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Screening and Interventions to Prevent Dental Caries in Children Younger Than Age Five Years: A Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: In 2014, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to assess the benefits and harms of screening for dental caries, but recommended that primary care clinicians prescribe oral fluoride supplementation to preschool children starting at age 6 months whose primary water source is deficient in fluoride and apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption.

Purpose: To systematically review the current evidence on primary care screening for and prevention of dental caries in children younger than 5 years old.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through April, 2021), and MEDLINE (2013 to April, 2021); with surveillance through July 23, 2021, and manually reviewed reference lists.

Study Selection: Randomized controlled trials (RCTs) and controlled observational studies on benefits and harms of screening versus no screening and referral to dental care from primary care versus no referral; studies on the diagnostic accuracy of oral examination and risk assessment by primary care clinicians; RCTs on benefits and harms of oral health education and preventive interventions; and systematic reviews on risk of fluorosis associated with early childhood ingestion of dietary fluoride supplements.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): Thirty-three studies (reported in 36 publications) were included in this update (19 RCTs, four non-randomized trials, nine observational studies, and one systematic review [19 studies]). Seventeen studies were newly identified as part of this update and 16 studies (including the systematic review) were carried forward from the previous review. No randomized trial or observational study compared clinical outcomes between children younger than 5 years of age screened and not screened by primary care clinicians for dental caries. One good-quality cohort study (n=258) found primary care pediatrician examination following 2 hours of training associated with a sensitivity of 0.76 (95% confidence interval [CI], 0.55 to 0.91) for identifying a child with one or more cavities and 0.63 (95% CI, 0.42 to 0.81) for identifying children younger than 36 months of age in need of a dental referral, compared with a pediatric dentist evaluation. One study (n=697) found a novel risk assessment tool administered by home visitor nurses associated with suboptimal accuracy for predicting future caries in children 1 year of age. The prior USPSTF review found oral fluoride supplementation associated with reduced caries incidence versus no supplementation in children younger than 5 years of age in settings with inadequate water fluoridation, though only one trial was randomized; we identified no new trials. The prior USPSTF review included a systematic review of observational studies which found an association between early childhood ingestion of systemic fluoride and enamel fluorosis. Topical fluoride (all trials except for one evaluated varnish) associated with decreased caries increment (13 trials in updated meta-analysis, N=5733, mean difference in decayed, missing, and filled teeth or surfaces -0.94, 95% CI, -1.74 to -0.34) and decreased likelihood of incident caries (12 trials, N=8177, RR 0.80, 95% CI, 0.66 to 0.95; absolute risk difference -7%, 95% CI, -12% to -2%) versus placebo or no varnish, with no increase in risk of fluorosis or other adverse events. Almost all trials of topical fluoride were conducted in higher risk populations or settings. Evidence on other preventive interventions was limited (xylitol) or unavailable (silver diamine fluoride). Evidence on educational or counseling interventions is very sparse and no studies directly evaluated the effectiveness of primary care referral to a dentist versus no referral.

Limitations: Only English-language articles were included. Graphical methods were not used to assess for publication bias, due to diversity in populations, settings, and outcomes, and substantial statistical heterogeneity. Statistical heterogeneity was present in pooled analyses of fluoride varnish and not explained by stratification on a variety of factors. Studies conducted in resource-poor settings may be of limited applicability to screening in the United States. Most studies had methodological limitations.

Conclusions: Dietary fluoride supplementation and fluoride varnish appear to be effective at preventing caries outcomes in higher risk children younger than 5 years of age. Dietary fluoride supplementation in early childhood is associated with risk of enamel fluorosis, which is usually not severe. More research is needed to understand the accuracy of oral health examination and caries risk assessment by primary care clinicians, primary care referral for dental care, and effective parental and caregiver/guardian educational and counseling interventions.

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Chapter 1. Introduction and Background

Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2014 recommendation on the prevention of dental caries in children younger than 5 years of age.[1] In 2014, the USPSTF recommended that primary care clinicians prescribe oral fluoride supplementation starting at age 6 months for children whose water supply is deficient in fluoride (B recommendation) and that primary care clinicians apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption (B recommendation).[2] The recommendation was based on evidence from randomized trials that fluoride varnish is more effective than placebo or no varnish in preventing caries, and evidence previously reviewed by the USPSTF on the effectiveness of oral fluoride.[3,4] The USPSTF found insufficient evidence to assess the balance of benefits and harms of routine screening examinations for dental caries performed by primary care clinicians in children younger than 5 years of age (I statement). The 2014 recommendation expanded on the 2004 USPSTF recommendation, which also recommended fluoride supplementation and found insufficient evidence on screening by primary care clinicians, but did not address use of fluoride varnish.[5]

Condition Background

Condition Definition

Dental caries, or tooth decay, is a common chronic disease that can cause pain and diminished function and quality of life throughout one's lifespan.[6] Caries lesions form in teeth through a complex interaction among cariogenic, acid-producing bacteria in combination with fermentable carbohydrates and other dietary, genetic, behavioral, social, and cultural factors.[7-9]

Children are susceptible to caries as soon as the first teeth appear, which usually occurs at about 6 months of age. Early childhood caries is defined as the presence of one or more decayed (noncavitated or cavitated), missing (due to caries), or filled tooth surfaces in any primary tooth in a preschool-age child between birth and 71 months of age.[10] Early childhood caries is often measured using the dmfs index for decayed, missing, or filled primary tooth surfaces, and dmft for decayed, missing, or filled primary teeth. In a particular child, the number of dmfs can be higher than the number of dmft because one tooth may have more than one affected surface. Over the years the dental research and practice communities have developed and used different dental caries classification systems to describe the degree of decay, such as describing the progression of decay through the tooth tissues from the dentin to the pulp (d_1-d_4 lesions), the International Caries Detection and Assessment System (ICDAS)[11] and the American Dental Association Caries Classification System.[12] The American Dental Association Council on Scientific Affairs has published a comparative overview of these classifications.[11]

Prevalence and Burden of Disease/Illness

Dental caries is the most common chronic disease of children in the United States.[13,14] The National Health and Nutrition Examination Study (NHANES) found that among 2 to 5 year olds, the prevalence of dental caries in primary teeth increased from approximately 24 percent between 1988 to 1994 to 28 percent between 1999 to 2004, with a subsequent decrease in caries prevalence to approximately 23 percent in 2011 to 2016.[6,15,16] In 2011 to 2016, approximately 10 percent of children 2 to 5 years of age had untreated dental caries and in 2011 to 2014, approximately 4.6 percent had severe caries (defined as 3 or more decayed surfaces).

Dental caries disproportionately affects minority and economically disadvantaged children. NHANES data indicate that in 2011 to 2016, the prevalence of caries in children 2 to 5 years of age was 34 percent in those living in households below the federal poverty guidelines, compared with 16 percent in children from households at 200 percent or greater of the federal poverty guidelines; the proportion with untreated caries was 17 percent versus 6.02 percent.[6] The prevalence of caries among children aged 2 to 5 years was higher in Mexican American children (33%) and black non-Hispanic children (28%) than white non-Hispanic children (18%). Dental caries were also more likely to be untreated in black non-Hispanic (15%) and Mexican American (15%) than white non-Hispanic children (6.7%).[15]

Early childhood caries is associated with pain and loss of teeth, as well as impaired growth, decreased weight gain, and negative effects on quality of life.[7,17] Filling placement or extractions of carious teeth can be traumatic experiences for young children, and occasionally result in serious complications. Early childhood caries is also associated with failure to thrive and can affect appearance, self-esteem, speech, and school performance, and is associated with future caries in both the primary and permanent dentitions.[18] A systematic review found poor oral health associated with significantly increased risk of poor academic performance (pooled odds ratio [OR] 1.5, 95% confidence interval [CI], 1.20 to 1.83) and school absenteeism (pooled OR 1.43, 95% CI, 1.24 to 1.63).[19] Premature loss of primary molars due to early childhood caries can result in loss of arch space, leading to crowding of the permanent teeth, affecting esthetics and potentially requiring orthodontic correction.[7] In 2000, the U.S. Surgeon General estimated that over 50 million school hours are lost each year nationally due to dental related concerns.[14] In the state of North Carolina, a study based on 2008 data estimated that more than 4 million school hours are lost each year due to poor oral health status, with over 700,000 of these hours lost due to dental pain or infection.[19]

Etiology and Natural History

Dental caries is a disease process during which various strains of bacteria colonize the tooth surface and metabolize dietary carbohydrates (especially refined sugars) to produce lactic and other acids, resulting in demineralization of teeth.[7,20] In children ages 12 to 30 months, caries typically initially affects the maxillary primary incisors and first primary molars, reflecting the pattern of eruption. Dental caries first manifests as white spot lesions, which are small areas of demineralization under the enamel surface. At this stage, the caries lesion is usually reversible, if appropriate preventive action is taken (e.g., change in dietary behaviors or application of fluoride varnish). If oral conditions do not improve, demineralization progresses, and eventually results in irreversible cavities, with a loss of the normal tooth shape and contour. Continued progression of the caries process leads to pulpitis (inflammation due to bacterial infection of the dental pulp, or soft tissue in the center of a tooth) and tooth loss, and can be associated with complications such as facial cellulitis and systemic infections.[20,21]

Risk Factors

Risk factors for dental caries in young children are multifactorial comprising biological as well as non-biological factors/social determinants of health. Biological factors include high levels of cariogenic bacterial colonization, low saliva flow rates, developmental defects of tooth enamel, and high maternal levels of cariogenic bacteria. Non-biological/social determinants of health factors include, frequent exposure to dietary sugar and refined carbohydrates, inappropriate bottle feeding (e.g., child put to sleep with a bottle containing something other than water), low socioeconomic status, previous caries, maternal caries, , and poor maternal oral hygiene.[20,22] Other risk factors include lack of access to dental care, low community water fluoride levels, inadequate tooth brushing/use of fluoride-containing toothpastes, and lack of parental knowledge regarding oral health.[14]

Rationale for Screening/Screening Strategies

Screening for dental caries and caries risk factors in young children prior to school entry could identify caries lesions at an earlier and reversible stage and lead to interventions to treat existing caries lesions, prevent progression of caries lesions, and reduce incidence of future lesions, including lesions in the permanent dentition. Screening strategies typically include oral health risk assessment and visual examination to identify high-risk children, including those already with caries. Primary care clinicians can play an important role in screening for dental caries because many young children routinely see a primary care clinician starting shortly after birth, but do not see a dental health care professional until they are older.[23] Approximately three-quarters of children under 6 years of age did not have even one visit to a dental health care professional in the previous year, though the proportion with a visit increased from 21 percent in 1996 to 25 percent in 2004.[24] Access to dental care is impacted by many factors, including social determinants of health and shortages in dental health care professionals treating young children, particularly for children who are not insured or who are publicly insured.[25] Once children enter school, there are additional opportunities for screening and treatment.[26]

Preventive Interventions

In young children at risk for dental caries, interventions to prevent development of caries lesions focus on reducing the burden of bacteria, reducing the intake of refined sugars, and increasing the resistance of teeth to caries development.[7,22] Strategies to reduce the burden of bacteria include the use of fluoride, parental counseling to improve oral hygiene, xylitol, and topical antimicrobials such as chlorhexidine or povidone-iodine.[3,4] Educational and behavioral interventions can also address reduced intake of refined sugars through changes in diet and feeding practices. Children with caries or at risk of caries can also be referred for needed dental care.

Use of fluorides primarily focuses on promoting remineralization of the enamel. Fluoride exposure can be topical (fluoride dentifrices, rinses, gels, foams, varnishes) or systemic (dietary fluoride supplements).[7,22] Fluoridated water has topical as well as systemic effects. The main effect, however, is now believed to be topical. Fluoride is incorporated into the biofilm (dental plaque), saliva and tooth enamel and increases tooth resistance to acid decay, acts as a reservoir for remineralization of caries lesions, and inhibits cariogenic bacteria.[7,21] A potential harm of excessive systemic fluoride exposure is enamel fluorosis, a visible change in enamel opacity due to altered mineralization. The severity of enamel fluorosis depends on the dose, duration and timing of fluoride intake, and is most strongly associated with cumulative intake during enamel development; risk of fluorosis is related to exposure from birth to 6 to 8 years of age, though children are most susceptible between 15 to 30 months of age.[27,28] Mild fluorosis manifests as small opaque white streaks or specks in the tooth enamel.[29] Severe fluorosis results in discoloration and pitted or rough enamel.[21] In 1999 to 2004, the prevalence of severe enamel fluorosis in the United States was estimated at less than 1 percent.[29,30]

Topical fluoride is typically applied as a varnish with a small brush in young children. Unlike fluoride gels, which are more commonly used in older, school-aged children, fluoride varnish does not require specialized dental devices or equipment and can be applied quickly by both dental professional and non-dental health professionals in a variety of settings without the risk of the child swallowing large amounts, which can cause transient gastric irritation.[7,31] Compared with other topical fluoride application methods (such as acidulated phosphate fluoride or sodium fluoride gel), systemic exposure to fluoride is low following application of fluoride varnish.[32,33] The varnish results in prolonged contact time between the fluoride and the tooth surface, which maintains a higher level of the calcium fluoride in the biofilm; later the released fluoride promotes remineralization. Fluoride varnish is typically available in the United States as 5 percent sodium fluoride (2.26% F). Fluoride varnish is cleared for marketing by the U.S. Food and Drug Administration (FDA) as a cavity liner and tooth desensitizer; its use for prevention of caries is off-label.[34]

Silver diamine fluoride (SDF) is a topical medication that is noninvasive, relatively inexpensive, and easy to apply.[35] The most common concentration is 38 percent, though it has been evaluated in 10 percent to 38 percent formulations. SDF was cleared for marketing by the FDA in 2014 as a desensitizing agent in adults, similar to fluoride varnish 20 years earlier;[36] it has long been used in other parts of the world to arrest progression of existing caries lesions and avoid restorative treatment. SDF works by the combined effects of silver and fluoride on promoting remineralization, as a short-term germicide, and inhibits enzymes involved in collagen degradation, all of which result in an arrest of the carious process;[35,37] SDF is also being evaluated for preventing future caries in school-age children.[38,39] A potential disadvantage of SDF is cosmetic concerns, due to the permanent dark discoloration of active caries lesions by the silver component. However, SDF will not discolor healthy enamel, caries lesions themselves cause discoloration, and in young children discoloration would impact primary (non-permanent) teeth. Based on its potential as a caries treatment, SDF has been granted “breakthrough therapy” designation by the FDA, providing the opportunity for expedited approval for this indication, and a number of clinical trials of SDF for treating caries are in progress.

Xylitol is a naturally occurring sugar that cannot be metabolized by the oral microflora and thus has the potential to reduce levels of caries-forming mutans streptococci in the plaque and saliva.[40] In young children, xylitol can be administered as a syrup or topically via wipes. In older children, xylitol can also be administered in gum, lozenges, or snack foods. FDA allows foods (including chewing gums) that contain xylitol to make the following statement: “Xylitol may reduce the risk of tooth decay”.[41] Other topical antimicrobials such as chlorhexidine varnish or gel and povidone-iodine rinses are not commonly used in the United States in young children or are not available, as in the case of chlorhexidine varnish. Neither chlorhexidine nor povidone iodine has been approved by FDA to be used for caries reduction or prevention.[42]

Current Clinical Practice/Recommendations of Other Groups

Since the publication of the Surgeon General's Report on Oral Health in 2000,[14] many organizations (see below) have emphasized the importance of preventive oral health care for young children, particularly in the primary care setting. The American Academy of Pediatrics (AAP) has developed an oral health risk assessment tool for use in primary care settings starting at the 6 month visit, along with suggested interventions for children at risk.[43] The American Academy of Pediatric Dentistry (AAPD) developed the Caries-risk Assessment Tool (CAT), designed for use by dental and non-dental personnel.[44] Although the vast majority of pediatricians agree with recommendations on oral health screening, only about half report examining the teeth of more than half of their 0 to 3 year old patients, and few (4%) reported regularly applying fluoride varnish.[25] Data on rates of SDF use in primary care settings are not available.

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[45] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created two analytic frameworks with the key questions and the patient populations, interventions, and outcomes reviewed (**Figures 1 and 2**). Screening and preventive interventions were addressed in a single analytic framework in the prior USPSTF review. For this update, screening and preventive interventions have been split into separate analytic frameworks to more clearly distinguish treatment of children with existing caries identified on screening (screening analytic framework) from treatment of children without caries to prevent the development of future caries (interventions to prevent dental caries analytic framework).

Key Questions

Screening for Dental Caries in Children Younger Than Age 5 Years

1. How effective is oral screening (including risk assessment) performed by a primary care clinician in preventing dental caries in children younger than age 5 years?
2. How accurate is screening performed by a primary care clinician in identifying children younger than age 5 years who:
   a. Have cavitated or noncavitated caries lesions?
   b. Are at increased risk for future dental caries?
3. What are the harms of oral health screening performed by a primary care clinician in children younger than age 5 years?

Interventions to Prevent Dental Caries in Children Younger Than Age 5 Years

1. How accurate is screening performed by a primary care clinician in identifying children younger than age 5 years who are at increased risk of future dental caries*?
2. How effective is parental or caregiver/guardian oral health education provided by a primary care clinician in preventing dental caries in children younger than age 5 years?
3. How effective is referral by a primary care clinician to a dental health care professional in preventing dental caries in children younger than age 5 years?
4. How effective are preventive interventions (dietary fluoride supplementation, topical fluoride application, silver diamine fluoride, or xylitol) in preventing dental caries in children younger than age 5 years?
5. What are the harms of specific oral health interventions to prevent dental caries in children younger than age 5 years (parental or caregiver/guardian oral health education, referral to a dental health care professional, and preventive interventions)?

*This is the same question as Screening Key Question 2b.

Contextual Question

One Contextual Question was also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology.

1. How effective is silver diamine fluoride in preventing dental caries in children age 5 years or older?

Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through April, 2021), and Ovid MEDLINE (2013 through April, 2021) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles. Ongoing surveillance was conducted to identify major studies published since April 2021 that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on July 23, 2021 and identified no studies affecting review conclusions.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix A2**). Articles were selected for full review if they were about dental caries in preschool children (younger than 5 years old), were relevant to a key question, and met the pre-defined inclusion criteria. We restricted inclusion to English-language articles and excluded studies only published as abstracts. Studies of non-human subjects were also excluded, and studies had to report original data. We included an update[46] to a systematic review[28] included in the prior USPSTF report on risk of fluorosis; otherwise, inclusion was restricted to primary studies and systematic reviews were used as source of potentially eligible studies.

For all key questions, we included studies of children younger than 5 years of age, including those with dental caries at baseline. We focused on studies of screening or diagnostic accuracy performed in primary care settings for identifying caries or children at increased risk of caries. For preventive treatments, we included studies of primary care feasible treatments (not requiring extensive dental specific training) administered in primary care or non-primary care settings (e.g., daycare or preschool), but noted the setting and whether the treatment was administered by persons with dental training. Interventions were parental or caregiver education, referral to a dentist by a primary care clinician, and preventive treatments including dietary fluoride supplementation, topical fluoride application (varnish, foam, or gel), xylitol, and SDF; the comparison for each was no intervention or placebo. Antimicrobial rinses and antimicrobial varnishes, which were included in the prior USPSTF review, were not included in this update because they are not widely used in children or not available in the United States. Outcomes were decreased incidence of dental caries, morbidity, quality of life, function, and associated harms, including dental fluorosis. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists the included studies, and **Appendix A5** lists the excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we created data abstraction forms to summarize characteristics of study populations, interventions, comparators, outcomes, study designs, settings (including human development index classification, preschool or daycare, and community fluoridation level) and methods. One investigator conducted data abstraction, which was reviewed for completeness and accuracy by another team member.

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies by using criteria developed by the USPSTF; studies were rated as "good," "fair," or "poor" per USPSTF criteria, depending on the seriousness of the methodological shortcomings (**Appendix A6**).[45] For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus.

Data Synthesis

We performed a random effects meta-analysis using the profile likelihood model to summarize the effects of topical fluoride versus placebo or no fluoride on likelihood of developing caries (dichotomous outcome) or caries burden (continuous outcome, measured based on the number of decayed, missing, or filled teeth [dmft] or surfaces [dmfs]). Effects on caries burden were based on mean difference in followup caries index if available; otherwise difference in change from baseline caries index (caries increment) was used. Adjusted differences were utilized when reported. For caries burden, we used dmfs when available and otherwise used dmft. Data for dentin caries were used if available; otherwise data for any (enamel or dentin) caries were used. We combined arms of comparable interventions within the same study in the primary analysis, so each study was represented once in a meta-analysis, in order to avoid overweighting. For cluster randomized trials, we used treatment differences that accounted for the intracluster correlation, if reported. Otherwise, we corrected for clustering using the intracluster correlation by calculating the design effect and the effective sample sizes before combining with individually randomized trials. If the intracluster correlation was not reported, we imputed it based on the intracluster correlation reported in the other cluster trials. We conducted prespecified study-level subgroup analyses on the following factors: use of cluster design (yes or no), varnish frequency (every 4, 6, or 12 months), trial conducted in very high human development index (HDI) setting (yes or no, based on a United Nations Development Programme HDI score of 0.800 or higher for the country or geographic setting), trial conducted in preschool or daycare setting (yes or no), high-risk population (yes or no; high-risk defined as high baseline caries, high community caries burden, low socioeconomic status, or low rates of oral health behaviors [e.g., brushing with fluoridated toothpaste]), mean age (<2 vs. ≥2 years), enrollment restricted to caries-free children at baseline (yes or no), adequate water fluoridation (yes or no; adequate fluoridation defined as ≥0.7 parts per million [ppm] F), use of additional oral health measures (yes or no; additional oral health measures defined as education and/or provision of toothbrush and toothpaste), followup duration (1 vs. <1 year), and risk of bias (fair vs. good). We also conducted a sensitivity analysis excluding a trial[47] that used acidulated phosphate fluoride foam instead of fluoride varnish.

For all meta-analyses, statistical heterogeneity was assessed using the Cochran Q-test and I^2 statistic.[48] All meta-analyses were conducted using Stata/SE 16.1 (StataCorp, College Station, TX).

For all key questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[45] Evidence was rated "good", "fair", or "poor" based on study quality, consistency of results between studies, precision of estimates, study limitations, risk of reporting bias, and applicability.[45]

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and USPSTF members participated in developing the scope of the work and reviewed draft reports, but the authors are solely responsible for the content.

Expert Review and Public Comment

The draft Research Plan was posted for public comment on the USPSTF website from September 19 to October 16, 2019. The comments were reviewed and the Research Plan was revised by adding a footnote to clarify that in the screening analytic framework interventions are provided to children found to have caries on screening and in the prevention analytic framework interventions are provided to children without caries; changed "dentist" to "dental health care professional"; and revised the exclusion criteria to clarify that dental clinics providing interventions not available in primary care clinics are excluded from the review (interventions that can be provided in primary care practices are included even if they were administered in other settings). Also, the Research Plan was revised to clarify that information regarding the skill level or training of primary care clinicians participating in studies of screening and preventive interventions would be abstracted, and effects of skill level/training on effectiveness analyzed (data permitting).

A draft version of this report has been reviewed by content experts and representatives of Federal partners (**Appendix A7**), USPSTF members, and AHRQ Project Officers, and edits were made for clarity. The draft report was posted for public comment from May 11 to June 7, 2021, and minor edits were made for clarity, prior to finalization.

Chapter 3. Results

A total of 2674 new references from electronic database searches and manual searches of recently published studies were reviewed and 368 full-text papers were evaluated for inclusion. We included a total of 33 studies (reported in 36 publications). Seventeen trials were newly identified as part of this update and 16 studies (in 17 publications) were carried forward from the previous review. We excluded 16 studies (in 17 publications) that were included in the prior review; one was excluded for not being an included preventive intervention,[49] two for including children 5 years and older,[50,51] two for treatment of existing caries,[52,53] four for comparing active interventions,[54-57] and eight for being poor-quality.[58-65] Included studies and quality ratings are described in **Appendix B**.

Screening for Dental Caries in Children Younger Than Age 5 Years

Key Question 1. How Effective Is Oral Screening (Including Risk Assessment) Performed by a Primary Care Clinician in Preventing Dental Caries in Children Younger Than Age 5 Years?

No study compared clinical outcomes between children younger than 5 years of age screened and not screened by primary care clinicians.

Key Question 2a. How Accurate Is Screening Performed by a Primary Care Clinician in Identifying Children Younger Than Age 5 Years Who Have Cavitated or Noncavitated Caries Lesions?

Summary

- One study (n=258) included in the prior USPSTF review found a pediatrician oral examination of children younger than 36 months of age associated with a sensitivity of 0.76 and specificity of 0.95 for identifying a child with one or more cavities, a sensitivity of 0.49 and specificity of 0.99 for identifying a tooth with a cavity, and a sensitivity of 0.63 and specificity of 0.98 for identifying children in need of a dental referral, compared with a pediatric dentist evaluation.
- One study included in the prior USPSTF review found a pediatrician oral health examination of children 18 to 36 months of age associated with a sensitivity of 1.0 and specificity of 0.87 for identifying nursing caries (n=61) compared with a pediatric dentist examination.
- No new studies on the accuracy of screening performed by a primary care clinician for identifying children younger than 5 years of age were identified.

Evidence

The prior USPSTF review included two studies on the accuracy of screening by a primary care clinician for identifying children with cavitated or noncavitated caries lesions (**Appendix B1**). In both studies, screening was based on examination of the dentition for caries lesions. One good-quality study (n=258) evaluated the accuracy of caries screening of children younger than 36 months of age by primary care pediatricians following 2 hours of oral health education.[66] The study enrolled Medicaid-eligible children (9.7% with a cavity, mean 0.3 cavities/child) attending a private pediatric group practice in North Carolina. Compared with a pediatric dentist evaluation, it found a pediatrician oral examination associated with sensitivity of 0.76 (95% CI, 0.55 to 0.91) and specificity of 0.95 (95% CI, 0.92 to 0.98) for identifying a child with one or more cavities, a sensitivity of 0.49 (95% CI, 0.37 to 0.60) and specificity of 0.99 (95% CI, 0.99 to 0.99) for identifying a tooth with a cavity, and a sensitivity of 0.63 (95% CI, 0.42 to 0.81) and specificity of 0.98 (95% CI, 0.95 to 0.99) for identifying children in need of a dental referral. The need for referral was based on the presence of a cavity, soft tissue pathology, or evidence of tooth or mouth trauma. A fair-quality study found a pediatrician oral health exam of children 18 to 36 months of age following 4 hours of training associated with a sensitivity of 1.0 and specificity of 0.87 for identifying nursing caries compared with a pediatric dentist exam (n=61, CIs not reported and could not be calculated).[67] The number of true positives, true negatives, false positives, and false negatives were not reported and could not be calculated. Nursing caries were defined as caries involving one or more of the maxillary central or lateral incisors of the primary molars, but excluding the mandibular incisors. Methodological limitations of this study were unclear application of the reference standard to all patients and unclear inclusion of all patients in the analysis (**Appendix B2**).

No new study evaluated the accuracy of primary care clinician screening for carious lesions in children younger than 5 years of age.

Key Question 2b. How Accurate Is Screening Performed by a Primary Care Clinician in Identifying Children Younger Than Age 5 Years Who Are at Increased Risk for Future Dental Caries?

Summary

- One new study found a novel caries risk assessment tool administered by health visitor nurses in children 1 year of age associated with sensitivity of 0.53 and specificity of 0.77 (n=697) for predicting any $d_3$mft lesion at age 4 years and sensitivity of 0.65 and specificity of 0.69 (n=784) for predicting presence of three or more $d_3$mft lesions.

Evidence

One new study (n=1681) reported on the development and testing of a novel caries risk assessment tool (Dundee Caries Risk Assessment Model) administered by health visitors (registered nurses of midwives in Scotland with Masters level training who provide services to families with young children by visiting them in their homes) (**Appendix B1**).[68] The cohort consisted of all children born and resident in Dundee, Scotland in one calendar year. The study examined 56 potential risk factors evaluated at age 1 year for prediction of caries at age 4 years, using a prediction tree-based analysis. The prevalence of any d_1 (enamel or dentin) caries at baseline was 3 percent and the prevalence of any d_3 (enamel of dentin) caries was 0.4 percent. At 4 years, the respective prevalence were 49 and 33 percent. Separate models were developed for prediction of any or at least three d_1 or d_3 caries. The final models included two to five risk factors, including health visitor assessment of risk, socioeconomic status, parental smoking status, being breast fed, use of a pacifier, housing type, use of vitamins, and food or drink intake at night. For predicting presence of any $d_3$mft lesion at age 4 years, the sensitivity of the model was 0.53 and specificity 0.77 (n=697, CIs not reported), based on three risk factors (health visitor assessment of risk, parental smoking, and food or drinks at night). For predicting presence of at least three $d_3$mft lesions at age 4 years, the sensitivity of the model was 0.65 and specificity was 0.69 (n=784, CIs not reported), based on three risk factors (type of housing, health visitor assessment of risk, and use of vitamins). Results were similar for prediction of any or at least three $d_1$mft lesions. The study was rated fair-quality because it was unclear if the reference standard was assessed independent from the screening test and the risk factors selected for the models were not predefined (**Appendix B2**). We identified no study with independent validation of the Dundee Caries Risk Assessment Model.

Key Question 3. What Are the Harms of Oral Health Screening Performed by a Primary Care Clinician in Children Younger Than Age 5 Years?

No study reported harms of children younger than 5 years of age screened and not screened by primary care clinicians.

Interventions to Prevent Dental Caries in Children Younger Than Age 5 Years

Key Question 1. How Accurate Is Screening Performed by a Primary Care Clinician in Identifying Children Younger Than Age 5 Years Who Are at Increased Risk of Future Dental Caries?

See Key Question 2b for Screening for Dental Caries in Children Younger Than Age 5 Years, which addresses the same question.

Key Question 2. How Effective Is Parental or Caregiver/Guardian Oral Health Education Provided by a Primary Care Clinician in Preventing Dental Caries in Children Younger Than Age 5 Years?

Summary

- The prior USPSTF review included two trials on effects of oral health education in preventing dental caries; however, the trials were rated poor-quality (not truly randomized) and not carried forward in the current review.
- One new fair-quality trial (n=104) found oral health education for mothers of caries-free children 12 to 36 months of age associated with reduced risk of incident dental caries versus usual care at 6 months (13.5% vs. 34.7%, RR 0.39, 95% CI, 0.18 to 0.85).

Evidence

The 2014 USPSTF review[3,4] included two trials (in 3 publications) of multicomponent health interventions that included an oral health education component targeted at medically underserved children younger than 5 years.[58,59,62] Both trials found the intervention associated with decreased caries incidence at 1 to 4 years. However, both trials were rated poor-quality and were not carried forward in the current review. Neither trial was truly randomized; both utilized cluster allocation, but there were only two clusters. In addition, one of the trials had high attrition and did not adjust for confounders.[58,59]

One new, randomized trial conducted in Ahvaz, Iran (fluoride level in drinking water 0.31 to 0.51 ppm)[69] compared provision of oral health education to mothers (n=104) of children age 12 to 36 months versus usual care without specific oral health education (**Appendix B3**).[70] Children (mean age 18 months) were caries-free at the time of enrollment, with at least eight erupted teeth. The oral health education was delivered by a dental student at a well-child visit and included an oral health pamphlet, a brief individual session, a group session, and text message reminders every 2 weeks for 6 months. Dental health behaviors were not reported at baseline or followup. The study was open-label and rated fair-quality (**Appendix B4**).

At 6 months, oral health education was associated with decreased incidence of dental caries based on World Health Organization criteria (including white spot lesions noncavitated and categorized as D1) versus usual care (13.5% [7/52] vs. 34.7% [17/49]; risk ratio [RR] 0.39, 95% CI, 0.18 to 0.85). Harms were not reported.

Key Question 3. How Effective Is Referral by a Primary Care Clinician to a Dental Health Care Professional in Preventing Dental Caries in Children Younger Than Age 5 Years?

Summary

- No study directly evaluated the effects of referral by a primary care clinician to a dentist on caries incidence.
- Four new additional observational studies (N=61,194) of children enrolled in Medicaid found receiving a preventive dental visit from a dentist versus primary care clinician associated with increased likelihood of subsequent caries-related treatment, though findings are susceptible to confounding by indication. The studies were not designed to determine the referral source or effects of dental referral from primary care versus no referral.
- One study included in the prior USPSTF review (n=19,888) and one additional study (n=11,394) of children enrolled in Medicaid found an earlier (versus later) first preventive dental visit associated with no difference in subsequent dental procedures among treatment in children without caries at baseline; an earlier visit was associated with higher caries burden when assessed in kindergarten, but lower likelihood of untreated caries.

Evidence

No study directly evaluated referral of children younger than 5 years of age by a primary care clinician to a dental care professional versus no referral and effects on caries incidence or other dental outcomes. One retrospective cohort study included in the prior USPSTF report (n=19,888)[71] and five subsequent retrospective cohort studies (N=72,588)[72-76] evaluated outcomes associated with earlier versus later timing of preventive visits or primary care clinician versus dental provision of preventive dental visits (**Appendix B5**). All of the studies were conducted in Medicaid populations in North Carolina or Alabama; populations overlapped for studies conducted in the same state. The studies did not directly address the key question because they were not designed to determine the referral source or effects of dental referral from primary care versus no referral. In addition, although all studies controlled for confounders (including demographic factors, socioeconomic factors, and risk factors for caries), findings are susceptible to confounding by indication related to the need for dental services. All studies were rated fair-quality (**Appendix B6**).

Two new studies compared children enrolled in North Carolina Medicaid who had preventive oral health visits from a primary care clinician versus a dentist (**Appendix B5**).[74,75] In both analyses, children who received oral health visits from a primary care clinician were less likely to receive caries-related treatment compared with those who received oral health visits from a dentist, likely because those who saw a dentist had greater dental health needs. In the larger study (n=41,453), the likelihood of receiving any caries-related treatment between 3 to 5 years of age was 26.7 percent among children who received preventive oral health visits from a primary care clinician, 51.8 percent among children who received preventive oral health visits from a dentist, and 47.6 percent among children who received preventive health visits from both.[74] However, among children at risk for caries, another analysis (n=5235) found receiving preventive health visits from a primary care clinician associated with higher likelihood of untreated decayed teeth than receiving preventive health visits from a dentist (OR 2.05, 95% CI, 1.28 to 3.30).[75]

Two new studies conducted among children enrolled in Alabama Medicaid reported similar results (**Appendix B5**).[73,76] One study (n=9732) found children who had at least one preventive dental visit by a dentist were more likely to receive any caries-related treatment (20.6% vs. 11.3%, $p<0.001$) than those without a preventive dental visit.[73] In the other study, children with at least one preventive dental visit by a dentist had more restorative dental visits (difference 11.1%, $p<0.05$) and emergency dental visits (difference 1.9%, $p<0.05$) than those without a preventive visit.[76]

Two studies compared children with a first earlier versus later preventive dental visit. A study included in the prior USPSTF report evaluated children enrolled in North Carolina Medicaid (n=19,888) (**Appendix B5**).[71] It found having a first tertiary (dental caries present at baseline) preventive dental visit after 18 months of age associated with increased risk of subsequent dental procedures between 43 and 72 months of age compared with having an earlier (before 18 months of age) first visit (incidence density ratio ranged from 1.1 to 1.4). Among children without dental disease at baseline, there was no difference in risk of subsequent dental procedures by timing of initial preventive dental visit. A subsequent, new study of children also enrolled in North Carolina Medicaid (n=11,394) found a first preventive visit by 37 to 48 or 49 to 60 months of age associated with higher dmft index when assessed in kindergarten compared with first visit by 24 months of age, a finding likely related to children with more severe dental issues receiving earlier preventive visits.[72] However, a later first visit was associated with decreased likelihood of having untreated caries.

Key Question 4. How Effective Are Preventive Interventions (Dietary Fluoride Supplementation, Topical Fluoride Application, Silver Diamine Fluoride, or Xylitol) in Preventing Dental Caries in Children Younger Than Age 5 Years?

Dietary Fluoride Supplementation

Summary

- We identified no new trials published since the 2004 USPSTF review.
- One randomized and four nonrandomized studies included in the 2004 review found dietary fluoride supplementation in settings with water fluoridation levels below 0.6 ppm F associated with decreased caries incidence versus no fluoridation.

Evidence

We identified no trials published since the 2004 USPSTF review of the effectiveness of fluoride supplementation on preventing dental caries in children younger than 5 years old. One randomized trial[77] and four nonrandomized trials (in 5 publications)[78-82] included in the 2004 USPSTF review found dietary fluoride supplementation in settings with water fluoridation levels below 0.6 ppm F associated with decreased caries incidence versus no fluoridation.[7] The randomized trial (n=140, fluoridation <0.1 ppm F) found use of 0.25 mg fluoride drops or chews associated with decreased incidence of caries versus no fluoride supplementation in Taiwanese children with cleft lip who were 2 years of age at enrollment.[77] The percent reduction in caries incidence ranged from 52 to 72 percent for dmft and from 51 to 81 percent for dmfs. In the nonrandomized trials (N=2,273), the reduction in caries incidence versus no fluoride supplementation ranged from mean dmft reduction of 32% to 69%.[78-82] Two of the nonrandomized trials with extended followup found dietary fluoride supplementation associated with decreased caries incidence at 7 to 10 years of age (reductions ranged from 33% to 80%).[78,82]

Topical Fluoride Application

Summary

- Based on 15 trials (5 trials in the prior USPSTF review and 10 new trials), topical fluoride (administered as fluoride varnish in all trials except for one) was associated with decreased caries increment (13 trials, N=5733, mean difference -0.94, 95% CI, -1.74 to -0.34, I^2=86%) and decreased likelihood of incident caries (12 trials, N=8177, RR 0.80, 95% CI, 0.66 to 0.95, I^2=79%; absolute risk difference [ARD] -7%, 95% CI, -12% to -2%) versus placebo or no varnish. Almost all trials were conducted in children at higher risk of caries.

- No trial evaluated effects of topical fluoride on quality of life, function, or other noncaries outcomes.

Evidence

The 2014 USPSTF review[3,4] included three randomized trials[83-85] that found fluoride varnish in children younger than 5 years of age more effective than no varnish (reduction in caries increment 18% to 59% and absolute mean reduction in the number of surfaces of 1.0 to 2.4). The trials enrolled children at high-risk of caries, based on low socioeconomic status, inadequate community fluoridation, or high baseline caries incidence. Two of the trials[83,84] were conducted in Aboriginal communities in Canada or Australia and one trial[85] was conducted in disadvantaged children in San Francisco. Results were consistent with findings from the 2004 USPSTF review,[7] which found fluoride varnish associated with a percent reduction in incident caries lesions that ranged from 37 to 63 percent (absolute reduction in the mean number of cavities per child of 0.67 to 1.24 per year), based on three trials (two randomized[50,86] and one with alternate allocation[61]). One other randomized trial[47] in the 2014 USPSTF review evaluated topical fluoride administered as acidulated phosphate fluoride foam rather than as a varnish; fluoride foam was associated with decreased risk of caries versus placebo (dmfs increment 3.8 vs. 5.0, p=0.03; reduction in caries increment 24%). Meta-analysis on the effects of topical fluoride on caries incidence was not conducted for the prior USPSTF review.

Five trials (N=2616) previously reviewed by the USPSTF on topical fluoride versus no varnish or placebo were carried forward for this update.[47,83-86] As indicated above, four trials evaluated fluoride varnish and one trial evaluated fluoride administered as a foam. Eight trials of fluoride varnish included in prior USPSTF reviews were excluded due to poor-quality (non-randomized, including use of alternating allocation),[60,61,63,65] age older than 5 years,[50] evaluation of topical fluoride for treatment of existing caries,[52] or comparisons of different frequencies of varnish application, without a no varnish or placebo control.[53,57]

Ten additional trials (in 12 publications) of topical fluoride (N=6925) versus no treatment or placebo were added for this update (**Table 1, Appendix B7**).[87-98] All of the new trials evaluated fluoride varnish.

Across all 15 trials (previously reviewed by the USPSTF and added for this update), sample sizes ranged from 123 to 2536 (total N=9541) (**Table 1**, **Appendix B7**). One trial was conducted in the United States,[85] six in Europe,[86-89,91,92,97,98] one in Brazil,[96] one in Chile,[95] two in China,[47,90] two in Iran,[93,94] and two in Aboriginal communities in Australia and Canada.[83,84] Trials conducted in Kosovo, Iran, China, and the Aboriginal communities were not classified as "very high" on the human development index; the other trials were conducted in very high human development index countries. The mean age of enrolled children was 1 year to younger than 2 years in six trials and 2 years to younger than 5 years in nine trials; one trial[83] did not report mean age but enrolled children 6 months to 5 years of age and was grouped with the trials of children 2 years to younger than 5 years. Five trials[47,87,91,92,95] were conducted in preschool or daycare settings and the others were conducted in clinics. Seven trials enrolled children who were caries-free at baseline; five trials reported the proportion of children with caries at baseline, ranging from 17 to 100 percent,[83,84,87,92,96] two trials reported mean baseline dmfs of 1.1 to 4.79,[86,91] and one trial reported mean baseline dmft of 1.6 to 1.7.[47] The trials with the highest proportion of children with caries at baseline (72% and 100%) were conducted in Aboriginal communities in Canada and Australia.[83,84] Two trials were conducted in communities with adequate fluoridation (defined as ≥0.7 ppm) of drinking water.[85,97,98] All trials except for one evaluated children classified as being at higher risk, based on low socioeconomic status, high community prevalence of caries, high baseline caries burden, or low rates of oral health behaviors (e.g., tooth brushing with fluoride toothpaste).

Five trials were cluster randomized[47,83,84,87-89] and the rest were individually randomized. Fluoride varnish was most commonly administered as 5 percent sodium fluoride varnish; single trials evaluated 1.5 percent ammonium fluoride,[91] 0.2 ml 0.9 difluorosilane fluoride varnish,[87] or 1.23 percent acidulated phosphate fluoride foam.[47] Topical fluoride was administered every 6 months, with the exception of two trials which administered varnish every 3 or 4 months.[91,94] One trial evaluated fluoride varnish every 6 or 12 months.[85] Topical fluoride was administered by a dental health professional in all trials in which this information was reported. Three trials[47,86,91] did not describe provision of oral health education; in the other trials, oral health education was provided in addition to the randomized intervention. The duration of followup ranged from 1 to 3 years. The trials focused on effects of topical fluoride on caries increment (reported as a continuous outcomes for number of incident caries surfaces or teeth) or on likelihood of a child developing incident caries (reported as a dichotomous outcome). No trial evaluated effects of fluoride varnish on quality of life, function, or other non-caries health outcomes.

Three trials were rated good-quality[90,92,96] and the rest were rated fair-quality (**Appendix B4**). Methodological limitations in the fair-quality trials included unclear randomization or allocation concealment methods, open-label design, or high attrition.

In a meta-analysis, topical fluoride was associated with decreased caries increment versus placebo or no topical fluoride at 1 to 3 years followup (13 trials, N=5733, mean difference -0.94, 95% CI, -1.74 to -0.34, I^2=86%; **Figure 3**).[47,83-87,90-92,94-96,98] All trials reported caries increment as dmfs except for three, which only reported dmft. Statistical heterogeneity was substantial (I^2=86%). Results consistently favored topical fluoride in analyses stratified according to use of cluster randomization, application frequency, classification as very high human development index setting, preschool setting, mean age (<2 years vs. ≥2 years), enrollment restricted to caries-free children at baseline, adequate community water fluoridation, provision of additional oral health measures, risk of bias, or duration of followup (1 vs. 2 vs. 3 years) (**Table 1**). Stratification on these factors had little effect on statistical heterogeneity and no statistically significant interactions between these factors and effects on caries increment were observed. Results were also similar when the trial[47] that evaluated fluoride foam or the trial[97,98] that was not conducted in a high-risk population was excluded from the analysis.

Topical fluoride was also associated with decreased likelihood of incident caries versus placebo or no topical fluoride (12 trials, N=8177, RR 0.80, 95% CI, 0.66 to 0.95; ARD -7%, 95% CI, -12% to -2%; **Figure 4**). Statistical heterogeneity was high (I^2=79%). Definitions for incident caries included any caries lesion or development of ICDAS 5 to 6 (distinct dentine cavity) lesions (**Table 2, Appendix B7**). Results were similar when the trial of fluoride foam[47] or the trial conducted in a nonhigh-risk population[97,98] was excluded from the analysis (**Table 2**). There were no statistically significant interactions between use of cluster design, very high human development index setting, varnish frequency, preschool setting, all children caries-free at baseline, adequate community fluoridation, provision of additional oral health measures, risk of bias, or duration of followup, and statistical heterogeneity remained present in the stratified analyses (**Table 2**). There was a statistically significant interaction between age and effects of fluoride varnish on likelihood of incident caries (p for interaction=0.008). In trials in which the mean age was younger than 2 years, fluoride varnish was associated with decreased likelihood of incident caries (5 trials, N=3669, RR 0.60, 95% CI, 0.39 to 1.03, I^2=49%),[85,89-91,93] but there was no effect in trials in which the mean age of children was 2 years or older (7 trials, N=4508, RR 0.92, 95% CI, 0.81 to 1.01, I^2=42%).[47,83,87,92,95,96,98]

Xylitol

Summary

- One fair-quality trial (n=115) included in the prior USPSTF review found xylitol tablets associated with lower dmfs increment versus no xylitol in children 2 years of age (mean reduction 0.42), but the difference was not statistically significant.
- One small (n=44), fair-quality trial included in the prior USPSTF review found xylitol wipes associated with markedly decreased risk of having incident caries versus placebo wipes in children 6 to 35 months of age (5% vs. 32%, RR 0.14, 95% CI, 0.02 to 1.07), but the difference was not statistically significant.
- No new trials of xylitol versus no xylitol were identified.

Evidence

The 2014 USPSTF review included three trials of xylitol versus no xylitol;[64,99,100] however, one of the trials was poor-quality (non-randomized)[64] and excluded from this update. The other two trials were carried forward (**Appendix B8**); both were rated fair-quality. Methodological limitations included unclear randomization and/or allocation concealment, not blinding care providers or patients, and differences in attrition between groups (**Appendix B4**).

One trial (n=115) compared xylitol tablets versus no xylitol in Swedish children 2 years of age.[100] Baseline caries prevalence was 6 percent and the proportion of children that brushed their teeth one to two times a day was 79 percent; water is not fluoridated in Sweden. Xylitol was administered as one 0.5 mg tablet at bedtime for 6 months, followed by two tablets daily. Xylitol was associated with lower dmfs increment versus no xylitol after 2 years, but the difference was not statistically significant (mean percent reduction 52%, mean dmfs reduction 0.42).

The other, smaller (n=44) trial compared xylitol wipes versus placebo wipes in U.S. (San Francisco) children 6 to 35 months of age (mean 17.3 months).[99] Most children attending the clinic at which recruitment took place were of low socioeconomic status. The proportion of children with caries at baseline was 7 percent, the proportion that brushed their teeth daily was 68 percent, and the proportion that used fluoride toothpaste was 32 percent. The San Francisco water supply is generally fluoridated to 1.0 mg/l. Xylitol was administered as a topical wipe to the teeth three times per day for 1 year. Xylitol wipes were associated with markedly decreased risk of having incident caries versus placebo, though the difference was not statistically significant (5% [1/22] vs. 32% [7/22], RR 0.14, 95% CI 0.02 to 1.07). In an on-treatment analysis of 37 children who completed the study, xylitol was associated with decreased risk of incident caries versus placebo (5% vs. 40%, p=0.03) and deceased dmfs increment (0.05 vs. 0.53, p=0.01); dmfs increment was not reported in the intention-to-treat population.

Silver Diamine Fluoride

We identified no trial meeting inclusion criteria of SDF versus placebo or no SDF for prevention of caries in children younger than 5 years of age. One trial[101] was excluded because of non-English language, but a systematic review[102] noted that methods and results were reported poorly and excluded the trial from meta-analysis. Evidence on SDF for prevention of caries in children 5 years of age or older is addressed in the Contextual Question.

Key Question 5. What Are the Harms of Specific Oral Health Interventions to Prevent Dental Caries in Children Younger Than Age 5 Years (Parental or Caregiver/Guardian Oral Health Education, Referral to a Dental Health Care Professional, and Preventive Interventions)?

Summary

- The prior USPSTF review included a systematic review of 19 studies which found an association between early childhood ingestion of systemic fluoride and enamel fluorosis of the permanent dentition. Studies were observational and had methodological shortcomings, including use of retrospective recall to determine exposures.
- Four new trials (N=4141) reported no differences between fluoride varnish versus placebo or no varnish in risk of fluorosis or the likelihood of any adverse event. Two studies reported children did not like the smell of the fluoride varnish and one study reported that a few children vomited due to the smell, texture, or taste.

Evidence

Dietary Fluoride Supplementation

No trial reported risk of dental fluorosis associated with early childhood ingestion of dietary fluoride supplements.

The prior USPSTF included a systematic review of 19 observational studies on the association between early childhood intake of fluoride supplements and risk of fluorosis, based on searches conducted through June 2006 (**Appendix B9 and B10**).[46] Early childhood exposures were based on retrospective parental recall in 15 studies and on supplement use recorded at the time of exposure in four studies. Fluorosis was assessed at 8 to 14 years of age. The prevalence of fluorosis ranged from 10 to 67 percent. The review found intake of fluoride supplements prior to 7 years of age (primarily before 3 years of age) associated with increased risk of mild to moderate fluorosis. The ORs for dental fluorosis ranged from 1.1 to 10.8 in the studies that relied on retrospective recall and ranged from 4.2 to 15.6 in the studies that recorded supplement use at the time of exposure. We identified no new study on the association between early childhood intake of dietary fluoride supplements and risk of enamel fluorosis.

Topical Fluoride Application

The prior report included one trial of fluoride varnish that reported one child with an allergy to lanolin experienced an adverse event.[83] The other studies did not report adverse events or reported that no adverse events were detected.

Four new trials (in 6 publications, N=4141) reported adverse events associated with fluoride varnish versus placebo or no varnish (**Appendix B4 and B7**).[87-89,97,98,103]

One trial (n=181) that followed children for 4 years reported no differences in the risk of fluorosis associated with the use of fluoride varnish compared with placebo (27% vs. 35%, p=0.44).[103] There was also no difference in esthetically objectionable fluorosis (4.8% vs. 8.3%, p=0.48). No other trial reported risk of fluorosis. However, the degree of systemic exposure following application of fluoride varnish is believed to be low.

One trial (n=1096) reported no difference in the rate of adverse events between fluoride varnish and no fluoride varnish (7.2% vs. 5.9%; RR 1.22, 95% CI, 0.80 to 1.85).[97,98] Two trials (N=2864) reported child complaints about varnish odor,[87,89] with one reporting a few children vomited directly after application.[88,89]

Xylitol

Trials of xylitol did not report rates of diarrhea, and either did not report adverse events or stated none were reported.[99,100]

Contextual Question. 1. How Effective Is Silver Diamine Fluoride in Preventing Dental Caries in Children Age 5 Years or Older?

SDF has primarily been evaluated as a treatment for arresting existing cavitated caries lesions. Systematic reviews have found SDF effective for arresting caries in primary teeth of children, though methodological limitations have been noted.[104,105] Evidence on the effectiveness of SDF for preventing caries in children is very limited. As described in the Results, we identified no trials on the effectiveness of SDF in preventing dental caries in children younger than 5 years of age. One trial (n=704) conducted in the Philippines allocated first graders in six schools based on class registration number to single application of SDF (administered by school nurses) or atraumatic restorative treatment (ART) sealants (administered by dentists).[106] Children in two other schools served as no-treatment controls. The proportion of children with D3 caries at baseline was 13.3 percent. All of the schools were supposed to provide an ongoing oral health care program that included daily school-based tooth brushing with fluoride toothpaste, but three schools were not in compliance with the program. Therefore, analyses were stratified according to school compliance with the tooth brushing program. There were no statistically significant differences between SDF versus controls in caries increment in children in the brushing schools (hazard ratio [HR] 1.16, 95% CI, 0.51 to 2.63) or nonbrushing schools (HR 0.71, 95% CI 0.45 to 1.11), though estimates were imprecise. Staining and other harms were not reported.

We identified no other completed trials of SDF for preventing dental caries in children older than 5 years of age. Two similarly designed ongoing trials in the United States are currently in progress, with expected completion in 2023.[107,108] Both are cluster randomized trials in elementary school children and compare a single application of SDF (administered by dental hygienists or registered nurses) versus glass ionomer sealants (administered by dental hygienists). All children will receive toothbrushes, fluoride toothpaste, and oral hygiene instruction. The trial will evaluate caries arrest after 2 years and prevalence of new caries after 4 years. The primary difference between trials is that one is focused on children in low-income rural settings[108] and in the other trial the primary study population is low-income urban Hispanic/Latino children.[107]

One other randomized trial (n=452) of 6 year old children found 38 percent SDF every 6 months associated with fewer new decayed surfaces in primary teeth and first permanent molars versus no SDF at 36 months (0.29 vs. 1.43 and 0.37 vs. 1.06, respectively).[109] However, applicability of this trial to prevention is uncertain, as SDF was used for caries arrest in deciduous teeth and baseline caries status in first permanent molars was unclear.

Chapter 4. Discussion

Summary of Review Findings

Table 3 summarizes the evidence reviewed for this update. Dental caries is highly prevalent in children younger than 5 years of age. A high proportion of children in this age group do not receive recommended dental care and important disparities in oral health and access to care exist,[110,111] suggesting a potential role for primary care clinicians in dental caries screening and prevention. This report builds upon prior reviews conducted for the USPSTF.[3,112] A difference between this report and the prior USPSTF reviews is that it utilizes separate analytic frameworks for screening and prevention, to more clearly distinguish treatment of children with existing caries identified on screening (screening analytic framework) from treatment of children without caries to prevent the development of future caries (interventions to prevent dental caries analytic framework).

Nonetheless, the main findings of this report are consistent with the prior USPSTF review.[3,4] With regard to screening, we found no direct evidence on the effects of screening for dental caries by primary care clinicians in children younger than 5 years of age versus no screening on caries incidence and related outcomes. Some interventions, in particular fluoride supplementation in children and fluoride varnish, appear to be effective in preventing caries, though findings appear most applicable to higher risk children.

Evidence remains limited on the accuracy of primary care clinicians in identifying caries lesions or predicting caries incidence in children younger than 5 years of age. Compared with a pediatric dentist examination, one study in the prior USPSTF review found low sensitivity of primary care pediatricians for identifying children in need of a dental referral or with caries[66] and another study in the prior review found high accuracy of a pediatrician oral examination for identifying nursing caries.[67] One new study found a novel caries risk assessment tool administered by health visitor nurses in 1 year old children associated with suboptimal diagnostic accuracy for predicting future caries.[68] Other studies have assessed caries risk assessment instruments in young children, but did not meet inclusion criteria because the instruments were not administered by primary care clinicians or in primary care settings. These instruments often incorporate findings from an oral examination by a dental health professional and include tests not commonly obtained or available in primary care (such as mutans streptococci levels, saliva secretion level, or saliva buffer capacity),[68,113] potentially limiting applicability of findings to primary care settings.[114,115]

Evidence on the effectiveness of parental or caregiver/guardian oral health education on caries outcomes also remains very limited. Two trials included in the prior USPSTF review were rated poor-quality (non-randomized) and not carried forward.[58,59,62] One new trial found oral health education for mothers of caries-free children associated with reduced risk of incident dental caries versus usual care, but the study was relatively small and it was conducted in Iran, potentially reducing applicability to the United States.[70]

As in the prior USPSTF review, we identified no direct evidence on the effects of referral by a primary care clinician to a dentist on caries incidence. Observational studies of children enrolled in Medicaid found receiving a preventive dental visit from a dentist (vs. a primary care clinician) associated with increased likelihood of subsequent caries-related treatment compared with a primary dental visit.[73-76] However, these findings are difficult to interpret because of susceptibility to confounding by indication related to greater need for dental services in children who have a dental visit and variation in provision of caries-related treatment. Two observational studies compared an earlier versus later first preventive dental visit in early childhood but are also difficult to interpret. None of the studies were designed to determine referral source to dental services or to compare effects of dental referral from primary care versus no referral.

We identified no new trials published since the 2004 USPSTF review on the effectiveness of dietary fluoride supplementation in children younger than 5 years of age. The 2004 USPSTF review found dietary fluoride supplementation to be effective at reducing caries incidence in children younger than 5 years of age in settings primarily with water fluoridation levels less than 0.6 ppm F, though conclusions were mostly based on non-randomized trials.[7] We also found no new evidence on the association between early childhood intake of dietary fluoride supplementation and risk of enamel fluorosis. A systematic review included in the prior USPSTF review found an association between early childhood ingestion of systemic fluoride and enamel fluorosis of the permanent dentition.[46] Risk of enamel fluorosis appears to be impacted by total intake of fluoride (from supplements, drinking water, other dietary sources, and dentifrices), as well as age at intake, with intake before 2 to 3 years of age appearing to confer highest risk.[116] Although the prevalence of fluorosis may have increased among U.S. adolescents,[117,118] observed trends could be related to variability in the accuracy or reliability of methods used to assess fluorosis.[119] Regardless, severe fluorosis remains uncommon, with a prevalence of less than 2 percent.[117]

Our findings on the effectiveness of topical fluoride were also consistent with the prior USPSTF review, based on ten new trials, and five trials carried forward from the prior USPTF review. Seven of the ten new trials were conducted in very high human development index settings (compared to two of five prior trials), potentially increasing applicability of findings to U.S. primary care settings. A meta-analysis found topical fluoride associated with decreased caries increment (mean difference -0.94, 95% CI, -1.74 to -0.34) and decreased likelihood of experiencing incident caries (RR 0.80, 95% CI, 0.66 to 0.95). The number needed to treat to prevent one child with incident caries was about 14. Topical fluoride was administered as a varnish in all trials except for one,[47] which used acidulated phosphate fluoride foam. Although pooled analyses were characterized by substantial statistical heterogeneity, results were consistent in stratified analyses based on a number of factors, including use of cluster randomization, varnish frequency, setting, baseline caries status, community water fluoridation status, provision of additional oral health measures, risk of bias, and followup duration. Although there was an interaction between younger age and greater effectiveness of topical fluoride in reducing the likelihood of experiencing incident caries, there was no interaction between age and mean caries increment. Because almost all trials were conducted in higher risk children (based on low socioeconomic status, high community caries burden, high baseline caries burden, or low rate of oral health behaviors), the applicability of findings to children not at increased risk may be reduced. Although some studies were conducted in countries and settings in which sources of fluoride and oral health behaviors differ markedly from the United States, findings were similar when trials were stratified according to whether they were conducting in very high human development index settings or not. In all trials the varnish was applied by dental personnel, though fluoride varnish is believed to be easily applied with minimal training.[120,121] Evidence on harms associated with topical fluoride was limited but indicated no increased risk of fluorosis[103] or adverse events[97,98] versus placebo; serious adverse events were not reported though some children had difficulty tolerating varnish due to the odor.

Evidence on other preventive interventions was limited or unavailable. There were no new trials of xylitol in children younger than 5 years of age and evidence in the prior USPSTF review was limited to two trials with imprecise estimates.[99,100] No trial evaluated SDF for prevention of caries in children younger than five years of age.

Limitations

Our review had limitations. First, we excluded non-English language articles, which could result in language bias. However, we did not identify non-English language articles that appeared likely to impact conclusions. Although one non-English language trial[101] evaluated SDF versus no treatment for prevention of caries in children younger than 5 years of age, a systematic review[102] that included this trial noted that methods and results were reported poorly and excluded it from meta-analysis. Second, we did not search for studies published only as abstracts. Third, we did not assess for publication bias with graphical or statistical methods because of differences in study design, populations, and outcomes assessed, with substantial statistical heterogeneity. Fourth, statistical heterogeneity was substantial in meta-analyses of topical fluoride. Results were consistent in prespecified stratified analyses based on factors related to study design, population characteristics, intervention characteristics, and setting, though stratification did not explain the heterogeneity. Fifth, some trials were conducted in countries and settings in which oral health care and behaviors may differ substantially from typical U.S. primary care settings, potentially reducing applicability. Sixth, most studies had methodological limitations, reducing certainty in findings, and some key questions and interventions were addressed by little or no evidence.

Emerging Issues/Next Steps

SDF was cleared for U.S. marketing by the FDA in 2014 as a desensitizing agent in adults.[36] Although it has been evaluated for effectiveness in arresting existing caries, this use is off-label. There is also interest in using SDF off-label for prevention of caries. Two U.S. trials in elementary school-aged children are ongoing[39,107] and could inform future trials in younger children. A potential disadvantage of SDF is permanent dark discoloration of active caries lesions by the silver component, which may impact acceptability, though this may be of less concern when applied prior to eruption of permanent teeth. In addition, active caries lesions themselves cause discoloration.

Relevance for Priority Populations

Dental caries disproportionately affects minority children and economically disadvantaged children. Contributing factors include lack of access to dental health services or insurance and suboptimal oral health behaviors. Recent data indicate that the largest improvements in burden of caries in children 2 to 5 years of age have occurred in those below the federal poverty threshold, though significant disparities remain. In children below the federal poverty threshold, 17.6 percent had untreated caries in 2011 to 2014 compared with 6.2 percent at 200 percent or more above the threshold; corresponding rates for severe caries were 7.0 percent and 3.2 percent.[15] Trials showing effectiveness of fluoride supplementation and topical fluoride have primarily been conducted in higher risk populations based on low socioeconomic status, caries burden, or low rates of oral health behaviors, indicating that increasing access and use of preventive treatments in disadvantaged populations could reduce disparities. Provision of oral care in primary care settings is considered an important strategy for improving access for vulnerable and underserved populations, because children who lack access to a dentist often have multiple encounters with a primary care clinician.[122-124] For children enrolled in Medicaid or the Children's Health Insurance Program (36 million as of May 2020), these programs are the primary source of dental coverage. In young children, receipt of preventive oral health services by nondental providers in medical settings is associated with reduced caries experience.[125] State Medicaid policies to support primary care clinicians' application of fluoride varnish to children expanded to all states following the publication of the 2014 USPSTF recommendation. Data indicate an association between implementation of such policies and increased likelihood of good or excellent teeth in this population.[126]

Future Research

Research is needed to identify effective oral health educational and counseling interventions for parents and caregiver/guardians of young children. Research is also needed to validate the accuracy and utility of caries risk assessment instruments for use in primary care settings, and to determine how referral by primary care clinicians of young children for dental care affects caries outcomes. Additional trials would strengthen conclusions regarding the effectiveness of dietary fluoride supplementation in young children, especially in the current U.S. context of exposure to multiple sources of fluoride. Trials of fluoride varnish administered in primary care settings would be useful for confirming that effectiveness of fluoride varnish are reproducible in primary care settings and trials of varnish in lower-risk children and settings would be useful for determining applicability of findings. Studies on the effectiveness of SDF will clarify usefulness for prevention (rather than caries arrest) in young children; trials of SDF for prevention of caries in school-age children are expected to be completed in 2023.[107,108]

Conclusions

Dietary fluoride supplementation and fluoride varnish appear to be effective at preventing caries outcomes in higher risk children younger than 5 years of age. Dietary fluoride supplementation in early childhood is associated with risk of enamel fluorosis, which is usually mild. More research is needed to understand the accuracy of oral health examination and caries risk assessment by primary care clinicians, primary care referral for dental care, and effective parental and caregiver/guardian educational and counseling interventions.

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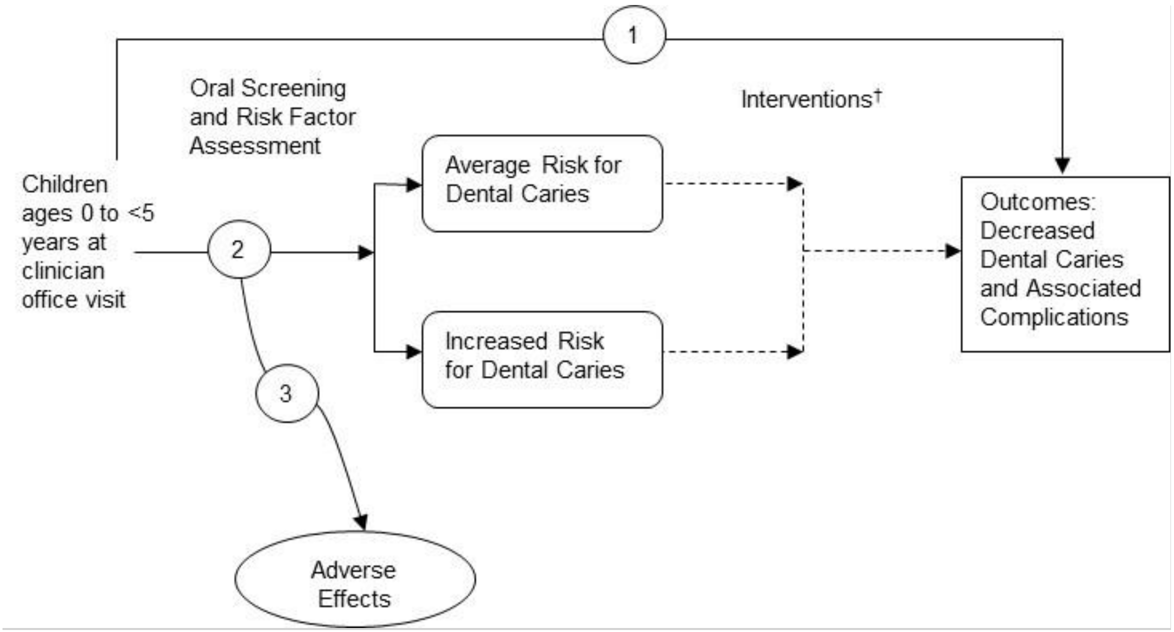
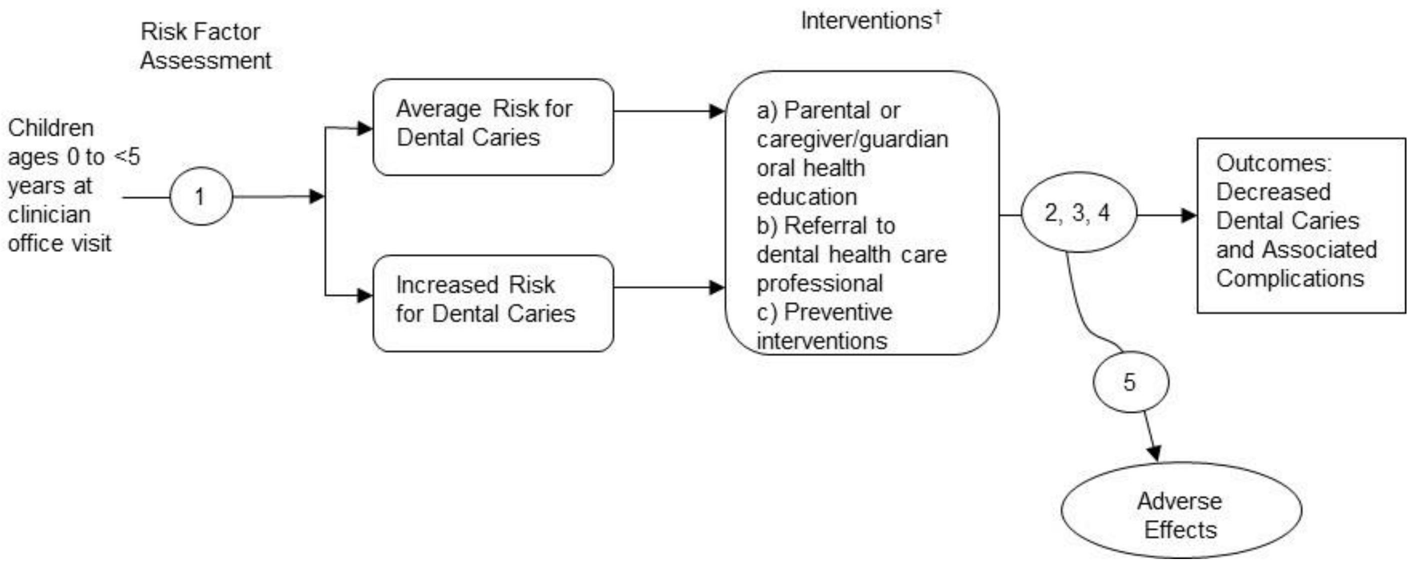
Figure 1. Analytic Framework: Screening for Dental Caries in Children Younger Than Age 5 Years*



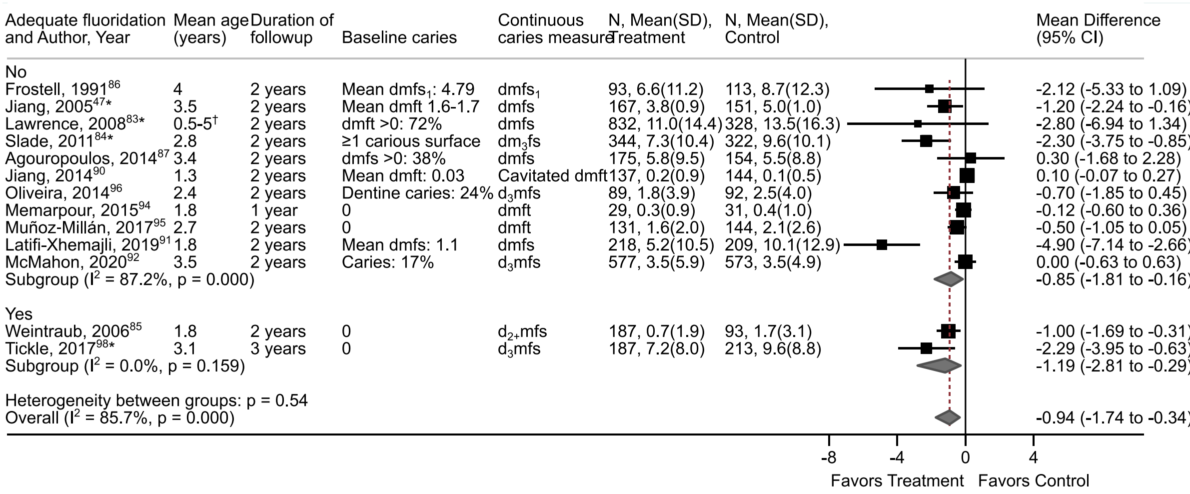
*The numbers in the analytic framework correspond to the Key Question numbers on page 9 in the report.
†Interventions are provided to children found to have caries on screening.

Figure 2. Analytic Framework: Interventions to Prevent Dental Caries in Children Younger Than Age 5 Years*



*The numbers in the analytic framework correspond to the Key Question numbers on page 9 in the report.
†Interventions are provided to children without caries.

Figure 3. Pooled Analysis of Topical Fluoride vs. Placebo or No Topical Fluoride on Mean Change in Number of Caries at Followup, by Fluoridation Status

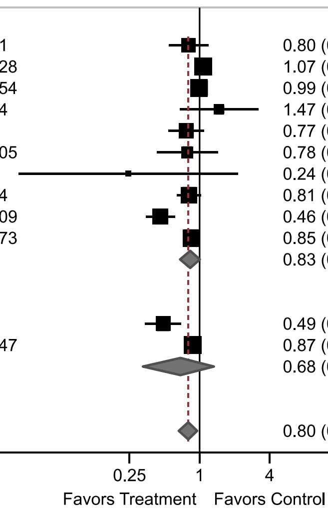


*Studies adjusted for clustering design or other confounding variables.
†Range of age.

Abbreviations: CI=confidence interval; DMFS=decayed, missing, and filled surfaces; DMFT=decayed, missing, and filled teeth; ICDAS=International Caries Detection and Assessment System.

Figure 4. Pooled Analysis of Topical Fluoride vs. Placebo or No Topical Fluoride on Caries Development at Followup, by Fluoridation Status

Adequate fluoridation and Author, Year	Mean age (years)	Duration of followup	Baseline caries	Outcome Definition	Treatment, n/N	Control, n/N	Risk Ratio (95% CI)
No							
Jiang, 2005[47]*	3.5	2 years	Mean dmft 1.6-1.7	dmfs increase ≥6	47/167	53/151	0.80 (0.54 to 1.19)
Lawrence, 2008[83]*	0.5-5†	2 years	dmft >0: 72%	New dmfs ≥1	595/832	247/328	1.07 (0.96 to 1.19)
Agouropoulos, 2014[87]	3.4	2 years	dmfs >0: 38%	dmfs >0	113/174	101/154	0.99 (0.85 to 1.16)
Jiang, 2014[90]	1.3	2 years	Mean dmft: 0.03	Incident caries	14/137	10/144	1.47 (0.68 to 3.20)
Oliveira, 2014[96]	2.4	2 years	Dentine caries: 24%	New caries lesion	32/89	43/92	0.77 (0.54 to 1.09)
Anderson, 2016[89]*	1	3 years	ICDAS 5-6: 0.2%	ICDAS 5 to 6	75/1231	99/1305	0.78 (0.43 to 1.44)
Memarpour, 2016[93]	1.7	1 year	0	dmft >0	1/87	4/85	0.24 (0.03 to 2.14)
Muñoz-Millán, 2017[95]	2.7	2 years	0	Cavitated caries	59/131	80/144	0.81 (0.64 to 1.03)
Latifi-Xhemajli, 2019[91]	1.8	2 years	Mean dmfs: 1.1	ICDAS 5 or 6	48/218	100/209	0.46 (0.35 to 0.61)
McMahon, 2020[92]	3.5	2 years	Caries: 17%	$d_3$mfs increment >0	165/577	193/573	0.85 (0.71 to 1.01)
Subgroup (I^2 = 75.4%, p = 0.000)							0.83 (0.68 to 1.00)
Yes							
Weintraub, 2006[85]	1.8	2 years	0	Incident caries	37/163	42/90	0.49 (0.34 to 0.70)
Tickle, 2017[98]	3.1	3 years	0	Became caries active	187/549	213/547	0.87 (0.75 to 1.02)
Subgroup (I^2 = 76.2%, p = 0.003)							0.68 (0.33 to 1.33)
Heterogeneity between groups: p = 0.43							
Overall (I^2 = 79.3%, p = 0.000)							0.80 (0.66 to 0.95)



*Studies adjusted for clustering design or other confounding variables.
†Range of age.

Abbreviations: CI=confidence interval; DMFS=decayed, missing, and filled surfaces; DMFT=decayed, missing, and filled teeth; ICDAS=International Caries Detection and Assessment System.

Table 1. Pooled Analyses of Mean Change in Number of Caries at Followup, Topical Fluoride vs. Placebo or No Topical Fluoride

	Number of trials	MD (95% CI)	I^2	p*
All trials	13[47,83-87,90-92,94-96,98]	-0.94 (-1.74 to -0.34)	86%	--
Fluoride type				0.57
• 5% NaF varnish	10[83-86,90,92,94-96,98]	-0.62 (-1.35 to -0.16)	75%	
• Other varnish	2[87,91]	-2.24 (-8.56 to 3.98)	83%	
• Foam	1[47]	-1.20 (-2.24 to -0.16)	Not applicable	
Quality				0.13
• Good-quality trials	3[90,92,96]	0.08 (-0.28 to 0.27)	0%	
• Fair-quality trials	10[47,83-87,91,94,95,98]	-1.33 (-2.36 to -0.54)	78%	
Fluoridation status				0.54
• Adequate	2[85,98]	-1.19 (-2.81 to -0.29)	0%	
• Not adequate	11[47,83,84,86,87,90-92,94-96]	-0.85 (-1.81 to -0.16)	87%	
Cluster RCT				0.27
• Yes	3[47,83,84]	-1.63 (-3.04 to -0.64)	0%	
• No	10[85-87,90-92,94-96,98]	-0.72 (-1.66 to -0.09)	86	
Setting				0.94
• Preschool	5[47,87,91,92,95]	-1.04 (-2.90 to 0.57)	88%	
• Other	8[83-86,90,94,96,98]	-0.89 (-1.86 to -0.21)	80%	
Mean age				0.93
• <2 years old	4[85,90,91,94]	-1.26 (-3.24 to 0.74)	98%	
• ≥2 years old	9[47,83,84,86,87,92,95,96,98]	-0.89 (-1.70 to -0.30)	50%	
High-risk of caries				0.34
• Yes	12[47,83-87,90-92,94-96]	-0.81 (-1.64 to -0.24)	84%	
• No	1[98]	-2.29 (-3.95 to -0.63)	Not applicable	
Caries free at baseline				0.33
• Yes	5[85,90,94,95,98]	-0.43 (-1.24 to 0.06)	74%	
• No	8[47,83,84,86,87,91,92,96]	-1.40 (-2.74 to -0.29)	74%	
High human development index				0.22
• Yes	7[85-87,90,92,95,98]	-0.43 (-1.16 to 0.06)	64%	
• No	6[47,83,84,91,94,96]	-1.62 (-3.26 to -0.33)	81%	
Additional oral health measures used				0.07
• Yes	10[83-85,87,90,92,94-96,98]	-0.53 (-1.18 to -0.10)	71%	
• No	3[47,86,91]	-2.57 (-5.45 to 0.03)	62%	
Duration of followup				0.35
• 1 year	2[87,94]	-0.09 (-0.73 to 0.71)	0%	
• 2 years	11[47,83-87,90-92,95,96]	-0.95 (-1.87 to -0.28)	84%	
• 3 years	1[98]	-2.29 (-3.95 to -0.63)	Not applicable	
Application Frequency				0.06
• Every 3 months	1[91]	-4.90 (-7.14 to -2.66)	Not applicable	
• Every 4 months	1[94]	-0.12 (-0.60 to 0.36)	Not applicable	
• Every 6 months	11[47,83-87,90,92,95,96,98]	-0.73 (-1.40 to -0.24)	70%	
• Every 12 months	1[85]	-1.00 (-1.72 to -0.28)	Not applicable	

*p value for interaction.

Abbreviations: CI=confidence interval; MD=mean difference; NaF=sodium fluoride; RCT=randomized controlled trial.

Table 2. Pooled Analyses of Risk of Caries Development at Followup, Topical Fluoride vs. Placebo or No Topical Fluoride

	Number of trials	RR (95% CI)	I^2	p*
All trials	12[47,83,85,87,89-93,95,96,98]	0.80 (0.66 to 0.95)	79%	--
Fluoride type				0.79
• 5% NaF varnish	11[83,85,87,89-93,95,96,98]	0.84 (0.69 to 0.99)	65%	
• Other varnish	2[87,91]	0.69 (0.27 to 1.71)	90%	
• Foam	1[47]	0.80 (0.54 to 1.19)	Not applicable	
Quality				0.49
• Good-quality trials	3[90,92,96]	0.85 (0.71 to 1.08)	0%	
• Fair-quality trials	9[47,83,85,87,89,91,93,95,98]	0.77 (0.60 to 0.96)	84%	
Fluoridation status				0.43
• Adequate	2[85,98]	0.68 (0.33 to 1.33)	76%	
• Not adequate	10[47,83,87,89-93,95,96]	0.83 (0.68 to 1.00)	75%	
Cluster RCT				0.37
• Yes	3[47,83,89]	1.04 (0.74 to 1.17)	0%	
• No	9[85,87,90-93,95,96,98]	0.76 (0.60 to 0.95)	78%	
Setting				0.63
• Preschool	5[47,87,91,92]	0.77 (0.58 to 1.01)	83%	
• Other	7[83,85,89,90,93,95,96,98]	0.83 (0.61 to 1.08)	74%	
Mean age				0.008
• <2 years old	5[85,89-91,93]	0.60 (0.39 to 1.03)	49%	
• ≥2 years old	7[47,83,87,92,95,96,98]	0.92 (0.81 to 1.01)	42%	
High-risk of caries				0.73
• Yes	11[47,83,85,87,89-93,95,96]	0.79 (0.64 to 0.96)	80%	
• No	1[98]	0.87 (0.75 to 1.02)	Not applicable	
Caries free at baseline				0.77
• Yes	6[85,89,90,93,95,98]	0.77 (0.57 to 1.04)	48%	
• No	6[47,83,87,91,92,96]	0.82 (0.62 to 1.05)	86%	
High human development index				0.57
• Yes	7[85,87,89,90,92,95,98]	0.84 (0.69 to 1.00)	48%	
• No	5[47,83,91,93,96]	0.74 (0.47 to 1.07)	79%	
Additional oral health measures used				0.11
• Yes	10[83,85,87,89,90,92,93,95,96,98]	0.86 (0.73 to 1.00)	64%	
• No	2[47,91]	0.59 (0.31 to 1.18)	59%	
Duration of followup				0.68
• 1 year	3[85,87,93]	0.71 (0.27 to 1.29)	58%	
• 2 years	9[47,83,85,87,90-92,95,96]	0.79 (0.63 to 0.99)	84%	
• 3 years	2[89,98]	0.87 (0.67 to 1.07)	0%	
Application Frequency				0.07
• Every 3 months	1[91]	0.46 (0.35 to 0.61)	Not applicable	
• Every 6 months	11[47,83,85,87,89,90,92,93,95,96,98]	0.88 (0.74 to 0.98)	52%	
• Every 12 months	1[85]	0.60 (0.40 to 0.91)	Not applicable	

*p value for interaction.

Abbreviations: CI=confidence interval; NaF=sodium fluoride; RCT=randomized controlled trial; RR=relative risk.

Table 3. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Screening KQ 1 and 3. Effectiveness and harms of screening by PCP	No studies	--	--	--	--	**--**
Screening KQ 2a. Accuracy of screening by PCP: Identifying caries lesion	k=2 (N=368) diagnostic accuracy studies (both in prior USPSTF review)	• Sensitivity of 0.76 and specificity of 0.95 for identifying a child with one or more cavities and sensitivity of 0.63 and specificity of 0.98 for identifying a child in need of a dental referral (1 study) • Sensitivity of 1.0 and specificity of 0.87 for identifying nursing caries (1 study)	Unable to assess consistency due to differences between studies Precision low to moderate	Nursing caries study rated fair-quality	Low	Primary care examiners underwent 2 or 4 hours of training; both studies conducted in the United States
Screening KQ 2b. Accuracy of screening by PCP: Predicting future caries	k=1 (n=1681) diagnostic accuracy study (new)	Dundee Caries Risk Assessment Model associated with sensitivity of 0.53 and specificity of 0.77 for predicting future dentin caries in children 1 year of age	Unable to assess consistency (single study) Precise	Fair-quality; factors selected for model not pre-defined; no validation available	Low	Administered by health visitor nurses in Scotland
Prevention KQ 1. Accuracy of screening by PCP*	See Screening KQ 2b	See Screening KQ 2b	See Screening KQ 2b	See Screening KQ 2b	See Screening KQ 2b	See Screening KQ 2b
Prevention KQ 2. Educational interventions	k=1 (n=104) RCT (new)	1 RCT found oral health education for mothers of caries-free children 12 to 36 months of age associated with reduced risk of incident dental caries vs. usual care at 6 months (RR 0.39, 95% CI, 0.18 to 0.85).	Unable to assess consistency (1 study) Precise	Fair-quality; dental health behaviors not reported at baseline or followup	Low	Conducted in Iran in region with inadequate fluoridation of drinking water

Table 3. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Prevention KQ 3. Referral to a dentist by a PCP	k=6 (N=92,476) observational studies; 1 study in prior review and 5 new	• No study directly compared referral by primary care clinician to a dentist vs. no referral • Receiving a dental visit from a dentist associated with increased likelihood of subsequent caries-related treatment versus a dental visit from a primary care provider (4 studies) • Earlier versus later first preventive dental visit associated with no difference in rate of subsequent dental procedures, higher subsequent caries burden, and lower rates of untreated caries	Consistent Precise	Observational studies; fair quality; studies not designed to determine referral source or compare effects of referral vs. no referral; findings susceptible to confounding by indication	Low	All studies conducted in U.S. children enrolled in Medicaid; some overlap in study populations conducted within the same state
Prevention KQ 4. Preventive interventions: Dietary fluoride supplementation	k=1 (n=140) RCT and k=4 (N=3172) non-randomized trials (all in prior USPSTF review)	Dietary fluoride supplementation in settings with water fluoridation levels below 0.6 ppm fluoride associated with decreased caries incidence versus no fluoridation (percentage reduction ranged from 48% to 72% for primary teeth and 51% to 81% for primary tooth surfaces)	Consistent Precise	4 of 5 trials were non-randomized	Moderate	2 trials conducted in Asia; 1 trial conducted in children with cleft lip; 3 trials conducted between 1967 and 1972

Table 3. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Prevention KQ 4. Preventive interventions: Topical fluoride	k=15 (N=9541) RCTs (5 in prior USPSTF review and 10 new)	Topical fluoride associated with decreased caries increment (13 trials, mean difference -0.94, 95% CI -1.74 to -0.34) and decreased likelihood of incident caries (12 trials, RR 0.80, 95% CI 0.66 to 0.95) vs. placebo or no varnish	Inconsistent (high statistical heterogeneity) Precise	11 trials rated fair quality (2 rated good quality); open-label design in some trials	Moderate	Almost all trials conducted in higher risk children or settings; almost all trials evaluated fluoride varnish; varnish applied by persons with dental training; some trials conducted in preschool or daycare setting; some trials conducted in non-very high human development index settings; some trials included children with high baseline caries burden
Prevention KQ 4. Preventive interventions: Xylitol	k=2 (N=159) RCTs (both in prior USPSTF review)	Estimates imprecise from 2 trials, but favored xylitol over placebo for caries outcomes	Consistent Imprecise	Trials rated fair-quality	Low	Trials conducted in U.S. and Sweden; 1 trial conducted in low socioeconomic status setting; xylitol administered as tablet or wipe
Prevention KQ 4. Preventive interventions: Silver diamine fluoride	No studies	--	--	--	--	--
Prevention KQ 5. Harms of interventions: Dietary fluoride supplements	k=1 SR of 19 observational studies (in prior USPSTF review)	Intake of fluoride supplements prior to 7 years of age (primarily before 3 years of age) associated with increased risk of mild to moderate fluorosis; odds ratio ranged from 1.1 to 10.8 in the studies that relied on retrospective recall and from 4.2 to 15.6 in the studies that recorded supplement use at the time of exposure	Consistent Precise	Observational studies; most studies relied on retrospective recall to determine fluoride exposure	Low-moderate	Studies conducted in a variety of settings and countries, variability in recommended levels of fluoride supplementation and water fluoridation levels

Table 3. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Prevention KQ 5. Harms of interventions	k=4 (N=4141) RCTs (all new)	No difference in risk of fluorosis or esthetically objectionable fluorosis (1 trial); no difference in risk of adverse events (1 trial); reports of complaints about odor	Consistency cannot be determined (single trials reported different adverse events) Precise	Harms not reported or suboptimal reporting in most trials	Low-moderate	See KQ 4
Prevention KQ 5. Harms of interventions	No studies	RCTs of xylitol vs. placebo or no xylitol did not report harms	--	--	--	--

*This is the same question as Screening KQ 2b.

Abbreviations: CI=confidence interval; KQ=key question; PCP=primary care physician; ppm=parts per million; RCT=randomized controlled trial; RR=relative risk; SR=systematic review; USPSTF=United States Preventive Services Task Force.

Appendix A1. Search Strategies

Database: OVID MEDLINE®

Search Strategy:

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1. exp Dental Caries/ (43963)
2. limit 1 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") (8321)
3. limit 2 to yr="2014 -Current" (1368)
4. limit 3 to (meta analysis or "systematic review") (36)
5. from 4 keep 11,13,18,20-22,24,31 (8)
6. limit 3 to randomized controlled trial (121)
7. from 6 keep 1,3-4,6-9,13,19,22,24-26,29,34,38,42-43,46,48-49,52,56,58-59,61,63-64,66,68,72-74,77,79,83-85,92-94,101,107-108,112,115-117 (48)
8. 5 or 7 (56)

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

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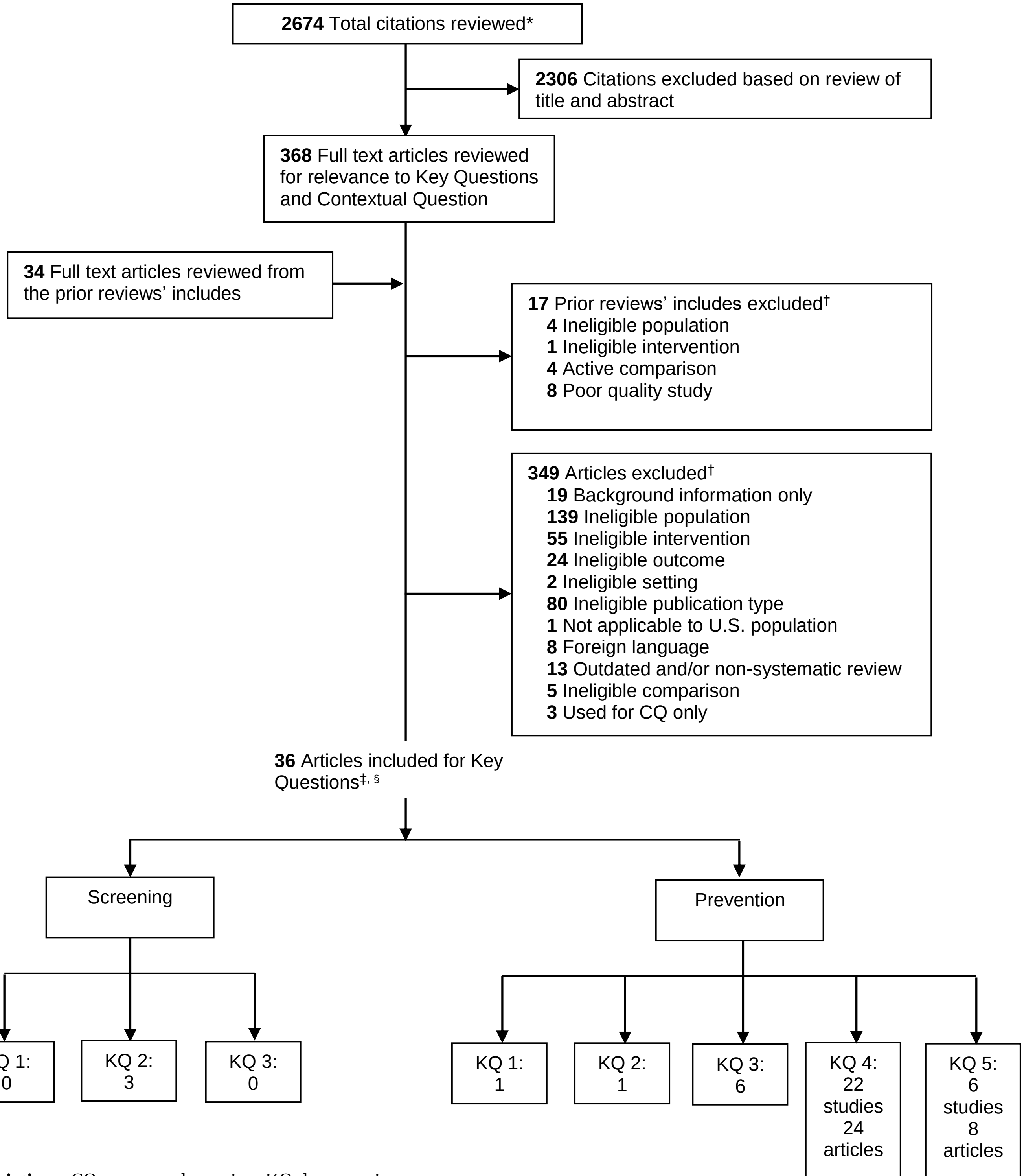
1. dental caries.mp. [mp=title, short title, abstract, full text, keywords, caption text] (113)
2. limit 1 to full systematic reviews (87)
3. 2 and prevention.mp. [mp=title, short title, abstract, full text, keywords, caption text] (62)
4. 3 and children.mp. [mp=title, short title, abstract, full text, keywords, caption text] (51)
5. from 4 keep 1,6,8,23,30,32-35,41-42 (11)

Appendix A2. Inclusion and Exclusion Criteria

Category	Included	Excluded
Populations	Asymptomatic children younger than age 5 years	Animal studies, adults, children older than preschool age (≥5 years), and children who are symptomatic for dental caries
Interventions	**KQs 1–3 (screening) and KQ 1 (preventive interventions):** Oral screening and risk factor assessment performed by a primary care clinician **KQs 2, 3, 5 (preventive interventions):** Parent/caregiver/guardian oral health education and/or referral to dental health care provider **KQs 4, 5 (preventive interventions):** Preventive interventions: oral fluoride supplementation, topical fluoride application, silver diamine fluoride, or xylitol (including xylitol given to the child or mother)	**KQs 1–3 (screening) and KQ 1 (preventive interventions):** Community- or school-based screening interventions **KQs 2, 3 (preventive interventions):** Education or referral not performed in primary care settings; education or referral for existing caries **KQs 4, 5 (preventive interventions):** Interventions not available for preschool children or not available in the United States; treatment for existing caries
Comparisons	No intervention or placebo	Active treatment
Outcomes	**KQs 1, 3 (screening) and KQs 2–5 (preventive interventions):** Dental caries, morbidity, quality of life, and function **KQ 2 (screening) and KQ 1 (preventive interventions):** Diagnostic accuracy and measures of risk prediction **KQ 3 (screening) and KQ 5 (preventive interventions):** Dental fluorosis, tooth staining, emotional stress, acute toxicity, and other associated complications	Cost effectiveness
Setting	Applicable to U.S. primary care practice	Schools; dental clinics providing interventions not available in primary care settings
Study Design	**KQ 1 (screening) and KQs 2–4 (preventive interventions):** Randomized, controlled trials; nonrandomized, controlled clinical trials; and cohort studies **KQ 2 (screening) and KQ 1 (preventive interventions):** Studies of diagnostic accuracy or risk prediction **KQ 3 (screening) and KQ 5 (preventive interventions):** Randomized, controlled trials; nonrandomized, controlled clinical trials; cohort studies or case-control studies (if data from randomized trials are lacking); and systematic reviews	**KQs 1, 2 (screening) and KQs 1–4 (preventive interventions):** Case-control studies; uncontrolled intervention studies **All KQs:** Opinions, editorials, or case reports
Study Quality	Good or fair quality	Poor quality

Appendix A3. Literature Flow Diagram



Abbreviations: CQ=contextual question; KQ=key question.
*Identified from reference lists, hand searching, suggested by experts, etc.
†We included 36 publications of 33 studies. See Appendix A5 for the list of excluded studies and Appendix A2 for the list of exclusion criteria.
‡Studies that provided data and contributed to the body of evidence were considered 'included'.
§Studies may have contributed data for more than one key question.

Appendix A4. List of Included Studies

1. Agouropoulos A, Twetman S, Pandis N, et al. Caries-preventive effectiveness of fluoride varnish as adjunct to oral health promotion and supervised tooth brushing in preschool children: a double-blind randomized controlled trial. J Dent. 2014 Oct;42(10):1277-83. doi: 10.1016/j.jdent.2014.07.020. PMID: 25123352.

2. Anderson M, Dahllof G, Soares FC, et al. Impact of biannual treatment with fluoride varnish on tooth-surface-level caries progression in children aged 1-3 years. J Dent. 2017 Oct;65:83-8. doi: 10.1016/j.jdent.2017.07.009. PMID: 28739318.

3. Anderson M, Dahllof G, Twetman S, et al. Effectiveness of early preventive intervention with semiannual fluoride varnish application in toddlers living in high-risk areas: A stratified cluster-randomized controlled trial. Caries Res. 2016;50(1):17-23. doi: 10.1159/000442675. PMID: 26795957.

4. Basir L, Rasteh B, Montazeri A, et al. Four-level evaluation of health promotion intervention for preventing early childhood caries: a randomized controlled trial. BMC Public Health. 2017 10 02;17(1):767. doi: 10.1186/s12889-017-4783-9. PMID: 28969655.

5. Beil H, Rozier RG, Preisser JS, et al. Effect of early preventive dental visits on subsequent dental treatment and expenditures. Med Care. 2012;50(9):749-56. doi: 10.1097/MLR.0b013e3182551713. PMID: 22525611.

6. Beil H, Rozier RG, Preisser JS, et al. Effects of early dental office visits on dental caries experience. Am J Public Health. 2014;104(10):1979-85. doi: 10.2105/AJPH.2013.301325.

7. Blackburn J, Morrisey MA, Sen B. Outcomes associated with early preventive dental care among Medicaid-enrolled children in Alabama. JAMA Pediatr. 2017;171(4):335-41. doi: 10.1001/jamapediatrics.2016.4514.

8. Dos Santos AP, Malta MC, de Marsillac MW, et al. Fluoride varnish applications in preschoolers and dental fluorosis in permanent incisors: results of a nested-cohort study within a clinical trial. Pediatr Dent. 2016 Oct 15;38(5):414-8. PMID: 28206898.

9. Frostell G, Birkhed D, Edwardsson S, et al. Effect of partial substitution of invert sugar for sucrose in combination with Duraphat treatment on caries development in preschool children: the Malmo Study. Caries Res. 1991;25(4):304-10. doi: 10.1159/000261381. PMID: 1913770.

10. Hamberg L. Controlled trial of fluoride in vitamin drops for prevention of caries in children. Lancet. 1971 Feb 27;1(7696):441-2. PMID: 4100412.

11. Hennon DK, Stookey GK, Muhler JC. Prophylaxis of dental caries: Relative effectiveness of chewable fluoride preparations with and without added vitamins. J Pediatr. 1972;80(6):1018-21. PMID: 5026023.

12. Hu D, Wan H, Li S. The caries-inhibiting effect of a fluoride drop program: a 3-year study on Chinese kindergarten children. Chin J Dent Res. 1998;1(3):17-20. PMID: 10557167.

13. Ismail AI, Hasson H. Fluoride supplements, dental caries and fluorosis: a systematic review. J Am Dent Assoc. 2008;139(11):1457-68. doi: 10.14219/jada.archive.2008.0071. PMID: 18978383.

14. Jiang EM, Lo EC, Chu CH, et al. Prevention of early childhood caries (ECC) through parental toothbrushing training and fluoride varnish application: a 24-month randomized controlled trial. J Dent. 2014 Dec;42(12):1543-50. doi: 10.1016/j.jdent.2014.10.002. PMID: 25448437.

15. Jiang H, Bian Z, Tai BJ, et al. The effect of a bi-annual professional application of APF foam on dental caries increment in primary teeth: 24-month clinical trial. J Dent Res. 2005;84(3):265-8. doi: 10.1177/154405910508400311. PMID: 15723868.

16. Kranz AM, Rozier RG, Preisser JS, et al. Preventive services by medical and dental providers and treatment outcomes. J Dent Res. 2014;93(7):633-8. doi: 10.1177/0022034514536731.

17. Kranz AM, Rozier RG, Preisser JS, et al. Comparing medical and dental providers of oral health services on early dental caries experience. Am J Public Health. 2014 Jul;104(7) doi: 10.2105/ajph.2014.301972. PMID: 24832418.

Appendix A4. List of Included Studies

18. Latifi-Xhemajli B, Begzati A, Veronneau J, et al. Effectiveness of fluoride varnish four times a year in preventing caries in the primary dentition: a 2 year randomized controlled trial. Community Dent Health. 2019 Aug 29;36(2):190-4. doi: 10.1922/CDH_4453Begzati05. PMID: 31436925.

19. Lawrence HP, Binguis D, Douglas J, et al. A 2-year community-randomized controlled trial of fluoride varnish to prevent early childhood caries in Aboriginal children. Community Dent Oral Epidemiol. 2008;36(6):503-16. doi: 10.1111/j.1600-0528.2008.00427.x. PMID: 18422711.

20. Lin YT, Tsai CL. Comparative anti-caries effects of tablet and liquid fluorides in cleft children. J Clin Dent. 2000 2000;11(4):104-6. PMID: 11460274.

21. MacRitchie HM, Longbottom C, Robertson M, et al. Development of the Dundee Caries Risk Assessment Model (DCRAM)--risk model development using a novel application of CHAID analysis. Community Dent Oral Epidemiol. 2012 Feb;40(1):37-45. doi: 10.1111/j.1600-0528.2011.00630.x. PMID: 21838824.

22. Margolis FJ, Macauley J, Freshman E. The effects of measured doses of fluoride. A five-year preliminary report. Am J Dis Child. 1967;113(6):670-2. PMID: 4381737.

23. Margolis FJ, Reames HR, Freshman E, et al. Flouride. Ten-year prospective study of deciduous and permanent dentition. Am J Dis Child. 1975;129(7):794-800. PMID: 1096595.

24. McMahon AD, Wright W, Anopa Y, et al. Fluoride Varnish in Nursery Schools: A Randomised Controlled Trial - Protecting Teeth @3. Caries Res. 2020 Sep 10;54(3):274-82. doi: 10.1159/000509680. PMID: 32911474.

25. Memarpour M, Dadaein S, Fakhraei E, et al. Comparison of oral health education and fluoride varnish to prevent early childhood caries: A randomized clinical trial. Caries Res. 2016;50(5):433-42. doi: 10.1159/000446877. PMID: 27504845.

26. Memarpour M, Fakhraei E, Dadaein S, et al. Efficacy of fluoride varnish and casein phosphopeptide-amorphous calcium phosphate for remineralization of primary teeth: a randomized clinical trial. Med Princ Pract. 2015;24(3):231-7. doi: 10.1159/000379750. PMID: 25895964.

27. Munoz-Millan P, Zaror C, Espinoza-Espinoza G, et al. Effectiveness of fluoride varnish in preventing early childhood caries in rural areas without access to fluoridated drinking water: A randomized control trial. Community Dent Oral Epidemiol. 2018 02;46(1):63-9. doi: 10.1111/cdoe.12330. PMID: 28850712.

28. Oliveira BH, Salazar M, Carvalho DM, et al. Biannual fluoride varnish applications and caries incidence in preschoolers: a 24-month follow-up randomized placebo-controlled clinical trial. Caries Res. 2014;48(3):228-36. doi: 10.1159/000356863. PMID: 24481085.

29. Oscarson P, Lif Holgerson P, Sjöström I, et al. Influence of a low xylitol-dose on mutans streptococci colonisation and caries development in preschool children. Eur Arch Paediatr Dent. 2006;7(3):142-7. doi: 10.1007/bf03262555. PMID: 17140543.

30. Pierce KM, Rozier RG, Vann WF, Jr. Accuracy of pediatric primary care providers' screening and referral for early childhood caries. Pediatrics. 2002;109(5):E82. doi: 10.1542/peds.109.5.e82. PMID: 11986488.

31. Sen B, Blackburn J, Kilgore ML, et al. Preventive Dental Care and Long-Term Dental Outcomes among ALL Kids Enrollees. Health Serv Res. 2016;51(6):2242-57. doi: 10.1111/1475-6773.12469.

32. Serwint JR, Mungo R, Negrete VF, et al. Child-rearing practices and nursing caries. Pediatrics. 1993;92(2):233-7. PMID: 8337022.

33. Slade GD, Bailie RS, Roberts-Thomson K, et al. Effect of health promotion and fluoride varnish on dental caries among Australian Aboriginal children: results from a community-randomized controlled trial. Community Dent Oral Epidemiol. 2011;39(1):29-43. doi: 10.1111/j.1600-0528.2010.00561.x. PMID: 20707872.

Appendix A4. List of Included Studies

34. Tickle M, O'Neill C, Donaldson M, et al. A randomised controlled trial to measure the effects and costs of a dental caries prevention regime for young children attending primary care dental services: the Northern Ireland Caries Prevention In Practice (NIC-PIP) trial. Health Technol Assess. 2016 09;20(71):1-96. doi: 10.3310/hta20710. PMID: 27685609.

35. Tickle M, O'Neill C, Donaldson M, et al. A randomized controlled trial of caries prevention in dental practice. J Dent Res. 2017 Jul;96(7):741-6. doi: 10.1177/0022034517702330. PMID: 28375708.

36. Weintraub JA, Ramos-Gomez F, Jue B, et al. Fluoride varnish efficacy in preventing early childhood caries. J Dent Res. 2006;85(2):172-6. doi: 10.1177/154405910608500211. PMID: 16434737.

37. Zhan L, Cheng J, Chang P, et al. Effects of xylitol wipes on cariogenic bacteria and caries in young children. J Dent Res. 2012;91(7 Suppl):85S-90S. doi: 10.1177/0022034511434354. PMID: 22699675.

Exclusion key: 2: background information only; 3: contextual information only; 4: ineligible population; 5: ineligible intervention; 6: ineligible publication type; 7: ineligible outcome; 8: ineligible setting; 9: not applicable to U.S. population; 10: non-English paper; 11: outdated and/or non-systematic review; 12: ineligible comparison; 13: poor-quality study.

Full-text papers excluded from the prior review

1. Alamoudi NM, Hanno AG, Masoud MI, et al. Effects of xylitol on salivary mutans streptococcus, plaque level, and caries activity in a group of Saudi mother-child pairs. An 18-month clinical trial. Saudi Med J. 2012;33(2):186-92. PMID: 22327761. Exclusion: 12.

2. Autio-Gold JT, Courts F. Assessing the effect of fluoride varnish on early enamel carious lesions in the primary dentition. J Am Dent Assoc. 2001;132(9):1247-53. PMID: 1665349. Exclusion: 4.

3. Chu CH, Lo ECM, Lin HC. Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children. J Dent Res. 2002;81(11):767-70. doi: 10.1177/0810767. PMID: 12407092. Exclusion: 4

4. Davies GM, Duxbury JT, Boothman NJ, et al. Challenges associated with the evaluation of a dental health promotion programme in a deprived urban area. Community Dent Health. 2007;24(2):117-21. PMID: 17615828. Exclusion: 13.

5. Davies GM, Duxbury JT, Boothman NJ, et al. A staged intervention dental health promotion programme to reduce early childhood caries. Community Dent Health. 2005;22(2):118-22. PMID: 15984138. Exclusion: 13.

6. Du MQ, Tai BJ, Jiang H, et al. A two-year randomized clinical trial of chlorhexidine varnish on dental caries in Chinese preschool children. J Dent Res. 2006;85(6):557-9. doi: 10.1177/154405910608500615. PMID: 16723655. Exclusion: 4.

7. Grodzka K, Augustyniak L, Budny J, et al. Caries increment in primary teeth after application of Duraphat fluoride varnish. Community Dent Oral Epidemiol. 1982 Apr;10(2):55-9. doi: 10.1111/j.1600-0528.1982.tb00362.x. PMID: 6952970. Exclusion: 13.

8. Holm AK. Effect of fluoride varnish (Duraphat) in preschool children. Community Dent Oral Epidemiol. 1979 Oct;7(5):241-5. doi: 10.1111/j.1600-0528.1979.tb01225.x. PMID: 295702. Exclusion: 13.

9. Kovari H, Pienihäkkinen K, Alanen P. Use of xylitol chewing gum in daycare centers: a follow-up study in Savonlinna, Finland. Acta Odontol Scand. 2003;61(6):367-70. doi: 10.1080/00016350310007806. PMID: 14960009. Exclusion: 12.

10. Kressin NR, Nunn ME, Singh H, et al. Pediatric clinicians can help reduce rates of early childhood caries: effects of a practice based intervention. Med Care. 2009;47(11):1121-8. doi: 10.1097/MLR.0b013e3181b58867. PMID: 19786919. Exclusion: 13.

11. Lopez L, Berkowitz R, Spiekerman C, et al. Topical antimicrobial therapy in the prevention of early childhood caries: a follow-up report. Pediatr Dent. 2002 May-Jun;24(3):204-6. PMID: 12064491. Exclusion: 5.

12. Milgrom P, Ly KA, Tut OK, et al. Xylitol pediatric topical oral syrup to prevent dental caries: a double-blind randomized clinical trial of efficacy. Arch Pediatr Adolesc Med. 2009;163(7):601-7. doi: 10.1001/archpediatrics.2009.77. PMID: 19581542. Exclusion: 12.

13. Petersson LG, Twetman S, Pakhomov GN. The efficiency of semiannual silane fluoride varnish applications: a two-year clinical study in preschool children. J Public Health Dent. 1998 Winter;58(1):57-60. doi: 10.1111/j.1752-7325.1998.tb02991.x. PMID: 9608447. Exclusion: 13.

14. Seki M, Karakama F, Kawato T, et al. Effect of xylitol gum on the level of oral mutans streptococci of preschoolers: block-randomised trial. Int Dent J. 2011;61(5):274-80. doi: 10.1111/j.1875-595X.2011.00073.x. PMID: 21995376. Exclusion: 13.

15. Twetman S, Petersson LG, Pakhomov GN. Caries incidence in relation to salivary mutans streptococci and fluoride varnish applications in preschool children from low- and optimal fluoride areas. Caries Res. 1996;30(5):347-53. PMID: 8877088. Exclusion: 13.

16. Weinstein P, Riedy C, Kaakko T, et al. Equivalence between massive versus standard fluoride varnish treatments in high caries children aged 3-5 years. Eur J Paediatr Dent. 2001;2(2):91-6. Exclusion: 4.

17. Weinstein P, Spiekerman C, Milgrom P. Randomized equivalence trial of intensive and semiannual applications of fluoride varnish in the primary dentition. Caries Res. 2009;43(6):484-90. doi: 10.1159/000264686. PMID: 20016179. Exclusion: 12.

Full-text papers excluded from update searches

1. Agouropoulos A, Birpou E, Twetman S, et al. Validation of Three Caries Risk Assessment Tools for Preschool Children From Areas with High Caries Prevalence. Pediatr Dent. 2019 Sep 15;41(5):391-9. PMID: 31648671. Exclusion: 5.

2. Ahovuo-Saloranta A, Forss H, Hiiri A, et al. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents. Cochrane Database Syst Rev. 2016 Jan 18(1):CD003067. doi: 10.1002/14651858.CD003067.pub4. PMID: 26780162. Exclusion: 4.

3. Ahovuo-Saloranta A, Forss H, Walsh T, et al. Sealants for preventing dental decay in the permanent teeth. Cochrane Database Syst Rev. 2013 Mar 28(3):CD001830. doi: 10.1002/14651858.CD001830.pub4. PMID: 23543512. Exclusion: 4.

4. Ahovuo-Saloranta A, Forss H, Walsh T, et al. Pit and fissure sealants for preventing dental decay in permanent teeth. Cochrane Database Syst Rev. 2017 07 31;7:CD001830. doi: 10.1002/14651858.CD001830.pub5. PMID: 28759120. Exclusion: 4.

5. Al Dehailan L, Martinez-Mier EA. Prevention program including fluoride varnish and 1450-ppm fluoride toothpaste targeting young children in clinical setting in UK did not Stop sental caries from developing but slowed lesion progression. J Evid Based Dent Pract. 2019 06;19(2):207-9. doi: 10.1016/j.jebdp.2019.05.013. PMID: 31326059. Exclusion: 6.

6. Al-Batayneh OB, Bani Hmood EI, Al-Khateeb SN. Assessment of the effects of a fluoride dentifrice and GC Tooth Mousse on early caries lesions in primary anterior teeth using quantitative light-induced fluorescence: a randomised clinical trial. Eur Arch Paediatr Dent. 2020 Feb;21(1):85-93. doi: 10.1007/s40368-019-00451-7. PMID: 31134470. Exclusion: 5.

7. Alamoudi NM, Hanno AG, Almushayt AS, et al. Early prevention of childhood caries with maternal xylitol consumption. Saudi Med J. 2014 Jun;35(6):592-7. PMID: 24888659. Exclusion: 5.

8. Alamoudi NM, Hanno AG, Sabbagh HJ, et al. Impact of maternal xylitol consumption on mutans streptococci, plaque and caries levels in children. J Clin Pediatr Dent. 2012 Winter;37(2):163-6. doi: 10.17796/jcpd.37.2.261782tq73k4414x. PMID: 23534323. Exclusion: 4.

9. Alayadi H, Sabbah W, Bernabe E. Effectiveness of school dental screening on dental visits and untreated caries among primary schoolchildren: study protocol for a cluster randomised controlled trial. Trials. 2018 Apr 13;19(1):224. doi: 10.1186/s13063-018-2619-2. PMID: 29653545. Exclusion: 6.

10. Alrashdi M, Mendez MJC, Farokhi MR. A randomized clinical trial preventive outreach targeting dental caries and oral-health-related quality of life for refugee children. International journal of environmental research and public health. 2021;18(4):1-10. PMID: CN-02245225. Exclusion: 4.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

11. Alves APS, Rank R, Vilela JER, et al. Efficacy of a public promotion program on children's oral health. J Pediatr (Rio J). 2018 Sep - Oct;94(5):518-24. doi: 10.1016/j.jped.2017.07.012. PMID: 28958799. Exclusion: 6.

12. American Academy of Pediatric D. Guideline on fluoride therapy. Pediatr Dent. 2013 Sep-Oct;35(5):E165-8. PMID: 24290545. Exclusion: 6.

13. American Academy Of Pediatric Dentistry. Guideline on periodicity of examination, preventive dental services, anticipatory guidance/counseling, and oral treatment for infants, children, and adolescents. Pediatr Dent. 2013 Sep-Oct;35(5):E148-56. PMID: 24290543. Exclusion: 6.

14. American Academy of Pediatric Dentistry. Periodicity of examination, preventive dental services, anticipatory guidance/counseling, and oral treatment for infants, children, and adolescents. Pediatr Dent. 2017;39:188-96. Exclusion: 2.

15. Anonymous. Systematic review and meta-analysis of randomised controlled trials on the effectiveness of school-based dental screening versus no screening on improving oral health in children. Br Dent J. 2017 May 12;222(9):675. doi: 10.1038/sj.bdj.2017.403. PMID: 28496244. Exclusion: 6.

16. Anttonen V, Halunen I, Päkkilä J, et al. A practice-based study on the effect of a short sucrose/xylitol exposure on survival of primary teeth caries free. Int J Paediatr Dent. 2012;22(5):356-62. doi: 10.1111/j.1365-263X.2011.01205.x. PMID: 22211678. Exclusion: 4.

17. Autio-Gold J. Recommendations for fluoride varnish use in caries management. Dent Today. 2008 Jan;27(1):64-7. PMID: 18240633. Exclusion: 2.

18. B T. A two-year study of 40% chlorhexidine varnish on the prevention of dental caries. J Oral Sci Res. 2003;19:521-3. Exclusion: 10.

19. Bader JD, Rozier RG, Lohr KN, et al. Physicians' roles in preventing dental caries in preschool children: a summary of the evidence for the U.S. Preventive Services Task Force. Am J Prev Med. 2004 May;26(4):315-25. PMID: 15110059. Exclusion: 2.

20. Bader JD, Vollmer WM, Shugars DA, et al. Results from the Xylitol for adult caries trial (X-ACT). J Am Dent Assoc. 2013 Jan;144(1):21-30. doi: 10.14219/jada.archive.2013.0010. PMID: 23283923. Exclusion: 4.

21. Bakhshandeh A, Ekstrand K. Infiltration and sealing versus fluoride treatment of occlusal caries lesions in primary molar teeth. 2-3 years results. Int J Paediatr Dent. 2015 Jan;25(1):43-50. doi: 10.1111/ipd.12096. PMID: 24460688. Exclusion: 5.

22. Batra M, Shah AF, Virtanen JI. Integration of oral health in primary health care through motivational interviewing for mothers of young children: A pilot study. J Indian Soc Pedod Prev Dent. 2018 Jan-Mar;36(1):86-92. doi: 10.4103/JISPPD.JISPPD_19_17. PMID: 29607846. Exclusion: 6.

23. Bawden JW. Fluoride varnish: a useful new tool for public health dentistry. J Public Health Dent. 1998;58(4):266-9. PMID: 10390707. Exclusion: 2.

24. Baygin O, Tuzuner T, Kusgoz A, et al. Antibacterial effects of fluoride varnish compared with chlorhexidine plus fluoride in disabled children. Oral Health Prev Dent. 2014;12(4):373-82. doi: 10.3290/j.ohpd.a32129. PMID: 24914426. Exclusion: 4.

25. Berger C, Bachman J, Casalone GG, et al. An oral health program for children. Nurse Pract. 2014 Feb 15;39(2):48-53. doi: 10.1097/01.NPR.0000441912.47395.46. PMID: 24441318. Exclusion: 6.

26. Bidwell J. Fluoride mouthrinses for preventing dental caries in children and adolescents. Public Health Nurs. 2018 01;35(1):85-7. doi: 10.1111/phn.12364. PMID: 28944499. Exclusion: 4.

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131. Green E. A clinical evaluation of two methods of caries prevention in newly-erupted first permanent molars. Aust Dent J. 1989 Oct;34(5):407-9. doi: 10.1111/j.1834-7819.1989.tb00696.x. PMID: 2818298. Exclusion: 4.

132. Gruner D, Paris S, Schwendicke F. Probiotics for managing caries and periodontitis: Systematic review and meta-analysis. J Dent. 2016 May;48:16-25. doi: 10.1016/j.jdent.2016.03.002. PMID: 26965080. Exclusion: 5.

133. Guedes RS, Piovesan C, Ardenghi TM, et al. Validation of Visual Caries Activity Assessment: A 2-yr Cohort Study. J Dent Res. 2014 Jul;93(7 Suppl):101S-7S. doi: 10.1177/0022034514531017. PMID: 24713370. Exclusion: 5.

134. Gugnani N, Gugnani S. Remineralisation and arresting caries in children with topical fluorides. Evid Based Dent. 2017 06 23;18(2):41-2. doi: 10.1038/sj.ebd.6401234. PMID: 28642564. Exclusion: 6.

135. Günay H, Dmoch-Bockhorn K, Günay Y, et al. Effect on caries experience of a long-term preventive program for mothers and children starting during pregnancy. Clin Oral Investig. 1998;2(3):137-42. doi: 10.1007/s007840050059. PMID: 9927915. Exclusion: 4.

136. Hallas D, Fernandez JB, Lim LJ, et al. OHEP: an oral health education program for mothers of newborns. J Pediatr Health Care. 2015 Mar-Apr;29(2):181-90. doi: 10.1016/j.pedhc.2014.11.004. PMID: 25547319. Exclusion: 7.

137. Hanno AG, Alamoudi NM, Almushayt AS, et al. Effect of xylitol on dental caries and salivary Streptococcus mutans levels among a group of mother-child pairs. J Clin Pediatr Dent. 2011 Fall;36(1):25-30. doi: 10.17796/jcpd.36.1.d4g77616714w3372. PMID: 22900440. Exclusion: 4.

138. Hansel Petersson G, Twetman S, Bratthall D. Evaluation of a computer program for caries risk assessment in schoolchildren. Caries Res. 2002 Sep-Oct;36(5):327-40. doi: 10.1159/000065963. PMID: 12399693. Exclusion: 4.

139. Hanwatkar P, Gajendra S, Veazie P, et al. Fluoride Varnish: Knowledge, Preferences and Practices of General and Pediatric Dentists. N Y State Dent J. 2017 Mar;83(2):37-42. PMID: 29920030. Exclusion: 6.

140. Harrison R, Benton T, Everson-Stewart S, et al. Effect of motivational interviewing on rates of early childhood caries: a randomized trial. Pediatr Dent. 2007 Jan-Feb;29(1):16-22. PMID: 18041508. Exclusion: 5.

141. Harrison RL, Veronneau J, Leroux B. Effectiveness of maternal counseling in reducing caries in Cree children. J Dent Res. 2012;91(11):1032-7. doi: 10.1177/0022034512459758. PMID: 22983408. Exclusion: 4.

142. Harrison RL, Wong T. An oral health promotion program for an urban minority population of preschool children. Community Dent Oral Epidemiol. 2003;31(5):392-9. doi: 10.1034/j.1600-0528.2003.00001.x. PMID: 14667011. Exclusion: 6.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

143.Hashizume LN, Mathias TC, Cibils DM, et al. Effect of the widespread use of fluorides on the occurrence of hidden caries in children. Int J Paediatr Dent. 2013 Jan;23(1):72-6. doi: 10.1111/j.1365-263X.2012.01231.x. PMID: 22348554. Exclusion: 4.

144.Hatefnia E, Alinasab A, Ghorbani M. Impact of theory-based educational intervention on promotion of caries-prevention behaviors in iranian mothers with 3-6-year-old children. Biomedical research (india). 2017;28(5):1969-74. Exclusion: 7.

145.Heavey E. Open wide: Oral health in primary care. Nursing. 2014 Mar;44(3):59-62. doi: 10.1097/01.NURSE.0000441882.95371.8c. PMID: 24531586. Exclusion: 6.

146.Hebbal M, Ankola A, Metgud S. Caries risk profile of 12 year old school children in an Indian city using Cariogram. Med Oral Patol Oral Cir Bucal. 2012 Nov 1;17(6):e1054-61. doi: 10.4317/medoral.17880. PMID: 22926464. Exclusion: 4.

147.Hedayati-Hajikand T, Lundberg U, Eldh C, et al. Effect of probiotic chewing tablets on early childhood caries--a randomized controlled trial. BMC Oral Health. 2015 Sep 24;15(1):112. doi: 10.1186/s12903-015-0096-5. PMID: 26403472. Exclusion: 5.

148.Henshaw MM, Borrelli B, Gregorich SE, et al. Randomized Trial of Motivational Interviewing to Prevent Early Childhood Caries in Public Housing. JDR Clin Trans Res. 2018 Oct;3(4):353-65. doi: 10.1177/2380084418794377. PMID: 30238060. Exclusion: 8.

149.Herndon JB, Tomar SL, Catalanotto FA. Effect of training pediatricians and family physicians in early childhood caries prevention. J Pediatr. 2015 Apr;166(4):1055-61.e1. doi: 10.1016/j.jpeds.2014.12.040. PMID: 25662286. Exclusion: 5.

150.Hinze ES, Casamassimo PS, Seale NS, et al. Relative value of oral health in well-child care: a survey of pediatricians in Texas and Ohio. J Dent Child (Chic). 2014 May-Aug;81(2):84-90. PMID: 25198951. Exclusion: 6.

151.Hodge P. Mouthwashes: Do They Work and Should We Use Them? Part 2: Anticaries, Antihalitosis and Dry Mouth Relief Efficacy of Mouthwashes. Dent Update. 2016 Sep;43(7):631-2, 4-6, 9-40. PMID: 29148673. Exclusion: 4.

152.Hofmeyr GJ, Lawrie TA, Atallah AN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018 10 01;10:CD001059. doi: 10.1002/14651858.CD001059.pub5. PMID: 30277579. Exclusion: 4.

153.Holgerson PL, Twetman S, Stecksen-Blicks C. Validation of an age-modified caries risk assessment program (Cariogram) in preschool children. Acta Odontol Scand. 2009;67(2):106-12. doi: 10.1080/00016350802714734. PMID: 19152150. Exclusion: 4.

154.Holley MA, Wiley LA, Marass AD. Watch Me Grow: A Well-Child Examination Protocol to Improve Preventive Care in Dominican Children. J Pediatr Health Care. 2019 May - Jun;33(3):263-9. doi: 10.1016/j.pedhc.2018.09.003. PMID: 30472029. Exclusion: 4.

155.Holmes R, Howe D, Landes DP. Oral health education and disease prevention in primary dental care: insight from a pilot intervention targeting children aged 0-7 years in northeast England. Community Dent Health. 2013 Sep;30(3):134-7. PMID: 24151785. Exclusion: 4.

156.Holt RD, Morris CE, Winter GB, et al. Enamel opacities and dental caries in children who used a low fluoride toothpaste between 2 and 5 years of age. Int Dent J. 1994 1994/08//;44(4):331-41. PMID: 7822059. Exclusion: 4.

157.Hom JM, Lee JY, Silverman J, et al. State Medicaid Early and Periodic Screening, Diagnosis, and Treatment guidelines: adherence to professionally recommended best oral health practices. J Am Dent Assoc. 2013 Mar;144(3):297-305. PMID: 23449906. Exclusion: 6.

158.Hong M, Vuong C, Herzog K, et al. Sealed primary molars are less likely to develop caries. J Am Dent Assoc. 2019 08;150(8):641-8. doi: 10.1016/j.adaj.2019.04.011. PMID: 31352965. Exclusion: 4.

159.Honkala S, Runnel R, Saag M, et al. Effect of erythritol and xylitol on dental caries prevention in children. Caries Res. 2014;48(5):482-90. doi: 10.1159/000358399. PMID: 24852946. Exclusion: 4.

160. Horst JA, Heima M. Prevention of Dental Caries by Silver Diamine Fluoride. Compend Contin Educ Dent. 2019 Mar;40(3):158-63; quiz 64. PMID: 30829497. Exclusion: 4.

161. Horst JA, Tanzer JM, Milgrom PM. Fluorides and Other Preventive Strategies for Tooth Decay. Dent Clin North Am. 2018 04;62(2):207-34. doi: 10.1016/j.cden.2017.11.003. PMID: 29478454. Exclusion: 2.

162. Hou J, Gu Y, Zhu L, et al. Systemic review of the prevention of pit and fissure caries of permanent molars by resin sealants in children in China. J Investig Clin Dent. 2017 Feb;8(1) doi: 10.1111/jicd.12183. PMID: 26272130. Exclusion: 4.

163. Hultquist AI, Brudin L, Bagesund M. Early childhood caries risk assessment in 1-year-olds evaluated at 6-years of age. Acta Odontol Scand. 2020 Jul 22:1-9. doi: 10.1080/00016357.2020.1795247. PMID: 32697607. Exclusion: 4.

164. Ijaz S. Low quality evidence for effectiveness of fluoridated milk. Evid Based Dent. 2015 Dec;16(4):99. doi: 10.1038/sj.ebd.6401126. PMID: 26680513. Exclusion: 6.

165. Innes NP, Clarkson JE, Douglas GVA, et al. Child caries management: A randomized controlled trial in dental practice. J Dent Res. 2020;99(1):36-43. doi: 10.1177/0022034519888882. PMID: 31771385. Exclusion: 5.

166. Ismail A, Razak IA, Ab-Murat N. The impact of anticipatory guidance on early childhood caries: a quasi-experimental study. BMC Oral Health. 2018;18(1):126-. doi: 10.1186/s12903-018-0589-0. Exclusion: 6.

167. Isokangas P, Söderling E, Pienihäkkinen K, et al. Occurrence of dental decay in children after maternal consumption of xylitol chewing gum, a follow-up from 0 to 5 years of age. J Dent Res. 2000;79(11):1885-9. doi: 10.1177/00220345000790111201. PMID: 11145360. Exclusion: 4.

168. Jackson EB. Outcomes of a quality improvement project examining early childhood caries and improving identification of at risk patients in a pediatric medical home setting. J Pediatr Nurs. 2015 Jul-Aug;30(4):543-9. doi: 10.1016/j.pedn.2014.10.020. PMID: 25448475. Exclusion: 7.

169. Jamieson L, Bradshaw J, Lawrence H, et al. Fidelity of Motivational Interviewing in an Early Childhood Caries Intervention Involving Indigenous Australian Mothers. J Health Care Poor Underserved. 2016;27(1A):125-38. PMID: 27763436. Exclusion: 7.

170. Jamieson L, Smithers L, Hedges J, et al. Follow-up of intervention to prevent dental caries among indigenous children in australia: A secondary analysis of a randomized clinical trial. JAMA Netw Open. 2019 Nov 01;2(11) doi: 10.1001/jamanetworkopen.2019.15611. PMID: 31774519. Exclusion: 4.

171. Jamieson L, Smithers L, Hedges J, et al. Dental Disease Outcomes Following a 2-Year Oral Health Promotion Program for Australian Aboriginal Children and Their Families: A 2-Arm Parallel, Single-blind, Randomised Controlled Trial. EClinicalMedicine. 2018 Jul;1:43-50. doi: 10.1016/j.eclinm.2018.05.001. PMID: 31193658. Exclusion: 4.

172. Jamieson LM, Smithers LG, Hedges J, et al. Follow-up of an intervention to reduce dental caries in indigenous Australian children: A secondary analysis of a randomized clinical trial. JAMA Netw Open. 2019 Mar 01;2(3):e190648. doi: 10.1001/jamanetworkopen.2019.0648. PMID: 30874781. Exclusion: 4.

173. Janakiram C, Deepan Kumar CV, Joseph J. Xylitol in preventing dental caries: A systematic review and meta-analyses. Journal of Natural Science Biology & Medicine. 2017 Jan-Jun;8(1):16-21. doi: 10.4103/0976-9668.198344. PMID: 28250669. Exclusion: 2.

174. Jiang M, Xie QY, Wong MCM, et al. Association between dental conditions, sliver diamine fluoride application, parental satisfaction, and oral health-related quality of life of preschool children. Clin Oral Investig. 2020 Sep 07;07:07. doi: 10.1007/s00784-020-03542-8. PMID: 32895767. Exclusion: 4.

175. Jiang S, McGrath C, Lo EC, et al. Motivational interviewing to prevent early childhood caries: a randomized controlled trial. J Dent. 2020;97(103349) doi: 10.1016/j.jdent.2020.103349. PMID: 32330548. Exclusion: 5.

176. Jordan KH, McGwin G, Childers NK. Overestimation of Early Childhood Caries Using the dmfs Index. Pediatr Dent. 2020 May 15;42(3):208-11. PMID: 32522324. Exclusion: 5.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

177. Jorgensen MR, Twetman S. A systematic review of risk assessment tools for early childhood caries: is there evidence? Eur Arch Paediatr Dent. 2020 Apr;21(2):179-84. doi: 10.1007/s40368-019-00480-2. PMID: 31559535. Exclusion: 4.

178. Joury E, Alghadban M, Elias K, et al. Impact of providing free preventive dental products without health workers' counselling on infants' tooth-brushing and bottle-feeding termination practices: a randomised controlled trial. Community Dent Health. 2016 Sep;33(3):213-7. doi: 10.1922/CDH_3841Joury05. PMID: 28509517. Exclusion: 6.

179. Joury E, Bernabe E, Sabbah W, et al. Systematic review and meta-analysis of randomised controlled trials on the effectiveness of school-based dental screening versus no screening on improving oral health in children. J Dent. 2017 Mar;58:1-10. doi: 10.1016/j.jdent.2016.11.008. PMID: 27884719. Exclusion: 4.

180. Joury E, Khairallah M, Sabbah W, et al. Inequalities in the frequency of free sugars intake among Syrian 1-year-old infants: a cross-sectional study. BMC Oral Health. 2016 Sep 8;16(1):94. doi: 10.1186/s12903-016-0287-8. PMID: 27608712. Exclusion: 6.

181. Kalhan TA, Un Lam C, Karunakaran B, et al. Caries risk prediction models in a medical health care setting. J Dent Res. 2020 Apr 20 doi: 10.1177/0022034520913476. PMID: 32311276. Exclusion: 5.

182. Karasz A, Bonuck K. Reducing pediatric caries and obesity risk in South Asian immigrants: randomized controlled trial of common health/risk factor approach. BMC Public Health. 2018 05 31;18(1):680. doi: 10.1186/s12889-018-5317-9. PMID: 29855352. Exclusion: 6.

183. Kavvadia K, Agouropoulos A, Gizani S, et al. Caries risk profiles in 2- to 6-year-old Greek children using the Cariogram. Eur J Dent. 2012 Oct;6(4):415-21. PMID: 23077422. Exclusion: 7.

184. Keightley AJ, Taylor GD. Fluoride varnish applications and caries incidence in pre-schoolers. Evid Based Dent. 2014 Sep;15(3):83-4. doi: 10.1038/sj.ebd.6401045. PMID: 25343395. Exclusion: 6.

185. Kemparaj U, Chavan S, Shetty NL. Caries risk assessment among school children in davangere city using cariogram. Int J Prev Med. 2014 May;5(5):664-71. PMID: 24932401. Exclusion: 4.

186. Kilinc G, Uzuner N, Karaman O. Effect of dental care programme and fluoridation in the prevention of dental caries in asthmatic children. JPMA J Pak Med Assoc. 2016 11;66(11):1378-84. PMID: 27812052. Exclusion: 4.

187. Kramer MS, Chalmers B, Hodnett ED, et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. JAMA. 2001;285(4):413-20. doi: 10.1001/jama.285.4.413. PMID: 11242425. Exclusion: 5.

188. Kranz AM, Lee J, Divaris K, et al. North Carolina physician-based preventive oral health services improve access and use among young Medicaid enrollees. Health Aff (Millwood). 2014 Dec;33(12):2144-52. doi: 10.1377/hlthaff.2014.0927. PMID: 25489032. Exclusion: 6.

189. Laitala ML, Alanen P, Isokangas P, et al. Long-term effects of maternal prevention on children's dental decay and need for restorative treatment. Community Dent Oral Epidemiol. 2013 Dec;41(6):534-40. doi: 10.1111/cdoe.12057. PMID: 23786466. Exclusion: 5.

190. Lalloo R, Kroon J, Tut O, et al. Effectiveness, cost-effectiveness and cost-benefit of a single annual professional intervention for the prevention of childhood dental caries in a remote rural Indigenous community. BMC Oral Health. 2015 Aug 29;15:99. doi: 10.1186/s12903-015-0076-9. PMID: 26318162. Exclusion: 6.

191. Lapinleimu H, Viikari J, Jokinen E, et al. Prospective randomised trial in 1062 infants of diet low in saturated fat and cholesterol. Lancet. 1995;345(8948):471-6. doi: 10.1016/s0140-6736(95)90580-4. PMID: 7861873. Exclusion: 5.

192. Lebrun-Harris LA, Canto MT, Vodicka P. Preventive oral health care use and oral health status among US children: 2016 National Survey of Children's Health. J Am Dent Assoc. 2019 Apr;150(4):246-58. doi: 10.1016/j.adaj.2018.11.023. PMID: 30922456. Exclusion: 2.

193. Lenkkeri AM, Pienihäkkinen K, Hurme S, et al. The caries-preventive effect of xylitol/maltitol and erythritol/maltitol lozenges: results of a double-blinded, cluster-randomized clinical trial in an area of natural fluoridation. Int J Paediatr Dent. 2012 May;22(3):180-90. doi: 10.1111/j.1365-263X.2011.01182.x. PMID: 21951305. Exclusion: 4.

194. Leverett DH, Adair SM, Vaughan BW, et al. Randomized clinical trial of the effect of prenatal fluoride supplements in preventing dental caries. Caries Res. 1997;31(3):174-9. doi: 10.1159/000262394. PMID: 9165186. Exclusion: 4.

195. Levey C, Innes N, Schwendicke F, et al. Outcomes in randomised controlled trials in prevention and management of carious lesions: a systematic review. Trials. 2017;18(1). Exclusion: 2.

196. Lewis CW. Fluoride and dental caries prevention in children. Pediatr Rev. 2014 Jan;35(1):3-15. doi: 10.1542/pir.35-1-3. PMID: 24385561. Exclusion: 6.

197. Li X, Zhong Y, Jiang X, et al. Randomized clinical trial of the efficacy of dentifrices containing 1.5% arginine, an insoluble calcium compound and 1450 ppm fluoride over two years. J Clin Dent. 2015;26(1):7-12. PMID: 26054185. Exclusion: 4.

198. Li Y, Tanner A. Effect of Antimicrobial Interventions on the Oral Microbiota Associated with Early Childhood Caries. Pediatr Dent. 2015 May-Jun;37(3):226-44. PMID: 26063552. Exclusion: 2.

199. Lima TJ, Ribeiro CCC, Tenuta LMA, et al. Low-Fluoride Dentifrice and Caries Lesion Control in Children with Different Caries Experience: A Randomized Clinical Trial. Caries Res. 2008;42(1):46-50. doi: 10.1159/000111749. Exclusion: 12.

200. Lin HK, Fang CE, Huang MS, et al. Effect of maternal use of chewing gums containing xylitol on transmission of mutans streptococci in children: a meta-analysis of randomized controlled trials. Int J Paediatr Dent. 2016 Jan;26(1):35-44. doi: 10.1111/ipd.12155. PMID: 25684114. Exclusion: 7.

201. Liu BY, Lo EC, Li CM. Effect of silver and fluoride ions on enamel demineralization: a quantitative study using micro-computed tomography. Aust Dent J. 2012 Mar;57(1):65-70. doi: 10.1111/j.1834-7819.2011.01641.x. PMID: 22369560. Exclusion: 4.

202. Llodra JC, Rodriguez A, Ferrer B, et al. Efficacy of silver diamine fluoride for caries reduction in primary teeth and first permanent molars of schoolchildren: 36-month clinical trial. J Dent Res. 2005 Aug;84(8):721-4. PMID: 16040729. Exclusion: 3.

203. Lo EC, Chu CH, Lin HC. A community-based caries control program for pre-school children using topical fluorides: 18-month results. J Dent Res. 2001 Dec;80(12):2071-4. doi: 10.1177/00220345010800120901. PMID: 11808764. Exclusion: 4.

204. Maguire A. ADA clinical recommendations on topical fluoride for caries prevention. Evid Based Dent. 2014 Jun;15(2):38-9. doi: 10.1038/sj.ebd.6401019. PMID: 24971851. Exclusion: 6.

205. Makinen KK, Jarvinen KL, Anttila CH, et al. Topical xylitol administration by parents for the promotion of oral health in infants: a caries prevention experiment at a Finnish Public Health Centre. Int Dent J. 2013 Aug;63(4):210-24. doi: 10.1111/idj.12038. PMID: 23879257. Exclusion: 6.

206. Marghalani AA, Guinto E, Phan M, et al. Effectiveness of Xylitol in Reducing Dental Caries in Children. Pediatr Dent. 2017 Mar 15;39(2):103-10. PMID: 28390459. Exclusion: 2.

207. Marinho CCV, Higgins PTJ, Logan S, et al. Fluoride toothpastes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2009(1). Exclusion: 4.

208. Marinho CCV, Higgins PTJ, Logan S, et al. Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2009 or 2003(1). Exclusion: 11.

209. Marinho CCV, Higgins PTJ, Sheiham A, et al. Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2009(1). Exclusion: 4.

210. Marinho VC, Chong LY, Worthington HV, et al. Fluoride mouthrinses for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2016 Jul 29;7:CD002284. doi: 10.1002/14651858.CD002284.pub2. PMID: 27472005. Exclusion: 4.

211. Marinho VC, Worthington HV, Walsh T, et al. Fluoride gels for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2015 Jun 15(6):CD002280. doi: 10.1002/14651858.CD002280.pub2. PMID: 26075879. Exclusion: 2.

212. Marinho VC, Worthington HV, Walsh T, et al. Fluoride varnishes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2013 Jul 11(7):CD002279. doi: 10.1002/14651858.CD002279.pub2. PMID: 23846772. Exclusion: 2.

213. Masoud MI, Allarakia R, Alamoudi NM, et al. Long-term clinical and bacterial effects of xylitol on patients with fixed orthodontic appliances. Prog Orthod. 2015;16(1). Exclusion: 4.

214. Medeiros PB, Otero SA, Frencken JE, et al. Effectiveness of an oral health program for mothers and their infants. Int J Paediatr Dent. 2015;25(1):29-34. doi: 10.1111/ipd.12094. PMID: 24393627. Exclusion: 4.

215. Megalaa N, Thirumurugan K, Kayalvizhi G, et al. A comparative evaluation of the anticaries efficacy of herbal extracts (Tulsi and Black myrobalans) and sodium fluoride as mouthrinses in children: A randomized controlled trial. Indian J Dent Res. 2018 Nov-Dec;29(6):760-7. doi: 10.4103/ijdr.IJDR_790_16. PMID: 30589005. Exclusion: 4.

216. Mei ML, Zhao IS, Ito L, et al. Prevention of secondary caries by silver diamine fluoride. Int Dent J. 2016 Apr;66(2):71-7. doi: 10.1111/idj.12207. PMID: 26689611. Exclusion: 4.

217. Mejare I, Axelsson S, Dahlen G, et al. Caries risk assessment. A systematic review. Acta Odontol Scand. 2014 Feb;72(2):81-91. doi: 10.3109/00016357.2013.822548. PMID: 23998481. Exclusion: 6.

218. Milgrom P, Horst JA, Ludwig S, et al. Topical silver diamine fluoride for dental caries arrest in preschool children: A randomized controlled trial and microbiological analysis of caries associated microbes and resistance gene expression. J Dent. 2018 01;68:72-8. doi: 10.1016/j.jdent.2017.08.015. PMID: 28866468. Exclusion: 4.

219. Milgrom P, Tut O, Rothen M, et al. Efficacy evaluation of an anti-caries varnish: protocol for a phase II randomised controlled trial. BMJ Open. 2017 06 30;7(6):e017866. doi: 10.1136/bmjopen-2017-017866. PMID: 28667230. Exclusion: 6.

220. Milgrom P, Tut O, Rothen M, et al. Addition of Povidone-Iodine to Fluoride Varnish for Dental Caries: A Randomized Clinical Trial. JDR Clin Trans Res. 2020 May 21:2380084420922968. doi: 10.1177/2380084420922968. PMID: 32437626. Exclusion: 4.

221. Mohammadi TM, Hajizamani A, Hajizamani HR, et al. Fluoride varnish effect on preventing dental caries in a sample of 3-6 years old children. Journal of International Oral Health. 2015 Jan;7(1):30-5. PMID: 25709364. Exclusion: 4.

222. Moyer VA, Force USPST. Prevention of dental caries in children from birth through age 5 years: US Preventive Services Task Force recommendation statement. Pediatrics. 2014 Jun;133(6):1102-11. doi: 10.1542/peds.2014-0483. PMID: 24799546. Exclusion: 2.

223. Muhoozi GKM, Atukunda P, Diep LM, et al. Nutrition, hygiene, and stimulation education to improve growth, cognitive, language, and motor development among infants in Uganda: A cluster-randomized trial. Matern Child Nutr. 2018;14(2):e12527-e. doi: 10.1111/mcn.12527. PMID: 28925580. Exclusion: 5.

224. Muthu MS, Ankita S, Renugalakshmi A, et al. Impact of Pharmacological Interventions in Expectant Mothers Resulting in Altered Mutans Streptococci Levels in their Children. Pediatr Dent. 2015 Sep-Oct;37(5):422-8. PMID: 26531084. Exclusion: 4.

225. N T. Studies on topical application of Ag (NH3)2F for the control of interproximal caries in human primary molars: 3. Clinical trial of Ag(NH3)2F on interproximal caries in human primary molars. Jpn J Pediatr Dent. 1981;19(3):537-45. Exclusion: 10.

226.Nakai Y, Shinga-Ishihara C, Kaji M, et al. Xylitol gum and maternal transmission of mutans streptococci. J Dent Res. 2010;89(1):56-60. doi: 10.1177/0022034509352958. PMID: 19948944. Exclusion: 4.

227.Nguyen TM, Christian B, Koshy S, et al. A Validation and Cost-Analysis Study of a Targeted School-Based Dental Check-Up Intervention: Children's Dental Program. Children (Basel). 2020 Nov 26;7(12):26. doi: 10.3390/children7120257. PMID: 33256020. Exclusion: 4.

228.Nguyen Y, Ueno M, Zaitsu T, et al. Caries arresting effect of silver diamine fluoride in vietnamese preschool children. International Journal of Clinical Preventive Dentistry. 2017 09/30;13:147-54. doi: 10.15236/ijcpd.2017.13.3.147. Exclusion: 4.

229.Nicol P, Anthonappa R, King N, et al. Caries burden and efficacy of a referral pathway in a cohort of preschool refugee children. Aust Dent J. 2015 Mar;60(1):73-9. doi: 10.1111/adj.12269. PMID: 25721281. Exclusion: 5.

230.Nicolae A, Levin L, Wong PD, et al. Identification of early childhood caries in primary care settings. Paediatr Child Health. 2018 Apr;23(2):111-5. doi: 10.1093/pch/pxx155. PMID: 29686495. Exclusion: 6.

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348. Zukanovic A. Caries risk assessment models in caries prediction. Acta Med Acad. 2013 Nov;42(2):198-208. doi: 10.5644/ama2006-124.87. PMID: 24308399. Exclusion: 7.

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:
Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls, with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on above criteria:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80%; accurate diagnostic procedures and measurements applied equally to cases and controls; and appropriate attention to confounding variables.
Fair: Recent, relevant, and without major apparent selection or diagnostic workup bias, but response rate less than 80% or attention to some but not all important confounding variables.
Poor: Major selection or diagnostic workup bias, response rate less than 50%, or inattention to confounding variables.

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
    - For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
    - For cohort studies: consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions

- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria:
Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup greater than or equal to 80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies
Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:
Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.
Poor: Has a fatal flaw, such as: uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

*Reference: U.S. Preventive Services Task Force Procedure Manual.
https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-

processes/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies. Accessed on August 9, 2021.

Appendix A7. Expert and Federal Reviewers

Expert Reviewers

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National Institute on Minority Health and Health Disparities

Appendix B1. Diagnostic Accuracy Studies for the Prevention of Dental Caries

Author, year*	Screening test	Reference standard	Country Setting Screener	Population	Sample size Proportion with condition	Definition of a positive screening exam	Proportion unexaminable by screening test	Analysis of screening failures	Proportion who underwent reference standard and included in analysis
Prior review									
Pierce et al., 2002	Primary care pediatrician exam following 2 hours of training	Pediatric dentist exam	United States Pediatric group practice Primary care pediatrician	Children <36 months of age with erupted teeth participating in the "Into the Mouths of Babes" program. Excluded if they had received fluoride varnish and oral screening within 3 months or were very ill	n=258 children Cavitated lesions: 9.7% (mean 0.3/child)	Identification of a cavitated lesion Identification of need for referral	Appears to be none	Not applicable	Appears to be all
Serwint et al., 1993	Pediatrician exam (not primary care provider) following 4 hours of training	Pediatric dentist exam	United States General pediatric clinic Pediatrician	Children 18 to 36 months of age, mother primary caretaker. Excluded for developmental delay or facial abnormalities	n=110 children Nursing caries (caries involving ≥1 teeth including the maxillary central or lateral incisors or the primary molars but sparing the mandibular incisors): 20% (22/110)	Identification of nursing caries	Not reported	Not reported	55% (61/110)

Appendix B1. Diagnostic Accuracy Studies for the Prevention of Dental Caries

Author, year*	Screening test	Reference standard	Country Setting Screener	Population	Sample size Proportion with condition	Definition of a positive screening exam	Proportion unexaminable by screening test	Analysis of screening failures	Proportion who underwent reference standard and included in analysis
Current review									
MacRitchie et al., 2012	DCRAM	Dental exam following criteria developed for the Dundee selective threshold methods for caries detection.	Scotland Setting unclear, likely home-based Screening by nurse 'health visitor'	Children born and resident in Dundee, Scotland, in 1 complete calendar year and followed longitudinally for 4 years.	n=1681 Any d_1 at year 1: 3% Any d_3 at year 1: 0.4% Any d_1 at year 4: 49% Any d_3 at year 4: 33%	At age 4 years: $d_1$mft ≥1 or ≥3 $d_3$mft ≥1 or ≥3	Appears to be none	Not applicable	99.8%

Appendix B1. Diagnostic Accuracy Studies for the Prevention of Dental Caries

Author, year*	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC (95% CI)	Quality rating
Prior review						
Pierce et al., 2002	Patient-level analysis: 0.76 (19/25), 95% CI, 0.55 to 0.91 Tooth-level analysis: 0.49 (39/80), 95% CI, 0.37 to 0.60 Need for referral: 0.63 (17/27), 95% CI, 0.42 to 0.81	Patient-level analysis: 0.95 (222/233), 95% CI, 0.92 to 0.98 Tooth-level analysis: 0.99 (3210/3235), 95% CI, 0.99 to 0.99 Need for referral: 0.98 (225/231), 95% CI, 0.95 to 0.99	Patient-level analysis: 0.63 (19/30), 95% CI, 0.48 to 0.76; 0.83 (25/30) if precavitated lesions re-classified as true-positives Tooth-level analysis: 0.61 (39/64), 95% CI, 0.50 to 0.71 Need for referral: 0.74 (17/23), 95% CI, 0.55 to 0.87	Patient-level analysis: 0.97 (222/228), 95% CI, 0.95 to 0.99 Tooth-level analysis: 0.99 (3210/3251), 95% CI, 0.98 to 0.99 Need for referral: 0.96 (225/235), 95% CI, 0.93 to 0.97	NR	Good
Serwint et al., 1993	1.0 (n/N not calculable)	0.87 (n/N not calculable)	Not calculable	Not calculable	NR	Fair
Current review						
MacRitchie et al., 2012	$d_1$mft >0: 0.67 $d_3$mft >0: 0.53 $d_1$mft ≥3: 0.69 $d_3$mft ≥3: 0.65	$d_1$mft >0: 0.57 $d_3$mft >0: 0.77 $d_1$mft ≥3: 0.60 $d_3$mft ≥3: 0.69	NR	NR	NR	Fair

*See Appendix A4 for full citations of included studies.

Abbreviations: AUC=area under the curve; DCRAM=Dundee Caries Risk Assessment Model; CI=confidence interval; NR=not reported.

Appendix B2. Quality Ratings for Diagnostic Accuracy Studies

Author, year*	Representative spectrum	Random or consecutive sample	Screening test adequately described	Screening cutoffs predefined	Credible reference standard	Reference standard applied to all screened patients	Same reference standard applied to all patients
MacRitchie, 2012	Yes	Yes	Yes	No	Yes	Yes (99%)	Yes
Serwint, 1993	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Pierce, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix B2. Quality Ratings for Diagnostic Accuracy Studies

Author, year*	Reference standard and screening examination interpreted independently	Reference standard assessed by blinded assessor	Screening test assessed by blinded assessor	High rate of uninterpretable results, noncompliance with screening test, or attrition	Analysis includes patients with uninterpretable results or noncompliance	Quality rating
MacRitchie, 2012	Yes	Unclear	Unclear	No	No	Fair
Serwint, 1993	Yes	Yes	Yes	Unclear	Unclear	Fair
Pierce, 2002	Yes	Yes	Yes	No	Not applicable	Good

*See Appendix A4 for full citations of included studies.

Appendix B3. Trials of Educational Interventions for the Prevention of Dental Caries

Author, year*	Study Design	Interventions	Baseline population characteristics	Eligibility criteria	Number approached, eligible, enrolled, analyzed	Country Setting	Sponsor
Current report							
Basir et al., 2017	RCT	A. 2 brief in-person sessions (1 individual, 1 group; ≤30 minutes each), text message reminders every 2 weeks for 6 months, and pamphlet containing tips on the promotion of educational items and the need for oral health care for their children B. Usual well baby visit care without an oral health component	A vs. B Mean child age (SD): 1.5 (0.6) years Mean maternal age (SD): 31 (6.7) years Female: 50% Race/ethnicity: NR No prior dental visit: 71% vs. 73% Education >high school: 90% Caries at baseline: NR Toothbrushing: NR	Mothers of children age 12 to 36 months without caries and with ≥8 completely erupted teeth, 4 maxillary anteriors, and 4 mandibular anteriors	Approached: 140 Eligible: 107 Enrolled: 104 (52 vs. 52) Analyzed: 104 (52 vs. 52)	Iran Maternal-child health wards Water fluoridation: NR	No external funding

Appendix B3. Trials of Educational Interventions for the Prevention of Dental Caries

Author, year*	Duration of followup	Confounders adjusted for in analysis	Outcomes	Adverse events/harms	Attrition	Quality rating	Comments
Current report							
Basir et al., 2017	6 months	NA	A vs. B Caries incidence (WHO criteria, including white spot lesions non-cavitated and categorized as D1): 13.5% (7/52) vs. 34.7% (17/49); RR 0.39 (95% CI, 0.18 to 0.85)	Not reported	Unclear	Fair	Fig 1 show all pts were analyzed at followup but that math doesn't work for the reported caries incidence (35% of 52=18). I calculated the N based on an n=17 and incidence of 35%.

*See Appendix A4 for full citations of included studies.

Abbreviations: CI=confidence interval; NA=not applicable; NR=not reported; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; WHO=World Health Organization.

Appendix B4. Quality Ratings of Randomized, Controlled Trials of Topical Fluoride

Author, year*	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis	Patients with missing data analyzed?
Agouropoulos et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Anderson et al., 2016 Anderson et al., 2017	Unclear	No	Yes	No	No	No	Yes	No
Basir et al., 2017	Yes	Yes	Yes	Yes	No	No	Yes	No
Frostell et al., 1991	NR	NR	NR	Unclear	No	No	Unclear	No
Jiang et al., 2005	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No
Jiang et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Latifi-Xhemajli et al., 2019	Yes	Unclear	Yes	Yes	No	No	Yes	No
Lawrence et al, 2008	Yes	Unclear	Yes	Unclear	No	No	Yes	No
McMahon et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Memarpour et al, 2015	Yes	Unclear	Yes	Yes	No	No	Yes	No
Memarpour et al, 2016	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	No
Muñoz-Millán, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oliveira et al., 2014 dos Santos et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Oscarson et al., 2006	NR	NR	Yes	Yes	No	No	Yes	No
Slade et al, 2011	Yes	Yes	Yes	No	No	No	Yes	Yes
Tickle et al., 2016 Tickle et al., 2017	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No
Weintraub et al., 2006	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Zhan et al., 2012	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes

Appendix B4. Quality Ratings of Randomized, Controlled Trials of Topical Fluoride

Author, year*	Acceptable levels of overall attrition and between-group differences in attrition?	Post-randomization exclusions	Avoidance of selective outcomes reporting	Adjusted for cluster correlation?	Quality rating
Agouropoulos et al., 2014	No/Yes	No	Yes	NA	Fair
Anderson et al., 2016 Anderson et al., 2017	No/Yes	No	Yes	Yes	Fair
Basir et al., 2017	Yes/Yes	No	Yes	NA	Fair
Frostell et al., 1991	Unclear	No	Yes	NA	Fair
Jiang et al., 2005	Yes/Yes	No	Yes	Yes	Fair
Jiang et al., 2014	Yes/Yes	No	Yes	NA	Good
Latifi-Xhemajli et al., 2019	Yes/Yes	No	Yes	NA	Fair
Lawrence et al, 2008	Yes/Yes	No	Yes	Yes	Fair
McMahon et al., 2020	Yes/Yes	No	Yes	NA	Good
Memarpour et al, 2015	Yes/Yes	No	Yes	NA	Fair
Memarpour et al, 2016	Yes/Yes	No	Yes	NA	Fair
Muñoz-Millán, 2018	No/Yes	No	Yes	NA	Fair
Oliveira et al., 2014 dos Santos et al., 2016	Yes/Yes	No	Yes	NA	Good
Oscarson et al., 2006	Yes/Yes	No	Yes	NA	Fair
Slade et al, 2011	Yes/Yes	No	Yes	Yes	Fair
Tickle et al., 2016 Tickle et al., 2017	Yes/Yes	No	Yes	NA	Fair
Weintraub et al., 2006	No/Yes	No	Yes	NA	Fair
Zhan et al., 2012	Yes/No (10% vs. 23%)	No	Yes	NA	Fair

*See Appendix A4 for full citations of included studies.

Abbreviations: NA=not applicable; NR=not reported.

Appendix B5. Cohort Studies of Dental Referral From a Primary Care Clinician for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Population characteristics	Eligibility criteria	Number approached, eligible, enrolled, analyzed	Country	Sponsor
Prior Report							
Beil et al., 2012	Cohort	A: First preventive dental visit by age 18 months B: First preventive dental visit after age 18 months	A vs. B Female: 46% vs. 48-51% Non-white race: 67% vs. 66-67% Number of well-child visits: 1.8 vs. 1.4-1.7 Percent of population in county under 18 months of age enrolled in Medicaid: 30% vs. 31-33% Dentists per capita in county: 5.1 vs. 4.5-4.9	Children enrolled in North Carolina Medicaid prior to first birthday, enrolled for at least 12 months, with a paid claim for dental care (1999-2006) Excluded if they received dental services in medical office as part of the Into the Mouths of Babes fluoride varnish program.	Approached: 165,383 Eligible: 19,888 Enrolled: 19,888 Analyzed: 19,888	United States	AHRQ and NIDCR
Current Report							
Beil et al., 2014	Cohort	A: First preventive dental visit by age 24 months B: First preventive dental visit at age 24 to 36 months C: First preventive dental visit at age 37 to 48 months D: First preventive dental visit at 49 to 60 months	A vs. B vs. C vs. D Female: 47.5% vs. 50.6% vs. 49.5% vs. 48.2% White: 42.0% vs. 38.7% vs. 36.6% vs. 39.2% Black: 44.0% vs. 48.4% vs. 51.6% vs. 46.0% Hispanic: 11.6% vs. 11.4% vs. 9.7% vs. 12.1% Other race: 2.4% vs. 1.5% vs. 2.0% vs. 2.7% Mean (SD) number of well-child visits: 1.68 (1.13) vs. 1.34 (1.11) vs. 1.24 (1.12) vs. 1.15 (1.09) Medicaid enrollees under age 18 years in county of residence: 34.8% vs. 34.7% vs. 36.0% vs. 35.8% Mean (SD) number of dentists per 10,000 population: 4.11 (2.04) vs. 4.10 (2.01) vs. 3.83 (1.97) vs. 3.79 (1.91)	Children enrolled in North Carolina Medicaid prior to first birthday, still enrolled after turning 1 year, and did not receive preventive dental services in a medical office (2005-2006)	Approached: NR Eligible: 11,394 Enrolled: 11,394 Analyzed: 11,394	United States	AHRQ and NIDCR

Appendix B5. Cohort Studies of Dental Referral From a Primary Care Clinician for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Population characteristics	Eligibility criteria	Number approached, eligible, enrolled, analyzed	Country	Sponsor
Blackburn et al, 2017	Cohort	A: ≥1 preventive dental visit delivered by dental health care professional B: No preventive dental visits	A vs. B Female: 50.9% vs. 50.7% Black: 44.0% vs. 43.4% White: 37.6% vs. 38.3% Hispanic: 16.3% vs. 16.5% Other race: 2.0% vs. 1.8%	Children enrolled in Alabama's Medicaid program from birth for 3 or more years (2008-2012)	Approached: NR Eligible: NR Enrolled: 9732 Analyzed: 9732	United States	Lister Hill Center for Health Policy at the University of Alabama at Birmingham School of Public Health
Kranz, et al., 2014a	Cohort	A: Received ≥2 preventive oral health visits from a PCC B: Received ≥2 preventive oral health visits from a dental health care professional C: Received ≥2 preventive oral health visits from a PCC and a dental health care professional	A vs. B vs. C Female: 48.4% vs. 50% vs. 46.6% White: 39.4% vs. 34.4% vs. 36.4% Black: 41.6% vs. 42.1% 42.7% Hispanic: 7.0% vs. 14.2% vs. 11.9% Mean (SD) number of well-child visits before age 3 years: 5.0 (1.4) vs. 4.0 (2.2) vs. 4.9 (1.6) Medicaid eligible people under 18 years old per 10,000 people: 511.2 (SD 144.0) vs. 417.7 (SD 123.5) vs. 452.8 (SD 124.4) Mean (SD) number of dentists per 10,000 people: 3.3 (1.4) 4.6 (1.7) vs. 3.8 (1.7)	Children enrolled in North Carolina Medicaid prior to first birthday, still enrolled after turning 1 year, and received preventive dental services before the age of 3 years (2005-2006)	Approached: NR Eligible: 5235 Enrolled: 5235 Analyzed: 5235	United States	AHRQ and NIDCR

Appendix B5. Cohort Studies of Dental Referral From a Primary Care Clinician for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Population characteristics	Eligibility criteria	Number approached, eligible, enrolled, analyzed	Country	Sponsor
Kranz, et al., 2014b	Cohort	A: Received preventive oral health visits from a PCC B: Received preventive oral health visits from a dental health care professional C: Received preventive oral health visits from a PCC and a dental health care professional	A vs. B vs. C Age: 3-5 years overall Female: 48.7% vs. 48.9% vs. 47.2% White: 37.8% vs. 29.4% vs. 33.8% Black: 39.1% vs. 39.3% vs. 39.0% Hispanic: 12.6% vs. 20.1% vs. 18.2% Mean (SD) number of well-child visits before age 3 years: 4.8 (1.3) vs. 3.9 (1.9) vs. 4.6 (1.4) Medicaid eligible people <18 years old per 10,000 people: 0.2 (SD 0.1) vs. 0.2 (SD 0.1) vs. 0.2 (SD 0.1) Mean (SD) number of dentists per 10,000 people: 43.6 (1.6) vs. 5.2 (1.8) vs. 4.3 (1.9)	Children enrolled in North Carolina Medicaid prior to first birthday, enrolled for ≥12 months before age 3 years, enrolled for ≥7 months after turning 3 years, with >1 visit to PCPs, dentists, or both before age 3 years (2000-2006)	Approached: NR Eligible: 41,453 Enrolled: 41,453 Analyzed: 41,453	United States	AHRQ and NIDCR
Sen et al., 2016	Cohort	A: ≥1 preventive dental visit B: No preventive dental visits	A vs. B Age, mean (SD), years: 4.5 (0.7) vs. 4.0 (0.8) Female: 49.5% vs. 47.6% White: 67.2% vs. 72.5% Black: 23.6% vs. 17.3% Other race: 9.2% vs. 10.2% Well-child visits by 3 years, mean (SD) per child: 6.1 (3.7) vs. 6.6 (3.7)	Children enrolled in Alabama's CHIP program from birth to 4 years old (1998-2012)	Approached: NR Eligible: NR Enrolled: 4774 Analyzed: 4774	United States	Alabama Department of Public Health and Alabama Children's Health Insurance Program

Appendix B5. Cohort Studies of Dental Referral From a Primary Care Clinician for the Prevention of Dental Caries

Author, year*	Duration of followup	Confounders adjusted for in analysis	Outcomes	Adverse events/ harms	Attrition	Quality rating
Prior Report						
Beil et al., 2012	Through 72 months of age	Age, race/ethnicity, caregiver employment, caregiver education, language spoken at home, diet score, hygiene score, tooth monitoring score	Subsequent dental treatment, first preventive visit at 18-24, 25-30, 31-36, or 37-42 months vs. <18 months (reference) Primary or secondary preventive visit: Incidence density ratio 0.98 (0.87-1.1), 1.1 (0.94-1.2), 1.1 (0.96-1.2), and 1.1 (0.95-1.2) Tertiary preventive visit: Incidence density ratio 1.2 (1.0-1.4), 1.2 (1.1-1.4), 1.1 (0.99-1.3), and 1.4 (1.2-1.6)	Not reported	None reported	Fair
Current Report						
Beil et al., 2014	Up to 5 years of age (assessment in kindergarten)	Child-level: gender, race, number of well-child visits from age 12 to 24 months, and whether child was continuously enrolled in Medicaid County-level: % of population under age 18 enrolled in Medicaid, metropolitan status, and number of dentists per 10,000 population	A vs. B vs. C vs. D Any with untreated caries among those with caries (n=6749): 41.3% vs. 33.9% vs. 38.8% vs. 42.2%, p<0.01 for B vs. others B vs. C vs. D (reference A) Adjusted IRR (95% CI) for dmft index: 0.98 (0.90 to 1.07) vs. 0.88 (0.81 to 0.95) vs. 0.75 (0.69 to 0.82); p<0.05 for A vs. C and D Adjusted OR (95% CI) for having any untreated dental disease among children with any dental disease (n=6749): 0.71 (0.56 to 0.90) vs. 0.82 (0.66 to 1.03) vs. 0.97 (0.77 to 1.22), p<0.01 for A vs. B	Not reported	None reported	Fair
Blackburn et al, 2017	3 years	Propensity score matching of health services utilization, race, rural-urban community, age, fluoridation level	A vs. B Received any caries-related treatment visit: 20.6% vs. 11.3%, p<0.001 Any annual dental visit: 80.1% vs. 42.8%, p<0.001 Received fluoride varnish during the first 2 years of life: 84.3% vs. NA Number of fluoride varnishes received, mean (SD): 1.1 (0.7) vs. NA Difference in number of annual caries-related visits: 0.15 (95% CI, 0.11 to 0.16) Difference in caries-related expenditures: -0.01 (95% CI, -0.13 to 0.12) Different in annual dental expenditures: 0.03 (95% CI, -0.06 to 0.13)	Not reported	None reported	Fair

Appendix B5. Cohort Studies of Dental Referral From a Primary Care Clinician for the Prevention of Dental Caries

Author, year*	Duration of followup	Confounders adjusted for in analysis	Outcomes	Adverse events/ harms	Attrition	Quality rating
Kranz, et al., 2014a	Up to 3 years of age	Propensity score matching of sex, race, Hispanic ethnicity, total number of months enrolled in Medicaid, number of well-child visits, indicators of special heal care needs, receipt of caries-related treatment, whether any preventive oral health services were received in a federally qualified health center, health department, or rural health clinic, proportion of population with access to fluoridated public drinking water, rural or urban status, number of dentists, pediatricians, and family practice physicians per 10,000, and Medicaid-eligible children younger than 18 years	A vs. B vs. C Received any caries-related treatment before age 3 years: 24.0% vs. 39.2% vs. 31.0% A vs. C (reference B) OR (95% CI) of >0 dmft: 1.06 (0.78 to 1.46) vs. 0.77 (0.52 to 1.14) IRR (95% CI) of expected number of dmft for children at risk for dmft (n=2521): 0.95 (0.82 to 1.09) vs. 0.94 (0.82 to 1.08) OR (95% CI) of untreated decayed teeth of those at risk for dmft (n=2521): 2.05 (1.28 to 3.30) vs. 1.34 (0.82 to 2.19), p<0.01 for A vs. B	Not reported	None reported	Fair
Kranz, et al., 2014b	Up to 5 years of age	Child-level: sex, race, Hispanic ethnicity, months enrolled in Medicaid per year, number of well-child visits, indicators of special health care needs, whether any preventive oral health services were received in a public clinic, year that treatment was received County-level: proportion of population with access to fluoridated drinking water; rural or urban status; and the number of dentists, pediatricians, and family practice physicians, and Medicaid-eligible children under 18 years per 10,000 population	A vs. B vs. C Received any caries-related treatment between ages 3 to 5 years: 26.7% vs. 51.8% vs. 47.6%	Not reported	None reported	Fair
Sen et al., 2016	3 years	Propensity score matching of health services utilization, race, rural-urban community, age, fluoridation level	A vs. B Difference in number of restorative dental visits (adjusted): 11.1%, p<0.001 Difference in number of emergency dental visits (adjusted): 1.9%, p<0.05	Not reported	None reported	Fair

*See Appendix A4 for full citations of included studies.

Appendix B5. Cohort Studies of Dental Referral From a Primary Care Clinician for the Prevention of Dental Caries

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; CHIP=Children's Health Insurance Program; CI=confidence interval; IRR=incidence rate ratio; NIDCR=National Institute of Dental and Craniofacial Research; NA=not applicable; NR=not reported; OR=odds ratio; PCC=primary care clinician; SD=standard deviation.

Appendix B6. Quality Ratings of Included Cohort Studies

Author, year* Country	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders (i.e., age, sex, other medications)?	Were outcome assessors and/or data analysts blinded to exposure being studied?	Did the article report attrition or missing data?	Is there important differential loss to followup or overall high loss to followup or missing data?	Were appropriate confounders analyzed (i.e., age, sex, other medications)?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating
Beil et al., 2012 United States	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Beil et al., 2014 United States	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Blackburn et al, 2017 United States	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Kranz, et al., 2014a United States	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Kranz, et al., 2014b United States	Yes	Mostly	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Sen et al, 2016 United States	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair

*See Appendix A4 for full citations of included studies.

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Baseline population characteristics	Eligibility criteria
Prior Report				
Frostell et al., 1991	RCT	A: Duraphat treatment twice a year B: No treatment Most children were exposed to fluoride toothpaste and some use fluoride tablets and mouth rinse solutions. Interventionist: NR	Age: 4 years Female: NR Race: NR Mean $dmfs_1$: 4.79	4 year old children Excluded: Those who developed ≥10 caries between 3 and 4 years of age.
Jiang et al., 2005	Cluster RCT (15 clusters)	A: 0.6 to 0.8 g of 1.23% acidulated phosphate fluoride foam applied every 6 months, max 4 applications B: Placebo foam No oral health education described Interventionist: 2 dental health care professionals and 2 assistants	Age, mean (SD): 3.6 (0.6) years Female: 46% Race: NR dmft, mean (SD): 1.6 (2.5) dmfs, mean (SD): 2.6 (4.3) Use of fluoride toothpaste: 22% Daily toothbrushing: 46%	Children 3 to 4 years of age Excluded: Not reported
Lawrence et al., 2008	Cluster RCT (20 clusters)	A: 0.3 to 0.5 ml 5% sodium fluoride varnish (Duraflor) applied every 6 months B: No fluoride varnish All children: Parental oral health education at baseline, 12 and 24 months Interventionist: dental health care professionals	Age, mean (SD): 2.5 (1.2) years Female: 51%% Race: 100% aboriginal dmft, mean (SD): 7.0 (6.2) dmft >0: 72% Daily toothbrushing: NR	Children 6 month to 5 years of age, with at least one primary tooth Excluded: No teeth, stainless steel crowns only, ulcerative gingivitis, stomatitis or allergy to colophony component.
Slade et al., 2011	Cluster RCT (30 clusters)	A: 0.25 ml 5% sodium fluoride varnish (Duraphat) every 6 months, parental oral health education and provision of toothbrush and toothpaste (low concentration fluoride) B: No interventionsInterventionist: dental health care professionals	Age, mean: 2.8 years Female: 49% Race: All aboriginal dmfs >0: 62.5% $d_3$mfs, mean: 4.7 Daily toothbrushing: NR	Aboriginal identity, 18 to 48 months of age Excluded: Asthma

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Baseline population characteristics	Eligibility criteria
Weintraub et al., 2006	RCT	A: 0.1 mL 5% sodium fluoride varnish (Duraphat) applied at 6 month intervals with 4 intended applications B: 0.1 mL 5% sodium fluoride varnish (Duraphat) applied once per year with 2 intended applications C: No fluoride varnish (gauze dipped in varnish, then folded and dry area applied to teeth) All children: Parental oral health education annually Interventionist: dental health care professionals	Age, mean (SD): 1.8 (0.6) years Female: 53% Hispanic: 47% Asian: 46% Other race/ethnicity: 7% dmfs: 0 (excluded) Daily toothbrushing: NR	6 to 44 months if age, 4 erupted maxillary incisors, caries-free without demineralized white spots Excluded: Medical problems or medications affecting oral health e.g. cleft lip/palate
Current Report				
Agouropoulos et al., 2014	Cluster RCT (10 clusters)	A: 0.2 ml 0.9% diflurosilane (1000 ppm fluoride) at 6 month intervals B: Placebo varnish without fluoride at 6 month intervals All children: Supervised toothbrushing at school with fluoride toothpaste, parental oral health education, and toothbrushing instructions Interventionist: dental health care professionals	Age, mean (SD): 3.4 (0.8) years Female: 49.6% Race: NR dmfs, mean (SD): 2.8 (6.4) Caries: 37.5% Daily toothbrushing: NR	Children ages 2 to 5 years attending one of the preselected public preschools. Excluded: Born outside of Greece, antibiotics within the last 2 weeks
Anderson et al., 2016Same as Anderson et al., 2017	Cluster RCT (23 clusters)	A: 0.25 ml sodium fluoride varnish (5.65 mg Duraphat) on the buccal surface of teeth every 6 months B: No fluoride varnish All children: Parental oral health education, toothpaste, and toothbrush at 12, 24, and 36 months Interventionist: examiner, not specified, or dental assistant	Age: 1 year Female: 51.5% Race: NR ICDAS 1-6: 5.2% ICDAS 3-6: 0.6% ICDAS 5-6: 0.2% Daily toothbrushing: 55.1%	All children born in 2010 and living in the selected areas. Excluded: Not reported

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Baseline population characteristics	Eligibility criteria
Anderson et al., 2017 Same as Anderson et al., 2016	Cluster RCT (23 clusters)	A: 0.25 ml sodium fluoride varnish (Duraphat) on the buccal surface of teeth every 6 months B: No fluoride varnish All children: Parental oral health education, toothpaste, and toothbrush at 12, 24, and 36 months Interventionist: examiner, not specified, or dental assistant	Age: 1 year old Female: 53% Race: NR ICDAS 3-6 score: 3% Daily toothbrushing: 50%	Children enrolled in "Stop Caries Stockholm" (see Anderson et al., 2016) who developed caries between 1 and 3 years of the study period.
Jiang et al., 2014	RCT	A. 5% sodium fluoride varnish (Clinpro White Varnish) at 6 month intervals, also hands-on training on brushing child's teeth at baseline and toothbrush provided at 6 month intervals B: Hands-on training on brushing child's teeth at baseline; toothbrush provided and toothpaste without fluoride (placebo) administered at 6 month intervals C. No additional intervention All children: Parental health education at baseline Interventionist: dental health care professionals	Age, mean (SD): 1.3 (0.3) years Female: 56% Race: NR dmft, mean (SD): 0.03 (0.24) Daily toothbrushing: 12%	Children 8 to 23 months of age Excluded: Major systemic disease or on long-term medication; not cooperative and refused examination
Latifi-Xhemajli et al., 2019	RCT	A: 1.5% (7700 ppm) ammonium fluoride (Fluor Protector S) applied every 3 months for 2 years B: Usual care (control group had no F-varnish applied, unless their parents were advised for their child's basic oral health care) Interventionist: 2 pediatric dental health care professionals	Age, mean: 21 months Female: NR Race: NR dmfs, mean (SD): 1.1 (2.9) Daily toothbrushing: NR	Children 6 to 30 months with parental permission.
McMahon et al., 2020	RCT	A: Duraphat 50 mg/mL applied every 6 months B: Placebo varnish applied every 6 months All children: daily supervised toothbrushing Interventionist: dental health care professionals	Age, mean: 3.53 years (SD 0.24) Female: 50% Race: NR Caries at baseline: 17% Mean $d_3$mfs: 1.1 (SD 3.5) SIMD 1 (most deprived): 21%	3 year old children attending their first year of education in nursery schools. Excluded: Those with contraindications for fluoride varnish, history of bronchial asthma requiring hospitalization, history of allergic episodes requiring hospital admission, showing signs of distress on

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Baseline population characteristics	Eligibility criteria
				the day of baseline inspection, or showing signs of verbal or nonverbal reluctance.
Memarpour et al., 2015	RCT	A: 5% (22,600 ppm) sodium fluoride varnish (DuraShield) and parental oral health education every 4 months B: Educational pamphlet and motivational oral health counseling every 4 months C: CPP-ACP twice a day after teeth brushing and information on oral hygiene D: Dental examination onlyInterventionist: dental health care professionals	Age, mean (SD): 1.8 (0.6) years Female: NR Race: NR dmft: 0 (excluded) Daily toothbrushing: NR	Children 12 to 36 months, having lived since birth in towns with a similar water fluoridation level (<0.7 ppm) and at least 4 erupted maxillary primary incisors with at least 2 white spot lesions Excluded: Those who showed signs of cavitated caries or who did not use any oral hygiene methods, fluoride-containing products, or other preventive measures at home or at dental clinics; history of systemic disease, congenital physical or mental disability, oral or dental anomalies or disabilities, a history of drug allergies, allergies to milk protein or benzoate preservatives.
Memarpour et al., 2016	RCT	A. 5% sodium fluoride varnish at 6 month intervals; parental oral health education and training on proper toothbrushing at baseline B: Placebo varnish at 6 month intervals; parental oral health education and training on proper toothbrushing at baseline C. Placebo varnish at 6 month intervals without oral health education or training Interventionist: dental health care professionals	Age, mean (SD): 1.7 (0.7) years Female: 46% Race: NR Maternal high school diploma or higher: 55% dmft: 0 (excluded) Daily toothbrushing: 0%	Children age 12 to 24 months Excluded: Systemic diseases, drug allergies, congenital physical or mental disabilities, oral or dental anomalies or disabilities
Muñoz-Millán et al., 2018	RCT	A: 0.5 mL of fluoride varnish (Profluorid Varnish®) every 6 months B: 0.5 mL innocuous placebo varnish every 6 months All children: twice a year received a toothbrush and a tube of children's 500 ppm fluoride toothpaste, and supervised daily toothbrushing Interventionist: not described	Age, mean (SD): 32.9 (6.2) months Female: 54% Race: NR Daily toothbrushing: 100% -Brushing ≥2/day: 72% Good to fair oral hygiene index: 58% Visible plaque: 76%	2 to 3 year old children without cavitated carious lesions or previous dental treatments Excluded: Children with systemic diseases, disabilities or developmental enamel defects, and those with temporary residences.

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Baseline population characteristics	Eligibility criteria
Oliveira et al., 2014 dos Santos et al., 2016	RCT	A: 5% (22,600 ppm) sodium fluoride varnish at 6 month intervals B: Placebo varnish All children: Parental oral health education, free toothpaste and toothbrush at baseline Interventionist: trained undergraduate or graduate dental students	Age, mean (SD): 2.4 (0.9) years Female: 47% Race: NR $d_2$mfs, mean (SD): 0.9 (2.1) $d_3$mfs, mean (SD): 0.8 (1.9) Caries: 23.5% Daily toothbrushing: 80%	1 to 4 years of age Excluded: Fluoride application in the previous 6 months, >10 dental surfaces with dentine caries lesions, dental abscess, or systemic disease that could be aggravated by a dental problem.
Tickle et al., 2016 Tickle et al., 2017	RCT	A: 22,600 ppm fluoride varnish at 6 month intervals; also provided toothbrush and 50 mL tube of 1,450 ppm fluoride toothpaste B: No fluoride intervention All children: Parental oral health education every 6 months Interventionist: dental health care professionals	Age, mean (SD): 3.1 (0.53) years Female: 54% Race: NR dmft: 0 (excluded) Daily toothbrushing: NR	2 to 3 years of age Excluded: Dentin caries, history of fillings or extractions due to caries, fissure sealants on primary molar teeth, and/or a history of severe allergic reactions requiring hospitalization.

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Number approached, eligible, enrolled, analyzed	Country Setting	Sponsor	Duration of followup
Prior Report				
Frostell et al., 1991	Approached: NR Eligible: NR Enrolled: 206 Analyzed: 206 (113 vs. 93)	Sweden Suburban areas Fluoridation status NR	Swedish Sugar Company, Swedish Odonatological Patents Revenue Research Fund	2 years
Jiang et al., 2005	Approached: NR Eligible: NR Enrolled: 392 (209 vs. 183) Analyzed: 318 (167 vs. 151) at 2 years	China Recruitment setting: Kindergarten Water fluoridation status: 0.1 to 0.3 ppm	National Key Technologies R&D Program of the Tenth-five Year Plan, Ministry of Science and Technology China	2 years
Lawrence et al., 2008	Approached: 1,793 Eligible: 1,275 Enrolled: 1,275 (915 vs. 360) Analyzed: 1,146 (818 vs. 328)	Canada Recruitment setting: Rural Aboriginal communities Water fluoridation status: No fluoridation	Institute of Aboriginal Peoples' Health/Canadian Institutes of Health Research; Toronto Hospital for Sick Children Foundation	2 years
Slade et al., 2011	Approached: 685 Eligible: 666 Enrolled: 666 (344 vs. 322) Analyzed: 666 (344 vs. 322)	Australia Recruitment setting: Rural Aboriginal communities Water fluoridation status: See population characteristics Water fluoride concentration <0.6 ppm: 87%	Australian National Health and Medical Research Council	2 years
Weintraub et al., 2006	Approached: NR Eligible: NR Enrolled: 376 (126 vs. 124 vs. 126) Analyzed: 280 (87 vs. 93 vs. 100)	U.S. Recruitment setting: Family dental center and public health center serving primarily low-income, underserved Hispanic and Chinese populations Water fluoridation status: ~1 ppm	National Institute of Dental and Craniofacial Research; the National Center for Minority Health and Health Disparities; UCSF Department of Preventive and Restorative Dental Sciences	2 years
Current Report				
Agouropoulos et al., 2014	Approached: NR Eligible: 424 Enrolled: 409 (216 vs. 193) Analyzed: 328 (181 vs. 162)	Greece Recruitment setting: Public preschools located in medium and low socioeconomic areas of Athens, Greece Water fluoridation: NR (no fluoridated water in Greece)	"Live.Learn.Laugh" programme by FDI/Unilever and by Ivoclar-Vivadent	2 years
Anderson et al., 2016 Same as Anderson et al., 2017	Approached: NR Eligible: 4847 Enrolled: 3403 Analyzed: 2536 (1231 vs. 1305)	Sweden Recruitment setting: Dental clinics located in areas with a multicultural population and families predominantly of medium or low socioeconomic status	Stockholm County Council and Karolinska Institute	2 years

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Number approached, eligible, enrolled, analyzed	Country Setting	Sponsor	Duration of followup
		Water fluoridation: No added fluoride (concentration "close to zero")		
Anderson et al., 2017 Same as Anderson et al., 2016	Approached: NR Eligible: 3403 Enrolled: 801 Analyzed: 664 (314 vs. 350)	Sweden Recruitment setting: Dental clinics located in areas with a multicultural population and families predominantly of medium or low socioeconomic status Water fluoridation: NR	Stockholm County Council and Karolinska Institute	3 years
Jiang et al., 2014	Approached: 512 Eligible: 483 Enrolled: 450 (149 vs. 152 vs. 149) Analyzed: 415 (137 vs. 144 vs. 134)	China Recruited from parenting education centers and child day care centers Water fluoridation: 0.5 ppm	Hong Kong Research Grant Council	2 years
Latifi-Xhemajli et al., 2019	Approached: NR Eligible: NR Enrolled: 504 (255 vs. 249) Analyzed: 427 (218 vs. 209)	Kosovo Recruited from 11 preschools in the Pristina area Water fluoridation: NR	None	2 years
McMahon et al., 2020	Approached: 1,916 Eligible: 1284 Enrolled: 1284 (643 vs. 641) Analyzed: 1150 (577 vs. 573)	Scotland Recruited from 4 NHS Health Board areas Water fluoridation: NR	Scottish Government	2 years
Memarpour et al., 2015	Approached: NR Eligible: 220 Enrolled: 140 Analyzed: 123 (32 vs. 31 vs. 29 vs. 30)	Iran Recruitment setting: Public health care centers Water fluoridation status: <0.7 ppm	Vice-Chancellor of Research of the Shiraz University of Medical Science	12 months
Memarpour et al., 2016	Approached: NR Eligible: NR Enrolled: 300 (100 vs. 100 vs. 100) Analyzed: 260 (87 vs. 85 vs. 88) at 12 months	Iran Public health care centers Water fluoridation: <0.7 ppm	Shiraz University of Medical Sciences	1 year
Muñoz-Millán et al., 2018	Approached: NR Eligible: NR Enrolled: 275 Analyzed: 275 (131 vs. 144)	Chile Mainly low SES, rural preschools Fluoridation status: none	Comision Nacional de Investigacion	24 months
Oliveira et al., 2014 dos Santos et al., 2016	Approached: NR Eligible: 310 Enrolled: 200 Analyzed: 181 (89 vs. 92); 123 in nested-cohort (63 vs. 60)	Brazil Low-income families recruited at a pediatric ambulatory clinic located in a public health center "Access to fluoridated water", fluoridation status otherwise not reported	Colgate-Palmolive provided free supplies	24 months, 4 years for nested-cohort

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Number approached, eligible, enrolled, analyzed	Country Setting	Sponsor	Duration of followup
Tickle et al., 2016 Tickle et al., 2017	Approached: 2455 Eligible: 1248 Enrolled: 1248 Analyzed: 1096 (549 vs. 547)	Ireland National Health Services dental practices in Norther Ireland Fluoridation status not reported (national policy of mandatory water fluoridation at 0.6 to 0.8 ppm)	National Institute for Health Research Health Technology Assessment program	3 years

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Outcomes	Adverse events/harms	Attrition	Quality rating
Prior Report				
Frostell et al., 1991	A vs. B Mean $dmfs_1$: 2.26 vs. 3.60, p<0.01 Mean $dmfs_2$: 2.86 vs. 4.10, p=NS Mean $dmft_1$: 1.09 vs. 1.32, p=NS	NR	NR	Fair
Jiang et al., 2005	A vs. B dmfs increase >0: 61.7% (103/167) vs. 73.5% (111/151); RR 0.84 (95% CI, 0.72 to 0.98) dmfs increase ≥6: 28.1% (47/167) vs. 35.1% (53/151), RR 0.80 (95% CI, 0.58 to 1.11) dmfs increase ≥11: 11.4% (19/167) vs. 17.2% (26/151), RR 0.66 (95% CI, 0.38 to 1.14) dmfs increment (SD): 3.8 (0.9) vs. 5.0 (1.0); p=0.03; reduction in caries increment 24%	No adverse events detected	A vs. B: 20% (42/209) vs. 17% (32/183)	Fair
Lawrence et al., 2008	A vs. B Incident caries:† 71.5% (595/832) vs. 75.3% (247/328), adjusted OR 0.72 (95% CI, 0.42 to 1.25) -caries free at baseline:‡ 44.4% (157/354) vs. 57.9% (73/126); adjusted OR 0.63 (95% CI, 0.33 to 1.1 -0 to 1 years:‡ 61.1% (209/342) vs. 69.4% (84/121), adjusted OR 0.52 (95% CI, 0.23 to 1.19) -2 to 3 years:‡ 75.5% (336/445) vs. 82.0% (132/161), adjusted OR 0.52 (95% CI, 0.24 to 1.10) dmfs increment, adjusted mean (SD):† 11.0 (15.0) vs. 13.5 (15.0); adjusted mean difference -2.4 (SE 2.0), p=0.24, prevented fraction 18% -caries free at baseline, adjusted mean (SD):‡ 4.3 (8.5) vs. 6.1 (9.4); adjusted mean difference: -1.7 (SE 1.3), p=0.18 -0 to 1 year, adjusted mean (SD): 8.1 (10.5) vs. 11.2 (14.1); adjusted mean difference -3.9 (SE 2.4), p=0.10 -2 to 3 years: 13.6 (16.0) vs. 16.6 (17.5); adjusted mean difference -3.7 (SE 3.0), p=0.22	One child allergic to lanolin experienced an adverse event	A vs. B: 11% (96/915) vs. 9% (32/360)	Fair
Slade et al., 2011	A vs. B dmfs increment, adjusted mean (SD): 7.3 (10.4) vs. 9.6 (10.1), difference -2.3 (95% CI, -3.7 to -0.8), prevented fraction 24% -effect of additional 1 ppm F: -4.3 (95% CI, -7.0 to -1.6) -effect of age (years): -0.3 (95% CI, -0.3 to -0.2)	No adverse events detected	A vs. B: 19% (60/322) vs. 18% (63/344)	Fair

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Outcomes	Adverse events/harms	Attrition	Quality rating
Weintraub et al., 2006	A vs. B vs. C Incident caries ($d_2$mfs >0): 13.2% (11/83) vs. 15.1% (13/86) vs. 29.3% (27/92) at 12 months, RR 0.45 (95% CI, 0.24 to 0.83) A vs. C and RR 0.52 (95% CI, 0.28 to 0.93) for B vs. C; 17.3% (14/81) vs. 28.0% (23/82) vs. 46.7% (42/90) at 24 months, RR 0.37 (95% CI 0.22 to 0.63) for A vs. C and 0.60 (95% CI 0.40 to 0.91) for B vs. C $d_2$mfs, mean (SD): 0.7 (2.1) vs. 0.7 (1.8) vs. 1.7 (3.1); p<0.01 for A vs. C and B vs. C	No adverse events detected	A vs. B vs. C: 31% (39/126) vs. 25% (31/124) vs. 21% (26/126)	Fair
Current Report				
Agouropoulos et al., 2014	A vs. B Caries prevalence (dmfs>0): 63.0% (110/174) vs. 64.8% (100/154) at 1 year, RR 0.97 (95% CI, 0.83 to 1.14); 64.8% (113/174) vs. 65.8% (101/154) at 2 years, RR 0.99 (95% CI, 0.85 to 1.16) dmfs, mean (SD): 5.2 (9.2) vs. 4.9 (8.0) at 1 year; 5.8 (9.5) vs. 5.5 (8.8) at 2 years Caries increment (change in dmfs), mean (SD): 2.1 (4.5) vs. 2.3 (4.7) from baseline to 1 year; 0.8 (2.2) vs. 1.1 (2.3) from 1 to 2 years; 2.9 (5.3) vs. 3.0 (5.2) from baseline to 2 years	No serious adverse events were noted, in some cases, the smell of the varnish was unpleasant to the younger children	A vs. B: 19.5% (42/216) vs. 20.2% (39/193)	Fair
Anderson et al., 2016 Same as Anderson et al., 2017	A vs. B Scores at 24 months ICDAS 1-2: 6.8% (83/1223) vs. 6.2% (90/1452), RR 1.09 (95% CI 0.82 to 1.46) ICDAS 3-6: 3.4% (42/1223) vs. 4.3% (63/1452), RR 0.79 (95% CI 0.54 to 1.16) ICDAS 5-6: 2.5% (30/1223) vs. 2.5% (37/1452), RR 0.96 (95% CI 0.60 to 1.55) ICDAS 1-6: 10.2% (125/1223) vs. 10.5% (153/1452), RR 0.96 (95% CI 0.77 to 1.20) Scores at 36 months ICDAS 1-2: 11.5% (141/1231) vs. 9.6% (125/1305), RR 1.20 (95% CI 0.95 to 1.50) ICDAS 3-6: 10.4% (128/1231) vs. 13.7% (179/1305), RR 0.76 (95% CI 0.61 to 0.94) ICDAS 5-6: 6.1% (75/1231) vs. 7.6% (99/1305), RR 0.80 (95% CI 0.60 to 1.07) ICDAS 1-6: 21.9% (269/1231) vs. 23.3% (304/1305), RR 0.94 (95% CI 0.81 to 1.08)	No serious adverse events were noted, a few children vomited directly after application due to the smell, texture, or taste of the varnish	A vs. B: 25.5% (421/1652) vs. 25.5% (446/1751)	Fair

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Outcomes	Adverse events/harms	Attrition	Quality rating
Anderson et al., 2017 Same as Anderson et al., 2016	A vs. B No progression of caries between 12 and 24 months: 71.1% vs. 76.8%, p=0.002 No progression of caries between 24 and 36 months: 79.0% vs. 79.0%, p=0.912 Progression from a healthy or initial stage occlusal surface (ICDAS 0 to 2) to a moderate to an extensive decayed surface (ICDAS 3 to 6): 6.0% vs. 7.3%, p=0.17	NR	A vs. B: 26.3% (112/426) vs. 6.7% (25/375)	Fair
Jiang et al., 2014	A vs. B vs. C Incident cavitated caries lesions: 10.2% (14/137) vs. 6.9% (10/144) vs. 8.2% (11/134); RR 0.68 (95% CI, 0.31 to 1.48) for A vs. B, RR 1.24 (95% CI, 0.59 to 2.64) for A vs. C, RR 0.85 (95% CI, 0.37 to 1.93) for B vs. C; RR 1.48 (95% CI, 0.83 to 2.64) for A vs. B, RR 1.47 (95% CI, 0.82 to 2.64), RR 0.99 (95% CI, 0.52 to 1.88) for B vs. C Incident cavitated and noncavitated caries lesions: 17.5% (24/137) vs. 11.8% (17/144) vs. 11.9% (16/134); RR dmfs, mean (SD): 0.2 (0.9) vs. 0.1 (0.5) vs. 0.2 (1.0); MD -0.1 (95% CI, -0.27 to 0.07) for A vs. B, MD 0.00 (95% CI, -0.23 to 0.23) for A vs. C, MD -0.1 (95% CI, -0.29 to 0.09) for B vs. C	NR	8% (23/301)	Good
Latifi-Xhemajli et al., 2019	A vs. B at endpoint dmfs, mean (SD): 5.2 (10.5) vs. 10.1 (12.9), p<0.001 dmfs >0: 30.6% vs. 60.0%; RR 1.81 (95% CI, 1.49 to 2.20) ICDAS 5-6: 22.0% vs. 47.7%; RR 1.49 (95% CI, 1.29 to 1.73)	NR	15.3% (77/504)	Fair
McMahon et al., 2020	A vs. B Mean $d_3$mfs: 3.5 (5.9) vs. 3.5 (4.9) Worse $d_3$mft: 27% (155/577) vs. 32% (181/573), OR 0.80 (95% CI, 0.62 to 1.03) Worse $d_3$mfs: 29% (165/577) vs. 34% (193/573), OR 0.79 (95% CI, 0.61 to 1.01) Worse d_3t: 21% (119/577) vs. 26% (147/573), OR 0.75 (95% CI, 0.57 to 0.99) Worse mt: 5% (28/577) vs. 4% (21/573), OR 1.34 (95% CI, 0.75 to 2.39) Worse ft: 9% (52/577) vs. 11% (65/573), OR 0.77 (95% CI, 0.53 to 1.14) Extraction: 2% (11/577) vs. 1% (8/573), OR 1.37 (95% CI, 0.55 to 3.44) Fillings: 10% (55/577) vs. 11% (61/573), OR 0.88 (95% CI, 0.60 to 1.30) Pulpotomy: 1% (4/577) vs. 1% (3/573), OR 1.33 (95% CI, 0.30 to 5.95) Preformed metal crowns: 2% (13/577) vs. 2% (10/573), OR 1.30 (95% CI, 0.56 to 2.98) Extraction of deciduous teeth: 0% (1/577) vs. 0% (0/573) NNT to prevent 1 child from having a worsening of $d_3$mft: 21	NR	A vs. B: 10% (66/643) vs. 11% (68/641)	Good

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Outcomes	Adverse events/harms	Attrition	Quality rating
Memarpour et al., 2015	A vs. B vs. C vs. Ddmft at 12 months, mean (SD): 0.3 (0.90) vs. 0.42 (0.99) vs. 0.17 (0.53) vs. 2.0 (2.0); p<0.001 for C vs. others	NR	A vs. B vs. C vs. D: 82.9% (29/35) vs. 88.6% (31/35) vs. 85.7% (30/35) vs. 91.4% (32/35)	Fair
Memarpour et al., 2016	A vs. B vs. C Incident caries (dmft >0) At 4 months: 1.0% (1/95) vs. 2.1% (2/97) vs. 3.1% (3/96); RR 1.96 (95% CI, 0.18 to 21.24) for A vs. B, RR 0.34 (95% CI, 0.04 to 3.18) for A vs. C, RR 0.66 (95% CI, 0.11 to 3.86) for B vs. C At 8 months: 1.1% (1/93) vs. 3.2% (3/94) vs. 16.0% (15/94); RR 2.97 (95% CI, 0.31 to 28.02) for A vs. B, RR 0.07 (95% CI, 0.01 to 0.50) for A vs. C, RR 0.20 (95% CI, 0.06 to 0.67) for B vs. C At 12 months: 1.1% (1/87) vs. 4.7% (4/85) vs. 33.0% (29/88); RR 4.09 (95% CI, 0.47 to 35.89) for A vs. B, RR 0.03 (95% CI, 0.005 to 0.25) for A vs. C, RR 0.14 (95% CI, 0.05 to 0.39) for B vs. C	NR	13% (40/260)	Fair
Muñoz-Millán et al., 2018	A vs. B Incidence of caries: 45% (59/131) vs. 55.5% (80/144) , p=0.081 Mean (95% CI) incremental caries difference: -0.5 (-1.1 to 0.1) Mean (SD) dmft: 1.6 (2.0) vs. 2.1 (2.6) Preventive fraction: 18.9% (95% CI, -2.9% to 36.2%)	None reported by parents	A vs. B 32% (42/131) vs. 30% (44/144)	Fair
Oliveira et al., 2014dos Santos et al., 2016	A vs. B Children with new dentine caries lesions: 35.9% (32/89) vs. 46.7% (43/92); RR 0.77 (95% CI 0.54 to 1.09), ARD 11% (95% CI -3.5 to 25.0%) $d_2$mfs, mean (SD): 2.0 (4.0) vs. 2.8 (4.2); difference -0.8 (95% CI, -1.9 to 0.4) $d_3$mfs, mean (SD): 1.8 (3.9) vs. 2.5 (4.0); difference -0.7 (95% CI, -2.0 to 0.4)	2 complaints reported; 1 child's mother was bothered by the color of the child's teeth after fluoride varnish application and 1 child's mother reported the child complained of a burning sensation in her mouth on the first day of placebo varnish application No withdrawals due to AEs, and of 11 (8 vs. 3) children with asthma at baseline none reported any Aes Followup for subgroup evaluated at 4 years (n=123) Fluorosis: 27% (17/63) vs. 35% (21/60); p=0.44	A vs. B: 11% (11/100) vs. 8% (8/100)	Good

Appendix B7. Trials of Topical Fluoride for the Prevention of Dental Caries

Author, year*	Outcomes	Adverse events/harms	Attrition	Quality rating
		Esthetically objectionable fluorosis: 4.8% (3/63) vs. 8.3% (5/60); p=0.48		
Tickle et al., 2016 Tickle et al., 2017	A vs. B Converted from caries free to caries active: 34% (187/549) vs. 39% (213/547); adjusted OR 0.81 (95% CI, 0.64 to 1.04); p=0.11 $d_3$mfs affected by caries in children who developed caries, mean (SD): 7.18 (7.99) vs. 9.61 (8.75); adjusted mean difference -2.29 (95% CI, -3.96 to -0.63); p=0.007 Teeth extraction, among those developing caries: 11.2% (11/187) vs. 13.1% (28/547)	A vs. B Any AE: 7.2% (45/624) vs. 5.9% (37/624); RR 1.22 (95% CI 0.80 to 1.85)	A vs. B: 12% (75/624) vs. 12% (77/624)	Fair

*See Appendix A4 for full citations of included studies.

†Restricted to aboriginal children, including 14 non-randomized children who received fluoride varnish.

‡Includes 102 non-randomized children (88 nonaboriginal) who received fluoride varnish (or subgroup from this population).

Abbreviations: AE=adverse event; CI=confidence interval; CPP-ACP=casein phosphopeptide-amorphous calcium phosphate; ICDAS=international caries detection and assessment system; MD=mean difference; NR=not reported; NS=not significant; OR=odds ratio; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; SE=standard error; UCSF=University of California, San Francisco.

Appendix B8. Trials of Xylitol for the Prevention of Dental Caries

Author, year*	Type of study	Interventions	Population characteristics	Eligibility criteria	Number approached, eligible, enrolled, analyzed
Prior report					
Oscarson et al., 2006	RCT	A: One 0.48 gram xylitol tablet at bedtime after brushing for 6 months; then one tablet twice daily to age 3 years and 6 months B: No tablets	Age: 25 vs. 25 months Female: 49% vs. 46% (p>0.05) Non-white: NR Seldom/irregular tooth-brushing: 7% vs. 3% (p>0.05) High (>100 CFU) mutans streptococci counts: 11% vs. 6% (p>0.05) Daily sugary soft drinks: 17% vs. 27% (p>0.05) Daily sugars sweets: 0% vs. 2% (p>0.05)	Healthy 2 year old children. Excluded: Children with severe disabilities or uncooperative for oral exam	Number approached: NR Number eligible: NR Number enrolled: 132 (66 vs. 66) Number analyzed: 115 (55 vs. 63)
Zhan et al., 2012	RCT	A: Xylitol wipes, two at a time, three times per day (estimated daily dosage 4.2 g) every 3 months B: Placebo wipes	Age: 6 to 35 months vs. 6 to 35 months Female: 36% vs. 40% Non-white: 90% vs. 95% Brush teeth daily: 68% vs. 68% Use fluoride toothpaste: 36% vs. 27%	Mothers with healthy children aged 6 to 35 months; mothers were primary care givers (>8 hours daily) and with minimum of one active caries lesion within a year; no children with oral or systemic diseases; no mothers or children who took antibiotics or other medication affecting oral flora in previous 3 months.	Number approached: 82 Number eligible: 57 Number enrolled: 44 (22 vs. 22) Number analyzed: 44 (22 vs. 22) ITT; 37 (20 vs. 17) on-treatment analysis

Appendix B8. Trials of Xylitol for the Prevention of Dental Caries

Author, year*	Country Setting	Sponsor	Duration of followup	Outcomes	Adverse events/harms	Attrition	Quality rating
Prior report							
Oscarson et al., 2006	Sweden Recruitment setting: Public dental clinic Water fluoridation status: Not reported	County of Vasterbotten, The Patent Revenue Fund for Dental Prophylaxis and Swedish Dental Society	2 years	A vs. B Dental caries: 18% (10/55) vs. 25% (16/63), OR 0.65 (95% CI 0.27 to 1.59) dmfs, mean: 0.38 vs. 0.80 (p>0.05) Absolute reduction in caries increment: 0.42 Reduction in caries increment: 52%	A vs. B Withdrawals due to adverse events: NR	A vs. B: 16.7% (11/66) vs. 4.5% (3/66)	Fair
Zhan et al., 2012	United States Recruitment setting: University pediatric clinic Water fluoridation status: Not reported	California Society of Pediatric Dentistry Foundation, a Graduate Scientific Research Award from American Academy of Pediatric Dentistry, and NIH/NIDCR grant U54 DEO19285	1 year	A vs. B Mean new decayed surfaces: 0.05 vs. 0.53 (p=0.01) New caries lesions at 1 year: 5% vs. 40% (p=0.03); NNT 3 ITT analysis of new caries lesions at 1 year: 5% vs. 32%; RR 0.14 (95% CI 0.02 to 1.07); NNT 4 Absolute reduction in caries increment: 0.48 Reduction in caries increment: 91%	None	A vs. B 9% (2/22) vs. 23% (5/22)	Fair

*See Appendix A4 for full citations of included studies.

Abbreviations: CFU=colony-forming unit; CI=confidence interval; ITT=intention to treat; NIDCR=National Institute of Dental and Craniofacial Research; NIH=National Institutes of Health; NNT=number needed to treat; NR=not reported; OR=odds ratio; RCT=randomized controlled trial; RR=relative risk.

Appendix B9. Systematic Review of Fluorosis Due to Fluoride Supplements

Author, year*	Databases searched, date of last search	Number and type of studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Adverse events	Quality rating
Ismail and Hasson, 2008	MEDLINE: 1966-June 2006 Cochrane: up to 2nd quarter 2006 EMBASE: 1974-2006	5 observational studies	Cochrane Handbook of Systematic Reviews	Qualitative analyses only, due to high heterogeneity of subjects, outcomes, and duration of followup	Not reported	5 observational studies reported fluorosis outcomes associated with early childhood use of fluoride supplementation - All studies found an association between fluoride supplementation in early childhood and risk of fluorosis - 1 study (n=383) found OR increased by 84% per year of use of fluoride supplements (95% CI, 1.4 to 2.5) - 1 study (n=188) OR 10.3 in children started on fluoride supplements within the first 2 years of life (95% CI, 1.9 to 61.6) - Largest study (n=3978) found slightly increased risk that ranged	Good

Appendix B10. Quality Ratings of Systematic Reviews

Author, year*	1. Did the research questions and inclusion criteria for the review include the components of PICO?	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Critical Domain)	3. Did the review authors explain their selection of the study designs for inclusion in the review?	4. Did the review authors use a compre-hensive literature search strategy? (Critical Domain)	5. Did the review authors perform study selection in duplicate?	6. Did the review authors perform data extraction in duplicate?	7. Did the review authors provide a list of excluded studies and justify the exclusions? (Critical Domain)	8. Did the review authors describe the included studies in adequate detail?	9a. Did the review authors use a satisfactory technique for assessing the ROB in individual studies that were included in the review? (Critical Domain) RCTs	9b. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? (Critical Domain) NRSI
Ismail and Hasson, 2008	Yes	Yes	Yes	Yes	Not reported	Not reported	No	Yes	Yes	Yes

Appendix B10. Quality Ratings of Systematic Reviews

Author, year*	10. Did the review authors report on the sources of funding for the studies included in the review?	11a. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (Critical Domain)	11b. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (Critical Domain) NRSI	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? (Critical Domain)	14. Did the review authors provide a satisfactory explanation for, and discussion of, any hetero-geneity observed in the results of the review?	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Critical Domain)	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Overall rating
Ismail and Hasson, 2008	No	Not applicable	Not applicable	Not applicable	No	No	No	Yes	Good