxide'/exp/mj	1,970
#19	'zinc oxide':ti OR eugenol:ti OR 'nano hydroxyapatite':ti OR 'casein phosphopeptide':ti OR 'amorphous calcium phosphate':ti OR 'cpp acp':ti	4,757
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	167,708
#21	'dental caries'/exp/mj	30,831
#22	'dental cavity preparation'/exp/mj	31,117
#23	caries:ti,ab OR carious:ti,ab OR karies*:ti,ab OR cariës:ti,ab OR carie:ti,ab	42,959
#24	((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR 'white spots' OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel OR caries OR filling*)):ti,ab	39,458
#25	icdas:ab,ti OR 'icdas ii':ab,ti	347
#26	#21 OR #22 OR #23 OR #24 OR #25	105,853
#27	#20 AND #26	18,202
#28	'adolescent'/exp OR 'child'/exp OR 'infant'/exp OR 'infant disease*':ti,ab,de OR 'childhood disease*':ti,ab,de OR adolescen*:ti,ab,de OR babies:ti,ab,de OR baby:ti,ab,de OR 'boy?':ti,ab,de OR boyfriend:ti,ab,de OR boyhood:ti,ab,de OR child*:ti,ab,de OR 'girl?':ti,ab,de OR infant*:ti,ab,de OR juvenil*:ti,ab,de OR 'kid?':ti,ab,de OR minors:ti,ab,de OR minors*:ti,ab,de OR neonat*:ti,ab,de OR newborn*:ti,ab,de OR 'new born*':ti,ab,de OR paediatric*:ti,ab,de OR peadiatric*:ti,ab,de OR pediatric*:ti,ab,de OR perinat*:ti,ab,de OR preschool*:ti,ab,de OR puber*:ti,ab,de OR pubescen*:ti,ab,de OR school*:ti,ab,de OR teen*:ti,ab,de OR 'toddler?':ti,ab,de OR 'underage?':ti,ab,de OR 'under-age?':ti,ab,de OR youth*:ti,ab,de	4,624,095
#29	'tooth, deciduous'/exp OR (((deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) NEAR/2 (tooth OR teeth OR dentition)):ti,ab,de,tn)	15,719
#30	'pediatric dentistry'/exp OR 'dental care for children'/exp OR pedodontic*:ti,ab	311,714
#31	'pediatrics'/exp	107,989
#32	#28 OR #29 OR #30 OR #31	4,875,774

#33	#27 AND #32	16,403
#34	'systematic review (topic)'/exp OR 'systematic review'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp	319,736
#35	'biomedical technology assessment'/exp	13,584
#36	(systematic* NEAR/3 (review* OR overview*)):ti,ab,de	269,828
#37	(methodologic* NEAR/3 (review* OR overview*)):ti,ab,de	3,887
#38	((quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab,de) OR ((research NEAR/3 (integrati* OR overview*)):ti,ab,de)	28,728
#39	((integrative NEAR/3 (review* OR overview*)):ti,ab,de) OR ((collaborative NEAR/3 (review* OR overview*)):ti,ab,de) OR ((pool* NEAR/3 analy*):ti,ab,de)	32,053
#40	'data synthes*':ti,ab,de OR 'data extraction*':ti,ab,de OR 'data abstraction*':ti,ab,de	35,045
#41	handsearch*:ti,ab,de OR 'hand search*':ti,ab,de	10,020
#42	'mantel haenszel':ti,ab,de OR peto:ti,ab,de OR 'der simonian':ti,ab,de OR dersimonian:ti,ab,de OR 'fixed effect*':ti,ab,de OR 'latin square*':ti,ab,de	30,211
#43	'met analy*':ti,ab,de OR metanaly*:ti,ab,de OR 'technology assessment*':ti,ab,de OR hta:ti,ab,de OR htas:ti,ab,de OR 'technology overview*':ti,ab,de OR 'technology appraisal*':ti,ab,de	22,826
#44	'meta regression*':ti,ab,de OR metaregression*:ti,ab,de	8,730
#45	'meta analy*':ti,ab,de OR metaanaly*:ti,ab,de OR 'systematic review*':ti,ab,de OR 'biomedical technology assessment*':ti,ab,de OR 'bio-medical technology assessment*':ti,ab,de	404,048
#46	medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab	227,729
#47	cochrane:ab,ti,de OR ((health NEAR/2 'technology assessment'):ab,ti,de) OR 'evidence report':ab,ti,de	98,351
#48	'meta analysis':ti,ab,de OR 'systematic review':ti,ab,de	374,906
#49	(comparative NEAR/3 (efficacy OR effectiveness)):ti,ab,de	75,080
#50	'outcomes research':ti,ab,de OR 'relative effectiveness':ti,ab,de	80,570
#51	((indirect OR 'indirect treatment' OR 'mixed treatment') NEAR/3 'comparison*'):ti,ab,de	4,392
#52	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	703,034
#53	**#33 AND #52**	**288**

Q4: Alternatives to amalgam, caries, adults and systematic reviews: Elsevier Embase		
#1	'dental alloys'/exp/mj OR 'dental alloys' OR alloy*:ti	17947
#2	'dental cements'/exp/mj OR cement*:ti OR ionomer*:ti OR 'glass ionomer*':ti OR glassionomer*:ti OR rmgic:ti OR cermet:ti OR 'glass polyalkenoate':ti	27147
#3	((polycarboxylat* OR polyalkenoat* OR silicat*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	310
#4	'resins, synthetic'/exp/mj OR resin*:ti OR composite*:ti OR nanocomposite*:ti OR 'white filling*':ti	79877
#5	'fluor protector':ti OR 'nuva seal':ti OR panavia:ti OR 'rely x':ti OR retroplast:ti OR geristore:ti OR 'fleck s':ti OR epoxylite:ti	94
#6	'vertise flow':ti OR filtek:ti OR sonicfill:ti OR clearfil:ti OR smartcem2:ti OR scotchbond:ti OR sbmp:ti OR dyract:ti OR heliomolar:ti OR compoglass:ti OR adaptic:ti	145
#7	vidrion:ti OR meron:ti OR optiband:ti OR multicure:ti OR 'ultra band lok':ti OR helioseal:ti OR 'xeno iii':ti OR delton:ti	21
#8	'fissure sealant'/exp/mj OR sealant*:ti OR 'orthodontic adhesive*':ti	4387
#9	'bisphenol a glycidyl methacrylate':ti OR 'bis gma':ti OR bisgma:ti OR tegdma:ti OR uedma:ti	270
#10	'dental bonding'/exp/mj OR 'enamel bond*':ti OR 'dentine bond*':ti OR 'single bond*':ti	13,604
#11	'bulk fill':ti OR nanofill:ti OR microhybrid:ti OR nanohybrid:ti	702
#12	((compomer* OR polymer* OR carbomer* OR ormocer*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	983
#13	'crowns'/exp/mj OR crown*:ti OR 'hall s technique':ti OR 'hall technique':ti	18894
#14	'root canal filling materials'/exp/mj OR 'root canal filling':ti	3978
#15	'dental ceramics'/exp/mj OR porcelain*:ti OR ceramic*:ti OR nanoceramic*:ti	16486
#16	'dental inlay'/exp/mj OR inlay:ti OR inlays:ti OR 'in lay':ti OR 'in lays':ti OR onlay:ti OR onlays:ti OR 'on lay':ti OR 'on lays':ti	3394
#17	'dental pulp capping'/exp/mj OR 'pulpectomy'/exp/mj OR 'pulpotomy'/exp/mj OR 'pulp cap*':ti OR 'pulp therap*':ti OR pulpotom*:ti OR pulpect*:ti OR 'mineral trioxide aggregate':ti OR formocresol:ti	2490
#18	'calcium hydroxide'/exp/mj	1970
#19	'zinc oxide':ti OR eugenol:ti OR 'nano hydroxyapatite':ti OR 'casein phosphopeptide':ti OR 'amorphous calcium phosphate':ti OR 'cpp acp':ti	4,757
#20	#1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7 AND #8 AND #9 AND #10 AND #11 AND #12 AND #13 AND #14 AND #15 AND #16 AND #17 AND #18 AND #19	167,708

#21	'dental caries'/exp/mj	30831
#22	'dental cavity preparation'/exp/mj	31,117
#23	caries:ti,ab OR carious:ti,ab OR karies*:ti,ab OR cariës:ti,ab OR carie:ti,ab	42959
#24	((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR 'white spots' OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel OR caries OR filling*)):ti,ab	39458
#25	icdas:ab,ti OR 'icdas ii':ab,ti	347
#26	#21 AND #22 AND #23 AND #24 AND #25	105,853
#27	#20 AND #26	18202
#28	'systematic review (topic)'/exp OR 'systematic review'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp	319,736
#29	'biomedical technology assessment'/exp	13584
#30	(systematic* NEAR/3 (review* OR overview*)):ti,ab,de	269828
#31	(methodologic* NEAR/3 (review* OR overview*)):ti,ab,de	3,887
#32	((quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab,de) OR ((research NEAR/3 (integrati* OR overview*)):ti,ab,de)	28,728
#33	((integrative NEAR/3 (review* OR overview*)):ti,ab,de) OR ((collaborative NEAR/3 (review* OR overview*)):ti,ab,de) OR ((pool* NEAR/3 analy*):ti,ab,de)	32,053
#34	'data synthes*':ti,ab,de OR 'data extraction*':ti,ab,de OR 'data abstraction*':ti,ab,de	35,045
#35	handsearch*:ti,ab,de OR 'hand search*':ti,ab,de	10,020
#36	'mantel haenszel':ti,ab,de OR peto:ti,ab,de OR 'der simonian':ti,ab,de OR dersimonian:ti,ab,de OR 'fixed effect*':ti,ab,de OR 'latin square*':ti,ab,de	30,211
#37	'met analy*':ti,ab,de OR metanaly*:ti,ab,de OR 'technology assessment*':ti,ab,de OR hta:ti,ab,de OR htas:ti,ab,de OR 'technology overview*':ti,ab,de OR 'technology appraisal*':ti,ab,de	22,826
#38	'meta regression*':ti,ab,de OR metaregression*:ti,ab,de	8,730
#39	'meta analy*':ti,ab,de OR metaanaly*:ti,ab,de OR 'systematic review*':ti,ab,de OR 'biomedical technology assessment*':ti,ab,de OR 'bio-medical technology assessment*':ti,ab,de	404,048
#40	medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab	227,729
#41	cochrane:ab,ti,de OR ((health NEAR/2 'technology assessment'):ab,ti,de) OR 'evidence report':ab,ti,de	98,351
#42	'meta analysis':ti,ab,de OR 'systematic review':ti,ab,de	374906

#43	(comparative NEAR/3 (efficacy OR effectiveness)):ti,ab,de	75,080
#44	'outcomes research':ti,ab,de OR 'relative effectiveness':ti,ab,de	80,570
#45	((indirect OR 'indirect treatment' OR 'mixed treatment') NEAR/3 'comparison*'):ti,ab,de	4,392
#46	#28 AND #29 AND #30 AND #31 AND #32 AND #33 AND #34 AND #35 AND #36 AND #37 AND #38 AND #39 AND #40 AND #41 AND #42 AND #43 AND #44 AND #45	703,034
#47	#27 AND #46	319
#48	'adult'/exp OR adult:ab,ti,de OR 'middle aged':ab,ti OR age*:ab,ti,de	12,783,311
#49	#47 AND #48	94

Q3. Alternatives to amalgam, caries, paediatrics, systematic reviews. Cochrane Library		
#1	MeSH descriptor: [Dental Alloys] explode all trees	930
#2	MeSH descriptor: [Dental Cements] explode all trees	2405
#3	MeSH descriptor: [Resins, Synthetic] explode all trees	3652
#4	MeSH descriptor: [Pit and Fissure Sealants] explode all trees	361
#5	MeSH descriptor: [Pulpectomy] explode all trees	70
#6	MeSH descriptor: [Pulpotomy] explode all trees	146
#7	MeSH descriptor: [Crowns] explode all trees	724
#8	MeSH descriptor: [Root Canal Filling Materials] explode all trees	512
#9	MeSH descriptor: [Dental Porcelain] explode all trees	330
#10	MeSH descriptor: [Dental Bonding] explode all trees	1824
#11	(alloy OR alloys):ti,ab,kw	1084
#12	(cement* or Ionomer* or Glass-ionomer* or Glassionomer* or RMGIC or Cermet or glass-polyalkenoate):ti,ab,kw	4846
#13	(Polycarboxylat* or polyalkenoat* or silicat*):ti,ab,kw	774
#14	(Resin* OR Composite* OR nanocomposite* OR "white filling" OR "white fillings"):ti,ab,kw	16423
#15	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite):ti,ab,kw	309
#16	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic):ti,ab,kw	818
#17	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton):ti,ab,kw	152
#18	(Sealant* OR Orthodontic adhesive*):ti,ab,kw	1644
#19	("bisphenol A Glycidyl methacrylate" OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA):ti,ab,kw	585
#20	(Enamel bond* OR dentine bond* OR single bond*):ti,ab,kw	2087
#21	("Bulk fill" OR nanofill OR Microhybrid OR nanohybrid):ti,ab,kw	163

#22	(compomer* OR Polymer* OR carbomer* OR ormocer*):ti,ab,kw	11658
#23	(crown OR crowns OR "Hall's technique" OR "Hall technique"):ti,ab,kw	1574
#24	("root canal filling"):ti,ab,kw	554
#25	(porcelain* or ceramic* or nanoceramic*):ti,ab,kw	1217
#26	(Inlay OR inlays OR "in-lay" OR "in-lays" OR onlay OR onlays OR "on-lay" OR "on-lays"):ti,ab,kw	1901
#27	(pulp cap* OR Pulp therap* OR pulpotom* OR pulpect* OR mineral trioxide aggregate OR formocresol):ti,ab,kw	1337
#28	("Calcium hydroxide" OR "Ca(OH)2"):ti,ab,kw	453
#29	("Zinc oxide" OR eugenol OR "Nano-hydroxyapatite" OR "casein phosphopeptide" OR "amorphous calcium phosphate" OR "CPP-ACP"):ti,ab,kw	708
#30	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	36433
#31	MeSH descriptor: [Dental Caries] explode all trees	2180
#32	MeSH descriptor: [Dental Cavity Preparation] explode all trees	628
#33	(ICDAS OR ICDAS-II):ti,ab,kw	94
#34	(Caries OR carious OR karies* OR "cariës" OR carie):ti,ab,kw	4670
#35	(((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR white spots OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel))):ti,ab,kw	3713
#36	#31 OR #32 OR #33 OR #34 OR #35	6929
#37	#30 AND #36	3299
	Apply Limits: Cochrane Reviews only	41
#38	MeSH descriptor: [Child] explode all trees	1111
#39	MeSH descriptor: [Adolescent] explode all trees	97793
#40	MeSH descriptor: [Infant] explode all trees	15008
#41	MeSH descriptor: [Tooth, Deciduous] explode all trees	551
#42	(((deciduous or milk or primary or natal or baby or exfoliat* or transitional) NEAR/2 (tooth or teeth or dentition))):ti,ab,kw	976
#43	#38 OR #39 OR #40 OR #41 OR #42	112471
#44	**#37 AND #43. Apply Limits: Cochrane Reviews only**	**18**

Q4. Alternatives to amalgam, caries, adults, systematic reviews. Cochrane Library		
#1	MeSH descriptor: [Dental Alloys] explode all trees	930
#2	MeSH descriptor: [Dental Cements] explode all trees	2405
#3	MeSH descriptor: [Resins, Synthetic] explode all trees	3652
#4	MeSH descriptor: [Pit and Fissure Sealants] explode all trees	361
#5	MeSH descriptor: [Pulpectomy] explode all trees	70
#6	MeSH descriptor: [Pulpotomy] explode all trees	146
#7	MeSH descriptor: [Crowns] explode all trees	724

#8	MeSH descriptor: [Root Canal Filling Materials] explode all trees	512
#9	MeSH descriptor: [Dental Porcelain] explode all trees	330
#10	MeSH descriptor: [Dental Bonding] explode all trees	1824
#11	(alloy OR alloys):ti,ab,kw	1084
#12	(cement* or Ionomer* or Glass-ionomer* or Glassionomer* or RMGIC or Cermet or glass-polyalkenoate):ti,ab,kw	4846
#13	(Polycarboxylat* or polyalkenoat* or silicat*):ti,ab,kw	774
#14	(Resin* OR Composite* OR nanocomposite* OR "white filling" OR "white fillings"):ti,ab,kw	16423
#15	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite):ti,ab,kw	309
#16	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic):ti,ab,kw	818
#17	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton):ti,ab,kw	152
#18	(Sealant* OR Orthodontic adhesive*):ti,ab,kw	1644
#19	("bisphenol A Glycidyl methacrylate" OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA):ti,ab,kw	585
#20	(Enamel bond* OR dentine bond* OR single bond*):ti,ab,kw	2087
#21	("Bulk fill" OR nanofill OR Microhybrid OR nanohybrid):ti,ab,kw	163
#22	(compomer* OR Polymer* OR carbomer* OR ormocer*):ti,ab,kw	11658
#23	(crown OR crowns OR "Hall's technique" OR "Hall technique"):ti,ab,kw	1574
#24	("root canal filling"):ti,ab,kw	554
#25	(porcelain* or ceramic* or nanoceramic*):ti,ab,kw	1217
#26	(Inlay OR inlays OR "in-lay" OR "in-lays" OR onlay OR onlays OR "on-lay" OR "on-lays"):ti,ab,kw	1901
#27	(pulp cap* OR Pulp therap* OR pulpotom* OR pulpect* OR mineral trioxide aggregate OR formocresol):ti,ab,kw	1337
#28	("Calcium hydroxide" OR "Ca(OH)2"):ti,ab,kw	453
#29	("Zinc oxide" OR eugenol OR "Nano-hydroxyapatite" OR "casein phosphopeptide" OR "amorphous calcium phosphate" OR "CPP-ACP"):ti,ab,kw	708
#30	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	36433
#31	MeSH descriptor: [Dental Caries] explode all trees	2180
#32	MeSH descriptor: [Dental Cavity Preparation] explode all trees	628
#33	(ICDAS OR ICDAS-II):ti,ab,kw	94
#34	(Caries OR carious OR karies* OR "cariës" OR carie):ti,ab,kw	4670
#35	(((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR white spots OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel))):ti,ab,kw	3713
#36	#31 OR #32 OR #33 OR #34 OR #35	6929
#37	#30 AND #36	3299

	Apply Limits: Cochrane Reviews only	**41**
#38	MeSH descriptor: [Adult] explode all trees	3037
#39	(age* OR middle-age* OR adult):ti,ab,kw	744300
#40	#38 OR #39	744301
#41	#37 AND #40	31

Alternatives to amalgam, caries, children and RCTs. Ovid Medline			
Alternatives to Amalgam	1	exp Dental Alloys/ or alloy$.mp.	50916
	2	exp Dental Cements/ or (cement$.mp. or Ionomer$ or Glass-ionomer$ or Glassionomer$ or RMGIC or Cermet or glass-polyalkenoate).mp.	70180
	3	(Polycarboxylat$ or polyalkenoat$ or silicat$).mp.	23784
	4	exp Resins, Synthetic/ or Photoinitiators, Dental/ or (Resin$ or Composite$ or nanocomposite$ or white filling$).mp.	259060
	5	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite).mp.	2516
	6	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic).mp.	7063
	7	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton).mp.	590
	8	"Pit and Fissure Sealants"/ or (Sealant$ or Orthodontic adhesive$).mp.	7718
	9	(bisphenol A Glycidyl methacrylate or Bis-GMA or BisGMA or TEGDMA or UEDMA).mp.	5206
	10	exp Dental Bonding/ or (Enamel bond$ or dentin bond$ or single bond$).mp.	27123
	11	(Bulk fill or nanofill or Microhybrid or nanohybrid).mp.	2081
	12	(compomer$ or Polymer$ or carbomer$ or ormocer$).mp.	926109
	13	exp Crowns/ or (crown$ or "Hall's technique" or Hall technique).mp.	45763
	14	exp Root Canal Filling Materials/ or root canal filling.mp.	7884
	15	Dental Porcelain/ or exp Ceramics/ or (porcelain$ or ceramic$ or nanoceramic$).mp.	36080
	16	Inlays/ or (Inlay$ or in-lay$ or onlay$ or on-lay$).mp.	20668
	17	Dental Pulp Capping/ or Pulpectomy/ or Pulpotomy/ or "Pulp Capping and Pulpectomy Agents"/ or (pulp cap$ or Pulp therap$ or pulpotom$ or pulpect$ or mineral trioxide aggregate or formocresol).ab,ti,kf.	6673
	18	Calcium Hydroxide/ or Calcium hydroxide.ab,ti,kf. or "Ca(OH)2".ab,ti,kf.	6093
	19	(Zinc oxide or eugenol or Nano-hydroxyapatite or casein phosphopeptide or amorphous calcium phosphate or CPP-ACP).ab,ti,kf.	11418
	20	or/1-19	1322060
Caries	21	exp Dental Caries/	43589
	22	Dental Cavity preparation/	7584
	23	(ICDAS or ICDAS-II).af.	391
	24	(Caries or carious or karie* or "cariës" or carie).af.	61312
	25	((decalcif* or demineral* or hypomineral* or decay or fissures or white spots or cavit$ or defect$) adj10 (dent$ or tooth or teeth)).af.	35388
	26	or/21-25	87960
Children	27	exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or child* or girl? or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or	4172157

		paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.	
	28	exp Tooth, Deciduous/ or ((deciduous or milk or primary or natal or baby or exfoliat$ or transitional) adj2 (tooth or teeth or dentition)).mp.	16102
	29	Pediatric Dentistry/ or Dental Care for Children/ or pedodontic$.mp.	8307
	30	exp Child Health/ or Child Health Services/ or exp Pediatrics/	74405
	31	or/27-30	4182916
RCTs	32	Randomized Controlled Trial.pt.	476462
	33	Pragmatic Clinical Trial.pt.	973
	34	Randomized Controlled Trial/	476462
	35	exp Randomized Controlled Trials as Topic/	123549
	36	Random Allocation/	97675
	37	Double-Blind Method/	149615
	38	Single-Blind Method/	26288
	39	Placebos/	34243
	40	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1371107
	41	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	221822
	42	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	822
	43	or/32-42	1396177
Alternatives to amalgam AND Caries AND Children AND RCTs	**44**	**20 and 26 and 31 and 43**	**1259**

Alternatives to amalgam, caries, adults and RCTs. Ovid Medline			
Alternatives to amalgam	1	exp Dental Alloys/ or alloy$.mp.	50916
	2	exp Dental Cements/ or (cement$.mp. or Ionomer$ or Glass-ionomer$ or Glassionomer$ or RMGIC or Cermet or glass-polyalkenoate).mp.	70180
	3	(Polycarboxylat$ or polyalkenoat$ or silicat$).mp.	23784
	4	exp Resins, Synthetic/ or Photoinitiators, Dental/ or (Resin$ or Composite$ or nanocomposite$ or white filling$).mp.	259060
	5	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite).mp.	2516
	6	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic).mp.	7063
	7	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton).mp.	590
	8	"Pit and Fissure Sealants"/ or (Sealant$ or Orthodontic adhesive$).mp.	7718
	9	(bisphenol A Glycidyl methacrylate or Bis-GMA or BisGMA or TEGDMA or UEDMA).mp.	5206
	10	exp Dental Bonding/ or (Enamel bond$ or dentin bond$ or single bond$).mp.	27123
	11	(Bulk fill or nanofill or Microhybrid or nanohybrid).mp.	2081
	12	(compomer$ or Polymer$ or carbomer$ or ormocer$).mp.	926109
	13	exp Crowns/ or (crown$ or "Hall's technique" or Hall technique).mp.	45763
	14	exp Root Canal Filling Materials/ or root canal filling.mp.	7884

	15	Dental Porcelain/ or exp Ceramics/ or (porcelain$ or ceramic$ or nanoceramic$).mp.	36080
	16	Inlays/ or (Inlay$ or in-lay$ or onlay$ or on-lay$).mp.	20668
	17	Dental Pulp Capping/ or Pulpectomy/ or Pulpotomy/ or "Pulp Capping and Pulpectomy Agents"/ or (pulp cap$ or Pulp therap$ or pulpotom$ or pulpect$ or mineral trioxide aggregate or formocresol).ab,ti,kf.	6673
	18	Calcium Hydroxide/ or Calcium hydroxide.ab,ti,kf. or "Ca(OH)2".ab,ti,kf.	6093
	19	(Zinc oxide or eugenol or Nano-hydroxyapatite or casein phosphopeptide or amorphous calcium phosphate or CPP-ACP).ab,ti,kf.	11418
	20	or/1-19	1322060
	21	exp Dental Caries/	43589
	22	Dental Cavity preparation/	7584
	23	(ICDAS or ICDAS-II).af.	391
	24	(Caries or carious or karie* or "cariës" or carie).af.	61312
	25	((decalcif* or demineral* or hypomineral* or decay or fissures or white spots or cavit$ or defect$) adj10 (dent$ or tooth or teeth)).af.	35388
	26	or/21-25	87960
RCT	27	Randomized Controlled Trial.pt.	476462
	28	Pragmatic Clinical Trial.pt.	978
	29	Randomized Controlled Trial/	476583
	30	exp Randomized Controlled Trials as Topic/	123581
	31	Random Allocation/	97722
	32	Double-Blind Method/	149646
	33	Single-Blind Method/	26300
	34	Placebos/	34243
	35	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1372454
	36	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	221959
	37	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	822
	38	or/27-37	1397539
Alternatives to Amalgam AND Caries AND RCTs	39	20 and 26 and 38	4419
Adult	40	adult.mp. or middle aged.sh. or age:.tw.	8502650
Alternatives to Amalgam AND Caries AND RCTs AND adult	41	39 and 40	**1584**

Alternatives to amalgam, caries, children and RCTs. EBSCO CINAHL			
	S1	(MH "Dental Alloys+") OR (TX alloy*)	6,364

Alternatives to amalgam	S2	(MH "Dental Cements+") OR (TI (cement* OR Ionomer* OR Glass-ionomer* or Glassionomer* OR RMGIC or Cermet OR glass-polyalkenoate)) OR (AB (cement* OR Ionomer* OR Glass-ionomer* OR Glassionomer* OR RMGIC OR Cermet OR glass-polyalkenoate))	10,765
	S3	(MH "Resins, Synthetic+") OR (TI (resin* OR composite* OR nanocomposite* OR “white filling” OR “white filings”)) OR (AB (resin* OR composite* OR nanocomposite* OR “white filling” OR “white filings”))	28,970
	S4	(TI (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA)) OR (AB (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA))	85
	S5	(MH “Dental Bonding”) OR (TI (Enamel Bond* OR Dentin Bond* OR Single Bond*)) OR (AB (Enamel Bond* OR Dentin Bond* OR Single Bond*))	2,501
	S6	(TI (“bulk fill” OR “nano fill” OR nanofill OR microhybrid OR nanohybrid)) OR (AB (“bulk fill” OR “nano fill” OR nanofill OR microhybrid OR nanohybrid))	249
	S7	(TI (Polymer* or compomer* or carbomer* or ormocer*)) OR (AB (Polymer* or compomer* or carbomer* or ormocer*))	24,390
	S8	(MH “Crowns”) OR (TI (crown* OR “Hall’s technique” OR “Hall technique”)) OR (AB (crown* OR “Hall’s technique” OR “Hall technique”))	5,732
	S9	(TI (“root canal filling”)) OR (AB (“root canal filling”)) OR (MH "Root Canal Filling Materials")	1,161
	S10	(MH "Dental Porcelain") OR (TI (porcelain* OR ceramic* OR nanoceramic*)) OR (AB (porcelain* OR ceramic* OR nanoceramic*))	4,033
	S11	(MH “Inlays”) OR (AB (inlay OR inlays OR in-lay OR in-lays OR onlay OR onlays OR on-lay OR on-lays))	6,997
	S12	(MH "Pulpectomy") OR (MH "Pulpotomy") OR (TX pulp cap* OR pulp therap* OR pulpect* OR “mineral trioxide aggregate” OR formocresol)	1,026
	S13	(MH "Pit and Fissure Sealants") OR (TI (sealant* OR Orthodontic adhesive*)) OR (AB (sealant* OR Orthodontic adhesive*))	1,840
	S14	(TI polycarboxylat* OR polyalkenoat* OR Silicate*)) OR (AB (polycarboxylat* OR polyalkenoat* OR Silicate*))	934
	S15	(TI ("Calcium Hydroxide” OR “Ca(OH)2)”)) OR (AB ("Calcium Hydroxide” OR “Ca(OH)2)”))	429
	S16	(TI (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP)) OR (AB (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP))	695
	S17	(TI (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite)) OR (AB (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite))	180
	S18	(TI (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic)) OR (AB (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic))	563
	S19	(TI (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton)) OR (AB (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton))	57
	S20	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	79,592
Caries	S21	(MH “Dental Caries”)	10,434

	S22	(TX (ICDAS OR ICDAS-II))	325
	S23	(TI (Caries OR carious OR karies* OR "cariës" OR carie)) OR (AB (Caries OR carious OR karies* OR "cariës" OR carie))	9,105
	S24	(TX (decalcification or demineral?ation or hypomineral?ation or decay or fissures or white spots or cavit* or defect* or lesion*) N10 (dent* or tooth or teeth or enamel))	12,648
	S25	S21 OR S22 OR S23 OR S24	22,868
Alternatives to amalgam and caries	S26	(S20 AND S25)	3,782
Children	S27	(MH "Adolescence+") OR (MH "Child+") OR (MH "Infant+") OR (MH "Minors") OR (TI adolescen* or babies or baby or boy* or boyfriend or boyhood or child* or girl* or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler* or underage* or under-age* or youth*) OR (AB adolescen* or babies or baby or boy* or boyfriend or boyhood or child* o ...	1,166,284
	S28	(MH "Tooth, Deciduous+") OR (MH "Dentition, Primary") OR (MH "Dentition, Mixed")	2,491
	S29	(TI (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*)) OR (AB (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*))	2,908
	S30	(MH "Pediatric Dentistry") OR (MH "Pediatrics+") OR (MH "Dental Care for Children") OR (MH "Child Health") OR (MH "Child Health Services+") OR (TI pedodont*) OR (AB pedodont*)	52,344
	S31	S27 OR S28 OR S29 OR S30	1,167,628
Alternatives to amalgam and caries and paediatrics	S32	S26 AND S31	1,435
RCT	S33	(MH "Clinical Trial Registry") OR (MH "Clinical Trials+") OR (MH "Random Sample+") OR (MH "Random Assignment") OR (MH "Placebos")	311,117
	S34	TI (((singl* OR doubl*) N2 (blind* OR dumm* OR mask*))) OR AB (((singl* OR doubl*) N2 (blind* OR dumm* OR mask*))) OR MW (((singl* OR doubl*) N2 (blind* OR dumm* OR mask*)))	64,115
	S35	(PT "Clinical trial")	86,760
	S36	S33 OR S34 OR S35	320,797
Alternatives to amalgam and caries and paediatrics and RCTs	S37	S32 AND S36	280

Alternatives to amalgam, caries, adult (not children) and RCTs. EBSCO CINAHL			
Alternatives to amalgam	S1	(MH "Dental Alloys+") OR (TX alloy*)	6,364
	S2	(MH "Dental Cements+") OR (TI (cement* OR Ionomer* OR Glass-ionomer* or Glassionomer* OR RMGIC or Cermet OR glass-polyalkenoate)) OR (AB (cement* OR Ionomer* OR Glass-ionomer* OR Glassionomer* OR RMGIC OR Cermet OR glass-polyalkenoate))	10,765
	S3	(MH "Resins, Synthetic+") OR (TI (resin* OR composite* OR nanocomposite* OR "white filling" OR "white filings")) OR (AB (resin* OR composite* OR nanocomposite* OR "white filling" OR "white filings"))	28,970

	S4	(TI (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA)) OR (AB (bisphenol A Glycidyl methacrylate OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA))	85
	S5	(MH “Dental Bonding”) OR (TI (Enamel Bond* OR Dentin Bond* OR Single Bond*)) OR (AB (Enamel Bond* OR Dentin Bond* OR Single Bond*))	2,501
	S6	(TI (“bulk fill” OR “nano fill” OR nanofill OR microhybrid OR nanohybrid)) OR (AB (“bulk fill” OR “nano fill” OR nanofill OR microhybrid OR nanohybrid))	249
	S7	(TI (Polymer* or compomer* or carbomer* or ormocer*)) OR (AB (Polymer* or compomer* or carbomer* or ormocer*))	24,390
	S8	(MH “Crowns”) OR (TI (crown* OR “Hall’s technique” OR “Hall technique”)) OR (AB (crown* OR “Hall’s technique” OR “Hall technique”))	5,732
	S9	(TI (“root canal filling”)) OR (AB (“root canal filling”)) OR (MH "Root Canal Filling Materials")	1,161
	S10	(MH "Dental Porcelain") OR (TI (porcelain* OR ceramic* OR nanoceramic*)) OR (AB (porcelain* OR ceramic* OR nanoceramic*))	4,033
	S11	(MH “Inlays”) OR (AB (inlay OR inlays OR in-lay OR in-lays OR onlay OR onlays OR on-lay OR on-lays))	6,997
	S12	(MH "Pulpectomy") OR (MH "Pulpotomy") OR (TX pulp cap* OR pulp therap* OR pulpect* OR “mineral trioxide aggregate” OR formocresol)	1,026
	S13	(MH "Pit and Fissure Sealants") OR (TI (sealant* OR Orthodontic adhesive*)) OR (AB (sealant* OR Orthodontic adhesive*))	1,840
	S14	(TI polycarboxylat* OR polyalkenoat* OR Silicate*)) OR (AB (polycarboxylat* OR polyalkenoat* OR Silicate*))	934
	S15	(TI ("Calcium Hydroxide” OR “Ca(OH)2)”)) OR (AB ("Calcium Hydroxide” OR “Ca(OH)2)”))	429
	S16	(TI (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP)) OR (AB (Zinc oxide OR eugenol OR Nano-hydroxyapatite OR casein phosphopeptide OR amorphous calcium phosphate OR CPP-ACP))	695
	S17	(TI (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite)) OR (AB (Fluor-Protector OR Nuva Seal OR Panavia OR Rely X OR Retroplast OR Geristore OR "Fleck's" OR Epoxylite))	180
	S18	(TI (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic)) OR (AB (Vertise Flow OR Filtek OR SonicFill OR Clearfil OR SmartCem2 OR Scotchbond OR SBMP OR Dyract OR Heliomolar OR Compoglass OR Adaptic))	563
	S19	(TI (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton)) OR (AB (Vidrion OR Meron OR Optiband OR Multicure OR Ultra Band Lok OR Helioseal OR Xeno III OR Delton))	57
	S20	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	79,592
Caries	S21	(MH “Dental Caries”)	10,434
	S22	(TX (ICDAS OR ICDAS-II))	325
	S23	(TI (Caries OR carious OR karies* OR "cariës" OR carie)) OR (AB (Caries OR carious OR karies* OR "cariës" OR carie))	9,105
	S24	(TX (decalcification or deminerali?ation or hypominerali?ation or decay or fissures or white spots or cavit* or defect* or lesion*) N10 (dent* or tooth or teeth or enamel))	12,648
	S25	S21 OR S22 OR S23 OR S24	22,868
Alternatives to amalgam AND Caries	S26	(S20 AND S25)	3,782
Children	S27	(MH “Adolescence+”) OR (MH “Child+”) OR (MH “Infant+”) OR (MH “Minors”) OR (TI adolescen* or babies or baby or boy* or boyfriend or boyhood or child* or girl* or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or	1,166,284

		pubescen* or school* or teen* or toddler* or underage* or under-age* or youth*) OR (AB adolescen* or babies or baby or boy* or boyfriend or boyhood or child* or girl* or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler* or underage* or under-age* or youth*)	
	S28	(MH "Tooth, Deciduous+") OR (MH "Dentition, Primary") OR (MH "Dentition, Mixed")	2,491
	S29	(TI (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*)) OR (AB (deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) N2 (tooth OR teeth OR dent*))	2,908
	S30	(MH "Pediatric Dentistry") OR (MH "Pediatrics+") OR (MH "Dental Care for Children") OR (MH "Child Health") OR (MH "Child Health Services+") OR (TI pedodont*) OR (AB pedodont*)	52,344
	S31	S27 OR S28 OR S29 OR S30	1,167,628
RCTs	S32	(MH "Clinical Trial Registry") OR (MH "Clinical Trials+") OR (MH "Random Sample+") OR (MH "Random Assignment") OR (MH "Placebos")	311,117
	S33	TI (((singl* OR doubl*) N2 (blind* OR dumm* OR mask*))) OR AB (((singl* OR doubl*) N2 (blind* OR dumm* OR mask*))) OR MW (((singl* OR doubl*) N2 (blind* OR dumm* OR mask*)))	64,115
	S34	(PT "Clinical trial")	86,760
	S35	S32 OR S33 OR S34	320,797
Alternatives to amalgam AND caries AND RCTs	S36	(S26 AND S35)	572
(Alternatives to amalgam AND caries AND RCTs) NOT children	S37	S36 NOT S31	292

Alternatives to amalgam, caries, children and RCTs. Elsevier Embase			
Alternatives to amalgam	#1	'dental alloys'/exp/mj OR 'dental alloys' OR alloy*:ti	17,947
	#2	'dental cements'/exp/mj OR cement*:ti OR ionomer*:ti OR 'glass ionomer*':ti OR glassionomer*:ti OR rmgic:ti OR cermet:ti OR 'glass polyalkenoate':ti	27,147
	#3	((polycarboxylat* OR polyalkenoat* OR silicat*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	310
	#4	'resins, synthetic'/exp/mj OR resin*:ti OR composite*:ti OR nanocomposite*:ti OR 'white filling*':ti	79,877
	#5	'fluor protector':ti OR 'nuva seal':ti OR panavia:ti OR 'rely x':ti OR retroplast:ti OR geristore:ti OR 'fleck s':ti OR epoxylite:ti	94
	#6	'vertise flow':ti OR filtek:ti OR sonicfill:ti OR clearfil:ti OR smartcem2:ti OR scotchbond:ti OR sbmp:ti OR dyract:ti OR heliomolar:ti OR compoglass:ti OR adaptic:ti	145
	#7	vidrion:ti OR meron:ti OR optiband:ti OR multicure:ti OR 'ultra band lok':ti OR helioseal:ti OR 'xeno iii':ti OR delton:ti	21
	#8	'fissure sealant'/exp/mj OR sealant*:ti OR 'orthodontic adhesive*':ti	4,387
	#9	'bisphenol a glycidyl methacrylate':ti OR 'bis gma':ti OR bisgma:ti OR tegdma:ti OR uedma:ti	270
	#10	'dental bonding'/exp/mj OR 'enamel bond*':ti OR 'dentin bond*':ti OR 'single bond*':ti	13,604
	#11	'bulk fill':ti OR nanofill:ti OR microhybrid:ti OR nanohybrid:ti	702

	#12	((compomer* OR polymer* OR carbomer* OR ormocer*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	983
	#13	'crowns'/exp/mj OR crown*:ti OR 'hall s technique':ti OR 'hall technique':ti	18,894
	#14	'root canal filling materials'/exp/mj OR 'root canal filling':ti	3,978
	#15	'dental ceramics'/exp/mj OR porcelain*:ti OR ceramic*:ti OR nanoceramic*:ti	16,486
	#16	'dental inlay'/exp/mj OR inlay:ti OR inlays:ti OR 'in lay':ti OR 'in lays':ti OR onlay:ti OR onlays:ti OR 'on lay':ti OR 'on lays':ti	3,394
	#17	'dental pulp capping'/exp/mj OR 'pulpectomy'/exp/mj OR 'pulpotomy'/exp/mj OR 'pulp cap*':ti OR 'pulp therap*':ti OR pulpotom*:ti OR pulpect*:ti OR 'mineral trioxide aggregate':ti OR formocresol:ti	2,490
	#18	'calcium hydroxide'/exp/mj	1,970
	#19	'zinc oxide':ti OR eugenol:ti OR 'nano hydroxyapatite':ti OR 'casein phosphopeptide':ti OR 'amorphous calcium phosphate':ti OR 'cpp acp':ti	4,757
	#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	167,708
Caries	#21	'dental caries'/exp/mj	30,831
	#22	'dental cavity preparation'/exp/mj	31,117
	#24	((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR 'white spots' OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel OR caries OR filling*)):ti,ab 39,458	42,959
	#25	icdas:ab,ti OR 'icdas ii':ab,ti	347
	#26	#21 OR #22 OR #23 OR #24 OR #25	105,853
Alternatives to amalgam AND Caries	#27	#20 AND #26	18,202
Paediatrics	#28	'adolescent'/exp OR 'child'/exp OR 'infant'/exp OR 'infant disease*':ti,ab,de OR 'childhood disease*':ti,ab,de OR adolescen*:ti,ab,de OR babies:ti,ab,de OR baby:ti,ab,de OR 'boy?':ti,ab,de OR boyfriend:ti,ab,de OR boyhood:ti,ab,de OR child*:ti,ab,de OR 'girl?':ti,ab,de OR infant*:ti,ab,de OR juvenil*:ti,ab,de OR 'kid?':ti,ab,de OR minors:ti,ab,de OR minors*:ti,ab,de OR neonat*:ti,ab,de OR newborn*:ti,ab,de OR 'new born*':ti,ab,de OR paediatric*:ti,ab,de OR peadiatric*:ti,ab,de OR pediatric*:ti,ab,de OR perinat*:ti,ab,de OR preschool*:ti,ab,de OR puber*:ti,ab,de OR pubescen*:ti,ab,de OR school*:ti,ab,de OR teen*:ti,ab,de OR 'toddler?':ti,ab,de OR 'underage?':ti,ab,de OR 'under-age?':ti,ab,de OR youth*:ti,ab,de	4,624,095
	#29	'tooth, deciduous'/exp OR (((deciduous OR milk OR primary OR natal OR baby OR exfoliat* OR transitional) NEAR/2 (tooth OR teeth OR dentition)):ti,ab,de,tn)	15,719
	#30	'pediatric dentistry'/exp OR 'dental care for children'/exp OR pedodontic*:ti,ab	311,714
	#31	'pediatrics'/exp	107,989
	#32	#28 OR #29 OR #30 OR #31	4,875,774
Paediatrics, Alternatives to Amalgam AND caries	#33	#27 AND #32	16,403
RCTs	#34	'controlled clinical trial'/exp OR random*:ti OR placebo*:ti OR ((double NEXT/1 blind*):ti)	812,356
Alternatives to Amalgam AND caries AND	**#35**	**#33 AND #34**	**1,534**

Paediatrics
AND RCTs

Alternatives to amalgam, caries, adult and RCTs. Elsevier Embase			
Alternatives to amalgam	#1	'dental alloys'/exp/mj OR 'dental alloys' OR alloy*:ti	17,947
	#2	'dental cements'/exp/mj OR cement*:ti OR ionomer*:ti OR 'glass ionomer*':ti OR glassionomer*:ti OR rmgic:ti OR cermet:ti OR 'glass polyalkenoate':ti	27,147
	#3	((polycarboxylat* OR polyalkenoat* OR silicat*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	310
	#4	'resins, synthetic'/exp/mj OR resin*:ti OR composite*:ti OR nanocomposite*:ti OR 'white filling*':ti	79,877
	#5	'fluor protector':ti OR 'nuva seal':ti OR panavia:ti OR 'rely x':ti OR retroplast:ti OR geristore:ti OR 'fleck s':ti OR epoxylite:ti	94
	#6	'vertise flow':ti OR filtek:ti OR sonicfill:ti OR clearfil:ti OR smartcem2:ti OR scotchbond:ti OR sbmp:ti OR dyract:ti OR heliomolar:ti OR compoglass:ti OR adaptic:ti	145
	#7	vidrion:ti OR meron:ti OR optiband:ti OR multicure:ti OR 'ultra band lok':ti OR helioseal:ti OR 'xeno iii':ti OR delton:ti	21
	#8	'fissure sealant'/exp/mj OR sealant*:ti OR 'orthodontic adhesive*':ti	4387
	#9	'bisphenol a glycidyl methacrylate':ti OR 'bis gma':ti OR bisgma:ti OR tegdma:ti OR uedma:ti	270
	#10	'dental bonding'/exp/mj OR 'enamel bond*':ti OR 'dentin bond*':ti OR 'single bond*':ti	13,604
	#11	'bulk fill':ti OR nanofill:ti OR microhybrid:ti OR nanohybrid:ti	702
	#12	((compomer* OR polymer* OR carbomer* OR ormocer*) NEAR/10 (tooth OR teeth OR dent* OR enamel OR caries OR filling*)):ti	983
	#13	'crowns'/exp/mj OR crown*:ti OR 'hall s technique':ti OR 'hall technique':ti	18,894
	#14	'root canal filling materials'/exp/mj OR 'root canal filling':ti	3,978
	#15	'dental ceramics'/exp/mj OR porcelain*:ti OR ceramic*:ti OR nanoceramic*:ti	16,486
	#16	'dental inlay'/exp/mj OR inlay:ti OR inlays:ti OR 'in lay':ti OR 'in lays':ti OR onlay:ti OR onlays:ti OR 'on lay':ti OR 'on lays':ti	3,394
	#17	'dental pulp capping'/exp/mj OR 'pulpectomy'/exp/mj OR 'pulpotomy'/exp/mj OR 'pulp cap*':ti OR 'pulp therap*':ti OR pulpotom*:ti OR pulpect*:ti OR 'mineral trioxide aggregate':ti OR formocresol:ti	2,490
	#18	'calcium hydroxide'/exp/mj	1,970
	#19	'zinc oxide':ti OR eugenol:ti OR 'nano hydroxyapatite':ti OR 'casein phosphopeptide':ti OR 'amorphous calcium phosphate':ti OR 'cpp acp':ti	4,757
	#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	167708
Caries	#21	'dental caries'/exp/mj	30831
	#22	'dental cavity preparation'/exp/mj	31,117
	#23	caries:ti,ab OR carious:ti,ab OR karies*:ti,ab OR cariës:ti,ab OR carie:ti,ab	42959
	#24	((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR 'white spots' OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel OR caries OR filling*)):ti,ab	39,458
	#25	icdas:ab,ti OR 'icdas ii':ab,ti	347
	#26	#21 OR #22 OR #23 OR #24 OR #25	105853
Alternatives to amalgam AND caries	#27	#20 AND #26	18202
RCT	#28	'controlled clinical trial'/exp OR random*:ti OR placebo*:ti OR ((double NEXT/1 blind*):ti)	812,356

Alternatives to amalgam AND caries AND RCTs	#29	#27 AND #28	1605
Adult age	#30	'adult'/exp OR adult:ab,ti,de OR 'middle aged':ab,ti OR age*:ab,ti,de	12,783,311
Alternatives to amalgam AND caries AND RCTs AND adult	**#31**	**#29 AND #30**	**1,207**

Alternatives to amalgam, caries, children and RCTs. Cochrane Library			
Alternative to amalgam	#1	MeSH descriptor: [Dental Alloys] explode all trees	930
	#2	MeSH descriptor: [Dental Cements] explode all trees	2405
	#3	MeSH descriptor: [Resins, Synthetic] explode all trees	3652
	#4	MeSH descriptor: [Pit and Fissure Sealants] explode all trees	361
	#5	MeSH descriptor: [Pulpectomy] explode all trees	70
	#6	MeSH descriptor: [Pulpotomy] explode all trees	146
	#7	MeSH descriptor: [Crowns] explode all trees	724
	#8	MeSH descriptor: [Root Canal Filling Materials] explode all trees	512
	#9	MeSH descriptor: [Dental Porcelain] explode all trees	330
	#10	MeSH descriptor: [Dental Bonding] explode all trees	1824
	#11	(alloy OR alloys):ti,ab,kw	1084
	#12	(cement* or Ionomer* or Glass-ionomer* or Glassionomer* or RMGIC or Cermet or glass-polyalkenoate):ti,ab,kw	4846
	#13	(Polycarboxylat* or polyalkenoat* or silicat*):ti,ab,kw	774
	#14	(Resin* OR Composite* OR nanocomposite* OR "white filling" OR "white fillings"):ti,ab,kw	16423
	#15	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite):ti,ab,kw	309
	#16	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic):ti,ab,kw	818
	#17	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton):ti,ab,kw	152
	#18	(Sealant* OR Orthodontic adhesive*):ti,ab,kw	1644
	#19	("bisphenol A Glycidyl methacrylate" OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA):ti,ab,kw	585
	#20	(Enamel bond* OR dentin bond* OR single bond*):ti,ab,kw	2087
	#21	("Bulk fill" OR nanofill OR Microhybrid OR nanohybrid):ti,ab,kw	163
	#22	(compomer* OR Polymer* OR carbomer* OR ormocer*):ti,ab,kw	11658
	#23	(crown OR crowns OR "Hall's technique" OR "Hall technique"):ti,ab,kw	1574
	#24	("root canal filling"):ti,ab,kw	554
	#25	(porcelain* or ceramic* or nanoceramic*):ti,ab,kw	1217
	#26	(Inlay OR inlays OR "in-lay" OR "in-lays" OR onlay OR onlays OR "on-lay" OR "on-lays"):ti,ab,kw	1901
	#27	(pulp cap* OR Pulp therap* OR pulpotom* OR pulpect* OR mineral trioxide aggregate OR formocresol):ti,ab,kw	1337
	#28	("Calcium hydroxide" OR "Ca(OH)2"):ti,ab,kw	453
	#29	("Zinc oxide" OR eugenol OR "Nano-hydroxyapatite" OR "casein phosphopeptide" OR "amorphous calcium phosphate" OR "CPP-ACP"):ti,ab,kw	708
	#30	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	36433

Caries	#31	MeSH descriptor: [Dental Caries] explode all trees	2180
	#32	MeSH descriptor: [Dental Cavity Preparation] explode all trees	628
	#33	(ICDAS OR ICDAS-II):ti,ab,kw	94
	#34	(Caries OR carious OR karies* OR "cariës" OR carie):ti,ab,kw	4670
	#35	(((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR white spots OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel))):ti,ab,kw	3713
	#36	#31 OR #32 OR #33 OR #34 OR #35	6929
Alternatives to amalgam AND caries	#37	#30 AND #36	3299
Children	#38	MeSH descriptor: [Child] explode all trees	1111
	#39	MeSH descriptor: [Adolescent] explode all trees	97793
	#40	MeSH descriptor: [Infant] explode all trees	15008
	#41	MeSH descriptor: [Tooth, Deciduous] explode all trees	551
	#42	(((deciduous or milk or primary or natal or baby or exfoliat* or transitional) NEAR/2 (tooth or teeth or dentition))):ti,ab,kw	976
	#43	#38 OR #39 OR #40 OR #41 OR #42	112471
Alternatives to amalgam, caries, children and trials	**#44**	**#37 AND #43** **Apply Limits: Cochrane Protocols, Trials and Clinical Answers**	**794 trials** **1 protocol**

Alternatives to amalgam, caries, adults and RCTs. Cochrane Library			
Alternatives to amalgam	#1	MeSH descriptor: [Dental Alloys] explode all trees	930
	#2	MeSH descriptor: [Dental Cements] explode all trees	2405
	#3	MeSH descriptor: [Resins, Synthetic] explode all trees	3652
	#4	MeSH descriptor: [Pit and Fissure Sealants] explode all trees	361
	#5	MeSH descriptor: [Pulpectomy] explode all trees	70
	#6	MeSH descriptor: [Pulpotomy] explode all trees	146
	#7	MeSH descriptor: [Crowns] explode all trees	724
	#8	MeSH descriptor: [Root Canal Filling Materials] explode all trees	512
	#9	MeSH descriptor: [Dental Porcelain] explode all trees	330
	#10	MeSH descriptor: [Dental Bonding] explode all trees	1824
	#11	(alloy OR alloys):ti,ab,kw	1084
	#12	(cement* or Ionomer* or Glass-ionomer* or Glassionomer* or RMGIC or Cermet or glass-polyalkenoate):ti,ab,kw	4846
	#13	(Polycarboxylat* or polyalkenoat* or silicat*):ti,ab,kw	774
	#14	(Resin* OR Composite* OR nanocomposite* OR "white filling" OR "white fillings"):ti,ab,kw	16423
	#15	(Fluor-Protector or Nuva Seal or Panavia or Rely X or Retroplast or Geristore or "Fleck's" or Epoxylite):ti,ab,kw	309
	#16	(Vertise Flow or Filtek or SonicFill or Clearfil or SmartCem2 or Scotchbond or SBMP or Dyract or Heliomolar or Compoglass or Adaptic):ti,ab,kw	818
	#17	(Vidrion or Meron or Optiband or Multicure or Ultra Band Lok or Helioseal or Xeno III or Delton):ti,ab,kw	152
	#18	(Sealant* OR Orthodontic adhesive*):ti,ab,kw	1644
	#19	("bisphenol A Glycidyl methacrylate" OR Bis-GMA OR BisGMA OR TEGDMA OR UEDMA):ti,ab,kw	585
	#20	(Enamel bond* OR dentin bond* OR single bond*):ti,ab,kw	2087
	#21	("Bulk fill" OR nanofill OR Microhybrid OR nanohybrid):ti,ab,kw	163
	#22	(compomer* OR Polymer* OR carbomer* OR ormocer*):ti,ab,kw	11658
	#23	(crown OR crowns OR "Hall's technique" OR "Hall technique"):ti,ab,kw	1574
	#24	("root canal filling"):ti,ab,kw	554
	#25	(porcelain* or ceramic* or nanoceramic*):ti,ab,kw	1217

	#26	(Inlay OR inlays OR "in-lay" OR "in-lays" OR onlay OR onlays OR "on-lay" OR "on-lays"):ti,ab,kw	1901
	#27	(pulp cap* OR Pulp therap* OR pulpotom* OR pulpect* OR mineral trioxide aggregate OR formocresol):ti,ab,kw	1337
	#28	("Calcium hydroxide" OR "Ca(OH)2"):ti,ab,kw	453
	#29	("Zinc oxide" OR eugenol OR "Nano-hydroxyapatite" OR "casein phosphopeptide" OR "amorphous calcium phosphate" OR "CPP-ACP"):ti,ab,kw	708
	#30	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	36433
Caries	#31	MeSH descriptor: [Dental Caries] explode all trees	2180
	#32	MeSH descriptor: [Dental Cavity Preparation] explode all trees	628
	#33	(ICDAS OR ICDAS-II):ti,ab,kw	94
	#34	(Caries OR carious OR karies* OR "cariës" OR carie):ti,ab,kw	4670
	#35	(((decalcif* OR demineral* OR hypomineral* OR decay OR fissures OR white spots OR cavit* OR defect* OR lesion*) NEAR/10 (dent* OR tooth OR teeth OR enamel))):ti,ab,kw	3713
	#36	#31 OR #32 OR #33 OR #34 OR #35	6929
Alternatives to amalgam AND Caries	#37	#30 AND #36	3299
		Apply Limits: Cochrane Protocols, Trials and Clinical Answers	3037
Adult	#38	MeSH descriptor: [Adult] explode all trees	3037
	#39	(age* OR middle-age* OR adult):ti,ab,kw	744300
	#40	#38 OR #39	744301
	#41	#37 AND #40	2040
	#42	(mouse OR mice OR “in vitro”):ti,ab,kw	21000
	#43	#41 NOT #42	1772

Appendix 2 Numbers of primary papers and reviews retrieved from search

Alternatives to Amalgam + Caries + paediatric	Medline	Cinahl	Embase	Cochrane	**Totals before de-duplication**
RCT	1259	280	1534	794	**3867**
Systematic reviews	196	80	288	18	**519**

Alternatives to Amalgam + Caries + adult	**Medline**	**Cinahl**	**Embase**	**Cochrane**	**Totals before de-duplication**
RCT	1583	292	1207	1772	**3742**
Systematic reviews	133	96	94	31	**291**

Appendix 3 List of websites searched for information for Questions 1 and 2

General scoping searches were carried out in the search engine Google.com to gain an initial idea of terminology and likely key terms. Initial search terms used included combinations of mercury, dental amalgam, filling and caries. Further searches were carried out using the websites of national and international dental organisations.

These included the website of the UNEP Mercury Convention (http://mercuryconvention.org/Convention/), World Dental Federation (https://www.fdiworlddental.org), Council of European Dentists (https://cedentists.eu/, https://eudental.eu/), International Association for Dental Research (https://www.iadr.org/), Dental Council, Ireland (http://www.dentalcouncil.ie), Irish Dental Association (https://www.dentist.ie), Ireland: UCC Oral Health Services Guideline Initiative (https://www.ucc.ie/en/ohsrc/publications-guidelines/), Scottish Dental Clinical Effectiveness Programme (http://www.sdcep.org.uk), Scottish Dental: Accessible information about Dentistry (https://www.scottishdental.org/), Finnish Dental Association (https://www.hammaslaakariliitto.fi/en), The Finnish Dental Society Apolloni (https://www.apollonia.fi/en/), Dutch dental association KNMT (https://www.knmt.nl/), Danish Dental association (https://www.tandlaegeforeningen.dk/), France: Association Dentaire Francaise (https://adf.asso.fr), American Dental Association (https://www.ada.org/), Canadian Dental Association (https://www.cda-adc.ca), British Dental Association (https://www.bda.org/dentists/representation/gdps/gdpc/), Faculty of General Dental Practice UK (https://www.fgdp.org.uk/ https://www.fgdp.org.uk/guidance-standards), Federal Dental Association/Bundeszahnärztekammer (https://www.bzaek.de/), British Society for Restorative Dentistry (http://www.bsrd.org.uk/), British Society of Periodontology (http://www.bsperio.org.uk/).

Some guideline websites were also searched at a basic level. These included SIGN (https://www.sign.ac.uk/our-guidelines.html), G-I-N.net (http://www.g-i-n.net/), UCC OHSRC (https://www.ucc.ie/en/ohsrc/publications-guidelines/), ECRI (https://guidelines.ecri.org/), the UK guidelines websites (https://www.guidelines.co.uk/ and https://www.guidelinesinpractice.co.uk/), NICE http://www.nice.org.uk/guidance/index.jsp?action=byType&type=2&status=3, the Australian Clinical Guidelines website http://www.clinicalguidelines.gov.au/, the Canadian CPJ Infobase guidelines site (https://joulecma.ca/cpg/homepage), Royal College of Surgeons Dental Facilities Guidelines site (https://www.rcseng.ac.uk/dental-faculties/fds/publications-guidelines/), the Royal College of Physicians Guidelines & Policy site (https://www.rcplondon.ac.uk/guidelines-policy), the French Haute Autorité de Santé site (https://www.has-sante.fr/portail/jcms/c_2567683/en/portail-english-assessment-recommendation?portal=c_2567683), and the American Dental Association clinical practice guidelines site (https://ebd.ada.org/en/evidence/guidelines).

Some national governmental and organizational sites were also included, focusing on countries which were known to have taken action on dental amalgam, or who planned to. Language was a barrier for many of these websites. While it was planned to follow up citations from some key documents (such as the UNEP 2016 Lessons from countries phasing down dental amalgam, the CADTH 2018 *Dental Amalgams Compared With Composite Resin* review, and the World Alliance for Mercury Free Dentistry (WAMFD) 2014 report *Toward Mercury-Free Dentistry How to Successfully Implement the Dental Amalgam Phase-Down Measures of the Minamata Convention),* the extremely short time frame permitted for this review did not allow for these measures.

Appendix 4 Evidence for dental caries in children and adolescents

Eleven reviews on fluoride technologies for prevention

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
Marinho *et al.* (2003a)[65] (Cochrane review)	To assess the effectiveness and safety of fluoride toothpastes when compared with a placebo or non-fluoride toothpaste control group in the prevention of caries in children	Topical fluoride in the form of toothpastes only, using any of the following fluoride agents combined or not in the formulation: sodium fluoride (NaF), sodium monofluorophosphate (SMFP), stannous fluoride (SnF2), acidulated phosphate fluoride (APF), amine fluoride (AmF).	74 RCTs were included with 45073 children aged 16 or less 11 trials were judged to be at a low risk of bias, 7 trials at a high risk of bias and for the remaining trials the risk of bias was unclear. All trials used a placebo or non-fluoride toothpaste control group.	Children aged 5 to 16 years who used fluoridated toothpaste had fewer decayed, missing and filled permanent teeth after three years (regardless of whether their drinking water was fluoridated). Twice a day use increases the benefit. No conclusion could be reached about the risk that using fluoride toothpastes were associated with fluorosis. The authors conclude that '… Taken together, the trials are of relatively high quality, and provide clear evidence that fluoride toothpastes are efficacious in preventing caries…' p2	Adequate for fluoride toothpastes compared to controls for preventing caries in permanent teeth in children and adolescents aged 5-16
Marinho *et al.* (2003b) [68] (Cochrane review)	To assess the effectiveness and safety of fluoride varnishes, gels, mouthrinses, and toothpastes (Topical Fluoride Therapy) compared concurrently to a placebo or no	Topical fluoride therapy in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration (ppm F), amount or	There were 144 RCTs included; 133 that contributed data for meta-analysis (involving 65169 children aged 5-16 14 trials were judged to be at a low risk of bias,	Children aged 5 to 16 years who applied fluoride in the form of toothpastes, mouthrinses, gels or varnishes had fewer decayed, missing and filled teeth in both the permanent and	Adequate for topical fluoride therapy over controls for preventing caries in children and adolescents

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
	TFT group for preventing caries in children.	duration of application, and with any technique or method of application, provided the frequency of application was at least once a year.	21 trials were at a high risk of bias and the risk of bias in the remaining trials was unclear. Approximately two thirds of the children used toothpaste, followed by mouthrinse, gel and varnish applications.	the deciduous dentition regardless of whether their drinking water was fluoridated. According to the authors '…The benefits of topical fluorides have been firmly established on a sizeable body of evidence from randomized controlled trials…' p2	
Marinho *et al.* (2004a)[69] (Cochrane review)	To compare the effectiveness of two Topical Fluoride Therapies (TFT) combined with one of them alone (mainly toothpaste) when used for the prevention of dental caries in children	Topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration (ppm F), amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year.	12 RCTs were included, involving 4026 children aged 14 or less 2 of the trials were judged to be at a high risk of bias and the remaining 10 trials were unclear	Children and adolescents who used another form of topical fluoride in addition to fluoride toothpaste experienced a modest (10%) additional reduction in tooth decay compared with children who only used fluoride toothpaste.	Adequate for combining two Topical Fluoride Therapies over using toothpaste alone but the difference is modest
Marinho *et al.* (2004b)[70] (Cochrane review)	To compare the effectiveness of one form of topical fluoride intervention with another when used for the prevention of dental caries in children.	Topical fluoride therapy in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration (ppm F), amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year.	17 RCTs were included with participants aged 14 or less; 3243 analysed out of 4423 initially randomized 1 trial had a low risk of bias, 2 trials had a high risk of bias and the remaining 14 trials were judged to be unclear.	Fluoride toothpaste was not significantly different from Mouthrinse, or gel or both gel and mouthrinse Compared with each other, fluoride toothpaste and mouthrinse, and toothpaste and gel appear to be effective to a similar degree in the prevention of dental caries in children.	Inconclusive, it is not possible to tell which is superior

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
				Caries reduction from fluoride mouthrinse compared with gel, fluoride varnish compared with gel, and varnish compared with toothpaste (deciduous teeth only) are unclear. According to the authors '…fluoride toothpastes, mouthrinses and gels reduce tooth decay in children and adolescents to a similar extent…' p2	
Dos Santos *et al.* (2013)[66]	To assess the effectiveness of fluoride toothpaste compared to placebo or no intervention on the prevention of dental caries in the primary dentition of preschool children.	The intervention in six trials comprised of standard fluoride (1000-1500 ppm) and oral health education and in three trials low toothpaste (<600 ppm) and oral health education. One trial included both standard and low fluoride concentrations.	8 RCTs were included; total sample under analysis not reported; children were aged 7 or under. All 8 trials were judged to have a high risk of bias.	'…preschool children who brushed their teeth with standard fluoride toothpaste (1000-1500 ppm) experienced a significant reduction in the mean number of primary decayed, missing owing to caries and filled dental surfaces and teeth. They also had a significant lower risk of developing dental caries than those who receives no intervention…' p7 When standard fluoride toothpaste were compared to placebo or no intervention, significant caries reduction at surface (31%), tooth	Adequate for standard fluoride toothpaste (1000-1500 ppm) compared to controls

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
				(16%) and individual (RR = 0.86) levels were observed. The evidence for effectiveness on low fluoride toothpastes (<600 ppm) is equivocal.	
Tubert-Jeannin *et al.* (2011)[71] (Cochrane review)	Compared fluoride supplements (tablets, drops, lozenges) with no fluoride supplement or with other preventive measures such as topical fluorides for preventing dental caries in children less than 16 years of age	Fluoride supplements in the form of tablets, drops, lozenges (or chewing gums): • with or without the use of vitamins; • using any fluoride agent, at any concentration, amount, frequency of use, duration of application, and with any technique of application (sucked or not, chewed or not); • with or without the use of topical fluorides (fluoride rinse, topical fluoride application, fluoride varnish or fluoride toothpaste) or non-fluoride-based measures (chlorhexidine, xylitol, sealants, oral hygiene interventions p6-7	Eleven randomised controlled trials with 7196 children were included in this review. Ten trials were judged to have an unclear risk of bias and one at high risk of bias, and therefore the trials provide weak evidence about the efficacy of fluoride supplements.	When fluoride supplements were compared with no fluoride supplement (three studies), the use of fluoride supplements was associated with a 24% reduction in decayed, missing and filled surfaces in permanent teeth in children aged 5-12 For children aged less than 5 years, there was weak evidence that the use of fluoride supplements prevents dental caries in primary teeth. The effect of fluoride supplements was unclear on deciduous or primary teeth. When fluoride supplements were compared with topical fluorides or with other preventive measures, there was no differential effect on permanent or deciduous teeth.	Inadequate evidence to judge the effectiveness of using fluoride supplements to prevent dental caries in primary or permanent teeth in children and adolescents

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
				'…We rated 10 trials as being at unclear risk of bias and one athigh risk of bias, and therefore the trials provide weak evidence about the efficacy of fluoride supplements…' p2	
Walsh *et al.* (2019)[7]	Compare the effect of toothpaste of different fluoride concentrations (ppm) in preventing dental caries in children, adolescents, and adults.	The formulation and fluoride concentration of toothpaste is diverse, with a variety of fluoride compounds used singly and in combination including sodium fluoride, sodium mono-fluorophosphates, amine fluoride and stannous fluoride, and, according to each manufacturer's specifications, these must be compatible with other basic ingredients, especially abrasive systems (which account for almost half of the entire toothpaste formulation)	96 RCTs were included that included children aged up to 18. 1 trial was judged to have a low risk of bias, 14 trials were judged to have a high risk of bias, and for the remaining 81 trials, the risk of bias was unclear.	In primary teeth of young children, brushing teeth with a toothpaste containing 1500 ppm fluoride reduced the amount of new decay when compared with non-fluoride toothpaste; the amount of new decay was similar with 1055 ppm compared with 550 ppm fluoride toothpaste; and there was a slight reduction in the amount of new decay with 1450 ppm toothpaste compared with 440 ppm fluoride toothpaste. In permanent teeth of children and adolescents, there was less new decay when tooth-brushing with toothpaste containing 1000 to 1250 ppm or 1450 to 1500 ppm fluoride compared with non-fluoride	Adequate for fluoride in toothpaste Inconclusive for the dose of fluoride

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
				toothpaste, and tooth-brushing with 1450 to 1500 ppm fluoride toothpaste reduced the amount of new decay more than 1000 to 1250 ppm toothpaste. There was a similar amount of new decay when children and adolescents used a toothpaste of 1700 to 2200 ppm or 2400 to 2800 ppm fluoride compared to 1450 to 1500 ppm toothpaste. The evidence for the effects of other strengths of toothpaste was less certain. According to the authors '…The stronger the fluoride concentration, the more decay is prevented'.	
Singh and Purohit (2018)[67]	Determine the efficacy of high-fluoride toothpastes (>= 2500 ppm) as compared to standard fluoride toothpastes (<= 1500 ppm) in preventing dental caries		Eight randomised controlled trials were included in this review. The age range of participants was 6-16 years in six trials and 27-103 years in two trials. Allocation sequence was judged to be adequate in all eight trials. However, allocation concealment was not declared explicitly in any of the eight trials. Apart from two	High-fluoride toothpaste use (>= 2500 ppm) was statistically significantly associated with lower caries increment. High-fluoride toothpastes were also associated with a greater preventive effect compared with low-fluoride toothpastes. High-fluoride toothpastes are	Adequate in favour of high-fluoride over standard flouride

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
			studies with single blinding, knowledge of the allocated interventions was adequately prevented by double blinding in the remaining six trials.	superior to low-fluoride toothpastes in reducing caries.	
Marinho *et al.* (2016)[74] (Cochrane Review)	How effective and safe is the use of fluoride mouthrinse for preventing tooth decay (dental caries) in permanent teeth in children and adolescents compared with placebo (a mouthrinse without the active ingredient fluoride) or no treatment?	fluoride mouth rinses. The fluoride compound most commonly used in mouthrinse is sodium fluoride	37 RCTs involving 15,813 children and adolescents aged 6-14 Most studies (28) were at high risk of bias, and nine were at unclear risk of bias. Almost all children received a fluoride rinse formulated with sodium fluoride (NaF), mostly on either a daily or weekly/fortnightly basis and at two main strengths, 230 or 900 ppm F, respectively	'…Supervised regular use of fluoride mouth rinse by children and adolescents is associated with a large (27%) reduction in tooth decay in children's permanent teeth…' p28 Reports were published between 1965 and 2005, and studies took place in several countries	**Adequate for fluoride mouthrinse compared to control** The authors state moderate certainty in size of the effect GRADE
Marinho *et al* (2015)[73] (Cochrane Review Update)	Are fluoride gels effective for preventing dental caries in children and adolescents when compared with placebo or no treatment	Fluoride gels '…The 'classical' fluoride gels do not contain abrasives, their fluoride concentration is usually much higher than that of a fluoride toothpaste and they are applied at relatively infrequent intervals…' p6	28 RCTs (including 3 new trials since the original review) all trials involved 9,140 children and adolescents (aged 2-15) Most trials (20) were at high risk of bias, with 8 trials at unclear risk of bias. Trials were published between 1967 and 2005.	'…The application of fluoride gels, either by professionals or self-applied, is associated with a large reduction in caries increment in permanent teeth in children (the quality of evidence is moderate GRADE). There is less certainty of the large reduction observed in the first or baby teeth (low quality evidence: 3 trials)…' p27	**Adequate for fluoride gels compared to control in preventing caries in permanent teeth in children and adolescents** There is moderate quality evidence of a large effect GRADE

Author and year	Primary review focus	Intervention descriptor	Number of type of studies included	Author(s)' conclusion	Level of evidence
Marinho *et al* (2013)[72] (Cochrane review)	Fluoride varnishes for preventing dental caries in children and adolescents compared to placebo (a treatment without the active ingredient i.e. fluoride) or no treatment	Fluoride varnishes '…There are two main preparations commercially known as Duraphat and Fluor Protector. Duraphat contains 5% sodium fluoride (NaF), in a natural resin carrier with some alcohol included as a solvent. Fluor Protector contains 0.9%difluorosilane by weight (1000 ppm F) in polyurethane-based varnish and sets to a thin transparent film…' p6	Twenty-two RCTs with 12,455 participants; age range 1-15 Most of the trials (15) were at a high risk of bias in at least one domain and the remaining 7 trials are at unclear risk of bias.	'…the application of fluoride varnishes two to four times a year, either in the permanent or primary dentition, is associated with a substantial reduction in caries increment...' p21 '…in the 13 trials that looked at children and adolescents with permanent teeth the review found that the young people treated with fluoride varnish experienced on average a 43% reduction in decayed, missing and filled tooth surfaces. In the 10 trials looking at the effect of fluoride varnish on first or baby teeth the evidence suggests a 37% reduction in decayed, missing and filled tooth surfaces…' p3	**Adequate for fluoride varnishes compared to control in preventing caries in primary and permanent teeth in children and adolescents** There is moderate quality evidence GRADE

Ten reviews on non-fluroide technologies for prevention

Author and year	Primary review question	Intervention description	No and type of studies included	Authors conclusions	Level of Evidence
Ahovuo-Saloranta *et al* (2017)[75] (Cochrane Review; update of earlier reviews 2004, 2008 and 2013)	To compare the effects of different types of fissure sealants in preventing caries in occlusal surfaces of permanent teeth in children and adolescents	Dental sealant (resin-based and glass ionomer) is applied to a tooth surface to provide a physical barrier that prevents growth of biofilm by blocking nutrition. Although sealants were introduced for preventing caries on occlusal surfaces, they are now considered active agents in controlling and managing initial caries lesions on occlusal surfaces and, recently, on approximal surfaces as well	38 RCTs that involved a total of 7924 children; seven trials were new for this update (1693 participants; children were aged 5-16) Most of the studies included in this analysis were carried out in the 1970s. All studies were assessed as having a high risk of bias because the dental professionals who are measuring the outcomes can see whether or not sealant has been used and can discriminate between materials after follow-up	Resin-based sealants applied on occlusal surfaces of permanent molars (back teeth) are effective for preventing caries in children and adolescents reducing it by between 11% and 51% more than in children without sealant (measured two years after application) The above finding is based on moderate-quality evidence (reasonably certain: GRADE). Results were inconclusive when glass ionomer-based sealant was compared with no sealant and when one type of sealant material was compared with another.	**Adequate for resin-based sealants** Inconclusive for glass ionomer sealant Inconclusive for the superiority of one sealant over another
Marghalani *et al* (2017)[79]	To evaluate the effectiveness of Xylitol in reducing dental caries in children compared to no treatment, a placebo or preventive strategies. Decayed, missing and filled primary and permanent surfaces/teeth.	Xylitol is a five-carbon sugar alcohol derived primarily from birch trees.	5 randomised and 5 non-randomised controlled trials All 10 trials had a high risk of bias.	The evidence showed a small effect size from 5 RCTs with a very low quality of evidence (GRADE) and high heterogeneity; the evidence is **uncertain.**	**Inconclusive for xylitol *versus* control**
Wang *et al* (2017)[81]	To assess the effect of non-fluoride agents on the prevention of	non-fluoride agents Five chemical agents, namely arginine, casein phosphopeptide-	14 RCTs with total of 4,269 participants were	'…The current research evidence is not sufficient to	**INADEQUATE**

Author and year	Primary review question	Intervention description	No and type of studies included	Authors conclusions	Level of Evidence
	dental caries in primary dentition: A systematic review	amorphous calcium phosphate (CPP-ACP), chlorhexidine, triclosan and xylitol were investigated in included studies	evaluated, (age range, 0 to 11 years) The risk of bias assessment revealed that only one study had a low risk of bias, three studies had an unclear risk of bias and the remaining 10 were scored as high risk of bias	confirm that the use of these non-fluoride agents is more effective than placebo or fluoride for preventing dental caries in primary dentition…' p6	The authors describe weak and insufficient evidence
Ahovuo-Saloranta *et al.* (2016)[76] (Cochrane Review)	To compare fissure sealants with fluoride varnishes, or fissure sealants together with fluoride varnishes compared with fluoride varnishes alone, for preventing dental caries in the occlusal surfaces of permanent teeth of children and adolescents.	According to Ahovuo-Saloranta and colleagues '…A dental sealant is applied to a tooth surface to provide a physical barrier that prevents growth of biofilm by blocking nutrition. Although sealants were introduced for preventing caries on occlusal surfaces, they now are considered active agents in controlling and managing initial caries lesions on occlusal surfaces and, recently, on approximal surfaces as well…Along with resin-based sealants, other sealant materials [include] glass ionomer cements (combination of silicate and polyacrylate cement system). Glass ionomer cements contain fluoride and are thought to prevent caries through fluoride release over a prolonged period…Novel materials called Compomers, which were introduced in the 1990s to combine benefits of resins and those of glass ionomer cements have also been applied as sealants p6 The aim of topical fluoride varnish application is to treat hard tooth surfaces in	Eight randomised controlled trials with 1746 children aged 5-10 years. One trial was assessed as low risk and the remaining seven was either high risk or unclear risk.	'…Although we found evidence suggesting the superiority of resin-based fissure sealants over fluoride varnishes applied to prevent occlusal caries in permanent molars, and some evidence for benefit of resin-based sealant together with fluoride varnish over fluoride varnish alone, this evidence is of low quality. We conclude that current scarce data mean that it is not possible to reach conclusions [Inconclusive] about whether to apply sealants or fluoride varnishes on occlusal surfaces of permanent molars…' p25-26	Inconclusive evidence on whether sealants or fluoride varnish is better for preventing dental caries in the permanent teeth of young children Inadequate evidence upon which to compare glass-ionomer-based sealants with fluoride varnishes: Inconclusive evidence on whether resin-based sealant combined with fluoride varnish or using fluoride varnish alone is superior

Author and year	Primary review question	Intervention description	No and type of studies included	Authors conclusions	Level of Evidence
		such a way that caries is arrested or reversed. Fluoride acts to prevent caries in three ways: (1) by inhibiting the demineralisation and (2) promoting the remineralisation of dental enamel, and (3) by inhibiting acid formation by plaque bacteria p6			
Botton *et al* (2016)[84]	Are self-etch adhesive systems effective in the retention of occlusal pit and fissure sealants compared to sealants with prior-acid etching?	'…self-etch adhesive systems eliminate the prior acid etching and rinsing steps, reducing not only the technique sensitivity, but also the time of application and, consequently decreasing the chair time…' p403 The type of sealants included in the study are unclear in the reporting	5 RCTs were included Age range 4-21 Dentition under study; permanent teeth in four trials and primary teeth in one trial The authors note that '…all selected studies showed a good strength of evidence….' P410 However, they did not assess risk of bias using the Cochrane instrument; they used a quality appraisal scoring system for each included study; strong evidence 10-11, good evidence 6-9 and reasonable evidence 0-5. Four studies scored between 6-9 and one study scored 11	'…sealants applied in the conventional manner, with prior acid etching, present superior retention throughout time compared to the occlusal sealants combined with self-etch system …' p410 High heterogeneity was reported across the included studies and in the meta-analysis Quality of the evidence was not assessed using GRADE.	**Adequate for prior acid etching over self-etch adhesive**
Hou *et al* (2017)[77]	Evaluate the relationship between pit and fissure sealants and the prevention of dental caries in permanent (first)	…Pit and fissure sealants where an adhesive resin material is placed at the pits and fissures of molar teeth without removing the tooth structure.	20 RCTs trials were included in the meta-analysis	…pit and fissure [resin] sealants are an effective caries-preventive	**Adequate for pit and fissure resin sealant when compared with**

Author and year	Primary review question	Intervention description	No and type of studies included	Authors conclusions	Level of Evidence
	molars of children in China Compared to no intervention	Pit and fissure sealants can block these surfaces, stopping food and bacteria from accumulating, thereby protecting enamel from bacteria and metabolite erosion. …' p1	Age range of participants 6-20 The authors state that they used the Cochrane risk of bias assessment on all the trials but they don't provide an overall assessment of their conclusions on the risk of bias e.g. low, moderate, high. They do state that limitations in the included trials include poor description of randomisation and allocation concealment and blinding, suggesting high degree of selection bias, measurement bias.	intervention…' p6 The authors did not assess the quality of the evidence for their findings GRADE	no intervention
Riley *et al.* (2015)[80] (Cochrane review)	Compared different xylitol-containing products with a placebo (a substitute without xylitol) or no treatment for the prevention of dental caries in children and adults.	Xylitol is a 5-carbon sugar alcohol of crystalline structure, found in many fruits and plants. It achieves equal sweetness to sucrose without resulting in a physiological requirement for insulin production as it is not absorbed in the small intestine…Xylitol has been produced in a variety of preparations including chewing gum, syrup, lozenges, sprays, mouthwashes, gels, toothpaste, candies, and varnishes	Ten randomised controlled trials including 7969 participants (5903 of who were included in the analyses) were included in this review. One trial included adults, the others included children aged from 1 month to 13 years. One trial was assessed as being at low risk of bias; two were assessed as being at unclear risk of	The main finding of the review was that, over 2.5 to 3 years of use, a fluoride toothpaste containing 10% xylitol may reduce caries by 13% when compared to fluoride-only toothpaste in children; the finding is based on low-quality evidence. The remaining evidence on children, from small single studies with high risk of bias was insufficient to determine a benefit from	inadequate evidence on which to judge the effectiveness of xylitol as an intervention for preventing dental caries in children and adolescents

Author and year	Primary review question	Intervention description	No and type of studies included	Authors conclusions	Level of Evidence
			bias, with the remaining seven being at high risk of bias.	xylitol products. '…We found some low quality evidence to suggest that fluoride toothpaste containing xylitol may be more effective than fluoride-only toothpaste for preventing caries in the permanent teeth of children, and that there are no associated adverse effects from such toothpastes. The effect estimate should be interpreted with caution due to high risk of bias and the fact that it results from two studies that were carried out by the same authors in the same population. The remaining evidence we found is of low to very low quality and is insufficient to determine whether any other xylitol containing products can prevent caries in infants, older children, or adults…' p19-20	
Walsh *et al.* (2015)[82] (Cochrane review)	Compared chlorhexidine gels, toothpastes, varnishes, mouthrinses, chewing gums or	Chlorhexidine gluconate is a cationic bis-biguanide with a broad spectrum of antibacterial activity…chlorhexidine-	Eight randomised controlled trials with a total of 2876 participants	Six of the studies compared dental professionals applying	Inconclusive evidence

Author and year	Primary review question	Intervention description	No and type of studies included	Authors conclusions	Level of Evidence
	sprays with each other, placebo or no intervention for caries prevention in children and adolescents.	based preparations in a variety of formulations and a range of strengths [include] toothpastes (0.4%); mouthrinses in either alcohol-based (ethanol) or non-alcoholic formulations (0.12% and 0.2%); gels (1%); thymol-containing varnishes (1%, 10%, 20% and 35%); chewing gums; and sprays (0.2%)…' p6	aged 0-15 years, of whom 2276 (79%) were evaluated were included in this review. The focus of the trials was on both primary and permanent teeth. Six of the trials were judged to be at high risk of bias and two trials at unclear risk of bias.	different strengths of chlorhexidine varnishes versus placebo to the baby teeth, permanent teeth or both types of teeth in children and adolescents. The other two studies looked at the effects of parents placing chlorhexidine gel on their children's baby teeth. Overall, The results did not provide evidence that chlorhexidine varnish or gel reduces tooth decay or reduces the bacteria that encourage tooth decay. '…There is little evidence from the eight studies included in this review to either support or refute the assertion that chlorhexidine is more effective than placebo or no treatment in the prevention of caries in children and adolescents…' p22	
James *et al* (2010)[83]	Comparing chlorhexidine varnish to placebo/no treatment/fluoride varnish in children and adolescents: a systematic review	Chlorhexidine varnish is an antimicrobial agent that is particularly effective in reducing the levels of Mutans streptococci MS in saliva and dental plaque	12 RCTs were included Age range of participants 4-18 Risk of Bias (Cochrane) assessment: 4 trials; high, 4	'…The results of the trials included in this review are conflicting, but in general, the evidence does not support the use of chlorhexidine varnish for preventing	**Inconclusive evidence** Evidence regarding the effectiveness of chlorhexidine varnish for preventing

Author and year	Primary review question	Intervention description	No and type of studies included	Authors conclusions	Level of Evidence
			trials; low and 4 trials; unclear The quality of the evidence was not assessed (GRADE) The tooth type/surface treated varied across the trials e.g. in 5 trials ALL teeth/surface was treated and in the trials FPM = first permanent molar; SPM = second permanent molar; Occ. = occlusal surface; Approx. = approximal surface	caries in children and adolescents…' p338	caries is inconclusive. Further well-conducted randomised trials are required before chlorhexidine varnish can be recommended for caries prevention
Yengopal and Mickenautsch (2010)[78]	To compare resin-modified glass ionomer cement (RM-GIC) fissure sealants with resin-based fissure sealants on the absence of caries on sealed teeth.	resin-modified glass ionomer cement (RM-GIC) fissure sealants resin-based fissure sealants	6 randomised controlled trials were included All trials scored (B) unclear for selection bias and (D) not possible for detection bias and (A) adequate for attrition bias. Five trials included participants with age range of 5-27, the other trial is unclear but included pediatric patients and 1st molar and 2nd molar and premolar teeth were examined in the included trials.	No conclusive evidence that either material was superior to the other in preventing dental caries. Both materials appear to be equally suitable for clinical application as a fissure sealant for a period of up to 2 years.	**Inconclusive** evidence whether resin-modified glass ionomer cement (RM-GIC) fissure sealants or resin-based fissure sealants are superior for preventing dental caries

Seven reviews of procedures and techniques for restorative treatment of dental caries in children and adolescents

Author and year	**Primary review question**	**Intervention descriptor**	**No. Of studies, study design and quality**	**Authors conclusions**	Level of evidence
Schenkel *et al.* (2019)[100] (Cochrane Review)	To assess the effects of using dental cavity liners, compared to no liners, in the placement of Class I and Class II resin-based composite posterior restorations in permanent teeth in children and adults (measuring hypersensivity and restoration success)	Resin-based composite (RBC) is currently accepted as a viable material for the restoration of caries for posterior permanent teeth requiring surgical treatment. These materials are formulated to be placed into the prepared tooth cavity in a soft, viscous state, and then made to harden through a process known as polymerization. Liners are purported to protect the pulp from the toxic effects of some dental restorative materials and to prevent the pain of thermal conductivity by placing an insulating layer between restorative material and the remaining tooth structure	Eight randomised controlled trials, with over 700 participants, were included. Restorations in permanent teeth in adults or children 15 years or older. All studies were at unclear or high risk of bias.	There is inconsistent, low-quality evidence regarding the difference in postoperative hypersensitivity subsequent to placing a dental cavity liner under Class I and Class II posterior resin-based composite restorations in permanent posterior teeth in adults or children 15 years or older. Furthermore, no evidence was found to demonstrate a difference in the longevity of restorations placed with or without dental cavity liners. The quality of the evidence identified in this review is low and there is a lack of confidence in the effect estimates	**Inadequate for liners versus no liners to prevent postoperative sensitivity** **Inconclusive for liners versus no liners on the longevity of restorations**
Ruengrungsom *et al.* (2018)[98]	What is the clinical performance of different types of glass ionomer cements (original, resin modified, and high viscosity) applied using atraumatic restorative treatment techniques to single and multiple surface restorations in	Different types of glass ionomer cements (original, resin modified, and high viscosity) applied using atraumatic restorative treatment technique or conventional technique are compared to each other	67 studies; trials and observational studies included. Children and adolescents included in most studies. Studies on permanent and deciduous teeth. Total count of participants and teeth not provided 5 studies had all 7 scores rated as low	For single-surface occlusal or multi-surface glass ionomer cement restorations, the conventional technique showed better survival than atraumatic restorative treatment technique regardless of dentition type	**Inconclusive** for any type of glass ionomer being better than the other

Author and year	**Primary review question**	**Intervention descriptor**	**No. Of studies, study design and quality**	**Authors conclusions**	Level of evidence
	occlusal and approximal cavities in permanent and deciduous teeth? (restoration survival and annual failure rates)	The conventional restorative technique is not described in the paper.	risk of bias whereas 6 studies had one or two scores of serious risk. The remaining 56 had a one or more moderate risk of bias score.	(primary or permanent). When comparing the same treatment technique, annual failure rates of approximal or multi-surface glass ionomer cement restorations were greater than those of single-surface (occlusal) restorations, irrespective of dentition type. resin modified glass ionomer - conventional technique seems to be promising for restoring approximal cavities of primary teeth compared to other restorative materials.	
Tedesco *et al.* (2018)[97]	Compared the performance of the available treatments for dentine caries lesions, regardless of nearness to pulp or pulp involvement in primary teeth, on caries lesion arrestment (CLA) or the success rate (SR) and considered the different progression depths and surfaces involved. "Which is the best treatment for CLA or SR of the dentine caries lesions of primary teeth?"	'...All available approaches to treat dentine caries lesion of primary teeth was considered in this ystematic review. Atraumatic restorative treatment (ART) was considered as a restorative procedure that included caries removal using only hand instruments (i.e., spoon excavators) and restoration with high-viscous glass ionomer cement (HV) without the use of a rubber dam. Alternatively, conventional	Fourteen randomised controlled trials and one non-randomised observational study was included in this review. Participants in the trials were aged 2-10. Most of the studies were scored as having weak evidence because they did not provide most of the information required. The risk of bias analysis performed on the clinical trials showed that all studies received more unclear scores because of the uncertainty regarding potential bias in the questions,	For occlusal surfaces, only two studies presented data regarding the outer half of the dentine, with conventional restorative treatment (CRT) using composite resin showing superior results; five studies presented data regarding the depth of caries lesions, and CRT with Compomers resulted in the best results. Seven studies considered occlusoproxima	Inadequate evidence Tedesco et al. (2018) state that '...the treatment of dentine caries lesions in primary teeth depends on the progression depth and surface involved. However, few studies exist, and most have a high risk of bias to provide enough evidence to strongly recommend the best treatment option...' p16

Author and year	**Primary review question**	**Intervention descriptor**	**No. Of studies, study design and quality**	**Authors conclusions**	Level of evidence
		restorative technique (CRT) was considered as including caries removal using rotary instruments and restoration with any restorative material, including the use of a rubber dam. Thus, studies reporting treatment procedures that differed from those definitions were not included in the present review...' p3-4 ART: Atraumatic restorative treatment; CRT: Conventional restorative treatment; SSC: Stainless steel crown; NRCT: Nonrestorative caries treatment; UCT: Ultraconservative treatment; HT: Hall technique; IRT: Interim restorative treatment; SDF: Silver diamine fluoride; LVGIC: Low-viscosity glass ionomer cement; NaF: Sodium fluoride; RS: resin sealant; HVGIC: High-viscosity glass ionomer cement; RC: Resin composite; AM: Amalgam; RMGIC: Resin-modified glass ionomer cement;	especially those related to allocation concealment, incomplete outcome data and baseline imbalances given that we were unable to identify this information	l surfaces, and the Hall technique showed the best SR among the evaluated treatments. Finally, two annual applications of silver diamine fluoride showed the best nonrestorative approach to arrest caries lesions on occlusal and smooth surfaces.	
Dorri *et al.* (2017)[22]	To assess the effects of atraumatic restorative treatment (ART) compared with conventional treatment (the drill and fill	Atraumatic restorative treatment is a minimally invasive approach, which involves removal of decayed tissue using hand	15 eligible randomised controlled trials with 3,760 participants. All included studies were published	The available evidence suggests that atraumatic restorative treatment using high-viscosity glass ionomer may	**Inadequate** evidence upon which to compare ART with conventional treatment techniques

Author and year	**Primary review question**	**Intervention descriptor**	**No. Of studies, study design and quality**	**Authors conclusions**	Level of evidence
	approach) for managing dental caries lesions in the primary and permanent teeth of children and adults. (measuring restoration failure and pain)	instruments alone, usually without use of anaesthesia and electrically-driven equipment, and restoration of the dental cavity with an adhesive material (glass ionomer cement, composite resins, resin-modified glass-ionomer cement and compomers.	between 2002 and 2016. Eleven studies evaluated the effects of ART on primary teeth only, and four on permanent teeth. The authors judged all studies to be at high risk of bias. Two had industry backing. Any age, the mean age of the participants was 25.4 years (ranging from 3 to 101 years).	have a higher risk of restoration failure than conventional treatment for caries lesions in primary teeth, but the evidence is of low-quality and we cannot rely on the findings. We can draw no conclusions about the effects of ART *versus* conventional treatment when using resin-modified glass ionomer or composite because of the very low quality of the evidence. No studies reported on adverse events or costs	
Tedesco *et al.* (2016)[99]	What is the survival rate of atraumatic restorative treatment with the conventional approach (not sescribed) in occlusoproximal restorations in primary molars in children (measuring restoration survival)	Atraumatic restorative treatment is based on the minimal intervention philosophy [using hand tools only]	4 randomised controlled trials with 1,771 participants were included. Age of participants was 2 to 9 years. Primary molars were treated teeth Three studies had a high risk of bias for outcome assessment. All studies had an unclear risk of bias for allocation concealment	Atraumatic restorative treatment restorations have similar survival rates compared to conventional treatment and are a viable option to restore occlusoproximal cavities in primary molars. (No difference)	Inconclusive evidence for atraumatic restorative treatment *versus* conventional approach
Montedori *et al.* (2016)[101] (Cochrane Review)	Comparing laser-based methods to conventional mechanical methods for removing dental caries in deciduous and permanent teeth (pain, anaesthesia, durability of	Laser is an acronym standing for light amplification by stimulated emission of radiation. Laser is a device emitting a high coherence light beam with waves at single frequency (very	The authors included nine randomised controlled trials, published between 1998 and 2014, involving 662 participants. The population consisted of both children and adolescents in four trials, only adults in	Given the low quality of the body of evidence, the authors concluded that evidence was insufficient to support the use of laser as an alternative to traditional drill therapy for	**Inadequate evidence upon which to compare laser based methods with conventional mechanical methods**

Author and year	**Primary review question**	**Intervention descriptor**	**No. Of studies, study design and quality**	**Authors conclusions**	Level of evidence
	restoration, pulp damage). The conventional methods are: handpiece with a bur, chemomechanical system, sono-abrasion system, or air-abrasion system	narrow spectrum). The laser core is constituted of a material (positioned inside a highly reflective optical cavity) termed 'gainmedium' with properties that allow it to amplify light deriving from the energy source of the device	four trials, and both children/adolescents and adults in one trial. The age range of the participants was 3.5 to 84 years. Any tooth with caries All studies had a high for blinding participants, or most had an unclear risk of bias for blinding practitioners and outcome ascertainment	caries removal. The authors found some evidence in favour of laser therapy for pain control, need of anaesthesia and patient discomfort, but, again, the body of evidence was of low quality. Additional well-designed, randomised trials investigating the most relevant outcomes are needed.	
Ricketts *et al.* (2013)[102] (Cochrane Review)	To assess the clinical advantage of stepwise, partial or no caries removal compared with complete caries removal in previously unrestored primary and permanent teeth in children and adults	Three alternative operative caries management interventions were assessed by comparing them with the traditional treatment of removing all the decay in one go (complete caries removal). These interventions were: - Stepwise excavation - this technique removes caries in stages over two visits some months apart, allowing the dental pulp time to repair itself and lay down dentine. - Partial caries removal - the dentist removes part of the dentinal caries and seals what is left into the tooth permanently. - No dentinal caries removal - no dentinal	In this updated review, 4 new randomised controlled trials were included bringing the total to 8 trials with 934 participants and 1,372 primary or permanent teeth. Four studies investigated primary teeth, three permanent teeth and one included both. Any age considered in the included trials Most of the trials trials were assessed at high risk of bias for blinding of intervention, participants and outcome, although the new trials showed evidence of attempts to minimise bias.	Stepwise and partial excavation reduced the incidence of pulp exposure in symptomless, vital, carious primary as well as permanent teeth. Therefore these techniques show clinical advantage over complete caries removal in the management of dentinal caries. No dentinal caries removal was compared to complete caries removal in two very different studies. There was some moderate evidence of no difference between these techniques for the outcome of signs and symptoms of pulp disease and reduced	**Adequate evidence for stepwise, or partial caries removal when compared to complete caries removal** **Inconclusive evidence for no dentinal caries removal versus complete removal**

Author and year	**Primary review question**	**Intervention descriptor**	**No. Of studies, study design and quality**	**Authors conclusions**	Level of evidence
		caries is removed before sealing or restoring.		risk of restoration failure favouring no dentinal caries removal, from one study, and no instances of pulp disease or restoration failure in either group from a second quasi-randomised study. Due to the short term follow-up in most of the included studies and the high risk of bias, further high quality, long term clinical trials are still required to assess the most effective intervention.	

Six reviews of restorative materials for late treatment of dental caries in children and adolescents

Author and year	Primary review question	Intervention descriptor	Number, type and quality of studies	Authors conclusions	Level of evidence
Dias *et al.* (2018)[15]	compared glass-ionomer cement to composite resin in Class II restorations in primary teeth	According to Dias et al. "…GICs [glass-ionomer cements] are adhesive materials that release fluoride to the oral environment, and their insertion technique is faster compared to composite resin, making this material an important resource for the treatment of children…" p313	Ten randomised controlled trials were included in this review. The children participating in the ten trials were aged 3-11 years. The Cochrane instrument was used to assess the risk of bias in the ten trials. Six studies were classified as low risk of bias, and 4 as "unclear"	'…glass ionomer cement (GIC) and composite resin (CR) presented similar clinical performance to each other concerning the percentage of failures, marginal adaptation, marginal discoloration and anatomical form in Class II restorations in primary teeth, regardless of the type of GIC or isolation. However, regarding the occurrence of secondary carious lesions, GIC presented superior clinical performance, and this effect was more evident for the resin-modified GIC used with rubber dam isolation…' p12	Inconclusive evidence regarding whether glass-ionomer cement or composite resin is better on marginal discoloration, marginal adaptation, retention of restoration, and wear of the restorative material in Class II restorations in primary teeth Adequate evidence that glass-ionomer cements were significantly better than composite resins at preventing the occurrence of secondary carious lesions in primary teeth.
Raggio *et al.* (2016)[104]	To evaluate the ability of glass ionomer cement to prevent [secondary] caries lesions in margins of occlusal and occlusoproximal restorations in primary teeth compared with that of other restorative materials (amalgam, resin composite, or polyacid-modified resin composite)	Fluoride released glass ionomers cements may be capable of preventing caries The intervention group were either resin modified or high viscosity glass ionomer cement	8 randomised controlled trials were included in this review; all children under 10 years old Primary teeth. All 8 studies had two or more unclear risk of bias scores.	There is moderate strength of evidence for a positive association between of glass ionomer cement and prevention of post restoration caries lesions only in the margins of occlusoproximal restorations of primary teeth and no difference between restoration materials for	**Adequate evidence for secondary caries prevention in the margins of occlusoproximal restorations** **Inconclusive evidence for secondary caries prevention in the margins of occlusal restorations**

Author and year	Primary review question	Intervention descriptor	Number, type and quality of studies	Authors conclusions	Level of evidence
				occlusal restorations	
Ma *et al.* (2016)[10] (Cochrane Review)	To determine the effects of different materials used for retrograde filling (root canal therapy) in children and adults for whom retrograde filling is necessary in order to save the tooth.	Retrograde filling using different types of filling material: mineral trioxide aggregate (MTA), intermediate restorative material (IRM), super ethoxybenzoid acid (Super-EBA), dentine-bonded resin composite, glass ionomer cement, and amalgam.	The review included six randomised controlled trials (916 participants with 988 teeth) reported in English. All the studies had high risk of bias for blinding of participants. Any type of tooth in children and adults that required root canal therapy.	There is insufficient evidence to draw any conclusion as to the benefits of any one material over another. The authors conclude that more high-quality randomised controlled trials are required.	Inconclusive could not make any conclusions in favour of any one of the five interventions
Innes *et al.* (2015)[105] (Cochrane Review)	To evaluate the clinical effectiveness and safety of all types of preformed crowns for restoring primary teeth, compared with conventional filling materials (such as amalgam, composite, glass ionomer, resin modified glass ionomer and compomers), other types of crowns or methods of crown placement, non-restorative caries treatment or no treatment.	Restorations that can be provided can either be filling materials or preformed crowns. Traditionally, preformed crowns have been made of metal and referred to as either preformed metal crowns or stainless steel crowns. They are silver in colour. More recently, aesthetic preformed crowns have been developed and used for primary teeth, which are white in colour. For the purposes of this review, the term 'crown' will be used when referring to preformed crowns of any type, while ' preformed metal crowns' is used specifically to refer to preformed crowns made of metal and 'aesthetic crown' used specifically to refer to preformed crowns with a non-metallic appearance. Placement of a preformed crown is intended to	The authors identified five randomised controlled trials. Across the five trials, there were 438 child participants with 693 teeth. Primary teeth. All studies had high risk of bias for blinding because the participants knew which treatment they received and so did the people who treated them.	Crowns placed on primary molar teeth with carious lesions, or following pulp treatment, are likely to reduce the risk of major failure or pain in the long term compared to fillings. Crowns fitted using the Hall Technique may reduce discomfort at the time of treatment compared to fillings. The amount and quality of evidence for crowns compared to non-restorative caries, and for metal compared with aesthetic crowns, is very low. There are no RCTs comparing crowns fitted conventionally *versus* using the Hall Technique. There is moderate quality evidence that crowns are more effective than fillings for	Adequate evidence for crowns versus conventional filling materials

Author and year	Primary review question	Intervention descriptor	Number, type and quality of studies	Authors conclusions	Level of evidence
		provide a more durable restoration than a filling.		managing decay in primary molar teeth. There is moderate quality evidence that crowns fitted using the Hall Technique are less likely to cause abscesses and pain than fillings. The evidence comparing preformed crowns with non-restorative caries management, and comparing preformed metal crowns with preformed white crowns, is very low quality so we do not know which is better.	
Tedesco *et al.* (2016)[99]	To evaluate the evidence of the ability of glass ionomer cements compared to other restorative materials [amalgam] to prevent or arrest [secondary] caries lesions in approximal surface in contact with occlusoproximal restorations in children.	Glass ionomer cements contains a fluoride release property which is thought to help prevent caries.	Four longitudinal randomised controlled trials with 815 participants and six laboratory trials were included. Mix of primary and permanent teeth. Age 2.8 to 16 years. Three studies had a high risk of bias for one outcome and all studies had an unclear risk of bias for at least two outcomes.	In the longitudinal studies with children and adolecents, no benefit was identified to glass ionomer cements compared to other restorative materials [amalgam]. In the laboratory studies, glass ionomer cements shows better ability than other restorative materials to arrest caries lesions in adjacent surfaces, but this was not confirmed in the longitudinal clinical trials. Therefore, evidence is inconclusive.	Inconclusive evidence Children no difference Laboratory benefit
Santos *et al.* (2016)[103]	Assess the survival and	Restoration materials	11 randomised and non-	Adhesive materials with a	Inconclusive for resin survival

Author and year	Primary review question	Intervention descriptor	Number, type and quality of studies	Authors conclusions	Level of evidence
	clinical performance of glass ionomer cements, (conventional, resin-modified glass ionomer cement, silver-reinforced glass ionomer cement), composite resins, and compomers to determine which are superior on restoration survival for children with primary molars.	containing adhesive materials such as glass ionomer cements, composite resins, and compomers.	randomised trials with 483 children were included and most had a high risk of bias. Children aged 3-10 years and primary molars.	resin component (composite resin, compomer and resin-modified glass ionomer cement) have similar survival rates for 24 months and up to 48 months; this conclusion is based on weak evidence. There was no evidence that adhesive materials with a resin component have a greater survival rate in comparison to glass ionomer cement. Among the glass ionomers, silver-reinforced glass ionomer cement seemed to have the worst survival rateand is not recommended for restoring primary molars.	versus glass ionomer cement

Six reviews of remineralisation agents for early treatment of dental caries in children and adolescents

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
Oliveira *et al.* (2019)[86]	To investigate whether silver diamine fluoride (SDF) is effective in preventing new caries lesions in primary teeth when compared to no treatment, placebo or active treatments (sodium fluoride varnish, and high-viscosity glass ionomer cement).	SDF derives from the conjunction of silver nitrate and fluoride. It reduces the growth of cariogenic bacteria, hampers degradation of collagen in dentine, inhibits demineralisation and promotes remineralisation of both enamel and dentine.	6 reports of 4 randomised or non-randomised controlled trials that included 1118 children and analysed 915 of them were included. Age of children, Primary teeth. All studies had at least 1 domain with unclear or high risk of bias.	After 24 months of follow-up, in comparison to placebo, no treatment, and fluoride varnish, SDF applications significantly reduced the development of new dentine caries lesions. High-viscosity glass ionomer cement was better than SDF after 12 months of follow-up but the difference between them was not statistically significant	Adequate evidence that silver diamine fluoride was more effective than controls in arresting caries lesions in primary teeth and providing an anti-caries benefit for the entire dentition Inconclusive evidence when silver diamine fluoride was compared to other active treatments
Urquhart *et al.* (2019)[29]	Compare non-restorative treatments with other active intervention or no treatment or placebo for the arrest or reversal of non-cavitated and cavitated carious lesions on primary and permanent teeth in children and adults.	Interventions included sodium fluoride (NaF), stannous fluoride toothpaste or gel, acidulated phosphate fluoride (APF), difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, amorphous calcium phosphate (ACP), casein phosphopeptide–ACP (CPP-ACP), nano hydroxyapatite, tricalcium phosphate, prebiotics and/or 1.5% arginine, probiotics, silver diamine fluoride (SDF), silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, and carbamide peroxide p15	Forty-four randomised controlled trials based on 48 reports, which included 7378 participants and assessed the effect of 22 interventions, were included in this review. The precise age range of the participants is not reported in the review. Twelve trials included participants with primary dentition, 22 with permanent dentition and 9 with mixed dentition. The authors note that '…Information to judge most domains was often incomplete or missing. The domain of allocation concealment was judged to be the most serious methodological issue, and overall most studies had serious issues of risk of bias…' p17	Results from the Network Meta-analysis (NMA) shows that the combination of sealants and 5% NaF varnish was the most effective for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth (moderate certainty GRADE). The combination of resin infiltration and 5% NaF varnish may be the most effective for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth (low certainty GRADE). Similarly, 5000-ppm Fluoride (1.1% NaF) toothpaste or gel may be the most effective for non-cavitated and cavitated carious lesions on root surfaces in permanent teeth (low certainty GRADE). Results from the study-level data show that when compared with no intervention, 5% NaF varnish could be the most effective treatment for arresting	Adequate evidence that the combination of individual sealants and 5% sodium fluoride varnish were the most effective intervention for non-cavitated carious lesions on occlusal surfaces in primary and permanent teeth. Adequate evidence that 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth.

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
				or reversing non-cavitated facial/lingual lesions on primary and permanent teeth (low to moderate certainty). The use of 1.23% APF gel compared with oral health education on facial/lingual lesions, was effective only at longer follow-up times (12 months), moderate certainty GRADE). For arresting advanced cavitated carious lesions, study-level data suggest that 38% Silver Diamine Fluoride applied bi-annually was more effective on any coronal surface of primary teeth when compared with both 12% SDF solution applied bi-annually and 38% SDF solution applied annually (moderate to high certainty GRADE). '…The certainty in the evidence ranged from very low to high for the outcome of arrest or reversal across all surfaces, types of lesions, and dentition. We predominantly downgraded the certainty due to serious issues of risk of bias and imprecision…' p23	Adequate evidence the use of 1.23% acidulated phosphate fluoride gel on facial/lingual lesions at 12 months compared to oral health education was effective. Adequate evidence that 38% silver diamine fluoride applied twice per year was more effective than controls in arresting caries lesions in primary teeth and providing an anti-caries benefit for the entire dentition. Inadequate evidence the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective for non-cavitated carious lesions on approximal surfaces in primary and permanent teeth. Inadequate to suggest that 5,000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective for non-cavitated and cavitated carious lesions on root

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
					surfaces in permanent teeth.
Meyer *et al.* (2018)[87]	Calcium phosphates used in biomimetic oral care as a remineralising agent to manage early caries lesions in children and adolescents were compared to possibly fluoride (comparator not clear in review).	Calcium phosphates represent a group of common agents used in oral care that can be considered biomimetic, due to the fact that the mineral phase of teeth consists of the same basic compound.	Books, reviews, and original research papers with a focus on in vivo and in situ studies were included. 35 studies were included. The study design methods of the included studies are not provided. The quality of the studies included in the review was not assessed. Age and type of teeth not stated. However, the conclusion does mention children.	'…In conclusion, calcium phosphates represent a promising innovative approach for daily oral care that will broaden the range of future treatments in preventive dentistry…' p417	Inadequate evidence upon which to assess the performance of calcium phosphates.
Gao *et al.* (2016)[89]	Compared professionally applied fluoride therapy with other active treatments, placebo or no intervention in remineralising and arresting dental caries in primary and permanent teeth in children.	Professionally applied fluoride therapy is a relatively low-cost and easily operated treatment and has been used to arrest active dental caries. Fluoride inhibits plaque metabolism, alters plaque composition, affects plaque formation and reduces plaque bacteria's ability to produce a large amount of acid from carbohydrates. p2	Seventeen randomised controlled trials were included in this review. The age range of the children included in the trials is not reported in the review. The risk of bias of each study was undertaken using the Cochrane risk of bias instrument. The authors do make an overall judgement on the risk of bias in the included studies. However, they do state that '…blinding of outcome measurement and allocation concealment were either not achieved or not mentioned by the researchers. The sample size of some studies was small, while some studies didn't report the statistical procedure of sample size calculation or justified the sample size used in their studies…' p6	The results of the meta-analysis on four studies showed that 5% NaF varnish (fluoride varnish) remineralised approximately two-thirds of early enamel caries lesions. According to the authors '…Apart from NaF varnish, there is limited evidence to support the benefits of using other professional-applied fluoride agents such as 0.9 % silicon tetrafluoride, 0.42 % NaF gel and 10 % SDF in remineralising early enamel caries…' p7 38 % Silver Diamine Fluoride (SDF) (The most commonly used concentration) is superior to fluoride varnish in arresting dental caries in both the primary and permanent teeth in children. According to the authors '…There is no need to remove the soft decay (the infected dentine) before SDF application…' p7 According to the authors '…professionally applied	Adequate evidence to suggest that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth. Adequate evidence that silver diamine fluoride was more effective than controls for arresting the progression of active caries in both primary and permanent teeth in children and adolescents.

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
				5% sodium fluoride varnish shows the capability to remineralise early enamel caries in children. Silver diamine fluoride solution at 38% is effective in arresting active dentine caries…' p8	
Duangthip *et al.* (2015)[90]	Compared non-surgical methods with controls in arresting or slowing down the progression of active dentine caries in primary teeth in preschool children.	Various non-surgical intervention methods, such as fluoride agents (toothpaste, mouthrinse, gel, varnish, solution), silver diamine fluoride (SDF), dental sealant, resin infiltrant, chlorhexidine, xylitol, CPP-APC, ozone and oral health education were included in this review. p2	Three randomised controlled trials and one longitudinal study were included in this review. All children involved in the studies were aged 6 years and under. Assessment of risk of bias in the included studies was undertaken using the Cochrane risk of bias assessment tool. Two studies were judged to have a low risk of bias, one study had moderate risk and one study had high risk of bias.	Three studies reported significantly higher success rates of SDF treatment (65-91%) compared with no treatment (34%), sodium fluoride varnish (38-44%) and interim GI restorations (39-82%) in arresting dental caries in preschool children. one study reported a superior effect of daily brushing with 1100 ppm Fluoride toothpaste when compared to brushing with 500 ppm Fluoride toothpaste on enamel caries progression. According to Duangthip et al. (2015) '…There is limited evidence to support the effectiveness of SDF applications once/twice a year and that of daily tooth-brushing with fluoride toothpaste in arresting or slowing down the progression of active dentine caries in primary teeth in preschool children…' p8	Adequate evidence to suggest that brushing teeth with highly concentrated fluoride toothpaste is effective at slowing the progressing of early caries in preschool children. Adequate evidence that silver diamine fluoride was more effective than controls in arresting caries lesions in primary teeth in preschool children.
Benson *et al.* (2013)[91] (Cochrane review)	Compares the effects of various forms of fluoride used during orthodontic treatment on the development of demineralised white lesions (DWLs).	Methods of applying fluoride that were assessed included: 1. topical fluorides, for example, fluoride-containing varnish, mouthrinse, gel or toothpaste; 2. fluoride-releasing devices	Three randomised controlled trials with 458 participants were included in this updated review. One study was assessed at low risk of bias for all domains, in one study the risk of bias was unclear and in the remaining study, the risk of bias was high. Participants had a mean age of 15.7 in one trial, 14.3 plus/minus 1.6 in	One trial comparing fluoride varnish applied every six weeks at the time of orthodontic review with a placebo (253 participants, low risk of bias), provided moderate-quality evidence of an almost 70% reduction in DWLs. '...The quality of the evidence found is moderate in the case of one well-designed study and weak in the remaining studies...' p3	Adequate evidence to suggest that fluoride varnish can be an effective intervention to reduce the development of white spot lesions in children undergoing orthodontic treatment.

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
		attached to the braces; and 3. control group approaches - individuals did not receive additional fluoride as described, or they received a placebo or a different form of fluoride. p3	another trial and no age reported in the third trial. No particular type of teeth specified in the review.		
Ancira-González *et al.* (2018)[88]	Effect of fluoride varnishes, gels, and remineralisation agents on white spot lesion in primary teeth. The outcome was remineralisation of the white spot lesion.	A mix of topical agents to remineralise dental enamel of primary teeth. It would appear the authors main interest was caesein phosphopeptide-amorphous calcium phosphate.	9 randomised or non-randomised trials on children's primary teeth. The childrens age was between 1-8 years. 7 studies had one high risk of bias score and 4 studies had 2 or more high risk of bias scores.	Fluoride varnish is a better remineralisation agent than no intervention, placebo or chlorhexidine. Fuoride varnish was not better than pit and fissure sealants or ND: YAG laser treatment. Where fluoride varnishes were combined with chlorohexidine or laser treatment, the combination performed better remineralisation than fluoride varnish alone.	Adequate evidence to suggest that fluoride varnish is an effective remineralising agent for targeting white spot lesions in primary teeth.

Four reviews of micro-invasive strategies for early treatment of dental caries in children and adolescents

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
Krois *et al.* (2018)[92]	To compare micro-invasive treatments with non-invasive treatments or placebo to arrest early non-cavitated proximal carious lesions.	Micro-invasive strategies (sealing and infiltration) remove a few micro-meters of tissue during application, usually when conditioning the tooth surface with acids, and install a diffusion barrier onto (lesion sealing) or within (lesion infiltration) the carious tissue. The barrier (of resins or glass ionomer cements) impedes acid diffusion into the hard tissue and further mineral loss from it, thereby arresting the lesion. p15 Non-invasive strategies remove no carious tissue at all and include dietary control, biofilm control or control of de- and remineralisation (via fluorides etc,) often combined with each other p15	Fifteen reports of 13 randomised controlled trials with 486 participants were included. Four trials assessed lesions in primary teeth and nine trials assessed lesions in permanent teeth. Participants comprised children and adolescents with a mean age of 15 years. All trials showed low risk of bias with regards to blinding of the assessment, and there was also limited indication of selective reporting or issues of random sequence generation. In contrast, blinding of operators or participants was always rated as unclear or high risk, and allocation concealment was rated as unclear risk of bias in seven studies. Nearly all trials on infiltration were sponsored by the manufacturer; two trials were additionally conducted by the inventors.	Firm evidence on the superior efficacy of sealing/infiltration over non-invasive treatment was reached. Firm evidence was also reached on the superior efficacy of sealing and infiltration (both separately) over non-invasive treatment. There was no significant difference between infiltration versus sealing, and firm evidence was not reached. According to Krois et al. (2018) '…Based on our findings, sealing or infiltration instead of non-invasive treatment [non-invasive] would avoid 278 per 1000 treated lesions to progress (44% non-invasive treatment and 16% sealed or infiltrated lesions would progress). The certainty of the evidence was graded as moderate. Sealing instead of noninvasive treatment would avoid 282 per 1000 treated lesions to progress. The certainty of the evidence was graded as moderate. Infiltration instead of non-invasive treatment would avoid 266 per 1000 treated lesions to progress (as the control group event proportion was lower). The certainty of the evidence was graded as high…' p18	Adequate evidence that micro-invasive treatment (sealing and resin infiltration) is superior to non-invasive treatment. Inconclusive evidence regarding which is better - sealing or infiltration.
Wright *et al.* (2016)[93]	To summarise the evidence on effect of dental sealants for the prevention and management of pit-and-fissure occlusal carious lesions in primary	'…Occlusal surfaces, especially those on permanent molars, contain grooves called pits and fissures that can trap debris and	23 randomised controlled trials (24 papers) were included. Trials were assessed as having an unclear risk of bias (poor reporting in the original papers).	There is moderate quality evidence that the use of sealants when compared with control groups that did not have sealants reduces the incidence of carious lesions in the occlusal surfaces of permanent	Adequate evidence that sealants when compared with no sealant are better in preventing carious lesions and arresting

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
	and permanent molars, compared with a control without sealants, with fluoride varnishes, or with other head-to-head comparisons.	microorganisms, increasing the risk of caries lesions…Sealants are dental materials that dentists apply to the pit and fissure surface of teeth. The sealant material penetrates and hardens, acting as a physical barrier to inhibit the ingress of bacteria…' P283	Children/adolescents aged 6-16 yr. Primary and permanent molars were the teeth under treatment.	molars by approximately 80% in children and adolescents.	the progression of non-cavitated carious lesions in primary and permanent molars. Inconclusive evidence for which is better sealants or fluoride varnish. Inconclusive evidence regarding the superiority of one sealant over another.
Dorri *et al.* (2015)[95] (Cochrane Review)	To evaluate the effects of micro-invasive treatments for managing proximal caries lesions in primary and permanent dentition in children and adults. The controls were: non-invasive measures, invasive means, no intervention, or placebo. Theoutcome was lesion progression.	Micro-invasive treatments involve conditioning the tooth surface using organic acids prior to treating the caries lesion; The conditioning involves the loss of few micrometers of tooth enamel. There are two types of micro-invasive treatments: sealing and resin infiltration.	We included a total of eight trials, which randomised 365 participants. No age provided. Primary teeth, permanent teeth or both. The authors judged seven studies to be at high overall risk of bias, primarily due to lack of blinding of participants and personnel.	The available evidence shows that micro-invasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions and is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss). The authors are moderately confident that further research is unlikely to substantially change the estimate of effect.	Adequate evidence that micro-invasive treatment (sealing and resin infiltration) is superior to non-invasive treatment in primary and permanent molars.
Doméjean *et al.* (2015)[96]	To evaluate the *in vivo* scientific evidence of the ability of resin infiltration to arrest non-cavitated caries lesions compared to fluoride varnish, sealant microbrush or water application.	The porosities of an enamel lesion are infiltrated with a low viscosity resin, a technique known as 'resin infiltration'.	3 randomised controlled trials in 4 papers, including children, adolescents and adults. All 4 articles reported on proximal caries lesions. One study had been conducted on 48 high-caries-risk children while the other 3 (n = 22, 22 and 39, respectively) were on moderate- and low-caries-risk adolescents and adults. The quality of the studies was assessed	This systematic review revealed that the use of resin infiltration to arrest the progression of non-cavitated caries lesions is encouraging. This suggests that resin infiltration is a promising noninvasive approach and might be considered as an additional option to non-operative and operative treatment approaches. However, high-quality, long-term clinical trials, preferably in general dental practice settings, are required to confirm the efficacy of resin infiltration for non-	Inconclusive evidence that resin infiltration is effective in arresting the progression of caries when compared to controls.

Author and year	Primary review question	Intervention description	No. & type of studies included and quality of primary studies	Author(s)' conclusions	Level of evidence
			to be high with respect to randomization, split-mouth design and blinding.	cavitated caries lesions in both deciduous and permanent teeth.	

Studies examining the survival of interventions to treat or prevent caries in children and adolescents (3 studies)

Author and Year	Primary review question	Intervention descriptor	No. of studies , study design & quality	Author(s)' conclusions	Quality of evidence
de Amorim *et al.* (2018)[107]	To describe the survival of ART glass ionomer restorations and ART sealants in primary and permanent posterior teeth.	ART is done by hand, not drill and fill. Its restorative component is based on the selective removal of carious tissues down to the soft dentine in deep/very deep lesions and to firm dentine in non-deep lesions.	42 publications and 34 clinical trials from 22 countries. 28 studies were exclusively focused on children, 3 on children and adults and 1 on adults Only 2 studies scored low risk of bias across all parameters. 32 of the studies had a high risk of bias for one or more parameters.	Survival percentages of single-surface and multiple-surface ART restorations in primary posterior teeth over the first 2 years were 94.3% (± 1.5%) and 65.4% (± 3.9%), respectively. Single-surface ART restorations in permanent posterior teeth over the first 3 years were 87.1% (± 3.2%); and for multiple-surface ART restorations in permanent posterior teeth over the first 5 years were 77% (± 9.0%). Mean annual dentine-carious-lesion-failure percentages in previously sealed pits and fissures using ART sealants in permanent posterior teeth were 0.9% at 3 yr and 1.9% at 5 yr.	Adequate evidence that atraumatic restorative treatment technique to place high viscosity glass-ionomer cement sealants produce medium to high levels of survival. Adequate evidence that using the atraumatic restorative treatment technique to place high viscosity glass-ionomer cement sealants effectively prevents caries lesions in children and adolescents.
Chisini *et al.* (2018)[106]	To describe the longevity of primary teeth restorations and the reasons for failure	Restorative interventions included: amalgam (6 studies), compomer (9 studies), composite resin (6 studies), conventional glass ionomer resin (5 studies), modified resin glass ionomer (4 studies), resin	31 studies (mostly RCTs) included in the qualitative analysis, evaluating 12,047 posterior restorations in primary teeth in children. In general, studies had a high risk of selection,	Success rate: Amalgam: 82% at 3 yr. Compomer: 91% at 3 yr. Composite: 79% at 4 yr. Conventional glass ionomer resin: 89% at 4 yr. Modified resin glass ionomer: 57% at 3 yr. Resin modified glass ionomer: 94% at 4 yr.	Inconclusive evidence regarding the best material for posterior restorations in primary teeth due to wide ranges for failure or success and different endpoints

Author and Year	Primary review question	Intervention descriptor	No. of studies , study design & quality	Author(s)' conclusions	Quality of evidence
		modified glass ionomer (10 studies), steel crowns (3 studies).	performance, and detection bias.	Steel crowns: 96% at 3 yr. Overall annual failure rate range: Amalgam: 1-28% over 3 yr. Compomer: 1.7-15.4% over 3 yr. Composite: 1.7-12.9% over 4 yr. Glass ionomer: 0.8-16.6% over 4 yr. Modified resin GI: 10-29% over 3 yr. Resin modified GI: 0.9-16.9% over 4 yr. Steel crowns: 1.4-19% over 3 yr. Main reason for failure over 3-4 years: Secondary caries (36.5%), restoration loss (19.6%), marginal adaptation (15.6%), fractured teeth or restoration (8.3%)	
Papageorgiou *et al.* (2017)[108]	To assess the clinical performance or survival of pit and fissure sealants on various teeth to prevent caries or for management of early signs of caries. The control groups were any other active, control, or placebo modality	The procedure of 'sealing' the pits and fissures of teeth includes the placement of a liquid material onto the occlusal surface (i.e. pits and fissures) of posterior teeth, thereby forming a layer that is bonded micromechanically and acts mainly as a barrier against acids and the subsequent mineral loss from within the tooth. Pit-and-fissure sealants can be placed on either caries-free posterior teeth to prevent pit-and-fissure caries or on teeth with incipient caries lesions to prevent their progression to definitive caries p3	A total of 16 randomised clinical trials with 2,778 patients (male/female 49.1%/50.9%) and an average age of 8.4 years were included. The number of cohort years in primary studies is unclear and indications are that they are between 5 and 15 years. Both primary and permanent teeth were included. 9 trials had a high risk of bias for at least one domain, in particular, blinding of outcome assessment missing in all 50% of the trials.	Based on the results of this systematic review, the performance of pit and fissure sealants in terms of caries of the sealed tooth or retention loss of the sealant do not seem to be negatively affected by mouth side, jaw, and tooth type.	Inconclusive evidence that the characteristics of individual teeth had any influence on the clinical performance of pit and fissure sealants

Appendix 5 Evidence for dental caries in adults

Evidence for prevention of adult caries to minimise or override the need for amalgam

Author and year	Primary review focus	Author(s)' conclusion	Evidence Assessment
Walsh *et al.* (2019)[7] (Cochrane Review)	Determine and compare the effects of toothpastes of different fluoride (sodium fluoride and sodium monofluorophosphate) concentrations in preventing dental caries in children, adolescents, and adults. P11	For the mature permanent dentition of adults, toothbrushing with 1000 or 1100 parts per million fluoride toothpaste reduces decayed, missing, and filled surfaces when compared to non-fluoride toothpaste in adults of all ages (moderate-certainty evidence using GRADE and taking account of bias). P37	Adequate evidence for fluoride toothpaste Inconclusive evidence for size of the benefit of fluoride in toothpaste
Bagherian *et al.* (2018)[25]	Evaluate fissure sealant retention in clinical studies in which investigators used flowable composites as pit and fissure sealants compared to and fissure sealants. Age and type of teeth sealed and number of participants are not provided P92	It seems that the use of flowable composite as a fissure sealing material can slightly increase the retention rate of sealants compared to conventional resin-based sealants. P96 Of the 11 studies identified in the systematic review, four scored as having a low risk of bias, and seven scored as having a medium risk.	Inconclusive evidence for flowable composite as a sealing material over conventional resin-based sealants due to borderline significance and bias in primary studies.
Alirezaei *et al.* (2018)[26]	Evaluate the ability of glass-ionomer cement-based sealants and resin-based sealants to prevent the occurrence of caries and their retention in standards-based clinical studies. P641 There was no age limit and the type of teeth were not specified.	The results of the meta-analysis indicate that conventional resin-based sealants had a significant positive effect on retention rates compared to the effect of glass-ionomer cement -based sealants, but both materials exhibited the same caries prevention effect, which is the main goal of fissure sealant therapy. P647 Of the 31 studies included in the systematic review, 16 had a low risk of bias, and 15 had a medium risk.	Inconclusive evidence for sealing Adequate evidence for resin retention over glass-ionomer cements
Twetman and Keller (2016)[23]	Summarise the findings of clinical trials published after 2002 using fluoride mouth rinses, fluoride gels, or foams, compared to no intervention or placebo, among children (5 years and over) and adults for the prevention of dental caries. P39	All fluoride measures appeared to be beneficial in preventing crown caries and reversing root caries, but the quality of evidence was graded as low for fluoride mouth rinse, moderate for fluoride gel and very low for acidulated fluoride foam based on GRADE and taking account of bias. No conclusions could be drawn on the cost-effectiveness. P43	Inadequate evidence for fluoride mouth rinse Adequate evidence for fluoride gel Inadequate evidence for acidulated fluoride foam
Yengopal and Mickenautsch (2010) and correction in 2012 by Ritwik, P[154]	Appraise quantitatively current evidence regarding the caries-preventing effect of resin-modified glass-ionomer fissure sealants in comparison to that of resin-based fissure sealants. P18	This meta-analysis found no conclusive evidence that either material was superior to the other in preventing dental caries. P25 The authors described the included trials as poor quality.	Inadequate evidence that either material was superior to the other due to limited evidence quality Ritwik (2012) describes the certainity of the evidence as limited.

Evidence for early treatment of adult caries to minimise or override the need for amalgam

Author and year	Primary review focus	Author(s)' conclusion	Evidence Assessment
Urquhart *et al.* (2019)[29]	Synthesise the evidence on the benefits and harms of nonrestorative treatments to arrest or reverse existing noncavitated and cavitated carious lesions on primary and permanent teeth. P15 The nonrestorative or non- and microinvasive caries treatment are: sodium fluoride, stannous fluoride toothpaste or gel, acidulated phosphate fluoride, difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, amorphous calcium phosphate, casein phosphopeptide– amorphous calcium phosphate, nano hydroxyapatite, tricalcium phosphate, prebiotics and/or 1.5% arginine, probiotics, silver diamine fluoride, silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, and carbamide peroxide. They were compared to each other, placebo, and no intervention P15	Evidence suggests that 1) the combination of sealants and 5% sodium fluoride varnish was the most effective for noncavitated carious lesions on occlusal surfaces in permanent teeth (moderate certainty), and 2) the combination of resin infiltration and 5% sodium fluoride varnish may be the most effective for noncavitated carious lesions on approximal surfaces in permanent teeth (low certainty). Similarly, 5000 parts per million fluoride (1.1% sodium fluoride) toothpaste or gel may be the most effective for noncavitated and cavitated carious lesions on root surfaces in permanent teeth (low certainty). Study-level data show that when compared to no intervention, 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing noncavitated facial/lingual lesions on permanent teeth (low to moderate certainty). Also, study-level data compared the use of 1.23% acidulated phosphate fluoride gel with oral health education on facial/lingual lesions, although this treatment was effective only at longer follow-up times (12 months, moderate certainty). Overall most studies had serious issues of risk of bias. P23	Adequate evidence for combination of sealants and 5% sodium fluoride varnish for noncavitated carious lesions on occlusal surfaces in permanent teeth and 5% sodium fluoride varnish could be the most effective treatment for arresting or reversing noncavitated facial/lingual lesions on permanent teeth. Inadequate evidence for all other interventions
Tao *et al.* (2018)[30]	Evaluate the efficacy of "the combination of casein phosphopeptide-amorphous calcium phosphate and fluorides compared to fluorides monotherapy on patients with early caries lesions" P2 in permanent teeth (age of study participants unclear but young adults appear to be included)	Fluorides combined with casein phosphopeptide-amorphous calcium phosphate achieved the same efficacy for early caries lesions on smooth surfaces compared to fluorides monotherapy. The combination treatment showed significantly better efficacy than fluorides monotherapy alone for occlusal early caries lesions. The authors state that "the limited number of studies resulted in tiny subgroups, which suggests that the evidence is incomplete and is not generalisable" P8 Further well-designed studies are still needed. There was an unclear risk of bias in the majority of the included studies.	Inadequate evidence for fluorides combined with casein phosphopeptide-amorphous calcium phosphate over fluorides monotherapy for early caries lesions
Liang *et al.* (2018)[112]	Evaluate the caries-arresting effectiveness of micro-invasive interventions for non-cavitated proximal caries and analyse their efficacy for caries lesions of different depths. P2676 Compared to non-invasive measures, placebo, or no treatment. The age range was 6.5 to 39 years.	The subgroup analysis showed that resin infiltration and resin sealant, but not glass-ionomer cement could reduce the caries progression rate. Further analysis of their efficacies for caries lesions of different depths indicated that resin infiltration could arrest progression of enamel caries and caries around the enamel-dentine junction However, when the outer third of the dentine was involved, resin infiltration did not yield significantly different results compared to the control group. Resin	Adequate evidence in favour of resin infiltration and sealant for arresting the progression of non-cavitated proximal caries. Inadequate evidence for therapeutic effects of resin sealant for different caries depths

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		sealant, compared to other methods, was not more effective at different caries depths the caries depth (enamel enamel dentine junction and dentine). P2682	
Krois *et al.* (2018)[92]	Synthesise the evidence on sealing or infiltrating proximal carious lesions in primary and permanent teeth of children, adolescents and young adults compared to each other, no intervention, or placebo.	Firm evidence on the superior efficacy of sealing conbined with infiltration over noninvasive treatment was reached. Firm evidence was also reached on the superior efficacy of sealing and infiltration as separate interventions over noninvasive treatment. One study compared infiltration to sealing and found no significant difference. Based on Bayesian network meta-analyses, infiltration was ranked first in 80% of the simulations (sealing 20%, noninvasive treatment 0%). There is moderate to high evidence that sealing or infiltration are likely to be more efficacious for arresting early (non-cavitated) proximal lesions than noninvasive treatment. Bias was not a major feature in these studies.	Adequate evidence for sealing and/or infiltration to arresting early (non-cavitated) proximal lesions over no intervention
Indrapriyadharshini *et al.* (2018)[31]	Assess the long-term remineralising potential of casein phosphopeptide-amorphous calcium phosphate in paste form in both naturally occurring and post-orthodontic white spot lesions in vivo in any age or type of teeth, compared to fluoride varnish or placebo. P488	Four of the twelve studies evaluated the effect of casein phosphopeptide-amorphous calcium phosphate in paste form on naturally occurring early caries lesions compared to placebo or no treatment, out of which three studies concluded that there was a significant reduction in caries increment after using the paste (no meta analysis). The other eights examined secondary caries as a result of orthodontic treatment and are not of interest to this review. Seven studies had low risk of bias, three were unclear and two were at high risk. GRADE was not applied	Inconclusive evidence for using casein phosphopeptide-amorphous calcium phosphate in paste form compared to placebo to reduce caries due to inability to control for heterogeneity and bias in studies
da Silva *et al.* (2018)[113]	Assess whether HEMA [2-hydroxyethyl methacrylate] free adhesive systems in adults permanent teeth have better clinical performance than HEMA containing systems in noncarious cervical lesions.	HEMA-free and HEMA-containing adhesive systems showed a similar clinical performance in noncarious cervical lesion restorations. 13 studies were classified as "low" risk of bias and nine as "unclear".	Inconclusive evidence for either type of adhesive using limited and inconsistent evidence. Farsai assigned a SORT score B which indicates inconsistent or limited quality evidence.
Boing *et al.* (2018)[119]	Compare the loss of retention and color match of glass-ionomer cements and resin-based composites in noncarious cervical lesions in permanent adult teeth.	Glass-ionomer cement, when compared to resin-based composites, showed significantly higher retention rates in follow-ups between 1 and 5 years. Quality of evidence was graded as moderate to low due to unclear risk of bias and imprecision in some outcomes.	Adequate evidence in favour of glass-ionomer cement, when compared to resin-based composites for retention up to 5 years
Szesz *et al.* (2017)[120]	Do flowable resin composite restorations, compared to regular resin composites, improve the marginal adaptation, marginal discoloration and retention rates of restorations placed in	The authors have moderate confidence that the resin composite viscosity does not influence the retention rates at 3 years. Similar marginal discoloration and better marginal adaptation was observed for flowable composites but the quality of evidence is doubtful.	Adequate evidence that retention is similar for flowable resin composite compared to regular

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	non-carious cervical lesions in permanent adult teeth?	Two studies were high risk of bias and 6 were at unclear risk of bias.	Inadequate evidence for marginal discoloration and marginal adaptation
Paula *et al.* (2017)[110]	Investigate which remineralisation agents (fluoride, casein phosphopeptide-amorphous calcium phosphate, ICON resin) are effective for the treatment of white spot lesions. There was no age cut off and both permanent and primary teeth were included.	The majority of studies included in this review that therapy with remineralising agents reduces the white spot lesions (size or visual appearance). Three of four studies concluded that fluoride prooducts demonstrated remineralisation of white spot lesions. Studies with remineralising agents such as casein phosphopeptide-amorphous calcium phosphate, and ICON resin demonstrated regression of white spot lesions, either in size or in their clinical visual appearance. The high risk of bias in the primary studies seriously limits the conclusions about products to treat white spot lesions. More studies are required for scientific evidence in order to reach a conclusion of the most suitable therapeutic method for the treatment of surface and subsurface demineralization of the enamel.	Inadequate evidence for determining the most suitable product to remineralise white spot lesions
Schroeder *et al.* (2017)	Which adhesive strategy (self-etch and etch-and-rinse adhesives) for composite resin restorations in non-carious cervical lesions? The type of teeth and age of participants are not clear.	Composite resin restorations placed with self-etch and etch-and-rinse adhesives produce restoration with similar clinical service and sensitivity, however using etch-and-rinse adhesives one can reduce marginal discoloration at 18 months to 2 years and again at 4 to 5 years. All trials were at low risk of bias.	Adequate evidence in favour of etch and rinse for discolouration Inconclusive evidence for either product for sensitivity and retention
Szesz *et al.* (2016)[115]	Identify if selective etching of enamel margins (compared to no etching) improves the retention rates and marginal discoloration of cervical composite restorations in non-carious cervical lesions of adult patients	The selective enamel etching prior to application of self-etch adhesive systems in non-carious cervical lesions can produce composite restorations with better esthetics (lower marginal discoloration rates and better marginal integrity) and higher longevity (higher retention rates). P10 Three studies were at high risk of bias and 7 studies were considered to be at low risk of bias. The overall number of participants is small and the study periods varied from 1 to 5 years.	Inconclusive evidence for selective etching of enamel prior to application of self-etch adhesive systems in non-carious cervical lesions due to small sample sizes and some bias in the studies. The authors use "might" in the abstract
Schwendicke *et al.* (2015a)[28]	Compare noninvasive, microinvasive, and minimally invasive treatments for pit-and-fissure lesions in permanent teeth. P523 Various treatment options are available for pit-and-fissure lesions in permanent posterior teeth: (1) noninvasive treatments (like fluoride) to avoid any dental hard tissue removal; (2) microinvasive treatments (sealants) remove only a few micrometers of hard tissues by etching; and (3) minimally invasive methods (sealants and	Available treatment options seem suitable for treating shallow or moderately deep pit-and-fissure lesions in posterior permanent teeth; further conclusions are not possible. The evaluated data found micro-invasive and minimally invasive treatments efficacious to avoid invasive retreatments after treating pit-and-fissure lesions in permanent posterior teeth. Current evidence indicates that noninvasive treatments might also be suitable for this purpose, while effect estimates remain nonsignificant. The need for any retreatment was significantly higher in microinvasively (sealed) lesions than in those that received noninvasive or	Inadequate evidence for minimally invasive over microinvasive and over noninvasive

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	restoration) remove carious dentine but avoid sacrificing sound tissues. The interventions were compared to each other, no active or placebo treatment, or standard oral home care. The age of the participants was not clear.	minimally invasive treatments. The studies supporting these findings, however, were mostly of limited quality; thus, the overall certainty of the findings is thus low or very low. P531	
Schroeder *et al.* (2015)[116]	"Does enamel bevelling compared to no enamel bevelling improve the retention of composite restorations in non-carious cervical lesion of adult patients [permanent teeth]?" 778	There is not enough evidence to support the bevelled technique over non-bevelled for non-carious cervical lesions over longer periods of time. The authors conclude that "there is no difference between bevelled and non-bevelled technique over the short-term follow up of 12–18 months of clinical service, although this conclusion was based on two low-risk of bias randomised controlled trials with small sample sizes. Additionally, there is no evidence to support this conclusion over longer-term follow-ups." P786	Inconclusive evidence for bevelled restorations over no treatment
Raphael and Blinkhorn (2015)[111]	"Is there sufficient clinical evidence available to support the use of Tooth Mousse® (MI Paste®) and Tooth Mousse Plus® (MI Paste Plus®) over a routine oral care regimen for the prevention and treatment of early dental caries?" P3 Participants of any age and tooth type were included. Casein Phosphopeptide-Amorphous Calcium Phosphate	"The findings of this systematic review suggest there is a lack of evidence to support the use of Tooth Mousse® (MI Paste®) over a routine preventive fluoride regimen for the prevention of early dental caries. ... There is a lack of support for the use of fluoride-containing formulation - Tooth Mousse Plus® (MI Paste Plus®) over Tooth Mousse® (MI Paste®)." P11 The strength of evidence of the group of studies included in this systematic review is weakened by high risk of bias, small sample sizes, short observation periods and varying outcome measures.	Inadequate evidence for tooth-mousse plus as majority of studies had a high risk of bias and only two were included in metaanalysis. Hani *et al.* describes the evidence from this review as insufficient to support the use of tooth mousse.
Dorri, M. *et al.* (2015)[95] (Cochrane Review)	"Evaluate the effects of micro-invasive treatments for managing proximal caries lesions in primary and permanent dentition in children and adults." P7 Micro-invasive treatments were compared to non-invasive measures, invasive means, no intervention or placebo.	"The available evidence shows that micro-invasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions (limited to outer third of dentine, based on radiograph) and is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss). We can be moderately confident that further research is unlikely to substantially change the estimate of effect. Due to the small number of studies, it does remain unclear which micro-invasive technique offers the greatest benefit, or whether the effects of micro-invasive treatment confer greater or lesser benefit according to different clinical or patient considerations." P22 The authors assessed the quality of evidence for micro-invasive treatments and caries progression outcome as moderate. The authors judged seven studies to be at high overall risk of bias, primarily due to lack of blinding of participants and personnel.	Adequate evidence for microinvasive treatment over non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss), but high risk of bias

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Domejean *et al.* (2015)[96]	The aim of this review was to evaluate the in vivo scientific evidence regarding the ability of resin infiltration to arrest non-cavitated caries lesions (occlusal and proximal). P217. Resin infiltration was compared to fluoride varnish, sealant microbrush, or water application in high-caries-risk children and moderate- and low-caries-risk adolescents and adults.	This systematic review revealed that "resin infiltration appeared to be an effective method to arrest the progression of non-cavitated caries lesions." P219 "The compilation of the results was not deemed meaningful because one of the included studies was undertaken on primary teeth whereas the others involved permanent teeth where resin infiltration was compared to different control/placebo groups. The major limitation of this paper is the small sample which was due to the restricted search of the articles published in only one medical database, PubMed." P220 Each study had a different comparator group. GRADE was not used to assess the quality of evidence.	Inconclusive evidence for resin infiltration over fluoride varnish, sealant microbrush or water application as small sample sizes
Peumans *et al.* (2014)[117]	Evaluate the clinical effectiveness of contemporary adhesives for the restoration of non-carious cervical lesions in permanent teeth in terms of restoration retention as a function of time. P1090 The adhesives were compared to each other. Materials with adhesive potential were categorised into six main classes: 3-step etch&rinse adhesives, 2-step etch&rinse adhesives, 2-step self-etch adhesives, 1-step self-etch adhesives, glass-ionomers and self-adhesive composites. The first four can bond restorative composite to tooth tissue. The age of the participants was not described.	The lowest annual failure rate scores were recorded for glass-ionomer shortly followed by 2-step etch&rinse, 3-step etch&rinse and 1-step self-etch adhesives_mild. Significantly higher annual failure rate scores were recorded for 1-step self-etch adhesives, 2-step etch&rinse adhesives, and 2-step self-etch adhesives. In addition, significant differences in annual failure rate were noticed between adhesives of the same class , except for glass-ionomer and 2-step self-etch adhesives_mild. Finally, selective enamel etching (compared to non-etching) did not significantly influence the retention rate of self-etch adhesives.	Inconclusive evidence for lowest annual failure rate scores for glass-ionomer, shortly followed by 2-step etch&rinse adhesives. The HRB reduced score from adequate to inconclusive because the primary studies did not have a quality assessment and the results were not assessed for the certainity of evidence.
Li *et al.* (2014)[109]	"Assess the long-term (>3 months) remineralising effect of casein phosphopeptide-amorphous calcium phosphate on early caries lesions in vivo" P771 compared to fluoride toothpastes or mouthwashes, placebos, topical creams, or chewing gum. There were no age limits but nearly all participants were adolescents. The type of tooth would appear to be both primary and permanent teeth but once again it is not clear.	Casein phosphopeptide-amorphous calcium phosphate has a long-term remineralizing effect on early caries lesions in comparison with placebo, although this does not appear to be significantly different from that of fluorides. The advantage of using casein phosphopeptide-amorphous calcium phosphate as a supplement to fluoride-containing products is still unclear. Five studies had a high risk of bias, two had an unclear risk, and one had a low risk of bias.	Inadequate evidence for casein phosphopeptide-amorphous calcium phosphate over fluoride as most papers had a high risk of bias
Tellez *et al.* (2013)[27]	What is "the efficacy of nonsurgical caries preventive methods to arrest or reverse the progression of	"Fluoride interventions (varnishes, gels, and toothpaste) seem to have the most consistent benefit in decreasing the progression and incidence of non-carious cervical lesions. Studies using xylitol,	Inconsistent evidence for fluoride prevention methods due to high risk of bias

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	noncavitated carious lesions?" P80 The treatments were: fluorides in varying vehicles (toothpaste, gel, varnish, mouthrinse, and combination), chlorhexidine alone or in combination with fluoride, resin infiltration, sealants, xylitol in varying vehicles (lozenges, gum, or in combination with fluoride and/or xylitol), casein phosphopeptide amorphous calcium phosphate or in combination with calcium fluoride phosphate. The comparisons were: no treatment, placebo, saline, professional oral hygiene, fluoride toothpaste or mothwash or gel, each other. Two studies included adults.	chlorhexidine, and casein phosphopeptide-amorphous calcium phosphate vehicles alone or in combination with fluoride therapy are very limited in number and in the majority of the cases did not show a statistically significant reduction. Sealants and resin infiltration studies point to a potential consistent benefit in slowing the progression or reversing non-carious cervical lesions." P94 More than half of the trials assessed had moderate to high risk of bias or may be categorised as poor.	Inadequate evidence for non-fluoride preventive methods due to high risk of bias
Chee *et al.* (2012)[118]	"Establish whether simplified adhesives (self-etch) are as clinically effective as conventional adhesives (etch-and-rinse) with multiple application steps for treatment of non-carious cervical lesions in adults (permanent teeth)." P443 The comparisons were: three-step etch-and-rinse; two-step etch-and-rinse; two-step self-etch.	"There was insufficient evidence to make firm recommendations for the use of one adhesive system or bonding strategy over another. The proportion of information obtained from studies with an unclear or high risk of bias was high. The null hypothesis of no difference could not be supported or rejected with the data currently available, using the robust analysis planned. Studies with only one high or unclear risk of bias score found good clinical performance for adhesives with three-step etch-andrinse, two-step etch-and-rinse, two-step self-etch and one step self-etch bonding strategies.There is not enough evidence to support one adhesive or bonding strategy over another for treatment of non-carious cervical lesions." P450	Inadequate evidence for one step adhesives for treating non-carious cervical lesions over other adhesive systems
Mickenautsch and Yengopal (2010)	Identify whether "resin-modified glass-ionomers, in comparison to fluoride-containing composite resin, and composite resin without fluoride, are associated with a more effective reduction of demineralisation in hard tooth tissues under caries challenge." P348 Age and type of teeth not provided.	"The evidence suggests that resin-modified glass-ionomers is associated with a higher reduction of demineralization in adjacent hard tooth tissue than composite resin without fluoride. No difference was found when resin-modified glass-ionomers was compared to fluoride-containing composite resin. Resin-modified glass-ionomers showed efficacy in reducing demineralization." P356 The internal validity of the current evidence is limited as all four in vivo studies had an unclear risk of bias.	Inconsistent evidence for resin-modified glass-ionomers over composite resin with fluoride due to unclear risk of bias Inadequate evidence for resin-modified glass-ionomers over composite resin without fluoride due to unclear risk of bias

Evidence for late treatment of adult caries to minimise or override the need for amalgam

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Schenkel *et al.* (2019)[100] (Cochrane Review)	"Assess the effects of using dental cavity liners in the placement of Class I and Class II resin-based composite posterior restorations in permanent teeth in children and adults compared to no liners." P8 Dental cavity liners, in resin-based composite restorstions, have historically been used to protect the pulp from the toxic effects of some dental restorative materials and to prevent the pain of thermal conductivity by placing an insulating layer between restorative material and the remaining tooth structure.	"There is inconsistent, low-quality evidence regarding the difference in postoperative hypersensitivity subsequent to placing a dental cavity liner under Class I and Class II posterior resin-based composite restorations in permanent posterior teeth in adults or children 15 years or older. Furthermore, no evidence was found to demonstrate a difference in the longevity of restorations placed with or without dental cavity liners."P19 There is no evidence for children under 15 years. All studies were at unclear or high risk of bias.	Inadequate evidence for liners over no liners due to high risk of bias. The authors of this Cochrane review say this evidence though low quality is adequate
Kielbassa *et al.* (2017)[127]	Discuss the outcomes of high-viscosity glass-ionomer cement with a resinous coating in class 1 restorations of posterior primary or permanent teeth compared to amalgam (no studies) or resin composite or other glass-ionomer cements and to critically appraise the methodologies of the various studies. The age of the participants is not provided.	"Within the respective indications and cavity geometries, the high-viscosity glass-ionomer cement with a resinous coating in class 1 restorations of posterior primary or permanent teeth would seem possible, could merge the phase-down of mercury and the objectives of minimally invasive treatment to some extent, and might be a restorative alternative for patients with Class 1 cavities suffering from allergies to or not willing to afford other sophisticated or expensive techniques, such as composite resin. However, the quality of the randomised controlled trials needs improvement and the overall level of evidence is low." P16	Inadequate evidence for high-viscosity glass-ionomer cement with a resinous coating over amalgam, resin composite and other glass-ionomer cements
Dorri *et al.* (2017)[22] (Cochrane Review)	Assess the effects of atraumatic restorative treatment compared to conventional treatment for managing dental caries lesions in the primary and permanent teeth of children and adults.P7 Atraumatic restorative treatment is a minimally invasive approach, which involves removal of decayed tissue using hand instruments alone, usually without use of anaesthesia and electrically-driven equipment, and restoration of the dental cavity with an adhesive material (glass-ionomer cement, composite resins, resin-modified glass-ionomer cement, and compomers).P6	Given the very low quality of the evidence from single studies, the authors are uncertain about atraumatic restorative treatment using resin-modified glass-ionomer cement in the permanent teeth of older adults with root caries lesions over a six-month follow-up period. The authors judged all studies to be at high risk of bias.	Inadequate evidence for atraumatic restorative treatment compared to conventional treatment using resin-modified glass-ionomer cement in the permanent teeth of older adults

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	For the main comparison, atraumatic restorative treatment was compared to conventional treatment using the same material. There were four studies on permanent teeth		
Montedori *et al.* (2016)[101] (Cochrane Review)	"Compare laser-based methods to conventional mechanical methods for removing dental caries in deciduous and permanent teeth [pain, anaesthesia, durability of restoration, pulp damage]." P9 The conventional methods are: handpiece with a bur, chemomechanical system, sono-abrasion system, or air-abrasion system. The population consisted of both children and adolescents in four trials, only adults in four trials, and both children/adolescents and adults in one trial.	"Despite the inclusion of a fair number of studies in this systematic evaluation, only two studies with limited sample size assessed and provided data for the outcome removal of caries. The evidence was limited to either claim or refute a difference between laser and drill treatment for caries removal (low–quality evidence). Four studies that evaluated pain showed that laser treatment may have some advantage in terms of limiting pain in children, adolescents and adults. However, the quality of the evidence was low." P25	Inadequate evidence for laser-based methods over conventional mechanical methods for removing dental caries
Ma *et al.* (2016)[10] (Cochrane Review)	Determine the effects of different materials used for retrograde filling in children and adults permanent teeth for whom retrograde filling is necessary in order to save the tooth. P8 Root canal therapy is a sequence of treatments involving root canal cleaning, shaping, decontamination and obturation. Many materials, such as amalgam, zinc oxide eugenol and mineral trioxide aggregate, intermediate restorative material, super ethoxybenzoic acid cement, dentine-bonded resin composite and glass-ionomer cement are generally used.	There was very little evidence for each comparison. There is weak evidence of little or no difference between mineral trioxide aggregate and intermediate restorative material at the first year of follow-up (quality of evidence: low). Insufficient evidence of a difference between mineral trioxide aggregate and intermediate restorative material on success rate at the second year of follow-up (quality of evidence: very low). All the other outcomes were based on a single study. There is insufficient evidence of any difference between mineral trioxide aggregate and super ethoxybenzoic acid cement at the one-year follow-up (quality of evidence: very low), and only weak evidence indicating there might be a small increase in success rate at the one-year follow - up in favour of intermediate restorative material compared to super ethoxybenzoic acid cement (quality of evidence: very low). There was also insufficient and weak evidence to show that dentine-bonded resin composite might be a better choice for increasing retrograde filling success rate compared to glass-ionomer cement at the oneyear followup (quality of evidence: very low). And there was insufficient evidence of a difference between glass-ionomer cement and amalgam at both the one-year (quality of evidence: very low) and five-year follow-ups (quality of evidence: very low).	Inadequate evidence to support one type of retrograde filling over another

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Brodén *et al.* (2016)[124]	"Evaluate the available evidence on pulp capping procedures compared to root canal treatment in young permanent teeth with vital pulps exposed by caries" P201	"The search failed to disclose any article directly comparing pulp capping and root canal treatment." P205	Inadequate or no evidence for pulp capping procedures compared to root canal treatment
Boruziniat *et al.* (2016)[121]	"Evaluate existing evidence to verify whether an application of flowable composite as a liner provided less microleakage in Class 2 composite restorations", P94 compared to no liner. There was no restriction on age or type of tooth.	The results of this study indicate that flowable composite liners have no significant effect on microleakage of composite restorations. Data of studies were extracted if they were assessed as high or moderate level of evidence. Evaluation of the level of evidence was completed but not reported.	Adequate evidence in favour of not using flowable composite liners
Alqaderi *et al.* (2016)[21]	"Assess the success of coronal pulpotomy treatment to manage carious vital pulp exposure in permanent posterior teeth with closed root apices." P1 Pulp capping with calcium hydroxide, mineral trioxide aggregate or calcium enriched mixture cement; compared to amalgam or composite restoration	Differences in pulp capping and restoration materials did not significantly affect success rates. Two-year weighted mean success rate in the mineral trioxide aggergate and similar products group (92%) *versus* the calcium hydroxide (88%) was not significantly different; the amalgam group (92%) *versus* the composite group (93%) was not different either. The studies' quality and design indicate a low level of evidence.	Inadequate evidence to determine the best method of coronal pulpotomy treatment
Sequeira-Byron, P. *et al.* (2015)[20] (Cochrane Review)	"Assess the effects of restoration of endodontically treated permanent teeth (with or without post and core) by crowns *versus* conventional filling materials" P6	Only one trial met the inclusion criteria and it had a high risk of bias. There was no clear difference between the crown and composite group and the composite only group for non-catastrophic failures of the restoration or failures of the post at three years. The quality of the evidence for these outcomes is very low.	Inadequate evidence for crowns over conventional filling materials. McReynolds and Duane describes the evidence in this review as weak quality.
Schwendicke *et al.* (2015b)[122]	"Comparing antibacterial effects of different liners against each other or no liner." P1299 Treatments were categorised as: calcium hydroxide, mineral trioxide aggregate, antibiotic/disinfectant, calcium phosphates, zinc oxide eugenol, black copper cement, and glass-ionomer cement liners. There was no age limit and any type of teeth could be included.	Based on 11 studies, network meta-analysis found mineral trioxide lining to yield the greatest probability of achieving sterile cavities after a lining/sealing period (73%), followed by antibiotic/disinfectant (8%) and zinc oxide eugenol (7%). Only six studies assessed bacterial reduction after lining/sealing, and zinc oxide eugenol was found to have the highest probability of achieving a bacterial reduction. In both analyses, not providing any lining was found to have low antibacterial effects. Risk of bias was high or unclear. There is insufficient evidence to generally recommend cavity lining or the use of any specific liner based on their antibacterial effects	Inadequate evidence for antibacterial effects of different liners over no liners
Reis *et al.* (2015)[123]	Evaluate "the risk and intensity of postoperative sensitivity in posterior resin composite restorations bonded with self-etch and etch-and-rinse adhesives in permanent dentition (posterior	The overall relative risk of the spontaneous postoperative sensitivity was not different, and also, the stimuli-induced postoperative sensitivity was not different. No overall effect was revealed in the meta-analyses, meaning that no influence of the self-etch or etch-and-rinse adhesives strategy on	Inconclusive evidence for one adhesive over the other

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	restorations) of adult patients." P1053	postoperative sensitivity. The metaanaysis has limited generalisability. Five trials were considered to be "high" risk of bias and eleven were considered to be "unclear" in the key domains, and 13 studies (with 1,010 participants) were low risk of bias and used for meta-analysis.	
Rasines-Alcaraz *et al.* (2014)[9] (Cochrane Review)	Examine "restoration failure of direct composite resin fillings *versus* amalgam fillings for permanent posterior teeth". P7 Resin composites have become an esthetic alternative to amalgam restorations and there has been a remarkable improvement of its mechanical properties to restore posterior teeth. Amalgam has been the traditional material for filling cavities in posterior teeth for the last 150 years and, due to its effectiveness and cost, amalgam is still the restorative material of choice in certain parts of the world. There have been concerns over the use of amalgam restorations (fillings), relating to the mercury release in the body and the environmental impact following its disposal. The exact age of participants was also unclear in some studies; however, both children and adults with permanent teeth at the back of the mouth that required fillings were included.	Two trials were parallel group studies involving 1645 composite restorations and 1365 amalgam restorations (921 children only) in the analysis. The parallel group trials indicated that resin restorations had a significantly higher risk of failure than amalgam restorations (low-quality evidence) and increased risk of secondary caries (low-quality evidence) but no evidence of an increased risk of restoration fracture (moderate-quality evidence). The results from the split-mouth trials (which includes adults) were consistent with those of the parallel group trials. Adverse effects of dental restorations were reported in two trials. The outcomes considered were neurobehavioral function, renal function, psychosocial function, and physical development. The investigators found no difference in adverse effects between composite and amalgam restorations. However, the results should be interpreted with caution as none of the outcomes were reported in more than one trial. "The review found insufficient evidence to support or refute any adverse effects amalgam or composite restorations may have on patients. However, emerging research is highlighting issues around genetic susceptibility to mercury. The decision for a global phase-down of amalgam (Minamata Convention on Mercury) will restrict the future use of amalgam". P18	Adequate evidence that restoration fracture is the same for both amalgam and resin composite Inadequate evidence that resin composite has higher failure rates and secondary caries rates Sarkis-Onofre *et al.* describe the quality of the evidence as high.
Sharif *et al.* (2014)[12] (Cochrane Review)	Evaluate the effects of replacing (with resin composite) *versus* repair (with resin composite) in the management of defective resin composite dental restorations in permanent molar and premolar teeth. P4	No trials met the inclusion criteria	Inadequate evidence as no trials Faggion *et al.* also describes the evidence as inadequate
Ricketts *et al.* (2013)[102] (Cochrane Review)	Assess the effects of stepwise, partial or no dentinal caries removal compared to complete caries removal for the management of dentinal caries in previously unrestored primary and permanent teeth. Both adults and children.	Stepwise and partial excavation reduced the incidence of pulp exposure in symptomless, vital, carious primary as well as permanent teeth. The no dentinal caries removal studies investigating permanent teeth had a similar result with no difference in restoration failure (low to moderate quality evidence).	Adequate evidence in favour of stepwise, partial or no dentinal caries removal over complete removal

Author and year	Primary review focus	Author(s)' conclusion	Evidence Assessment
		Most of the trials were assessed at high risk of bias for blinding of intervention, participants and outcome, although the new trials showed evidence of attempts to minimise bias.	
Pereira-Cenci *et al.* (2013)[125] (Cochrane Review)	"Assess the effects of antibacterial agents incorporated into composite restorations for the prevention of dental caries", P3 compared to composite restorations containing no antibacterial agents. Adults and adolescents in any age group with restorations in the permanent dentition and children with restorations in the primary dentition.	No trials matched the inclusion criteria for this review.	Inadequate or no evidence as no trials met inclusion criteria
Fron Chabouis *et al.* (2013)[126]	Compare "the efficacy of composite and ceramic inlays or onlays in adult permanent teeth" P1210	"The 3-year overall failure risk ratio was in favor of ceramic inlays although not statistically significant." P1217 The authors have very limited evidence that ceramics have a better anatomical form than composite material for inlays in the short term; there was no difference for the three other parameters measured (colour match, occlusal marginal adaptation, or surface finish). However, this result may not be valid in the longterm, and other trials are needed. The authors identified two eligible randomised trials and these exhibited a high-risk of bias.	Inadequate evidence that composite inlays or onlays do not perform as well as ceramic as primary studies had a high risk of bias
Heintze and Rousson (2012)[14]	What is the data on resin composites that are placed without enamel/dentine conditioning in permanent teeth and resin composites placed with self-etching adhesive systems compared to amalgam restorations.	The overall success rate of composite resin restorations was about 90% after 10 years, which was not different from that of amalgam. Restorations with compomers had a significantly lower longevity. The main reason for replacement were bulk fractures and caries adjacent to restorations. Both of these incidents were infrequent in most studies and accounted only for about 6% of all replaced restorations after 10 years. Restorations with macrofilled composites and compomer suffered significantly more loss of anatomical form than restorations with other types of material. Restorations that were placed without enamel acid etching and a dentine bonding agent showed significantly more marginal staining and detectable margins compared to those restorations placed using the enamel-etch or etch-and-rinse technique; restorations with self-etching systems were between the other groups. Restorations with compomer suffered significantly more chippings (repairable fracture) than restorations with other materials, which did not statistically differ among each other. Restorations that	Inadequate evidence as no quality assessment of primary studies. Sarkis-Onofre *et al.* describe the quality of the evidence as critically low.

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		were placed with a rubber-dam showed significantly fewer material fractures that needed replacement, and this also had a significant effect on the overall longevity. The studies do not appear to have had a quality assessment.	
Mickenautsch *et al.* (2010)[128]	Compare the incidence of [secondary] carious lesions at margins of glass-ionomer cement and resin-modified glass-ionomer cement restorations. Two trials included children and two included adults. Both primary and permanent teets were included.	No difference between incidence of [secondary] carious lesions at margins of glass-ionomer cement and resin-modified glass-ionomer cement restorations. This finding was consistent across all datasets. Three of the four trials were at high risk of bias and the fourth scored unclear risk of bias.	Inadequate evidence that resin-modified glass-ionomer cement restorations prevent more secondary caries than other glass-ionomer cements

Evidence for survival and complications of dental interventions

Author and year	Primary review focus	Author(s)' conclusion	Evidence Assessment
Vagropoulou *et al.* (2018)[129]	Identify if different types of indirect restorations (inlay, onlay, and inlay/onlay and crown). used for single permanent anterior, premolar or molar teeth had different biological and technical complications, as well as survival rates. Mainly adults	The mean survival rate of inlays was 90.89% at five years, while for onlays and crowns it was 93.50% and 95.38%, respectively. For the fourth study group, consisting of both inlays and onlays, the survival rate was found to be 99.43%. Statistical analysis demonstrated caries to be the main biological complication for all types of restorations, followed by a root and/or tooth fracture incidence (11.34%) and endodontic incidence. Ceramic fractures represented the most common technical complication, followed by loss of retention and porcelain chipping. 7 of the 9 studies were assessed as high risk of bias and 2 as unclear risk of bias. The overall quality of evidence for the 9 studies was low. Due to the heterogeneity of the included studies no meaningful comparison could be made between types or restoration of materials.	Adequate evidence for survival Inadequate evidence for comparisons between indirect restorations
Abduo and Sambrook (2018)[17]	Evaluate the longevity of ceramic onlays in adults or adolescents (permanent teeth) and identify the factors that influence their survival P194	According to the 12 medium-term studies (2–5 years) the survival rate had a range of 91–100%. The 9 longer term studies (more than 5 years) generally indicated a reduced survival rate (71–98.5%). This review confirms that ceramic onlays have an acceptable medium-term survival and long-term survival. This finding is consistent with other reviews assessing survival of ceramic restorations. "The clinical performance of the ceramic onlay appears acceptable regardless of the follow-up duration." P211 Fracture of the ceramic onlay is the predominant cause of failure, and the most observed form of deterioration was associated with the restoration margin. The most observed form of deterioration was associated with margin integrity and discoloration. The studies' quality scores ranged from 7 to 12/12. A total of 16 studies (76.2%) had a quality rated as high, 3 studies (14.3%) had a quality rating of high-moderate and 2 studies (9.5%) were rated to have a moderate quality.	Adequate evidence for survival of onlays
van de Sande *et al.* (2016)[134]	"Investigate the influence of patient-related factors on restoration survival in posterior permanent teeth as well as to report the methods used to collect these factors." PS8 Participants were aged between 8 and 87 years.	"The assessment of patient factors along with other variables should become part of clinical studies investigating restoration survival, since several of these factors were shown to influence the failure of restorations, regardless of the material type."PS22 "Several studies lacked detailed information regarding the method used to classify patients." PS22 "For caries risk assessment, simplified methods based in caries activity were presented and seem appropriate for use in restoration survival	Inadequate evidence for determinants of survival as primary studies did not include a consistent set of determinants of survival

Author and year	Primary review focus	Author(s)' conclusion	Evidence Assessment
		analysis." PS22 "Few studies were found investigating the role of bruxism/parafunctional habits on restoration survival, and different results were reported." PS22 Primary studies were not quality assessed.	
Morimoto *et al.* (2016)[18]	"Evaluate the survival rate of resin and ceramic inlays, onlays, and overlays to [most likely permanent] and to identify the types of complications associated with the main clinical outcomes." P986	"This meta-analysis indicates that the survival rate of ceramic inlays, onlays, and overlays remains high, irrespective of the follow-up time{over 92% at 5 years and 91% at 10 years] and regardless of the ceramic material, study design, and study setting. Our results indicate that fractures remain the most frequent type of failure. The type of tooth does not seem to affect survival rates, but restorations survived longer on vital teeth." P993 The percentage of bias in the individual studies ranged from 46.1% to 76.9%.	Adequate evidence for survival Inadequate evidence for comparison of direct and indirect methods of restoration
Moraschini *et al.* (2015)[11]	Evaluate the "difference in failure rates between amalgam and composite resin posterior restorations [in permanent teeth]." P1044 No age was specified.	"The results of this review suggest that composite resin restorations in posterior teeth still have less longevity and a higher number of secondary caries when compared to amalgam restorations. In relation to fractures, there was no statistically significant difference between the two restorative materials regarding the time of follow-up." P1049 According to the risk of bias evaluation, all studies were classified as high quality.	Adequate evidence that resin composite has higher failure rates and secondary caries rates. Inconsistent evidence that restoration fracture is the same for both amalgam and resin composite Sarkis-Onofre *et al.* describe the evidence from this study as critically low. Alhareky and Travis assigned a SORT score B which indicates inconsistent or limited quality evidence.
Heintze *et al.* (2015)[133]	Verify whether specific material classes, tooth conditioning methods and operational procedures influence the result for Class III and Class IV composite resin restorations in anterior permanent teeth (of any age persons)	"The failure rate of anterior restorations was relatively low. Class IV restorations showed more fractures than Class III restorations. Class IV restorations with hybrid composites showed less fractures than microfilled composites. The overall performance of hybrid composites was better than that of microfilled composites. There was a consistent decrease in color match independent of the type of material. When the enamel was etched with phosphoric acid, less discoloration at the restorative margins was observed compared to restorations that involved other conditioning systems. Caries adjacent to the restoration was infrequent and not related to any factor evaluated except for the type of isolation: restorations that were placed with a rubber dam showed less caries at the margins than restorations that were placed without a rubber dam which, however, may becaused by additional confounding factors	Inadequate evidence as no quality assessment for primary studies

Author and year	Primary review focus	Author(s)' conclusion	Evidence Assessment
		(staining, etc.).- Bevelling of enamel had no significant influence on the outcome variables except for the anatomical form, which might be a random finding." P493 The studies do not appear to have had a quality assessment.	
Beck *et al.* (2015)[131]	"Review all published studies between 1996 and 2015 on the clinical performance of composite in posterior teeth and to compare the different failure rates and modes to those presented by Brunthaler *et al.* 12 years later." P961	"Significant findings were only observed by including all studies (irrespective of the observation period) and for studies lasting less than five years. The failure rate of composite restorations in posterior teeth increases with longer observation periods {at between 3% and 27% at 5 years and between 3% and 32% at 10 years]. In the study period of 1–4 years the most common reasons for failure reported were fracture, followed by marginal defects and secondary caries. For longer study periods (≥5 years), secondary caries and fracture turned out to be the predominant reasons and were simiarly distributed. Tetric Ceram, Surefil, Filtek Supreme (incl.XT) and Filtek Z250 were the most common composite materials investigated. The use of different materials/compositebrands had no influence on the overall failure rate." P982 There was no quality assessment of the primary studies.	Inadequate evidence no quality assessment for primary studies. Sarkis-Onofre *et al.* describe the quality of the evidence as critically low.
Astvaldsdottir *et al.* (2015)[130]	"Assess systematically the longevity of posterior resin composite restorations in adults" [permanent teeth]. P935 No comparison	The overall incidence rate for all causes of failure was 1.55 lost restorations per 100 restoration years within a four year period. The most common biological reason for failure (a total of 31 restorations) was secondary caries, with or without fracture of the restoration. The quality of the evidence was low.	Inadequate evidence as the quality of the evidence was low. Sarkis-Onofre *et al.* describe the quality of the evidence as critically low.
Opdam *et al.* (2014)[132]	Investigate the influence of patient-, materials-, and tooth-related variables on the survival of posterior resin composite restorations	The conclusion of the present meta-analysis of 12 clinical studies based on raw data is that caries risk and number of restored surfaces play a significant role in restoration survival, and that, on average, posterior resin composite restorations show a good survival, with annual failure rates of 1.8% at 5 years and 2.4% after 10 years of service. P948 Bias is disscussed but not formally assessed. The authors report that "the design of their present study leads to a number of restrictions on its generalisability. For inclusion, retrospective studies and prospective studies were allowed, practice- as well as university-based facilities, to provide a sufficient number of included restorations. However, differences in practice settings, survival criteria, number of included restorations per study, and the fact that 10 of the 12 studies were delivered by only 3 research groups lead to possible	Inadequate evidence as limited generalisability. Sarkis-Onofre *et al.* describe the quality of the evidence as critically low.

Author and year	Primary review focus	Author(s)' conclusion	Evidence Assessment
		bias." P946 Therefore, the authors want to make clear that this is not the ultimate degree of evidence for considering the longevity of posterior resin composites, which might be suggested from its meta-analytic design.	


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