Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL

TITLE: Fluoride Varnishes for Dental Health: A Review of the Clinical Effectiveness, Cost-effectiveness and Guidelines

DATE: 26 October 2016

CONTEXT AND POLICY ISSUES

The Canadian Pediatric Society[1] (CPS) indicates that oral health is a key part of an individual's overall health. As such, the CPS recommends all children and young adults should have appropriate access to dental care services.[1] Tooth decay can currently be considered one of the most common chronic conditions of childhood and should be considered to be a public health issue.[1,2] Early childhood caries (ECC) is defined as "the presence of one or more decayed, missing (due to caries) or filled tooth surfaces in any primary tooth in a preschool-aged child."[1] In those individuals at higher risk for developing caries, dental caries can begin to appear as soon as the first teeth erupt from the gums.[2] In Canada's urban areas, the prevalence of ECC is somewhere between six and eight percent; however, in areas of lower socioeconomic status, the prevalence can reach upwards of 90 percent.[1]

Sodium fluoride varnishes for professional application to prevent dental caries were developed in the 1960s.[2] Since that time, they have been used routinely in Europe and Canada.[2] Adults at high risk for the development of dental caries may also benefit from topical fluoride treatment.[2] Fluoride varnish has been described as an easy to use and inexpensive intervention and does not require special equipment to be applied.[2] Other types of topical fluoride treatments include gel, paste, and foam.[3] These treatments are available with various concentrations of fluoride and versions of these treatments can be applied professionally or at home.[3] Gels and foams are often applied to the teeth using disposable trays that fit over the teeth.[4]

The aim of this review is to examine the effectiveness, cost-effectiveness, and guidelines for use of fluoride varnishes compared with no treatment or other topical fluoride products.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of fluoride varnishes for dental health?

2. What is the clinical effectiveness of fluoride varnishes compared to other topical fluorides administered professionally?

3. What is the cost-effectiveness of fluoride varnishes for dental health?

4. What are the evidence-based guidelines regarding the use of fluoride varnish treatment?

KEY FINDINGS

Five systematic reviews and meta-analyses, nine randomized controlled trials, one economic evaluation and four evidence-based guidelines were identified regarding the use of fluoride varnishes for dental health.

The results of the included studies generally support the use of professionally applied topical fluoride varnish for the prevention and reversal of dental caries, remineralization of WSL and dental caries lesions, and decrease of dentin sensitivity. The effectiveness of fluoride varnish was not established for the remineralization of MIH in young children or for the prevention of new dental caries in adults with dry mouth. In the identified guidelines, fluoride varnish is recommended for routine use in children, particularly those at increased risk of developing dental caries. Adults with root caries were recommended to receive fluoride varnish treatment. No cost information that was directly applicable to the Canadian context was identified, but in a cost-effectiveness study of Native Alaskan children, fluoride varnish was considered to be a cost-effective treatment option.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and September 26, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Children (ages 0-11); Adolescents (ages 12-16); Adults (age 17+) in a dental care setting
Intervention	Fluoride varnish
Comparator	No professional treatment; Other topical fluorides (e.g. gels or rinses) administered professionally in a dental office
Outcomes	Clinical effectiveness (e.g. caries reduction, tooth remineralization, reduced dentine sensitivity), cost-effectiveness, guidelines (including indications for use)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Guidelines were excluded if their methodology was not clearly presented in the guideline document or through the body who produced them. Fluoride varnish interventions provided outside of a dental office or dental school were excluded from this review.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR, randomized studies were critically appraised using Downs and Black, economic studies were assessed using the Drummond checklist, and guidelines were assessed with the AGREE II instrument. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described. Details regarding the critical appraisal of included studies can be found in Appendix

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 382 citations were identified in the literature search. Following screening of titles and abstracts, 326 citations were excluded and 56 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 43 publications were excluded for various reasons, while 19 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of the characteristics of included publications are available in Appendix 2.

Study Design

Five systematic reviews (SRs) were included in this report.[5-9] Four reviews focused on children[5-8] and one review included studies conducted in adults and children.[9] The SRs included randomized controlled trials (RCTs),[5-9] quasi-randomized studies,[8] non-randomized studies,[7,9] and controlled clinical trials.[9] The literature search date cut-offs were 2013,[8,9] 2014,[5,7] and 2015[6] Nine RCTs[10-18] (five conducted in children,[10-13,15] two in adolescents and young adults,[17,18] and two in adults[14,16]) were included in this review. One economic analysis[19] focused on fluoride use in children was identified. Four evidence-based guidelines were included in the review.[4,9,20,21]

Country of Origin

Authors of the systematic reviews were located in the United States,[6,7,9] Hong Kong,[5] Denmark,[7] and the United Kingdom.[8] The included RCTs were conducted in Denmark,[10] Iran,[11,12] Brazil,[13,14] Hong Kong,[15,16] and China.[17,18] The economic analysis was undertaken with a United States (Alaska) healthcare payer perspective.[19] The evidence-based guidelines were produced in the United States by the American Academy of Pediatric Dentistry[20] (AAPD), the American Dental Association[9] (ADA), and Institute for Clinical Systems Improvement[21] (ICSI) and in Scotland by the Scottish Intercollegiate Guidelines Network[4] (SIGN).

Patient Population

Four systematic reviews,[5-8] five RCTs, [10-13,15] one economic evaluation,[19] and three guidelines[4,20,21] were focused on the use of fluoride varnishes for children. The ages of children included in the publications ranged from six months[9] up to 16 years of age.[8] The ages of children included in the identified RCTs ranged from eight months[15] to 12 years,[13] with four of the five RCTs including children aged 36 months or younger.[10-12,15] The economic evaluation aimed to determine the cost-effectiveness of fluoride treatment for children from six to 60 months of age.[19]

Two RCTs[17,18] included adolescents and young adults with patients aged 12 to 22[18] or 25[17] years of age. Two RCTs included adult patients.[14,16] One study included patients up to the age of 70[14] and one study included patients aged 26 to 75 years.[16] One guideline focused on dental interventions for patients of all ages.[9]

Interventions and Comparators

The publications identified for inclusion in this review included a range of interventions and comparators. The fluoride varnish interventions studied included:

- 5% (22,600 parts per million) sodium fluoride varnish
  - Duraphat (Colgate)[6,8,10,13,14,16-18]
  - Fluorniz[6,14]
  - Fluoridin[6,8]
  - Lawefluorid[8]
  - Fluor Protector[8]
  - Cavity Shield[8]
  - Duroflor[8]
  - DuraShield[10,12]
  - Fluorophat[14]
  - Duofluorid[14]

    - Unspecified brand(s)[5,7,9]
- 0.1% fluoride varnish (unspecified brands)[9]

The timing of fluoride varnish application varied between studies. Where specified, the reported frequency and timing of the interventions were as follows:

- Two applications, four months apart[6]
- Two applications, six months apart[10]
- Three applications, four months apart[6,12]
- Four applications, one week apart[6,13]
- Five applications, six months apart[11]
- Six applications, one month apart[18]
- Two to four times per year[7]
- Every three to 12 months[9]

The comparators included in the publications that were relevant to this review included:

- No treatment/intervention[5,7-9,11-13]
- Placebo[5,7-9,11,12,14-18]
- Tooth brushing technique[5,15]
- Fluoride gel[6]
- 5% fluoride film[17]
- Fluoride toothpaste[13,17]
- Oral health promotion/counseling[7,9-13,15,17]
- Other fluoride varnish[7,14]
- Oral health promotion plus varnish[7]

Outcomes

This review focused on the effectiveness of fluoride varnish for caries reduction, tooth remineralization, and the reduction of dentine sensitivity. The clinical outcomes reported in the included studies relevant to this review were:

- Caries prevention or reduction
    - Dimension change of caries lesions[5]
    - Caries prevalence or incidence[7,9,16] measured by ICDAS (International Caries Detection and Assessment System) criteria,[10,15] or dmft (decayed, missing, or filled teeth) index[11]
    - Caries increment change measured by damaged, missing, and filled surfaces (dmfs) score[8]
    - Caries risk reduction[11]
- Tooth remineralization[6]
    - Percentage of remineralized early enamel caries[5]
    - Mean change in fluorescence and area of the lesions (QLF)[13,17]
    - Reduction in size of white spot lesions[12,17]
    - White spot lesion depth[18]
- Dentine sensitivity using US Public Health Service Criteria[14]

Cost was examined in one study looking at the cost-effectiveness of various fluoride treatments, including fluoride varnish, for the prevention of dental caries in Alaskan native children.[19] The authors modelled the used of water fluoridation, dental sealants, fluoride varnish, tooth brushing

with fluoride toothpaste, or the conduct of an initial dental exams on children less than 18 months of age over a 10 year time horizon to evaluate the total cost of each intervention, as well as the cost per adverse health event (dental caries or full mouth dental restoration) avoided. Costs of existing dental procedures were obtained from Medicaid data. The authors assumed that all of the interventions had an ideal population coverage of 100 percent, that children were treated by a dentist or dental surgeon, that children would receive only one initial dental examination, and children would receive only one full mouth dental restoration per year.

Summary of Critical Appraisal

SRs

All five of the SRs included in this review clearly described an a priori design, a comprehensive literature search strategy, assessed the scientific quality of the included studies, and considered the scientific quality of the included studies when formulating their conclusions.[5-9] It was unclear whether Weyant et al.[9] performed duplicate study selection and data extraction. The other four SRs clearly stated that selection and data extraction were done in duplicate.[5-8] Only the SR by Lenzi et al.[6] clearly stated that the grey literature was included in their literature search strategy. The review by Marinho et al.[8] was the only one to provide a clear list of included and excluded studies. The reviews by Gao[5] and Weyant[9] did not provide detailed characteristics of the studies included in their analysis. It was unclear whether Weyant et al.[9] used appropriate methods to combine the findings of the studies included in their review and they did not mention whether the likelihood of publication bias was assessed. Of the five included SRs, only the review by Twetman et al.[7] did not clearly indicate whether the authors had potential conflicts of interest.

RCTs

The aim, research questions, interventions and comparators, clinical outcomes, and study results were clearly described in all of the included RCTs.[10-18] Block or cluster randomization was done in four studies[10,11,15,16] while five RCTs randomized individuals.[12-14,17,18] Randomization was achieved using computer software,[15,17] sequentially numbered, opaque, sealed envelopes,[14] random number tables,[12,18] and a randomization list.[13] In three studies, randomization was done by a third party not involved in the conduct of the study.[11,15,18] The exact method of random allocation was not described in two RCTs.[10,16]

Appropriate sample size and statistical power calculations were described in seven studies.[10,11,13,15-18] A lack of appropriate power calculations could results in uncertainty of the validity of the study results and the ability of the study to detect a true change in the population.

Four studies included patients,[10,14] and providers[10,11,14] or outcome assessors[11] who were not blinded to randomization. The lack of blinding of assessors could possibly impact their interpretation of the clinical outcomes and lead to bias in the reported results. Patients who were lost to follow-up were adequately described in seven studies.[10-12,15-18]

Potential confounding factors that could impact the applicability of results to the general population were described and accounted for in only three studies.[10,16,17] Anderson et al.[10] stratified dental clinics based on socioeconomic level, geographic area, and size of the clinic prior to randomization in an effort to have treatment and control groups that were as similar to each other as possible.

Seven studies recruited patients from a single treatment centre, or limited geographic or socioeconomic area which may have limited the generalizability of their overall findings as the study sample may not be representative of the general population as a whole.[12-18] Similarly, limited sample size (as determined by the authors) of two studies may have reduced the generalizability of their results.[11,16] Specific patient characteristics were not described by Restrepo,[13] Memarpour,[12] Du,[18] or Camilotti[14] which may limit the generalizability of their findings as we do not have a clear understanding of the exact characteristics of the original treatment population.

Economic Evaluation

The cost-effectiveness analysis by Atkins, et al.[19] appeared to be generally well conducted. The authors clearly stated the research question and economic importance of the analysis. The analysis was undertaken from a justified perspective appropriate to the question and scenario (health care payer) and the time horizon and discounting values (10 years, 3%) applied to resource costs were clearly identified. Costs and quantity of resources were reported separately and all relevant costs were considered. Sensitivity analyses were undertaken examining the minimum and maximum effectiveness of the interventions at both current and the ideal population coverage levels. The main limitation of this analysis is that it was conducted to examine the cost effectiveness of preventing dental caries and full mouth dental reconstructions in a very limited population of Alaska Native children in a specific geographic region. As such, the results cannot reasonably be generalized to any other region or population. The methods may help to inform approaches future cost-analyses in other regions. The evaluation assumed 100% coverage of children, and all interventions provided by a dentist or dental surgeon, and that children would receive one full mouth dental restoration per year, which may not be reflective of actual practice.

Guidelines

The four included guidelines[4,9,20,21] clearly described their overall objectives, population of interest, and target users. The health benefits and side effects appear to have been considered when forming the recommendations. The recommendations provided are specific, easily identifiable, and propose varied options for patient management. The composition of the AAPD guideline group was not clearly specified so it is unclear whether the group was composed of individuals from relevant professional groups.[20] Only the SIGN guideline clearly indicated that they incorporated the views and opinions of patients into their guideline.[4] The SIGN and ICSI guidelines considered potential resource implications of implementing the recommendations and also provide guidance as to how the recommendations could be put into practice.[4,21]

The search strategy used for the AAPD guideline was not described.[20] The SIGN, ADA, and ICSI groups undertook a systematic search of the literature to support their guidelines.[4,9,21] Additionally, the methods of critical appraisal and methods of evaluating the strength and quality of the included studies were not described.[20] The remaining three guidelines evaluated the level of evidence and grade of recommendations using established methodologies. The SIGN50,[4] USPSTF,[9] and GRADE[21] methods were used. The SIGN guideline was the only guideline that clearly indicated it was externally reviewed prior to publication.[4] The SIGN, ADA, and ICSI guidelines all described procedures for updating the document.[4,9,21] None of the four included guidelines described methods of guideline validation.

Summary of Findings

1. What is the clinical effectiveness of fluoride varnishes for dental health?

Five SRs[5-9] and seven RCTs[4,11-13,15,16,18] evaluated the clinical effectiveness of fluoride varnished for dental health.

Fluoride varnish alone versus no treatment or placebo treatment

Children

Four SRs[5-8] examined the use of fluoride varnish versus no treatment or a placebo treatment for the prevention of dental caries in children.

Gao et al.[5] systematically reviews studies of professionally applied fluoride treatment for preventing and improving dental caries in children. Six RCTs were identified regarding remineralization and meta-analysis was conducted on four of those RCTs that examined the same intervention and comparator.[5] In the meta-analysis, the overall percentage of remineralization was 63.6% greater than no treatment (95% confidence interval [CI], 36.0% to 91.2%; P <0.001).[5] The authors indicated that all six RCTs included in the review demonstrated an effectiveness of fluoride varnish for remineralization of early childhood caries (ECC).[5] Comparators studied in the individual trials included chlorhexidine and no treatment but the comparative effectiveness of fluoride versus those comparators were not reported in the review.

Lenzi et al.[6] identified three studies for meta-analysis comparing fluoride varnish (Duraphat, Fluorniz, or Fluoridin) with no treatment for the reversal of enamel carious lesions in children with a mean age from three to 12 years. The number of fluoride applications ranged from two quarterly applications to four weekly applications. The overall mean difference was a decrease of 2.04 (95% CI, -3.25 to -0.84; P = 0.0009) in the number of enamel carious lesions in the varnish versus control or no treatment group.[6] In the meta-analysis, there was a statistically higher decrease in caries prevalence in the fluoride varnish group as compared to the no treatment group. Despite a high level of heterogeneity identified in the meta-analysis, the authors concluded that fluoride varnish was an effective product to stop the progression of enamel carious lesions in both primary and permanent teeth.[6]

Marinho et al.[8] included 22 RCTs and quasi-randomized studies (13 analyzing permanent and 10 analyzing primary teeth) in their review. Data on 9,595 children up to the age of 16 years were included in the analysis. Various fluoride varnishes (Duraphat, Fluoridin, Lawefluorid, Fluor Protector, Cavity Shield, Duroflor) were compared with no treatment or placebo treatment. Pooled decayed, missing, and filled surfaces (dmfs) scores showed a prevented fraction estimate for permanent tooth surfaces of 43% (95% CI, 30% to 57%; P < 0.0001) when comparing fluoride varnish with placebo or no treatment.[8] The pooled dmfs prevented fraction estimate for primary tooth surfaces was 37% (95% CI, 24% to 51%; P <0.0001).[8]
The authors indicated that both analyses were based on moderate quality evidence. The authors concluded that fluoride varnish was effective for inhibiting caries development in both primary and permanent teeth.[8]

Tewtman et al.[7] undertook a review of self- and professionally-applied fluoride and other dental products for the prevention and management of ECC in children less than three years of age. Six studies (seven publications) were identified regarding the use of 5% sodium fluoride varnish

applied professionally two to four times per year combined with oral health education. Due to heterogeneity identified in the included studies and moderate to high risk of bias, the authors were not able to statistically combine results and provided a narrative synthesis of the evidence. The authors concluded that the findings of the identified studies provided limited quality evidence that fluoride toothpaste and fluoride varnish were each effective for the prevention of ECC when compared with no treatment or a placebo.[7] The authors did not compare the effectiveness of fluoride varnish with that of fluoride toothpaste.

All Ages

Weyant et al.[9] undertook a systematic review to support the development and update of the American Dental Association (ADA) guidelines regarding topical fluoride products for caries prevention. Topical fluorides, including 2.26% and 0.1% fluoride varnish, were compared with placebo, no treatment, or oral health counseling. Six RCTs and two non-randomized studies were identified for fluoride varnish use on primary teeth (children aged six months to eight years), 11 RCTs and two non-randomized studies were identified for permanent teeth (participants aged five to 79 years), and one controlled clinical trial examined both primary and permanent teeth.[9] The results of the analysis of the included studies were not clearly presented in the SR.

Based on the analysis of the included studies, the authors and the guideline panel concluded (with moderate certainty) that patients up to 18 years of age may benefit from the application of 2.26% fluoride varnish application at least twice a year for the prevention of dental caries. For adults, the guideline group concluded (with a low level of certainty) that 2.26% fluoride varnish may be beneficial to prevent root caries if applied at least twice a year.[9] For 0.1% fluoride varnish, the guideline group concluded (low to moderate certainty) that there was no benefit of twice or three times yearly application for caries prevention in children less than 18 years of age.[9]

<u>Fluoride varnish versus placebo gel for the prevention of caries in adults with dry mouth</u>

Adults

One RCT by Xin et al.[16] compared the use of fluoride varnish (Duraphat) and a placebo gel in 85 adults with Sjögren's syndrome, which results in dry mouth. All participants received oral health education at baseline. The type (enamel, dentin, or arrested) and number of caries lesions were recorded at 12 and 24 months. A higher mean number of new caries lesions were observed in the control group at the end of the study; however, the differences between groups were not statistically significant. The authors determined that there was no sufficient evidence to recommend for or against the quarterly use of fluoride varnish to prevent new dental caries in adults with Sjögren's syndrome.[16]

<u>Standard dental health intervention + fluoride varnish versus standard intervention alone with or without placebo varnish</u>

Children

Four RCTs[4,11,12,15] compared fluoride varnish plus a standard dental health intervention with the dental health intervention alone for reduction of dental caries in children.

Anderson et al.[4] undertook a non-blinded cluster RCT. Dental clinics were clustered and randomized and children attending the clinics born in 2010 received either topical fluoride varnish (Duraphat) over five visits (every six months) and family dental health education or dental health education alone. Clinical exams were conducted on all children at 12, 24, and 36 months of age.[10] The ICDAS score was measured at baseline (12 months), 24 and 36 months of age. No significant difference in the number of dental caries was observed between groups at 12, 24, or 36 months of age, thus the authors concluded that there was no additive effect fluoride varnish intervention for the prevention of dental caries.

Memarpour et al.[11] compared no treatment versus oral hygiene information and education versus fluoride varnish (DuraShield) plus education. One study examined the use of fluoride varnish for the prevention of ECC in children aged 12 to 24 months with two varnish applications at baseline and six months of follow-up.[11] Children in the fluoride varnish group had 31% fewer caries at 12 months as compared to the no treatment group. Both the varnish and education alone groups had significantly reduced caries incidence as compared to the no treatment group ($P < 0.001$); however, there were no significant differences reported between the two intervention groups.[11]

Jiang et al.[15] conducted an RCT comparing one-time oral parental oral hygiene education with hands on parental toothbrushing training with or without semi-annual fluoride varnish (Clinpro White Varnish) application for children less than three years of age at a low risk of dental caries. New dental caries were classified by ICDAS criteria as Level 1 (non-cavitated and cavitated lesions) or Level 2 (cavitated lesions only). At 24 months, the overall incidence of Level 1 caries was 13.7% (57 of 417 [control = 11.9%, hands-on = 11.8%, varnish = 17.5%]) and Level 2 caries was 8.4% (35 of 415 [control = 8.2%, hands-on = 6.9%, varnish = 10.2%])).[15] There were no statistically significant differences in the incidences of early childhood caries between the three study groups. The study was conducted in an area with public water supply fluoridation. The authors concluded that the use of fluoride varnish in this population of low risk children in an optimally fluoridated area may not be effective for the prevention of ECC.[15]

<u>Fluoride varnish versus no treatment for enamel remineralization</u>

Children

Restrepo et al.[13] conducted an RCT to evaluate the use of fluoride varnish (Duraphat, weekly application for four weeks) versus usual home care and placebo varnish for the remineralization of teeth with molar incisor hypomineralization (MIH) in children aged nine to 12 years. The most severe lesion was treated in each patient. The observed mean lesion volume and mean percentage of fluorescence loss were similar between the varnish and control groups at all five visits.[13] The authors concluded that four applications of fluoride varnish had no favorable effect on the remineralization of MIH lesions as compared to the control treatment.[13]

A second study by Memarpour et al.[12] examined fluoride varnish (DuraShield, three applications quarterly) versus no treatment plus placebo varnish) versus oral hygiene counseling alone for the remineralization of white spot lesions (WSL) on primary teeth of children aged 12 to 36 months.[12] The mean area of the WSL and dmft scores were reported. The mean area of WSL increased over time in the no treatment group and was significantly greater after 8 months ($P = 0.001$) but there was no significant difference observed in that group between eight and 12 months ($P = 0.221$).[12] The mean WSL size decreased significantly over time in the fluoride varnish group ($P < 0.001$) and there were significant differences in dmft only at 12 months (P

<0.001) between the control, fluoride varnish, and oral hygiene groups.[12] The authors observed that dmft did not change significantly over time in the varnish or oral hygiene groups but decreased in the control group and concluded that four applications of fluoride varnish in combination with oral hygiene education were effective to decrease the area of WSL.[12]

Adolescents and young adults

One parallel group RCT, conducted by Du et al.,[18] assessed the use of fluoride varnish (Duraphat, applied monthly for six months) versus saline placebo for the remineralization of WSL after fixed orthodontic treatment in patients aged 12 to 22 years. The depth of the WSL was assessed using a DIAGNOdent pen.[18] Lesion depth scores were significantly lower in the fluoride group as compared to the control group at both three and 6 months follow-up.[18] The authors concluded that the use of fluoride varnish was effective for the reversal of WSL after the removal of orthodontic brackets and they suggested the use of fluoride varnish should be considered as a routine measure in these cases.[18]

2. *What is the clinical effectiveness of fluoride varnishes compared to other topical fluorides administered professionally?*

Two RCTs[14,17] were identified that compared fluoride varnishes with other topical fluoride treatments.

<u>Fluoride varnish versus fluoride film for remineralization of post-orthodontic WSL</u>

Adolescents and young adults

He et al.[17] conducted a three-arm parallel RCT in patients aged 12 to 25 years who had recently completed orthodontic therapy and had at least one maxillary anterior tooth. The application of fluoride varnish (Duraphat) was compared with fluoride film (Sheer) and placebo. Participants in all groups received oral hygiene education and were required to use fluoridated toothpaste daily. Lesion volume was significantly reduced in the varnish, film, and control groups after six months.[17] There was a significantly greater decrease in lesion volume in the varnish group as compared to the film group. Although both fluoride varnish and fluoride film resulted in significant improvements in WSLs, the authors concluded that lesion volume decrease was greater with fluoride and fluoride varnish was determined to be significantly more effective than fluoride film or placebo.

One 14 year old boy suffered from nausea after swallowing fluoride varnish at one treatment.[17] No other adverse events were reported in any of the publications included in this review.

<u>Various fluoride varnishes versus placebo for the treatment of dentin sensitivity</u>

Adults

Camilotti et al.[14] conducted an RCT comparing four fluoride varnishes (Duraphat [50 mg NaF], Fluorniz [5.0g% NaF], Duofluorid XII [6% NaF + 6% CaF], Fluorophat [2% NaF]), sodium fluoride, potassium oxalate, and placebo for the improvement of dentin sensitivity in adult patients (18 to 70 years of age). All of the fluoride varnish treatments resulted in significant improvements in sensitivity scores from baseline; however, Duraphat and Flurophat resulted in the greatest improvements in mean sensitivity scores at final reassessment 30 days after the

last treatment.[14] There was some improvement in sensitivity scores in the placebo group but this change was not significant. The authors had originally hypothesized that there would be no difference in effectiveness between the different fluoride varnish treatments; however, they concluded that the final results disproved this theory.

3. What is the cost-effectiveness of fluoride varnishes for dental health?

One economic evaluation by Atkins et al.[19] was identified. The authors were interested in the cost-effectiveness of various dental interventions for Alaska native children ages six to sixty months of age. The aim was to reduce the number of carious teeth and full mouth dental reconstructions in the population. The analysis was modeled over a 10 year time horizon with a 3% discounting rate and was undertaken from the healthcare payer perspective. Cost-effectiveness was determined by calculating the cost-effectiveness ratio of the cost per prevented adverse health outcome. The authors concluded that a fluoride varnish program could result in 133 averted dental caries and averted costs of $195,347 in year 1. The authors concluded that fluoride varnish was a cost-effective solution with a 10 year total discounted cost of $1,252,021 USD to provide fluoride varnish to 100 percent of the population. However, in this geographical area, a general water fluoridation program was considered to be the most cost-effective solution for the prevention of ECC.[19]

4. What are the evidence-based guidelines regarding the use of fluoride varnish treatment?

Four evidence-based guidelines were identified regarding the use of fluoride varnish treatment in a dental office setting for the prevention and control of dental caries.[4,9,20,21] Three of these guidelines focused on patients 18 years of age and under[4,20,21] and one included patients of all ages.[9]

<u>Children at risk of caries</u>

The American Academy of Pediatric Dentistry guidelines[20] indicate that topical five percent sodium fluoride varnish and 1.23 percent fluoride gel preparations can effectively be used to reduce caries in children determined to be at risk and these children should receive a professionally applied fluoride treatment at minimum every six months. The Institute for Clinical Systems Improvement[21] guideline recommends fluoride for the prevention of dental caries in children from birth to 18 years of age. No frequency of treatment is provided but it is recommended children at high risk of cavities receive fluoride varnish if the facilities to deliver the fluoride in a clinic setting are available.[21]

<u>All children</u>

The Scottish Intercollegiate Guidelines Network[4] guideline recommends that a topical fluoride varnish should be applied at least twice per year in all children. Based on a balance of safety and effectiveness data, the American Dental Association[9] (ADA) recommends 2.26% fluoride varnish as the only topical fluoride option for children less than six years of age. Based on expert opinion, 2.26% fluoride varnish is recommended every three to six months for children up to 18 years of age. The ADA guideline also suggests that all patients who are determined to be at low risk of developing dental caries may not require the addition of topical fluoride treatment to their dental health care treatment if they also use fluoridated toothpaste and consume fluoridated water.[9]

Adults

Based on expert opinion, the ADA recommends that patients older than 18 years of age and adults with root caries should receive 2.26% fluoride varnish at least every three to six months.

Limitations

Weyant et al.[9] noted that their review included studies that included patients from different countries with and without additional fluoride use, with and without fluoridated public water supply, and with or without prophylaxis, making it difficult to determine the exact effect of the interventions of interest. Three of the nine RCTs[10,11,15] reported whether the study was conducted in an area with fluoridation of the public water supply. One study[10] was conducted in Denmark with a non-fluoridated water supply. Two studies conducted in Iran[11] and Hong Kong[15] reported water supplies with 0.5 and <0.7 parts per million of fluoride respectively. Other self-interventions, such as brushing or flossing rates could also be confounding.

Anderson et al.[10] indicated that cluster randomization may have been a limitation of their study. They suggested that individual randomization could have been preferable to demonstrate effectiveness but the cluster randomization of dental clinics was more practical. Stratification was undertaken in an effort to minimize confounders. Lack of blinding of providers and assessors may have resulted in interpretation bias of the results. The use of the standardized ICDAS tool was meant to minimize that probability. The overall study dropout rate of 25% was greater than expected but was evenly distributed between the intervention and control groups.

Jiang et al.[15] indicated that a high proportion of the children participating in the study came from families of middle and high socioeconomic status. Children in this population are generally at lower risk of developing dental caries and therefore the make-up of the study population may have limited its generalizability to the population as a whole.

This review focused on the application of varnish in a dental office setting. Varnish may also be applied in community, school, and medical office settings and may be applied by primary care physicians, nurses, and dental hygienists/assistants in the absence of the supervision of a dentist. Examining the use of fluoride varnish in other practice settings may be of interest for future research.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The results of the included studies generally support the use of professionally applied topical fluoride varnish for the prevention and reversal of dental caries, remineralization of WSL and dental caries lesions, and decrease of dentin sensitivity. The effectiveness of fluoride varnish was not established for the remineralization of MIH in young children or for the prevention of new dental caries in adults with dry mouth. In the identified guidelines, fluoride varnish is recommended for routine use in children, particularly those at increased risk of developing dental caries. Adults with root caries should also receive fluoride varnish treatment. Amongst the 19 included publications, only one minor adverse event was reported. The single centre design or limited geographical area of recruitment of the included studies may limit the generalizability of the findings. None of the identified reviews or RCTs were conducted in Canada, though the guidelines and recommendations were largely from the US and may provide a similar context to the Canadian population. No cost information that was directly applicable to the Canadian context was identified, but in a cost-effectiveness study of Native

Alaskan children, fluoride varnish was considered to be a cost-effective treatment option. Additionally, many of the identified studies did not indicate whether the public water supply in their region was fluoridated. Without this information it may be difficult to determine the effectiveness of fluoride varnish alone versus its effect in combination with other sources of fluoride.

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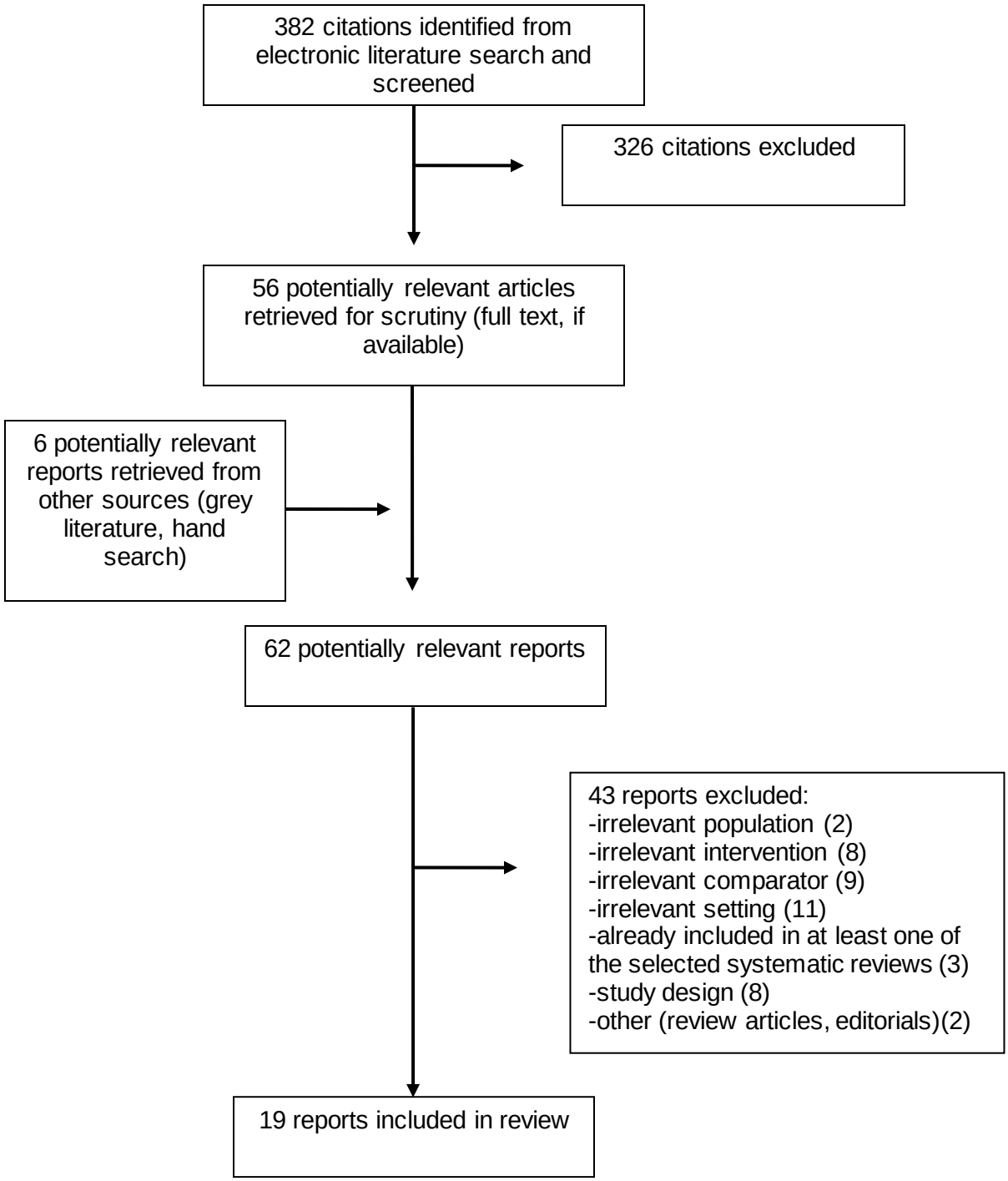
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Aim and Objectives of the review	Types and numbers of primary studies included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Children						

Gao, 2016[5]
 	
Hong Kong
	Professionally applied fluoride treatments for caries arresting effect and remineralization in children	• 17 RCTs
		  ○ 10 investigating remineralization (6 using NaF varnish)
		  ○ 7 investigating arresting effect on dentine caries
		• Search from 1948 to 2014
		• 4 studies included in meta-analysis of NaF varnish
			Not described	Remineralization
				• 5% NaF varnish
				• silicon tetrafluoride
				• fluoride gel
				• silver diamine fluoride
				
				Arresting
				• silver diamine fluoride
				• nano-silver fluoride
					• acidulated phosphate fluoride
					• saline
					• cross tooth brushing technique
					• glass ionomer
					• chlorhexidine
					• silicon tetrafluoride
					• no treatment
						• Dimension change of caries lesions
						• % of remineralized early enamel caries
						• 1 to 12 months follow-up

Lenzi, 2016[6]
 	
United States
	Evaluate the effectiveness of professional topical fluoride application (varnish or gel) on the reversal treatment of incipient enamel carious lesions in primary or permanent dentition	• 5 studies included in review
		  ○ 3 fluoride varnish
		  ○ 2 fluoride gel
		• 3 studies included in meta-analysis
		  ○ Only fluoride varnish
			Children
			• mean age ranged from 3 to 12
				Fluoride varnish
				• Duraphat (2 applications 4 months apart – all primary tooth surfaces)
				• Fluorniz (4 applications 1 weeks apart – all primary tooth surfaces)
				• Fluoridin (3 applications quarterly – all
					• No treatment	Reversal of carious lesions (remineralization)

	Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Aim and Objectives of the review**	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
				permanent tooth surfaces) Fluoride gel • 1.23% APF (7 or 8 applications at weekly intervals – buccal surfaces of maxillary permanent incisors or of mandibular permanent first molars)		
Twetman, 2015[7] Authors from Denmark and US	"…review the quality of evidence related to self-applied and professionally applied fluorides, antimicrobial agents, fissure sealants, temporary restorations and restorative care for the prevention and management of ECC."	• Prevention and arrest of ECC ○ Prospective randomized and non-randomized studies ○ n = 19 • Management and treatment of ECC ○ Prospective randomized and non-randomized studies, controlled non-randomized and observational studies	• Prevention ○ Children under 3 years of age	5% NaF varnish • 6 studies (7 papers) • applied 2 to 4 times per year + oral health promotion	• No intervention • oral health promotion • fluoride varnish • oral health promotion + varnish • placebo	Caries prevalence or incidence over at least one year

	Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Aim and Objectives of the review**	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
		○ n = 14 • Heterogeneity of included studies resulted in a narrative synthesis • Published 2000 and April 2014				
Marinho, 2013[8] United Kingdom	"To determine the effectiveness and safety of fluoride varnished in preventing dental caries in children and adolescents, and to examine factors potentially modifying their effect."	• 22 randomized and quasi-randomized trials ○ 13 analyzed for permanent teeth ○ 10 analyzed for primary teeth • Search up to May 2013	Children up to 16 years of age (n = 12, 455, 9595 in analysis)	• Topically-applied fluoride varnish ○ Duraphat ○ Fluoridin ○ Lawefluorid ○ Fluor Protector ○ Cavity Shield ○ Duroflor	Placebo or no treatment	• Caries increment change ○ dmfs in primary and permamen t teeth • Follow-up of at least one year
All ages						
Weyant, 2013[9] United States	Topical fluoride for caries prevention • SR to support ADA guidelines	71 trials (82 articles) • 2.26% NaF varnish ○ Primary dentition (6 RCTs and 2 NRS) ○ Permanent dentition (11 RCTs and 2	Fluoride varnish studies • Primary teeth ○ 6 months to 8 years • Permanent teeth ○ 5 to 79 years	NaF, stannous fluoride and APF for professional and prescription-strength home use • 2.26% and 0.1% NaF varnishes (professionally applied every 3 to 12 months)	• No topical fluoride • Oral health counseling • Placebo varnish	• Prevention of dental caries

	Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Aim and Objectives of the review**	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
		NRS) ○ Both (1 controlled clinical trial) • pre-1970s to 2013		• gels • foams • mouthrinses • prophylaxis pastes		

ADA = American Dental Association; APF = acidulated phosphate fluoride; dmfs = decayed, missing and filled tooth surfaces; ECC = early childhood caries; MA = meta-analysis; NaF = sodium fluoride; NRS = non-randomized studies; RCT = randomized controlled trial; SR = systematic review

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Children					
Anderson, 2016[10] Denmark Non-fluoridated public water supply	• Non-blinded cluster RCT • 23 dental clinics clustered and randomized • 36 months follow up	Children born in 2010 (1 year old) in predominately low to medium socioeconomic status areas N = 3,403 36 month follow-up n = 2,536	• Topical fluoride varnish (Duraphat, 22.6mg fluoride per mL) on the buccal surface of teeth at 12, 18, 24, 30, and 36 months of age (5 visits) plus standard preventive oral health program (tooth brushing instruction and information, and dietary counseling + fluoride toothpaste and toothbrush) at 12,	• Standard preventive oral health program • n = 1,751 ○ 36 months = 1,305 • Clinical examinations were conducted on all children in each group at 12, 24, and 36 months of age	• ICDASII criteria to detect and assess caries ○ Prevalence of dental caries and number of surfaces affected by caries

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
			24, and 36 months of age • n = 1,652 ○ 36 months = 1,231		
Memarpour, 2016[11] Iran Fluoridated public water supply (<0.7 ppm)	Single blind parallel group RCT for the prevention of ECC December 2012 to March 2014	• Children aged 12 to 24 months (mean = 20.49 ± 7.33, 54.3% male) with sound primary teeth • At least 4 erupted primary teeth with no signs of caries • Parents did not use an oral hygiene methods at home or in other clinics • N = 300 children • 12 months follow-up (n = 260 children)	• Oral health education + 5%NaF varnish (DuraShield) applied at baseline and 6 months	• No preventive intervention + placebo varnish • Oral health education + placebo varnish • Both groups received fluoride varnish and education after completion of the study	• Caries risk reduction • Presence of caries ○ dmft index
Restrepo, 2016[13] Brazil	RCT for the remineralization of teeth with MIH	• Children aged 9 to 12 years (mean = 10.25 ± 1.14, 68.6% male) selected according to clinically diagnosed levels of MIH • The most severe lesion was treated for each patient	• 5% NaF varnish (Duraphat) applied weekly for 4 weeks + oral hygiene instruction + fluoride toothpaste	• Usual home-care control + placebo varnish + oral hygiene instruction + fluoride toothpaste	• mean change in fluorescence and area of the lesion ○ QLF

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		• N = 51 patients (51 lesions)			
Memarpour, 2015[12] Iran	RCT for the remineralization of primary teeth June 2012 to June 2013	• Children aged 12 to 36 months (mean = 21.20 ± 6.76) with WSL in the anterior maxillary teeth • At least 4 erupted maxillary primary incisors • WSL were present in at least 2 teeth without signs of cavitated caries • N = 140 children • 12 months follow-up (n = 122 children) • Excluded children who did not use ant oral hygiene methods, fluoride containing products, or other preventive measures	• Oral hygiene and dietary counseling + 5% NaF varnish (DuraShield) at 4, 8, and 12 months	• No treatment + placebo varnish (oral health instruction and fluoride varnish provided after completion of the study) • Oral hygiene and dietary counseling • Oral hygiene and twice daily parental application of CPP-ACP tooth mousse for 12 months	• Reduction in size of WSL • dmft index

Jiang, 2014[15]
 	
Hong Kong
 	
Fluoridated public
	RCT for the prevention of early childhood caries	• Pre-school children aged 8 to 23 months (mean = 16 months) in general good	• Parental educational materials and toothbrushing training + semi-	• One-time oral parental educational talk and printed materials alone	• Incidence of new dental caries
					  ○ ICDAS criteria
					  ○ Level 1 – non-cavitated and

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
water supply (0.5 ppm)		health • N = 450 children • 24 months follow-up (n = 415 children)	annual application of 5% NaF varnish (Clinpro White Varnish) to all erupted teeth	• Oral parental educational talk and printed materials and hands-on toothbrushing training + follow-up with a dentist every 6 months + placebo varnish	cavitated lesions ○ Level 2 – cavitated lesions only • Parental and child self-toothbrushing • Use of fluoride toothpaste
Adolescents and Young Adults					
He, 2016[17] China	3-arm parallel RCT • 4 week pre-test washout period (tooth brushing only) • Treated monthly for 6 months • Randomized by patient, not by teeth • December 2011 to May 2012	• Patients aged 12 to 25 years (mean = 16.9) who had recently completed orthodontic treatment and had at least 1 maxillary anterior tooth with a white spot lesion • N = 240 patients (597 teeth)	• Fluoride varnish (Duraphat, 5% NaF)	• Fluoride film (Sheer, 5% acidulated NaF) • Placebo • All patients in the 3 groups received oral hygiene education and were required to use fluoride toothpaste daily	• Remineralization of WSLs ○ Measured with quantitative light-induced fluorescence images ○ Change in F (%) ○ Area (mm^2) ○ Change in Q (mm^2 x %)
Du, 2011[18] China	• Parallel-group, controlled RCT of fluoride varnish for the treatment of WSL after fixed orthodontic treatment • Recruitment from June to August	• Patients aged 12 to 22 years (mean = 16.6 ± 3.2, 32.3% male) with recently removed orthodontic brackets • N = 110 • 6 months follow-up	• 5% NaF varnish (Duraphat) applied monthly for 6 months	• Saline placebo applied monthly for 6 months	• WSL depth assessed with DIAGNOdent pen

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
	2008	(n = 96 patients, 209 teeth)			
Adults					
Xin, 2016[16] Hong Kong	Double-blind, placebo controlled RCT of fluoride varnish to prevent dental caries of Sjögren's syndrome patients • 24 months duration	• Adult patients with Sjögren's syndrome (mean age 50 years, 4% men) • N = 85 • 24 months follow-up (n = 78)	• 5% NaF varnish (Duraphat) + oral hygiene instruction	• Placebo gel (K-Y Gel)	• Development and arrest of coronal caries
Camilotti, 2012[14] Brazil	Randomized controlled trial • All patients had at least one lesion treated per quadrant • All treatments were applied by a single operator • 3 applications of the material selected for the group were made for each group and in each patient with 1 week between treatments • Dentin sensitivity was assessed	• Adults (age 18-70) with dentin sensitivity to thermal changes in the oral environment with good oral hygiene • Patients selected from the files at a single dental clinic • n = 36 teeth (42 patients)	• Fluoride varnish ○ Duraphat (50 mg NaF) ○ Fluorniz (5.0g% NaF) ○ Duofluorid XII (6% NaF + 6% CaF) ○ Fluorophat (2% NaF)	• Sodium fluoride ○ Flutop (5% NaF) • Potassium oxalate ○ Oxa-gel (3% potassium oxalate) • Placebo	Dental sensitivity • US Public Health Service Criteria ○ A = 0 (no sensitivity) ○ B = 2 (slight sensitivity) ○ C = 3 (high sensitivity) • Scores recorded before and after the application of treatments • Clinical probing and air blast

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
	weekly • Clinical reassessment at 30 days after the last application				

CaF = calcium fluoride; CPP-ACP = casein phosphopeptide-amorphous calcium phosphate; dmft = decayed, missing, and filled teeth; ICDAS = International Caries Detection and Assessment System; MIH = molar incisor hypomineralization; NaF = sodium fluoride; ppm = parts per million; QLF = quantitative light-induced fluorescence; RCT = randomized controlled trial, WSL = white spot lesion

Table A3: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Atkins, 2016[19] United States	Cost-effectiveness analysis Healthcare payer perspective	Water fluoridation, dental sealants, fluoride varnish, tooth brushing with fluoride toothpaste, initial dental exams on children <18 months	Alaska native children aged 6 to 60 months	10 year time horizon 3% discounting rate 2011 USD	Assumptions: • all of the interventions had an ideal population coverage of 100 percent • children were treated by a dentist or dental surgeon • children would receive only one initial dental examination • children would receive only one full mouth dental restoration per year. 2013 Alaska Medicaid Dental Fee schedule for costs

USD = United States dollars

Table A4: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
American Academy of Pediatric Dentistry, 2014[20]						
Dental practitioners and parents Pediatric patients	Fluoride therapy (systemic and topical)	Prevention and control of dental caries	• Electronic database searches resulted in too many results. • Relied on appraisal of references from recent evidence-based reviews and MAs and hand searching	• Critical appraisal of included evidence was not described • Strength and quality of the included evidence was not described	• Recommendations were developed based on current identified literature, expert opinion, and current best practices • No further information was provided regarding recommendations development • Strength of recommendations was not identified	NR
Scottish Intercollegiate Guidelines Network, 2014[4]						
Dental care teams within dental practices, parents, other primary care providers Pediatric patients (0 to 18 years)	Dental interventions for individuals (not population-based)	Prevalence of dental caries	• Key questions identified prior to systematic literature search • Title and abstract and full-text screening were done in duplicate	• Quality appraisal of included studies was done in duplicate • Level of evidence and grade of recommendation is determined for each question using	• Recommendations are based on the quality of, and confidence in, the identified evidence • Expert input is used to add clinical context to the recommendations • Recommendations are presented with the associated level of evidence to support	NR

Table A4: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
				SIGN50		
Weyant, 2013[9] – American Dental Association						
Dental practitioners Pediatric and adult patients	Professionally applied or Rx-strength home-use topical fluoride	Prevention and control of dental caries	• Update to 2006 guidelines • Multiple data bases and hand searching • Titles and abstracts were screened in duplicate • Excluded studies list confirmed by 2 expert panel members	• USPSTF grading system • Expert opinion in areas where evidence was lacking	• Recommendations based on balance of benefits and harms • Recommendations associated with the strength, direction of the evidence, and level of certainty • Panel approves drafted recommendations by majority vote • Updated every 5 years	NR
Wilkinson, 2013[21] – Institute for Clinical Systems Improvement						
Health care organizations Average-risk, asymptomatic children and adolescents under age 18	Used to develop systems of care	Prevention and treatment of dental caries	• Predefined database search was undertaken	• Guideline was formulated using GRADE methodology • Quality of evidence and strength of recommendation are specified	• Recommendations are drafted based on the strengths and weaknesses of the evidence as identified by the GRADE analysis of the identified literature	NR

MA = meta-analysis; NR = not reported; Rx = prescription; SR = systematic review; USPSTF = United States Preventive Services Task Force

APPENDIX 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[22]

AMSTAR Checklist	Gao, 2016[5]	Lenzi, 2016[6]	Twetman, 2015[7]	Marinho, 2013[8]	Weyant, 2013[9]
1. Was an 'a priori' design provided?	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y	Y	Y	CA
3. Was a comprehensive literature search performed?	Y	Y	Y	Y	Y
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	N	Y	N	N	CA
5. Was a list of studies (included and excluded) provided?	N	N	N	Y	N
6. Were the characteristics of the included studies provided?	N	Y	Y	Y	N
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	Y	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y	Y	Y	Y
9. Were the methods used to combine the findings of studies appropriate?	Y	Y	Y	Y	CA
10. Was the likelihood of publication bias assessed?	Y	Y	Y	Y	CA
11. Was the conflict of interest included?	Y	Y	N	Y	Y

CA = can't answer; N = no; NA = not applicable; Y = yes

Table A6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black Checklist[23]	
Strengths	**Limitations**
Children	
Anderson, 2016[10]	
• Hypothesis, clinical outcomes, patient characteristics, interventions, and distribution of confounders are clearly described • Main findings of the study are clearly described and no adverse effects were reported • Characteristics of patients lost to follow up are described • Actual probability values were provided • Subjects, staff and clinics included in the study were representative of the entire population from which they were recruited • Clinics were stratified based on socioeconomic levels, geographic area, and size of clinic prior to randomization by a third party • Appropriate statistical power calculations were done • Outcomes are reported at different lengths of follow-up accounting for all patients originally enrolled • The main outcome measure was valid and reliable	• The study was unblinded for both providers and participants
Memarpour, 2016[11]	
• The aim, interventions, patient characteristics, potential confounders, and study outcomes were well described • Parents were blinded to assigned study group • Block randomization and random numbers table • Patients lost to follow-up were described and did not differ significantly between groups • Appropriate sample size calculation described	• Limited sample size. geographic location, and limitation of socioeconomic backgrounds may limit the generalizability of results • Providers were also the outcome assessors and were not blinded • Confounders were not adjusted for in the analysis
Restrepo, 2016[13]	
• Aim of the study, interventions, and main study findings were well described • Power calculation was described • Control group received a placebo intervention	• Patient characteristics and confounding factors were not described • Confounders were not adjusted for in the analysis • Unclear whether assessors were blinded to assignment

Table A6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black Checklist[23]	
Strengths	**Limitations**
• Randomization list used to assign patients to groups. no further detail provided	• No mention of any patients lost to follow-up • Generalizability may have been limited due to patients being recruited from a single centre
Memarpour, 2015[12]	
• Aim of the study, interventions, and main study findings were well described • Patients were randomized by block randomization with a random number table and were recruited from the same population • Examiners (one dentist assessed teeth and a second applied treatment) and parents were blinded • Losses to follow-up were described and numbers were similar across groups • Statistical methods were well described	• Patient characteristics and confounding factors were not described • Power calculation was based on a previously published study • Limited geographic region of recruitment may have limited generalizability of the results
Jiang, 2014[15]	
• Hypothesis, clinical outcomes, patient characteristics, interventions, and distribution of confounders are clearly described • Stratified block randomization by a statistician not involved in the study • Parents and outcome assessors were blinded to the intervention • Sample size calculation was well described • Characteristics of patients lost to follow-up were described and were not significantly different than patients who remained in the study	• Subjects recruited were mainly from middle to high socioeconomic status and may not be representative of the population as a whole
Adolescents and Young Adults	
He, 2016[17]	
• The aim of the study, patient characteristics, interventions, and main findings of the study were clearly presented • Computer generated randomization sequence and allocation was concealed in opaque envelopes • Outcome examiners were blinded to treatment allocation • Sample size calculation was well described • Actual probability values were reported • Described patients lost to follow-up • Confounding factors were adjusted for in the statistical analysis	• Confounders were adjusted for in the statistical analysis but were not well described in the study. • Patients and providers were not blinded to treatment • Primary analysis was based on the per-protocol treatment rather than intention-to-treat but patients lost to follow-up were well described • Subjects were recruited from a single centre and may not be representative of the population as a whole

Table A6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black Checklist[23]	
Strengths	**Limitations**
Du, 2011[18]	
• The study aim, outcomes, interventions, and results were clearly described Sample size calculations were well described • Patients were randomized using a random number table and randomization was performed by a third party • Patients and the outcome assessor were blinded to treatment allocation • Patients lost to follow-up were described and drop-out rates did not differ significantly between groups	• Patient characteristics and potential confounding factors were not described • Generalizability of the results may be limited due to the short follow-up period (as defined by the authors) and single centre for recruitment of patients
Adults	
Xin, 2016[16]	
• Study aim, patient characteristics, confounders, outcomes, interventions, and results were clearly described. • Sample size calculation described • Patients chosen were representative of the overall patient group • Patients and assessors were blinded to treatment • Stratified block randomization was used • Concealment allocation was undertaken by a third party as was application of study treatment • Confounders were accounted for in a statistical analysis • Patients lost to follow-up were reported and were not significantly different between groups and between drop outs and those remaining in the study	• Generalizability of study results may be limited due to the limited patient population included and small sample size (as defined by the authors)
Camilotti, 2012[14]	
• Study hypothesis clearly stated • Interventions, main outcomes clearly described • Randomization via sequentially numbered, opaque, sealed envelopes prepared with unrestricted randomization • Main outcome measures were accurate	• Patient characteristics and confounders were not described • Sample size was determined from a previous pilot study. No further detail provided • *P*- values presented as <0.05 • Adverse events not mentioned • Participants were recruited from a single clinic. It is unclear whether they were representative of the general population • Patient and provider were not blinded to the treatment

Table A7: Strengths and Limitations of Guidelines using AGREE II[24]

Item	Guideline			
	AAPD, 2014[20]	SIGN, 2014[4]	Weyant, 2013[9] - ADA	Wilkinson, 2013[21] - ICSI
1. The overall objective(s) of the guideline is (are) specifically described.	✓	✓	✓	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	✓	✓	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	✓	✓	✓
4. The guideline development group includes individuals from all relevant professional groups.	X	✓	✓	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	X	✓	X	X
6. The target users of the guideline are clearly defined.	✓	✓	✓	✓
7. Systematic methods were used to search for evidence.	X	✓	✓	✓
8. The criteria for selecting the evidence are clearly described.	X	✓	✓	X
9. The strengths and limitations of the body of evidence are clearly described.	X	✓	✓	✓
10. The methods for formulating the recommendations are clearly described.	X	✓	✓	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓	✓	✓	✓
12. There is an explicit link between the recommendations and the supporting evidence.	X	✓	✓	✓
13. The guideline has been externally reviewed by experts prior to its publication	X	✓	X	X
14. A procedure for updating the guideline is provided.	X	✓	✓	✓
15. The recommendations are specific and unambiguous.	✓	✓	✓	✓
16. The different options for management of the condition or health issue are clearly presented.	✓	✓	✓	✓
17. Key recommendations are easily identifiable.	✓	✓	✓	✓
18. The guideline describes facilitators and barriers to its application.	X	✓	✓	X
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X	✓	X	✓
20. The potential resource implications of applying the recommendations have been considered.	X	✓	X	✓
21. The guideline presents monitoring and/or auditing criteria.	X	X	X	✓
22. The views of the funding body have not influenced the content of the guideline.	X	X	X	✓
23. Competing interests of guideline development group members have been recorded and addressed.	X	✓	X	✓

AAPD = American Academy of Pediatric Dentistry; ADA = American Dental Association; ICSI = Institute for Clinical Systems Improvement; SIGN = Scottish Intercollegiate Guidelines Network

Table A8: Strengths and Limitations of Economic Studies using Drummond[25]	
Strengths	**Limitations**
Atkins, 2016[19]	
• Research question, economic importance , and form of evaluation are clearly stated • Perspective of the analysis is stated and justified • Rationale for choosing interventions and alternatives is clear • Sources of effectiveness estimates are stated • Primary outcome measures are stated • Costs of resources are reported separately from quantity • Currency and price data are presented • Time horizon and discounting rates are appropriate • Sensitivity analyses were undertaken	• Results are not generalizable beyond the limited study population

APPENDIX 4: Main Findings and Author's Conclusions

Table A9: Summary of Findings of Included Systematic Reviews

Main Review Findings	Author's Conclusions
Children	
Gao, 2016[5]	

Six studies of 5% NaF varnish
• 1 study reported dimension change of caries lesions
  ○ Average size of early enamel caries was significantly smaller in children receiving professionally applied NaF varnish as compared to children receiving no fluoride treatment
• 5 studies reported % of remineralized early enamel caries
  ○ 1 study comparing 6% NaF + 6% calcium fluoride varnish found significant reversal of early enamel caries in the treatment vs no treatment groups
 	
Meta-analysis of 5% NaF varnish (4 studies) for remineralization
• overall % of remineralization = 63.6% (95% CI, 36.0 to 91.2; *P* <0.001)
	• Heterogeneity in the included studies meant not all studies could be included in meta-analysis
	• "Six trials were included in this review and they all demonstrated that NaF could remineralise early enamel caries." (page 7)
	• "Results of meta-analysis on four studies showed that 5% NaF varnish remineralised approximately two-thirds of early enamel caries lesions in children." (page 7)

Lenzi, 2016[15]	
Fluoride varnish versus no treatment for enamel carious lesions Overall mean difference = -2.04 (95% CI, -3.25 to -0.84; *P* = 0.0009) • There was a statistically higher decrease in caries prevalence in the fluoride varnish group as compared to the no treatment group **Fluoride gel on incipient carious lesions versus placebo or no treatment** • There was no evidence of effectiveness of fluoride gel for the reversal of active enamel carious lesions.	• "The meta-analysis showed that fluoride varnish is an effective approach for arresting the progression of enamel carious lesions in primary and permanent teeth." (page 88) • A high level of heterogeneity was identified in the meta-analysis • The duration of the included studies differed. Four applications once a week and two applications over four months were both effective. • "…we do not consider a bias risk with the inclusion of studies in which participants had access to fluoridated toothpaste or water." (page 89) • Because of the relatively small number of included studies, the authors indicated publication bias may have resulted in studies with negative or null results not being published.

Table A9: Summary of Findings of Included Systematic Reviews

Main Review Findings	Author's Conclusions
Marinho, 2013[8]	
Pooled dmfs prevented fraction estimate for permanent tooth surfaces – fluoride varnish vs placebo/no treatment • 43% (95% CI, 30% to 57%; *P* < 0.0001) • Substantial heterogeneity in the analyzed studies but moderate quality overall **Pooled dmfs prevented fraction estimate for primary tooth surfaces – fluoride varnish vs placebo/no treatment** • 37% (95% CI, 24% to 51%; *P* <0.0001) • Moderate quality evidence	• "The conclusions of this updated review remain the same as those when it was first published. The review suggests a substantial caries-inhibiting effect of fluoride varnish in both permanent and primary teeth, however the quality of the evidence was assessed as moderate, as it included mainly high risk of bias studies, with considerable heterogeneity." (page 2)
Twetman, 2015[7]	
Professionally applied fluorides for ECC prevention	• "Our present findings partly reinforced [the concept that sodium fluoride varnish was the treatment choice to prevent and control ECC in children at risk] but it should be emphasized that the prevented fraction was low and the quality of evidence was weaker than that of studies of fluoride varnish in young permanent dentition." (page 250) • "There is moderate and limited quality of evidence in support of fluoride toothpaste and fluoride varnish for ECC prevention…" (page 251)

Author	Intervention/ comparator	ECC outcome (PF)	Risk of bias
Lawrence, 2008	FV + OHP vs OHP	11.0 vs 13.4 dmfs (18%)	Mod
Milgrom, 2009	FV + FTP vs FV	8.2 vs 10.3 deft (20%)	Mod
Minah, 2010	FV +OHP vs historical	0.1 vs 1.3ds (93%)	High
Slade, 2011	FV + OHP vs NI	6.9 vs 9.9 dmfs (24%)	Mod
Ramos-Gomez, 2012	FV + OHP vs OHP	24 vs 34% (NS)	High
Divaris, 2013	FV + OHP vs NI	RR: 0.75 (25%)	Mod
Oliviera, 2014	FV vs placbo	36 vs 47% (11%)	Mod

Table A9: Summary of Findings of Included Systematic Reviews	
Main Review Findings	**Author's Conclusions**
All ages	
Weyant, 2013[9]	

Recommendations for 2.26% NaF Varnish
• Patients younger than six years of age and six to 18 years of age
  ○ "There is a benefit of 2.26 percent fluoride varnish application at least twice per year for caries prevention." [Moderate level of certainty] (page 21)
• Adult root caries
  ○ "There is a benefit of 2.26 percent fluoride varnish application at least twice per year for caries prevention in adults." [Low level of certainty] (page 21)
 	
Recommendations for 0.1% NaF Varnish
• Patients younger than six years of age
  ○ "There is no benefit of 0.1 percent fluoride varnish application twice per year for caries prevention." [Moderate level of certainty] (page 21)
• Patients aged six to 18
  ○ "There is no benefit of 0.1 percent fluoride varnish three times per week for caries prevention." [Low level of certainty] (page 21)
 	
• Harms
  ○ "Because of the low risk of experiencing harm in children younger than 6 years, unit doses of 2.26 percent fluoride varnish are the only topical fluoride agents that are recommended for this age group, even though other topical fluorides may have some evidence of benefit." (page 6)
 	
• Studies included patients from different countries with and without additional fluoride use, with and without fluoridated public water supply, and with or without prophylaxis
	• "The panel recommends the following for people at risk of developing dental caries: 2.26 percent fluoride varnish…for patients 6 years or older." (page 11)
	• "Only 2.26 percent fluoride varnish is recommended for children younger than 6 years." (page 11)

ECC = early childhood caries; FTP = fluoride toothpaste; FV = fluoride varnish; mod = moderate; NaF = sodium fluoride; NI = no intervention; OHP = oral health promotion; PF = prevented fraction

Table A10: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
Children	
Anderson, 2016[10]	

<u>Baseline caries scores [n(%)]</u>
Varnish group (n = 1,652)
• ICDAS 1-6 = 60 (4)
• ICDAS 3-6 = 11 (1)
• ICDAS 5-6 = 1 (0)
• Gingivitis = 82 (5)
Control group (n = 1,751)
• ICDAS 1-6 = 117 (7)
• ICDAS 3-6 = 11 (1)
• ICDAS 5-6 = 5 (0)
• Gingivitis = 78 (4)
 	
<u>24 months caries scores [n(%)]</u>
Varnish group (n = 1,223)
• ICDAS 1-2 = 83 (6.8)
• ICDAS 3-6 = 42 (3.4)
• ICDAS 5-6 = 30 (2.5)
Control group (n = 1,452)
• ICDAS 1-6 = 90 (6.2)
• ICDAS 3-6 = 63 (4.3)
• ICDAS 5-6 = 37 (2.5)
  ○ All reported *P* values were non-significant
 	
<u>36 months scores [n(%)]</u>
Varnish group (n = 1,231)
• ICDAS 1-2 = 141 (11.5)
• ICDAS 3-6 = 128 (10.4)
• ICDAS 5-6 = 75 (6.1)
Control group (n = 1,305)
• ICDAS 1-6 = 125 (9.6)
• ICDAS 3-6 = 179 (13.7)
• ICDAS 5-6 = 99 (7.6)
  ○ All reported *P* values were non-significant
 	
• No major adverse effects were reported
	• "…caries prevalence differed nonsignificantly between a group of children receiving a standard oral health program only and a group receiving the same program supplemented with semiannual fluoride varnish applications between 1 and 3 years of age." (page 21)
	• "…there were no differences in the number of tooth surfaces with moderate-to-severe carious lesions between children who had received fluoridated varnish on their teeth every 6 months and those who had not." (page 21)
	• "In conclusion, within the limitations of this field study, the extended preventive program of semiannual fluoride varnish applications had no additive effect in reducing the prevalence of early childhood caries in preschool children living in urban multicultural caries risk areas." (page 22)

Table A10: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
Memarpour, 2016[11]	

Reduction in caries incidence
dmft ≠ 0: Varnish / Oral Hygiene / Control
4 months (n = 95, 97, 96): 1 / 2 / 3
8 months (n = 93, 94, 94): 1 / 3 / 15
12 months (n = 87, 85, 88): 1 / 4 / 29
 	
Risk of caries experience (95% CI)
Overall risk: Varnish / Oral Hygiene / Control
4 months (n = 95, 97, 96): 1.05 (0.00 to 3.10) / 2.06 (0.00 to 4.92) / 3.12 (0.00 to 6.60)
8 months (n = 93, 94, 94): 1.08 (0.00 to 3.16) / 3.19 (0.00 to 6.74) / 15.96 (9.01 to 22.91)
12 months (n = 87, 85, 88): 1.15 (0.00 to 3.39) / 4.71 (0.21 to 9.21) / 32.95 (23.13 to 42.77)
• At 8 months
  ○ Reduction of caries risk was significantly reduced in the oral hygiene ($P = 0.005$) and fluoride varnish ($P < 0.001$) groups as compared to the control group
  ○ The risk value did not differ significantly between the two treatment groups
• At 12 months
  ○ Reduction of caries risk was significantly reduced in the oral hygiene ($P < 0.001$) and fluoride varnish ($P < 0.001$) groups as compared to the control group
  ○ The risk value did not differ significantly between the two treatment groups
 	
• No adverse effects were reported or observed in any group
	• "Our results showed a significant reduction in the number of caries in the [oral hygiene education] and [oral hygiene education + fluoride varnish] groups compared to the control group." (page 440)
	• Children in the fluoride varnish group had 31% fewer caries at 12 months as compared to the no treatment group.
	• There was no significant difference in the number of caries between the two treatment groups.

Table A10: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
Restrepo, 2016[13]	
Lesion volume (mean ± SD) Δ Q (ΔF x mm^2) — Varnish (n = 26) / Control (n = 25) Baseline: -0.87 ± 0.35 / -0.92 ± 0.25 2nd visit: -0.83 ± 0.38 / -0.88 ± 0.32 3rd visit: -0.95 ± 0.49 / -1.03 ± 0.27 4th visit: -1.08 ± 0.23 / -0.98 ± 0.30 5th visit: -0.89 ± 0.34 / -0.87 ± 0.29 **Percentage of fluorescence loss (mean ±SD)** Δ F (%) — Varnish (n = 26) / Control (n = 25) Baseline: -7.47 ± 0.43 / -7.22 ± 0.40 2nd visit: -6.84 ± 1.23 / -7.54 ± 0.87 3rd visit: -7.52 ± 0.92 / -7.31 ± 0.95 4th visit: -6.52 ± 1.14 / -6.76 ± 1.17 5th visit: -6.32 ± 0.50 / -6.43 ± 0.64 • There were no statistically significant changes in average change in fluorescence or extension of MIH lesions in either group • No adverse events were reported	• "We observed no favorable effect on the remineralization of MIH lesions in anterior teeth after four applications of fluoride varnish." (page 207)
Memarpour, 2015[12]	
Changes in mean WSL size over time (median [mean ± SD]) Mean % Change — Varnish / Oral Hygiene / Control 4 months (n = 35, 35, 35): -0.27 (-0.14 ± 0.36) / -0.09 (-0.14 ± 0.36) / 0.36 (+0.62 ± 1.04) 8 months (n = 32, 33, 33): -0.62 (-0.46 ± 0.54) / -0.29 (-0.06 ± 0.78) / 0.67 (+0.98 ± 1.22) 12 months (n = 29, 32, 31): -0.81 (-0.63 ± 0.62) / -0.50 (-0.10 ± 1.12) / 0.79 (+1.15 ± 1.26) • mean area of WSL increased over time in the control group and was significantly greater after 8 months (*P* = 0.001) but there was no significant difference between 8 and 12 months (*P* = 0.221) • mean WSL size decreased significantly over time in the fluoride varnish group (P <0.001)	• Surface area of WSL and dmft index increased over 12 months in the no treatment control group • "…oral health education and regular visits to the dentist are considered basic public dental health interventions intended to decrease dental caries." (page 236) • "…with time, oral hygiene measures alone were effective in decreasing dental caries but were insufficient to reverse WSL or stop ECC." (page 236) • "…four periodic applications of fluoride varnish combined with oral hygiene instruction was an effective method to reverse and decrease the WSL area and dmft index…" (page 236)

Table A10: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
dmft index during follow-up (mean ± SD) dmft index: Varnish / Oral Hygiene / Control 4 months (n = 35, 35, 35): 0.14 ± 0.52 / 0.06 ± 0.25 / 0.37 ± 1.21 8 months (n = 32, 33, 33): 0.31 ± 0.89 / 0.29 ± 0.86 / 0.84 ± 1.69 12 months (n = 29, 32, 31): 0.3 ± 0.90 / 0.42 ± 0.99 / 2 ± 2 • there were significant between group differences in dmft only at 12 months (*P* <0.001) • dmft did not change significantly in the varnish or oral hygiene groups • No adverse or unexpected effects were reported in the fluoride varnish or tooth mousse groups	
Jiang, 2014[15]	

<u>Overall incidences of ECC at 24 months</u>
• Level 1
  ○ 13.7% (57/415)
• Level 2
  ○ 8.4% (35/415)
• There were no statistically significant differences in the incidences of early childhood caries between the three treatment groups
• There were no statistically significant differences in parental toothbrushing between groups at 24 months
• Proportion of children who did not carry out self toothbrushing was significantly higher in the control group (*P* = 0.018)
• There were no statistically significant differences in the use of fluoride toothpaste between groups at 24 months
  ○ More than 70% of children in each group reported using fluoridated toothpaste
• No adverse events were reported
• Parents of children who dropped out of the study had significantly lower education and income levels than those who remained in the study.
	• "In an optimally water fluoridated area, semi-annual application of 5% sodium fluoride varnish may not be effective in preventing dental caries in young children aged below 3 years with low risk of dental caries." (page 1549)
	• "Based on the findings of this study and within limitations, it is concluded that the effectiveness of providing oral health education and hands-on training in parental toothbrushing to parents in preventing dental caries in young children with low risk of dental caries may not be different from that of providing oral health education alone." (page 1549)

Table A10: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
Adolescents and Young Adults	
He, 2016[17]	

Changes in QLF parameters over time

Lesion volume at 5% threshold (mean ± SD)

Δ Q (ΔF x mm^2)	Varnish (n = 69)	Film (n = 70)	Control (n = 72)
Baseline	-41.86 ± 45.29	-42.63 ± 49.02	-34.12 ± 41.32
3 months	-25.03 ± 30.18	-29.26 ± 38.16	-28.06 ± 35.00
6 months	-19.13 ± 23.77	-23.39 ± 32.67	-26.51 ± 31.96

- ΔQ was significantly decreased in all groups after 6 months
- "The decreases in ΔQ values among the three groups were statistically significant after adjusting for confounding factors…ΔQ values of the varnish and film groups decreased by a significantly greater amount than that of the control group (*P* <0.0001 for both comparisons)." (page 815)
- "…the ΔQ of the varnish group decreased by a significantly greater amount than that of the film group (*P* = 0.0266)." (page 815)
- Only two teeth healed completely

Lesion area (mean ± SD)

Area (mm^2)	Varnish (n = 69)	Film (n = 70)	Control (n = 72)
Baseline	2.54 ± 2.34	2.69 ± 2.70	2.07 ± 2.12
3 months	1.71 ± 1.76	2.00 ± 2.24	1.82 ± 1.91
6 months	1.37 ± 1.49	1.65 ± 1.96	1.70 ± 1.77

Percentage of fluorescence loss (mean ±SD)

Δ F (%)	Varnish (n = 69)	Film (n = 70)	Control (n = 72)
Baseline	-13.59 ± 3.75	-13.15 ± 3.75	-13.21 ± 3.39
3 months	-11.89 ± 3.27	-11.71 ± 3.30	-12.41 ± 3.09
6 months	-10.91 ± 3.42	-11.03 ± 3.15	-12.14 ± 3.02

- "This randomized clinical trial demonstrated the efficacy of fluoride varnish…and fluoride film…for enamel remineralization around orthodontic brackets after orthodontic treatment." (page 815)
- Both fluoride varnish and fluoride film resulted in significant improvements in white spot lesions.
- The authors concluded that fluoride varnish was significantly more effective than fluoride film or placebo.

Table A10: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
Adverse events • One 14 year old boy suffered from nausea after swallowing fluoride varnish at one treatment • No other adverse events were reported	
Du, 2011[18]	
Comparison of DD scores (lesion depth) between groups (mean ± SD)	• "Topical fluoride varnish application is effective in reversing WSLs after debonding and should be advocated as a routine caries prevention measure after orthodontic treatment." (page 463)

	Fluoride (n = 47)	Control (n = 49)	*P*-value
Baseline	17.66 ± 5.36	16.19 ± 5.70	0.196
3 months	11.88 ± 4.27	13.75 ± 4.76	0.046
6 months	10.10 ± 4.86	13.10 ± 5.19	0.004

• DD readings were significantly lower in the fluoride group at both 3 and 6 months follow-up
• No adverse events or safety concerns were reported

Adults

Xin, 2016[16]

Type of lesion by subject (%)

Lesion type	Fluoride (n = 40)	Control N = 38)
12 months		
No caries	15 (37.5)	19 (50)
Enamel	19 (47.5)	15 (39.4)
Dentin	4 (10)	8 (21.1)
Arrested	7 (17.5)	5 (13.2)
24 months		
No caries	11 (27.5)	12 (31.8)
Enamel	21 (52.5)	18 (47.4)
Dentin	13 (32.5)	16 (42.1)
Arrested	10 (25.0)	14 (37.5)

Type of lesion by surface (mean [SD])

Lesion type	Fluoride	Control
12 months		
Enamel	41 (1.0 [1.5])	34 (0.9 [1.5])
Dentin	8 (0.2 [0.6])	35 (0.9 [2.4])
Arrested	17 (0.4 [1.2])	13 (0.3 [1.2])
24 months		
Enamel	64 (1.6 [2.3])	60 (1.6 [2.5])
Dentin	55 (1.4 [2.6])	78 (2.1 [4.2])
Arrested	22 (0.6 [1.3])	25 (0.7 [1.3])

• "Although subjects in the placebo group developed higher mean new caries lesions than the fluoride group, the differences were not statistically significant." (page 7)
• "Results of this randomized clinical trial did not provide clear evidence to support or refute that quarterly applications of fluoride varnish can prevent development of dental caries in people with Sjögren's syndrome." (page 1)

Table A10: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
• No significant differences in lesion types were reported in either group. • When confounders were adjusted for, the odds ratio of dentin caries development was significantly lower in the fluoride group.	
Camilotti, 2012[14]	
Mean dentin sensitivity score values (SD) for fluoride varnish groups and placebo Fluorniz • Week 1 = 3 (0.000) • Week 2 = 1.83 (1.033) • Week 3 = 1.33 (1.033) • Reassessment = 1.33 (1.328) Duofluorid XII • Week 1 = 3 (0.000) • Week 2 = 1.83 (1.472) • Week 3 = 1.33 (1.033) • Reassessment = 1.33 (1.033) Flurophat • Week 1 = 3 (0.000) • Week 2 = 1.88 (0.560) • Week 3 = 0.89 (0.587) • Reassessment = 0.81 (0.599) Duraphat • Week 1 = 3 (0.000) • Week 2 = 2 (1.095) • Week 3 = 0.67 (1.033) • Reassessment = 0.33 (0.817) Placebo • Week 1 = 3 (0.000) • Week 2 = 2.92 (0.554) • Week 3 = 2.84 (0.532) • Reassessment = 2.80 (0.147)	• "As of the third week, all of the materials used presented statistically significant differences compared to baseline scores, with the exception of the placebo and sodium fluoride groups." (page 4) • "Fluorophat…and Duraphat… fluoridated varnishes presented the lowest sensitivity scores." (page 4) • The authors concluded that the study results disproved their hypothesis that there would be no difference between the different desensitizing agents.

CI = confidence interval; DD = DIAGNOdent pen; ECC = early childhood caries; ICDAS = International Caries Detection and Assessment System; MIH = molar incisor hypomineralization; QLF = quantitative light-induced fluorescence; SD = standard deviation; WSL = white spot lesions

Table A11: Summary of Findings of Included Cost Studies	
Main Study Findings	**Author's Conclusions**
Atkins, 2016[19]	
Undiscounted cost of applying fluoride varnish to the population = $62,923 Maximum annual cost of applying fluoride varnish to 100% of the population = $146,775 Total discounted 10 year cost = $1,252,021	• The authors concluded that all interventions were cost saving over the 10 year time horizon • Water fluoridation and dental sealants each showed the greatest cost benefit depending on the modelling scenario • Water fluoridation, tooth brushing, and fluoride varnish were found to prevent the most dental caries and full mouth dental restorations • The cost of a 10 year water fluoridation program would be less than either a 10 year tooth brushing or fluoride varnish program and would likely result in greater compliance

Table A12: Summary of Recommendations of Included Guidelines
American Academy of Pediatric Dentistry, 2014[20]
• "There is confirmation from evidence-based reviews that fluoride use for the prevention and control of caries is both safe and highly effective in reducing dental caries prevalence." (page 177) • "There is evidence from randomized controlled trials and meta-analyses that professionally applied topical fluoride treatments as five percent [sodium fluoride varnish] or 1.23 percent [fluoride] gell preparations are efficacious in reducing caries in children at risk." (page 177)
Scottish Intercollegiate Guidelines Network, 2014[4]
• "Fluoride varnish should be applied at least twice yearly in all children." (page 5)
HealthPartners Dental Group and Clinics, 2013[26]
Primary and transitional dentition • "…the application of a fluoride varnish using a disposable brush is equal to or more effective and less time consuming than the traditional application of a fluoride gel using disposable trays. For low-risk children, the recommended recall interval can be 12 months." • For "very young children" and "older children" at moderate or high risk of dental caries, the guideline recommends fluoride varnish be applied with a microbrush by the dentist as part of the standard dental visit and recommends the child be recalled every 3 to 6 months. Permanent dentition • Fluoride varnish for root caries, interproximal caries, and other smooth surface caries should be considered at clinic visits.
Weyant, 2013[9] – American Dental Association
• "For individuals at risk of dental caries: 2.26% fluoride varnish or 1.23% fluoride gel, or prescription strength, home-use 0.5% fluoride gel or paste, or 0.09% fluoride mouth rinse for children who are aged six or over." (page 3) • "Only 2.26% fluoride varnish is recommended for children younger than 6 years." (page 3)

Table A12: Summary of Recommendations of Included Guidelines
Wilkinson, 2013[21] – Institute for Clinical Systems Improvement
• "Fluoride should be recommended to prevent caries and cavities." (page 23) Birth to two years • "Use fluoride varnish for patients at high risk of cavities if mechanisms to successfully and consistently deliver this in the clinic setting are available." (page 24) Two to 18 years • "Consider fluoride varnish for patients at high risk of cavities if mechanisms to successfully and consistently deliver this in the clinic setting are available." (page 24)
Irish Oral Health Services Guideline Initiative, 2012[27]
Children at high risk of caries • Apply fluoride varnish every three or six months • "Apply fluoride varnish or consider glass ionomer as an interim sealant if moisture control is inadequate."