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Nonrestorative Treatments for Caries: Systematic Review and Network Meta-analysis

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Abstract
The goal of nonrestorative or non- and microinvasive caries treatment (fluoride- and nonfluoride-based interventions) is to manage the caries disease process at a lesion level and minimize the loss of sound tooth structure. The purpose of this systematic review and network meta-analysis was to summarize the available evidence on nonrestorative treatments for the outcomes of 1) arrest or reversal of noncavitated and cavitated carious lesions on primary and permanent teeth and 2) adverse events. We included parallel and split-mouth randomized controlled trials where patients were followed for any length of time. Studies were identified with MEDLINE and Embase via Ovid, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews. Pairs of reviewers independently conducted the selection of studies, data extraction, risk-of-bias assessments, and assessment of the certainty in the evidence with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Data were synthesized with a random effects model and a frequentist approach. Forty-four trials (48 reports) were eligible, which included 7,378 participants and assessed the effect of 22 interventions in arresting or reversing noncavitated or cavitated carious lesions. Four network meta-analyses suggested that sealants + 5% sodium fluoride (NaF) varnish, resin infiltration + 5% NaF varnish, and 5,000-ppm F (1.1% NaF) toothpaste or gel were the most effective for arresting or reversing noncavitated occlusal, approximal, and noncavitated and cavitated root carious lesions on primary and/or permanent teeth, respectively (low- to moderate-certainty evidence). Study-level data indicated that 5% NaF varnish was the most effective for arresting or reversing noncavitated facial/lingual carious lesions (low certainty) and that 38% silver diamine fluoride solution applied biannually was the most effective for arresting advanced cavitated carious lesions on any coronal surface (moderate to high certainty). Preventing the onset of caries is the ultimate goal of a caries management plan. However, if the disease is present, there is a variety of effective interventions to treat carious lesions nonrestoratively.

Keywords: systematic reviews and evidence-based dentistry, geriatric dentistry, pediatric dentistry, dental public health, evidence-based dentistry/health care, caries

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A supplemental appendix to this article is available online.

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Introduction

Dental caries is the most prevalent chronic disease in the world, affecting 60% to 90% of school-aged children and the majority of adults (World Health Organization 2018). The development of a carious lesion involves a dynamic biological process in which acids produced by bacterial glycolysis of dietary carbohydrates cause demineralization of dental hard tissues. Factors that modulate the ecology of oral biofilms are either protective or pathologic (Featherstone 2000; Slayton 2015). Early signs of caries consist of noncavitated coronal or root carious lesions (i.e., initial or white spot lesions). Progression of the disease process with further loss of tooth minerals leads to a cavitated lesion. Arresting cavitated lesions is more difficult, as loss of tooth structure creates niches for the biofilm that are not easily accessible. However, preserving tooth structure and pulpal health is also a guiding principle for the management of cavitated carious lesions (Schwendicke et al. 2016). Therefore, early detection, diagnosis, and the use of effective nonrestorative treatments are crucial for the management of noncavitated carious lesions. This strategy may also offer a conservative alternative to restorative care once lesions become cavitated.

Systematic reviews on the nonrestorative or non- and microinvasive treatment of carious lesions have historically focused on 1 or 2 interventions or been limited to 1 tooth surface; that is, they have not provided the comparative effectiveness of available strategies on all relevant surfaces (Schwendicke et al. 2015). The purpose of this review is to collect and synthesize the best available evidence on the benefits and harms of nonrestorative treatments for 1) the primary outcome of arrest or reversal of existing noncavitated and cavitated carious lesions on primary and permanent teeth and 2) the secondary outcome of adverse events. This review is based on network meta-analysis (NMA), which allows us to directly and indirectly compare >2 interventions at once (Salanti 2012). This systematic review informs a clinical practice guideline published in the *Journal of the American Dental Association* and is the product of an expert panel of clinicians convened by the American Dental Association's (ADA) Council on Scientific Affairs (Slayton et al. 2018). Evidence synthesis and drafting of manuscripts were led by methodologists from the ADA's Center for Evidence-Based Dentistry.

Methods

We followed the guidance from the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) Checklist to report this systematic review (Hutton et al. 2015).

Inclusion Criteria

Types of Studies. Studies included parallel or split-mouth randomized controlled trials, with follow-up of any length.

Participants. Participants included adults and children with noncavitated or cavitated carious lesions on primary or permanent teeth:

- Lesions were diagnosed by radiographs or visual/tactile assessment.
- Caries classification methods or lesion assessment criteria—such as the International Caries Detection and Assessment System (Ismail et al. 2007), Ekstrand criteria (Ekstrand et al. 1997) and Nyvaad criteria (Nyvad et al. 1999, 2003)—were used; DIAGNOdent and quantitative light-induced fluorescence, among others, were not included.
- Lesions were included in which no demineralized tissue was removed (beyond acid etching for bonding) before application of the intervention.

Interventions. Interventions included professionally applied or prescribed products available in the United States in which an active intervention was compared with another active intervention or no intervention/placebo: sodium fluoride (NaF), stannous fluoride toothpaste or gel, acidulated phosphate fluoride (APF), difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, amorphous calcium phosphate (ACP), casein phosphopeptide–ACP (CPP-ACP), nano hydroxyapatite, tricalcium phosphate, prebiotics and/or 1.5% arginine, probiotics, silver diamine fluoride (SDF), silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, and carbamide peroxide. SDF is the only intervention for which we included concentrations unavailable in the United States. We made this decision because although this intervention was initially studied in other countries in the 1970s, it has recently gained clinicians' and researchers' interest in the United States, warranting a full evaluation of its effect.

Outcomes. The primary outcome of this review was arrest or reversal of existing noncavitated and cavitated carious lesions. Secondary outcomes included adverse events, such as nausea, fluorosis, vomiting, allergic reactions, staining, tooth sensitivity, soft tissue trauma, symptomatic progression, pulpal health, lack of retention (for sealants), premature loss or extraction, and secondary caries.

Literature Search

A health sciences librarian (L.B.) in collaboration with methodologists and the expert panel developed a search strategy to retrieve studies assessing all the interventions of interest, except for sealants. The strategy was carried out in OVID Medline (Epub Ahead of Print, In Process, and Other Non-Indexed Citations; Daily; and 1946 to June 2017), Embase (1974 to June 2017), and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews per the OVID platform (inception to June 2017). The searches were not limited by language or study design (Appendix Methods).

In 2016, the ADA and the American Association of Pediatric Dentistry (AAPD) published a systematic review on the use of sealants for preventing and arresting carious lesions (Wright et al. 2016). Because the scope of that review was similar for this intervention, we updated the search strategy from that review in the same databases from January 2013 to June 2017 (Appendix Methods).

Selection of Primary Studies and Data Extraction

After we retrieved the references, titles and abstracts were screened in duplicate by 2 reviewers (O.U., M.P.T.) using Covidence (Veritas Health Innovation). Once we identified potentially included studies, we obtained and screened full text articles (O.U., M.P.T.). When agreement was elusive, we discussed eligibility until consensus was achieved. If this was not possible, a third reviewer (A.C.L.) acted as an arbiter. We also searched the reference sections of relevant primary studies, systematic reviews, and guidelines to identify additional studies.

Two pairs of reviewers used a tested data extraction form to abstract data independently and in duplicate (M.P.T., O.U., L.P., G.J.). We extracted the following study characteristics: country, study design, patient population (age, sex, dentition [primary and permanent teeth]), tooth surface (occlusal, approximal, facial/lingual), lesion type (noncavitated or cavitated), location (root or coronal), risk factors, follow-up times, interventions (brand name, manufacturer, active ingredient, concentration, dose, duration, frequency, mode of delivery, tooth preparation), adverse events, conflicts of interest, and funding source. We considered any arm described by the study authors as unsupervised at-home care or no treatment on the part of the clinician as "no treatment." We also extracted information related to the unit of analysis and the criteria used to define the outcome of arrest or reversal (Appendix Methods).

We extracted quantitative data from studies when arrest or reversal was reported dichotomously or continuously at the lesion level. When arrest or reversal was reported dichotomously, we extracted the number of total carious lesions at follow-up, as well as the number of arrested or reversed lesions in each arm. When arrest or reversal was reported continuously and the average number of lesions in each group that became arrested or reversed was reported, we extracted these data with the standard deviation.

Measures of Association

For dichotomous outcomes, we calculated relative risks (RRs) with 95% CIs, and for continuous outcomes, we calculated mean differences (MDs) with 95% CIs. For the outcome of arrest or reversal, we interpreted an RR >1 as an increase in the probability for arrest or reversal and an RR <1, a reduction in such probability. A negative MD represents an average reduction in the number of carious lesions arrested or reversed.

Statistical Analysis

We conducted NMA to obtain estimates of the relative effectiveness of all interventions on the primary outcome by combining direct and indirect evidence using a random-effects model that assumed a common between-study heterogeneity parameter across the network and a frequentist approach. P scores, which are analogous to SUCRA values in Bayesian NMA, were also obtained. These represent the average certainty that a treatment is better than all of the other treatments (Rucker and Schwarzer 2015). We provide details about NMA methods in the Appendix Methods.

We assessed global incoherence of the network using the design-by-treatment interaction model (Higgins et al. 2012). For details about the assessment of local incoherence and intransitivity in the context of the assessment of the certainty in the evidence, see the Appendix Methods. We conducted NMA using the package *netmeta* (Rucker et al. 2016) in the software R (version 3.1.1; R Foundation for Statistical Computing).

For studies on root surfaces, data on noncavitated and cavitated lesions, when separately reported, were combined within 1 network, as these may be difficult to distinguish in clinical practice and in the research context.

Within each network, if studies reported dissimilar follow-up times or lacked a common comparator or if pairwise meta-analysis was not possible, we categorized this as unpooled data and prioritized the calculation and reporting of RRs and MDs (and 95% CIs) at an individual study level. When we still failed to obtain these measures of association, we also considered these data unpooled and reported the results as described by the primary study authors.

Pairwise Subgroup Analyses

For studies on root surfaces, we conducted subgroup analysis at a pairwise level by lesion type, and for studies on coronal surfaces, by dentition. We used a test for interaction to explore the extent to which the effect of any included intervention varied according to the type of dentition or lesion. A level of significance of 0.05 was used for the interaction test. When there were no differences in treatment effects among primary, permanent, and mixed dentition, we combined the results.

Certainty in the Evidence

We assessed the certainty in the evidence (also known as the quality of the evidence) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach at the outcome level for each comparison between interventions (Guyatt et al. 2008). The certainty in the evidence can be high, moderate, low, or very low. When the certainty in the evidence is assessed from direct comparisons, randomized controlled trials start as high-certainty evidence. However, serious or very serious issues of risk of bias (Appendix Methods), inconsistency, indirectness, imprecision, and publication bias reduce the certainty (Guyatt et al. 2008). We assessed the certainty in the indirect evidence based on intransitivity, imprecision, and the lowest-certainty ratings for the direct comparisons, forming the first-order loop that contributed the most to an indirect estimate (Puhan et al. 2014). When assessing the certainty in the evidence for NMAs, we considered the certainty in the direct evidence and the indirect evidence, as well as their contribution to the network estimate, including local incoherence and imprecision (Puhan et al. 2014; Brignardello-Petersen, Bonner, et al. 2018). We provide details about this assessment in the Appendix Methods.

Results

After removing 7,124 duplicates, we screened 9,698 titles and abstracts. Of those, 379 citations were selected for screening at a full-text level. We included 44 studies (48 reports) in this review (Appendix Fig. 1, Tables 1 and 2).

Characteristics of Included Studies

These 44 trials were published between 1984 and 2018 and conducted in 22 countries: 34 trials were based on a parallel study design and 10 on a split-mouth design ($N_{patients}$ = 7,378). Twelve studies included participants with primary dentition, 22 with permanent dentition, and 9 with mixed dentition. For 1 study, type of dentition remained unclear (Appendix Table 1).

Risk-of-Bias Assessment

Information to judge most domains was often incomplete or missing. The domain of allocation concealment was judged to be the most serious methodological issue, and overall most studies had serious issues of risk of bias (Appendix Fig. 2).

Pairwise Subgroup Analyses

We were able to conduct subgroup analyses for the pairwise comparison of sealants versus no sealants on approximal surfaces (P = 0.52) and occlusal surfaces (P = 0.81) between primary and permanent teeth and found no evidence to suggest that the effect of these interventions varied according to dentition. We also conducted subgroup analysis for a pairwise comparison—5,000-ppm F (1.1% NaF) toothpaste or gel versus no treatment on root surfaces between cavitated and noncavitated lesions—and found no statistically significant difference in the treatment effect (P = 0.90).

Effects of Interventions on Caries Arrest or Reversal

We were able to conduct 4 NMAs according to lesion location and further stratified by tooth surface involved and lesion type.

Coronal Surfaces

Noncavitated carious lesions on occlusal surfaces. We identified 8 studies reporting the effectiveness of interventions in arresting or reversing noncavitated occlusal lesions, with 7 that could be included in the NMA (Agrawal and Pushpanjani 2011; Autio-Gold and Courts 2001; Bakhshandeh and Ekstrand 2015; Borges et al. 2010; da Silveira et al. 2012; Florio et al. 2001; Honkala et al. 2015; Table 1, Appendix Fig. 3a) and 1 that could not be pooled (Altenburger et al. 2010; Appendix Table 1). The relative effectiveness of 6 active interventions were assessed in the studies included in the NMA. These studies followed a total of 1,575 lesions in primary and permanent teeth for 8 to 12 mo. Network estimates for 0.2% NaF mouthrinse + supervised toothbrushing, 1.23% APF gel, 5% NaF varnish, resin infiltration + 5% NaF varnish, sealants + 5% NaF varnish, and sealants alone showed a 2- to 3-times-greater chance of arresting or reversing lesions as compared with no treatment (moderate certainty for all comparisons). The combination of sealants and 5% NaF varnish was the most effective in arresting or reversing lesions versus no treatment (RR, 3.35; 95% CI, 2.42 to 4.64; moderate certainty).

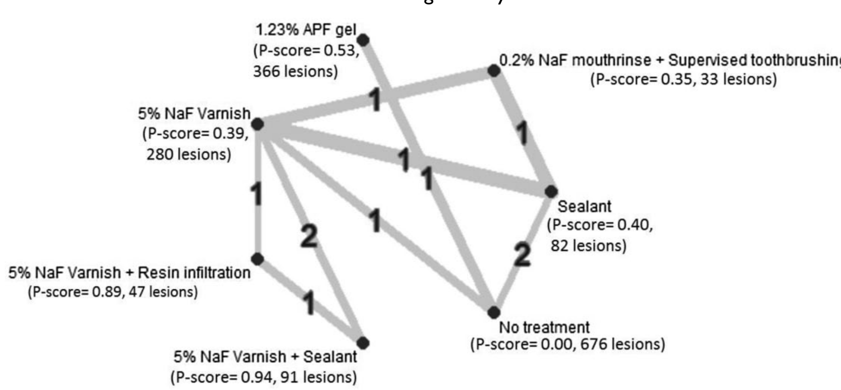
Noncavitated carious lesions on approximal surfaces. We identified 13 studies (14 reports) reporting the effectiveness of interventions in arresting or reversing noncavitated approximal lesions, with 6 studies (7 reports) that could be included in the NMA (Martignon et al. 2006; Ekstrand et al. 2010; Martignon et al. 2010; Paris et al. 2010; Martignon et al. 2012; Meyer-Lueckel et al. 2012; Gomez et al. 2015; Table 2, Appendix Fig. 3b) and 7 that could not be pooled (Modeer et al. 1984; Petersson et al. 1991; Peyron et al. 1992; Moberg Skold, Birkhed, et al. 2005; Moberg Skold, Petersson, et al. 2005; Trairatvorakul 2011; Meyer-Lueckel at al. 2016; Appendix Table 1). The relative effectiveness of 4 active interventions was assessed in the studies included in the NMA, which followed a total of 565 lesions in primary and permanent teeth for 12 to 36 mo. Studies included lesions with radiolucencies ranging from the enamel to lesions in the outer third of the dentin. Network estimates for resin infiltration and sealants after short-term tooth separation showed a 2-times-greater chance of arresting or reversing lesions as compared with no treatment (low certainty for all comparisons). Additionally, for the combination of resin infiltration and 5% NaF varnish, the network estimate suggested that there may be a 5-times-greater chance of arresting or reversing lesions versus no treatment (RR, 4.59; 95% CI, 1.00 to 20.88; very low certainty). For 5% NaF varnish alone, there may be a 2-times-greater chance of arresting or reversing lesions as compared with no treatment; however, these results were not statistically significant (RR, 2.29; 95% CI, 0.74, 7.10; very low certainty). Additional evidence from unpooled studies suggested similar results (Modeer et al. 1984; Petersson et al. 1991; Peyron et al. 1992; Moberg Skold, Petersson, et al. 2005).

Noncavitated carious lesions on facial/lingual surfaces. We identified 5 studies (Autio-Gold and Courts 2001; Bailey et al. 2009; Agrawal and Pushpanjani 2011; Bonow et al. 2013; Turska-Szybka et al. 2016) reporting the effectiveness of interventions in arresting or reversing noncavitated facial/lingual lesions, 3 (Autio-Gold and Courts 2001; Bailey et al. 2009; Agrawal and Pushpanjani 2011) of which could be used to calculate RRs Table 3 and Appendix Table 1). We did not create a network with the data coming from the 3 studies, due to the follow-up times being too dissimilar. In sum, 5% NaF varnish versus no intervention (low certainty) and 1.23% APF gel versus oral health education (moderate certainty) showed a 2- to 3-times-greater chance of arresting or reversing lesions in

Table 1. Relative Risks (95% CIs) and Certainty in the Evidence for Nonrestorative Treatments for the Arrest or Reversal of Noncavitated Carious Lesions on Occlusal Surfaces (8- to 12-mo Follow-up).

	Direct		Indirect		NMA	
Comparison	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence
0.2% NaF mouthrinse + supervised toothbrushing vs.						
1.23% APF gel			0.91 (0.68 to 1.22)	Low[a,b]	0.91 (0.68 to 1.22)	Low[a,b]
5% NaF varnish	0.99 (0.85 to 1.17)	Low[a,b]	0.76 (0.32 to 1.80)	Very low[a,c]	0.99 (0.84 to 1.15)	Low[a,b]
Resin infiltration + 5% NaF varnish			0.61 (0.43 to 0.85)	Moderate[a]	0.61 (0.43 to 0.85)	Moderate[a]
Sealant + 5% NaF varnish			0.58 (0.43 to 0.79)	Moderate[a]	0.58 (0.43 to 0.79)	Moderate[a]
Sealant	0.97 (0.83 to 1.14)	Low[a,b]	1.31 (0.51 to 3.33)	Very low[a,c]	0.98 (0.84 to 1.14)	Low[a,b]
No treatment			1.95 (1.54 to 2.46)	Moderate[a]	1.94 (1.54 to 2.46)	Moderate[a]
1.23% APF gel vs.						
5% NaF varnish			1.08 (0.83 to 1.40)	Low[a,b]	1.08 (0.83 to 1.40)	Low[a,b]
Resin infiltration + 5% NaF varnish			0.67 (0.45 to 0.99)	Low[a,b]	0.67 (0.45 to 0.99)	Low[a,b]
Sealant + 5% NaF varnish			0.64 (0.44 to 0.92)	Low[a,b]	0.64 (0.44 to 0.92)	Low[a,b]
Sealant			1.08 (0.82 to 1.41)	Low[a,b]	1.08 (0.82 to 1.41)	Low[a,b]
No treatment	2.13 (1.79 to 2.54)	Moderate[a]			2.13 (1.79 to 2.54)	Moderate[a]
5% NaF varnish vs.						
Resin infiltration + 5% NaF varnish	0.69 (0.50 to 0.97)	Low[a,b]	0.37 (0.19 to 0.73)	Moderate[a]	0.62 (0.46 to 0.83)	Moderate[a]
Sealant + 5% NaF varnish	0.59 (0.45 to 0.76)	Moderate[a]			0.59 (0.45 to 0.76)	Moderate[a]
Sealant	0.98 (0.84 to 1.14)	Low[a,b]	1.11 (0.75 to 1.65)	Low[a,b]	0.99 (0.86 to 1.15)	Low[a,b]
No treatment	2.05 (1.63 to 2.60)	Moderate[a]	1.80 (1.27 to 2.55)	Moderate[a]	1.97 (1.63 to 2.40)	Moderate[a]
Resin infiltration + 5% NaF varnish vs.						
Sealant + 5% NaF varnish	1.00 (0.78 to 1.28)	Low[a,b]	0.41 (0.14 to 1.17)	Low[a,b]	0.95 (0.75 to 1.21)	Low[a,b]
Sealant			1.61 (1.16 to 2.24)	Moderate[a]	1.61 (1.16 to 2.24)	Moderate[a]
No treatment			3.20 (2.24 to 4.56)	Moderate[a]	3.20 (2.24 to 4.56)	Moderate[a]
Sealant + 5% NaF varnish vs.						
Sealant			1.69 (1.26 to 2.27)	Moderate[a]	1.69 (1.26 to 2.27)	Moderate[a]
No treatment			3.35 (2.42 to 4.64)	Moderate[a]	3.35 (2.42 to 4.64)	Moderate[a]
Sealant vs. no treatment	1.84 (1.35 to 2.52)	Moderate[a]	2.10 (1.59 to 2.77)	Moderate[a]	1.98 (1.61 to 2.44)	Moderate[a]

Network geometry[d]



Seven studies contributed to this network (Autio-Gold and Courts 2001; Florio et al. 2001; Borges et al. 2010; Agrawal and Pushpanjali 2011; da Silveira et al. 2012; Bakhshandeh and Ekstrand 2015; Honkala et al. 2015). None of the indirect estimates were downgraded for intransitivity, and none of the NMA estimates were downgraded for incoherence.

APF, acidulated phosphate fluoride; NaF, sodium fluoride; NMA, network meta-analysis.

[a]Certainty in the evidence downgraded by 1 level due to serious risk of bias.

[b]Certainty in the evidence downgraded by 1 level due to serious imprecision.

[c]Certainty in the evidence downgraded by 2 levels due to very serious imprecision.

[d]Each black circle represents a node. Each line is an edge, and its thickness corresponds to the inverse variance of each direct estimate. The number next to each edge represents the number studies that compared those 2 interventions. P-scores represent the average certainty that a treatment is better than all of the other treatments. The higher the p-score, the more certain we are that it is superior to the other treatments (Rucker and Schwarzer 2015).

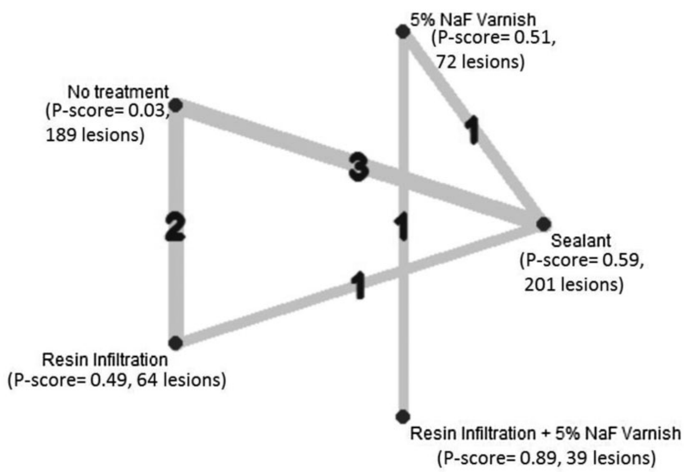
primary and permanent teeth. However, 10% CPP-ACP, when compared with placebo cream, may increase the chance of arresting or reversing lesions in primary and permanent teeth; however, these results were neither statistically nor clinically significant (low certainty; Table 3).

Noncavitated carious lesions on any coronal surface. Some studies did not report data by a specific surface and instead reported the total number of arrested or reversed lesions on a combination of surfaces (e.g., 2 studies presented the total arrested or reversed lesions on facial/lingual and occlusal

Table 2. Relative Risks (95% CIs) and Certainty in the Evidence for Nonrestorative Treatments for the Arrest or Reversal of Noncavitated Carious Lesions on Approximal Surfaces (12- to 36-mo Follow-up).

	Direct		Indirect		NMA	
Comparison	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence
5% NaF varnish vs.						
Resin infiltration			1.09 (0.32 to 3.65)	Very low[a,b]	1.09 (0.32 to 3.65)	Very low[a,b]
Resin infiltration + 5% NaF varnish	0.50 (0.18 to 1.37)	Very low[a,b]			0.50 (0.18 to 1.37)	Very low[a,b]
Sealant	0.95 (0.38 to 2.41)	Very low[a,b]			0.95 (0.38 to 2.41)	Very low[a,b]
No treatment			2.29 (0.74 to 7.10)	Very low[a,b]	2.29 (0.74 to 7.10)	Very low[a,b]
Resin infiltration vs.						
Resin infiltration + 5% NaF varnish			0.46 (0.09 to 2.23)	Very low[a,b]	0.46 (0.09 to 2.23)	Very low[a,b]
Sealant	1.27 (0.48 to 3.36)	Very low[a,b]	0.45 (0.12 to 1.65)	Very low[a,b]	0.88 (0.40 to 1.91)	Very low[a,b]
No treatment	1.82 (0.90 to 3.68)	Very low[a,b]	8.70 (0.99 to 76.92)	Very low[a,b]	2.11 (1.08 to 4.13)	Low[a,d]
Resin infiltration + 5% NaF varnish vs.						
Sealant			1.91 (0.48 to 7.52)	Very low[a,b]	1.91 (0.48 to 7.52)	Very low[a,b]
No treatment			4.59 (1.01 to 20.88)	Very low[a,b]	4.59 (1.01 to 20.88)	Very low[a,b]
Sealant vs. no treatment	2.56 (1.31 to 5.00)	Low[a,c]	1.13 (0.11 to 11.99)	Very low[a,b]	2.41 (1.26 to 4.58)	Low[a,c]

Network geometry[e]



Six studies contributed to this network (Gomez et al. 2005; Martignon et al. 2006; Ekstrand et al. 2010; Martignon et al. 2010; Paris et al. 2010; Martignon et al. 2012; Meyer-Lueckel et al. 2012). None of the indirect estimates were downgraded for intransitivity. None of the NMA estimates were downgraded for incoherence.
NaF, sodium fluoride; NMA, network meta-analysis.
[a]Certainty in the evidence downgraded by 1 level due to serious risk of bias.
[b]Certainty in the evidence downgraded by 2 levels due to very serious imprecision.
[c]Certainty in the evidence downgraded by 1 level due to serious inconsistency.
[d]Certainty in the evidence downgraded by 1 level due to serious imprecision.
[e]Each black circle represents a node. Each line is an edge, and its thickness corresponds to the inverse variance of each direct estimate. The number next to each edge represents the number studies that compared those 2 interventions. P-scores represent the average certainty that a treatment is better than all of the other treatments. The higher the p-score, the more certain we are that it is superior to the other treatments (Rucker and Schwarzer 2015).

combined). We identified 7 studies (Heidmann et al. 1992; Autio-Gold and Courts 2001; Duarte et al. 2008; Agrawal and Pushpanjani 2011; Sitthisettapong et al. 2012; Honkala et al. 2014; Hedayati-Hajikand et al. 2015) reporting the effectiveness of interventions in arresting or reversing noncavitated lesions on any coronal surface, with 3 that could be included in the NMA (Autio-Gold and Courts 2001; Agrawal and Pushpanjani 2011; Sitthisettapong et al. 2012; Table 4, Appendix Table 1, and Appendix Fig. 3c). The relative effectiveness of 3 active interventions was assessed in the studies included in the NMA. These studies followed a total of 4,672 lesions in primary and permanent teeth for 9 to 12 mo. Network estimates for 5% NaF varnish and 1.23% APF gel showed a 2-times-greater chance of arresting or reversing lesions versus no treatment (moderate certainty for all comparisons). However, 10% CPP-ACP may increase the chance of arresting or reversing lesions by only 3%; however, these results were neither statistically nor clinically significant (RR, 1.03; 95% CI, 0.90 to 1.18; low certainty; Table 4).

Cavitated lesions on any coronal surface. We identified 4 studies that reported the effectiveness of interventions in arresting advanced cavitated lesions on any coronal surface,

Table 3. Relative Risks (95% CIs) and Certainty in the Evidence for Nonrestorative Treatments for the Arrest or Reversal of Noncavitated Carious Lesions on Facial/Lingual Surfaces (1-mo to 12-mo Follow-up).

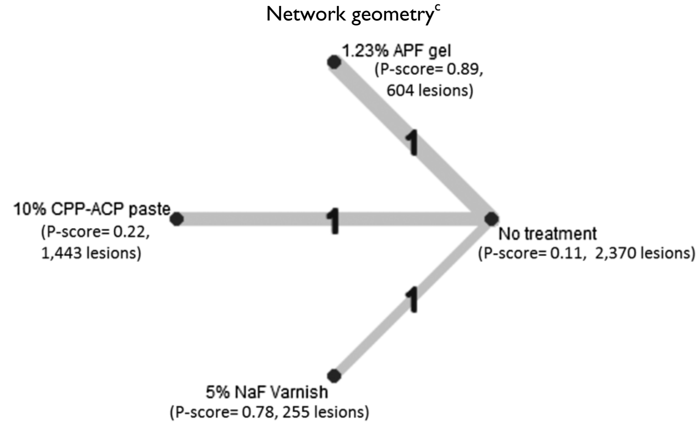
Study: *n* / *n*, Follow-up	Study Arm (Dose, Duration, Frequency)	Relative Risk (95% CI), Certainty in the Evidence
Bailey et al. (2009)[a] *n* = 45 people at follow-up, *n* = 408 lesions at longest follow-up 1, 2, and 3 mo	10% CPP-ACP cream + 900-ppm NaF mouthrinse +1,000-ppm NaF dentifrice (2 g morning and night for 12 wk + mouthrinse supervised at each visit) Placebo cream + 900-ppm NaF mouthrinse + 1,000-ppm NaF dentifrice	10% CPP-ACP cream + 900-ppm mouthrinse vs. 900-ppm mouthrinse: 1 mo: 1.28 (0.97 to 1.68), Low[b,c] 2 mo: 1.12 (0.93 to 1.36), Low[b,c] 3 mo: 1.23 (1.06 to 1.42), Low[b,c]
Autio-Gold et al. (2001) *n* = 142 people at follow-up,[d] *n* = 150 lesions at longest follow-up 9 mo	5% NaF varnish (baseline and 4 mo later) No treatment	5% NaF varnish vs. no treatment: 9 mo: 2.30 (1.58 to 3.34), Low[e]
Agrawal and Pushpanjali (2011) *n* = 257 people at follow-up,[d] *n* = 374 lesions at longest follow-up 12 mo	1.23% APF gel (baseline and 6 mo later) + oral health education Oral health education	1.23% APF gel + oral health education vs. oral health education: 12 mo: 2.47 (1.95 to 3.13), Moderate[b]

APF, acidulated phosphate fluoride; CPP-ACP, casein phosphopeptide–amorphous calcium phosphate; NaF, sodium fluoride; RR, relative risk.
[a]In this study, ≥1 adverse events were reported for 86% of participants (*n* = 39); however, there was no information on the arm or the nature of them. There was also ≥1 reported gastrointestinal symptoms in the CPP-ACP cream arm.
[b]Certainty in the evidence downgraded by 1 level due to serious risk of bias.
[c]Certainty in the evidence downgraded by 1 level due to serious imprecision.
[d]Authors did not report the number of participants that had lesions only on facial/lingual surfaces. This is the number of people at follow-up.
[e]Certainty in the evidence downgraded by 2 levels due to very serious risk of bias.

Table 4. Relative Risks (95% CIs) and Certainty in the Evidence for Nonrestorative Treatments for the Arrest or Reversal of Noncavitated Carious Lesions on Any Coronal Surface (9- to 12-mo Follow-up).

	Direct		Indirect		NMA	
Comparison	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence
1.23% APF gel vs.						
10% CPP-ACP paste			2.19 (1.83 to 2.61)	Moderate[a]	2.19 (1.83 to 2.61)	Moderate[a]
5% NaF varnish			1.05 (0.85 to 1.29)	Low[a,b]	1.05 (0.85 to 1.29)	Low[a,b]
No treatment	2.25 (2.00 to 2.53)	Moderate[a]			2.25 (2.00 to 2.53)	Moderate[a]
10% CPP-ACP paste vs.						
5% NaF varnish			0.48 (0.38 to 0.60)	Moderate[a]	0.48 (0.38 to 0.60)	Moderate[a]
No treatment	1.03 (0.90 to 1.18)	Low[a,b]			1.03 (0.90 to 1.18)	Low[a,b]
5% NaF varnish vs. no treatment	2.15 (1.80 to 2.57)	Moderate[a]			2.15 (1.80 to 2.57)	Moderate[a]

Network geometry[c]



Three studies contributed to this network (Autio-Gold and Courts 2001; Agrawal and Pushpanjali 2011; Sitthisettapong et al. 2012). None of the indirect estimates were downgraded for intransitivity.
APF, acidulated phosphate fluoride; CPP-ACP, casein phosphopeptide–amorphous calcium phosphate; NaF, sodium fluoride; NMA, network meta-analysis.
[a]Certainty in the evidence downgraded by 1 level due to serious risk of bias.
[b]Certainty in the evidence downgraded by 1 level due to serious imprecision.
[c]Each black circle represents a node. Each line is an edge, and its thickness corresponds to the inverse variance of each direct estimate. The number next to each edge represents the number studies that compared those 2 interventions. P-scores represent the average certainty that a treatment is better than all of the other treatments. The higher the p-score, the more certain we are that it is superior to the other treatments (Rucker and Schwarzer 2015).

Table 5. Relative Risks (95% CIs) and Certainty in the Evidence for Nonrestorative Treatments for the Arrest of Advanced Cavitated Carious Lesions on Any Coronal Surface (12- to 30-mo Follow-up).

Study: *n* / *n*, Surface, Follow-up	Study Arm (Dose, Duration, Frequency)	Relative Risk (95% CI), Certainty in the Evidence	
Duangthip et al. (2016), Duangthip, Wong, et al. (2018)[a] *n* = 309 people at follow-up, *n* = 1,228 lesions at longest follow-up[b] Mixed (occlusal, proximal, facial/lingual) 6,[c] 12, 18, and 30 mo	30% SDF solution (once a year, applied annually) 30% SDF solution (once a week for 3 wk, not applied annually) 5% NaF varnish (once a week for 3 wk, not applied annually)	30% SDF solution annually vs. 30% SDF solution once a week for 3 wk: 30 mo, 1.45 (1.21 to 1.73); High 18 mo, 1.13 (0.95 to 1.34); Moderate[d] 12 mo, 0.72 (0.56 to 0.91); Moderate[d] 30% SDF solution, once a week for 3 wk vs. 5% NaF varnish once a week for 3 wk: 30 mo, 0.97 (0.80 to 1.18); Moderate[d] 18 mo: 1.30 (1.07 to 1.57); High 12 mo: 2.08 (1.59 to 2.71); High	30% SDF solution annually vs. 5% NaF varnish once a week for 3 wk: 30 mo, 1.41 (1.20 to 1.66); High 18 mo, 1.47 (1.22 to 1.76); High 12 mo, 1.48 (1.11 to 1.97); High
Fung et al. (2016, 2018); Duangthip, Fung, et al. (2018) [a] *n* = 799 people at follow-up / *n* = 3,790 lesions at longest follow-up; Mixed (mesial, occlusal, facial, distal and lingual) 12, 18, and 30 mo	12% SDF solution (once a year, applied annually) 12% SDF solution (twice a year, applied biannually) 38% SDF solution (once a year, applied annually) 38% SDF solution (twice a year, applied biannually	12% SDF solution annually vs. 12% SDF solution biannually: 30 mo, 0.94 (0.87 to 1.02); High 24 mo, 0.91 (0.84 to 0.98); Moderate[d] 18 mo, 0.91 (0.83 to 0.99); Moderate[d] 12 mo, 0.85 (0.77 to 0.93); Moderate[d] 38% SDF solution biannually vs. 12% SDF solution biannually: 30 mo, 1.29 (1.21 to 1.38); High 24 mo, 1.29 (1.21 to 1.38); High 18 mo, 1.34 (1.25 to 1.43); High 12 mo, 1.30 (1.21 to 1.41); High	38% SDF solution biannually vs. 38% SDF solution annually: 30 mo, 1.13 (1.07 to 1.20); Moderate[d] 24 mo, 1.20 (1.13 to 1.27); High 18 mo, 1.15 (1.09 to 1.23); Moderate[d] 12 mo, 1.21 (1.12 to 1.30); High 38% SDF solution annually vs. 12% SDF solution annually: 30 m: 1.21 (1.13 to 1.30); High 24 mo: 1.19 (1.10 to 1.28); High 18 mo: 1.27 (1.18 to 1.38); High 12 mo: 1.27 (1.16 to 1.40); High

ICDAS, International Caries Detection and Assessment System; NaF, sodium fluoride; SDF, silver diamine fluoride.
[a]Adverse events: Black staining reported by Fung et al. (2018), Duangthip et al. (2016), and Duangthip, Wong, et al. (2018). In the study by Fung et al. (2018), there were no significant differences in tooth pain, gingival pain, gingival swelling, or gingival bleaching among the 4 groups; these adverse events affected a very small proportion of kids in each group.
[b]ICDAS 5 and 6 data are presented here (for ICDAS 3 and 4 data, see the Appendix).
[c]Data for 6 mo are reported in the studies but not shown here.
[d]Certainty in the evidence downgraded by 1 level due to serious imprecision.

from which RRs (2 studies [5 reports]: Duangthip et al. 2016; Duangthip, Fung, et al. 2018; Duangthip, Wong, et al. 2018; Fung et al. 2016; Fung et al. 2018); Table 5) and MDs (2 studies: Llodra et al. 2005; Yee et al. 2009; Appendix Table 1) were obtained. Results for moderate cavitated lesions can be found in Appendix Table 4. The lack of a common comparator across interventions prevented us from creating a network. After 30 mo of follow-up, 30% SDF solution applied annually on primary teeth showed a 1.5-times-greater chance of arresting advanced cavitated lesions in primary teeth versus 30% SDF solution applied once a week for 3 wk (RR, 1.45; 95% CI 1.21 to 1.73; high certainty). Also, 30% SDF solution applied annually on primary teeth is superior to 5% NaF varnish applied once a week for 3 wk (RR, 1.41; 95% CI, 1.20 to 1.66; high certainty). Additionally, after 30 mo of follow-up, 38% SDF solution applied biannually on primary teeth was superior to 12% SDF solution applied biannually (RR, 1.29; 95% CI, 1.21 to 1.38; high certainty) and 38% SDF solution applied annually (RR, 1.13; 95% CI, 1.07 to 1.20; moderate certainty).

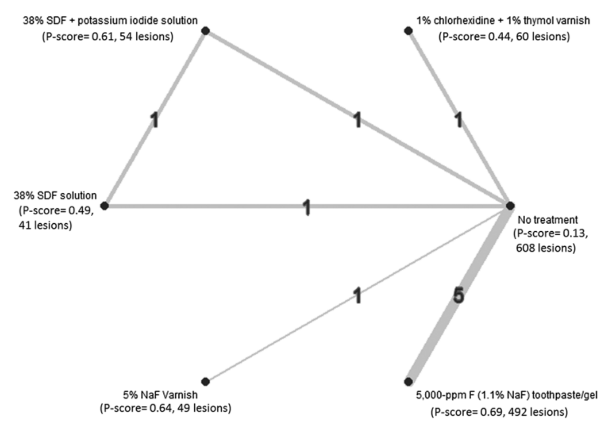
Root Surfaces

Noncavitated and cavitated lesions on root surfaces. We identified 11 studies (Schaeken et al. 1991; Wallace et al. 1993; Lynch et al. 2000; Baysan et al. 2001; Brailsford et al. 2002; Wyatt and MacEntee 2004; Ekstrand et al. 2008; Baca et al. 2009; Ekstrand et al. 2013; Zhang et al. 2013; Li et al. 2016) reporting the effectiveness of interventions in arresting or reversing noncavitated and cavitated root lesions, with 7 that could be included in the NMA (Schaeken et al. 1991; Lynch et al. 2000; Baysan et al. 2001; Ekstrand et al. 2008; Baca et al. 2009; Ekstrand et al. 2013; Li et al. 2016; Table 6, Appendix Table 1, and Appendix Fig. 3d). The relative effectiveness of 5 active interventions was assessed in the studies included in the NMA. These studies followed 1,304 lesions in permanent teeth for 3 to 12 mo. The network estimate for 5,000-ppm F (1.1% NaF) toothpaste or gel showed a 3-times-greater chance of arresting or reversing lesions as compared with no treatment (RR, 2.62, 95% CI, 1.49 to 4.63; low certainty). Also, network estimates for 1% chlorhexidine + 1% thymol varnish, 38%

Table 6. Relative Risks (95% CIs) and Certainty in the Evidence for Nonrestorative Treatments for the Arrest or Reversal of Noncavitated and Cavitated Carious Lesions on Root Surfaces (3- to 12-mo Follow-up).

	Direct		Indirect		NMA	
Comparison	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence	Relative Risk (95% CI)	Certainty in the Evidence
1% chlorhexidine + 1% thymol varnish vs.						
38% SDF solution			0.88 (0.14 to 5.60)	Very low[a,b]	0.88 (0.14 to 5.60)	Very low[a,b]
38% SDF + potassium iodide solution			0.71 (0.11 to 4.45)	Very low[a,b]	0.71 (0.11 to 4.45)	Very low[a,b]
5% NaF varnish			0.57 (0.04 to 8.69)	Very low[a,b]	0.57 (0.04 to 8.69)	Very low[a,b]
5,000-ppm F (1.1% NaF) toothpaste or gel			0.64 (0.15 to 2.70)	Very low[a,c,d]	0.64 (0.15 to 2.70)	Very low[a,c,d]
No treatment	1.67 (0.44 to 6.31)	Very low[a,b]			1.67 (0.44 to 6.31)	Very low[a,b]
38% SDF solution vs.						
38% SDF + potassium iodide solution	0.80 (0.25 to 2.61)	Low[a,c]			0.80 (0.25 to 2.61)	Low[a,c]
5% NaF varnish			0.64 (0.04 to 9.66)	Very low[a,b]	0.64 (0.04 to 9.66)	Very low[a,b]
5,000-ppm F (1.1% NaF) toothpaste or gel			0.72 (0.18 to 2.95)	Very low[a,c,d]	0.72 (0.18 to 2.95)	Very low[a,c,d]
No treatment	1.90 (0.52 to 6.87)	Very low[a,b]			1.92 (0.52 to 6.87)	Very low[a,b]
38% SDF + potassium iodide solution vs.						
5% NaF varnish			0.80 (0.05 to 11.95)	Very low[a,b]	0.80 (0.05 to 11.95)	Very low[a,b]
5,000-ppm F (1.1% NaF) toothpaste or gel			0.90 (0.22 to 3.62)	Very low[a,c,d]	0.90 (0.22 to 3.62)	Very low[a,c,d]
No treatment	2.36 (0.66 to 8.42)	Very low[a,b]			2.36 (0.66 to 8.42)	Very low[a,b]
5% NaF varnish vs.						
5,000-ppm F (1.1% NaF) toothpaste or gel			1.13 (0.10 to 13.12)	Very low[a,c,d]	1.13 (0.10 to 13.12)	Very low[a,c,d]
No treatment	2.96 (0.27 to 32.26)	Very low[a,b]			2.96 (0.27 to 32.26)	Very low[a,b]
5,000-ppm F (1.1% NaF) toothpaste or gel vs. no treatment	2.62 (1.49 to 4.63)	Low[a,d]			2.62 (1.49 to 4.63)	Low[a,d]

Network geometry[e]



Seven studies contributed to this network (Schaeken et al. 1991; Lynch et al. 2000; Baysan et al. 2001; Ekstrand et al. 2008; Baca et al. 2009; Ekstrand et al. 2013; Li et al. 2016). None of the indirect estimates were downgraded for intransitivity.
NaF, sodium fluoride; NMA, network meta-analysis; SDF, silver diamine fluoride.
[a]Certainty in the evidence downgraded by 1 level due to serious issues of risk of bias.
[b]Certainty in the evidence downgraded by 2 levels due to very serious imprecision.
[c]Certainty in the evidence downgraded by 1 level due to serious imprecision.
[d]Certainty in the evidence downgraded by 1 level due to serious inconsistency.
[e]Each black circle represents a node. Each line is an edge, and its thickness corresponds to the inverse variance of each direct estimate. The number next to each edge represents the number studies that compared those 2 interventions. P-scores represent the average certainty that a treatment is better than all of the other treatments. The higher the p-score, the more certain we are that it is superior to the other treatments (Rucker and Schwarzer 2015).

SDF solution applied annually, 38% SDF + potassium iodide solution applied annually, and 5% NaF varnish showed a range of 2- to 3-times-greater chance of arresting or reversing lesions versus no treatment; however, these results were not statistically significant (very low certainty).

Effect of Interventions on Other Outcomes for Coronal and Root Surfaces

Description of adverse events was reported in only 4 studies (7 reports: Bailey et al. 2009; Baca et al. 2009; Duangthip et al.

2016; Fung et al. 2016; Duangthip, Fung, et al. 2018; Duangthip, Wong, et al. 2018; Fung et al. 2018) and included black staining, tooth pain, gum pain, gingival swelling, gingival bleaching, and bitter taste. One study (Bailey et al. 2009) stated that 86% of the participants reported at least 1 adverse event but did not provide specifics regarding which treatment group experienced these (10% CPP-ACP or placebo group; Appendix Table 1). Other adverse events of interest—including nausea, fluorosis, vomiting, allergic reactions, tooth sensitivity, symptomatic progression, pulpal health, premature loss or extraction, or secondary caries—were not reported in the included studies, and thus no evidence was available to inform their occurrence. Among the studies examining the effect of sealants on occlusal noncavitated lesions, retention ranged from 41% to 89%, while no studies reported retention of sealants applied on approximal noncavitated lesions.

Discussion

Summary of Results

We used NMA to evaluate treatments regarding their ability to arrest or reverse noncavitated carious lesions on various tooth surfaces against a common comparator (no treatment). Evidence suggests that 1) the combination of sealants and 5% NaF varnish was the most effective for noncavitated carious lesions on occlusal surfaces in primary and permanent teeth (moderate certainty), and 2) the combination of resin infiltration and 5% NaF varnish may be the most effective for noncavitated carious lesions on approximal surfaces in primary and permanent teeth (low certainty). Similarly, 5,000-ppm F (1.1% NaF) toothpaste or gel may be the most effective for noncavitated and cavitated carious lesions on root surfaces in permanent teeth (low certainty).

Study-level data show that when compared with no intervention, 5% NaF varnish could be the most effective treatment for arresting or reversing noncavitated facial/lingual lesions on primary and permanent teeth (low to moderate certainty). Also, study-level data compared the use of 1.23% APF gel with oral health education on facial/lingual lesions, although this treatment was effective only at longer follow-up times (12 mo, moderate certainty). For arresting advanced cavitated carious lesions, study-level data suggest that 38% SDF solution applied biannually was more effective on any coronal surface of primary teeth when compared with both 12% SDF solution applied biannually and 38% SDF solution applied annually (moderate to high certainty).

Finally, 4 studies reported adverse events across the different interventions, including black staining, tooth/gum pain, gingival swelling and bleaching, and a bitter taste.

Certainty in the Evidence

The certainty in the evidence ranged from very low to high for the outcome of arrest or reversal across all surfaces, types of lesions, and dentition. We predominantly downgraded the certainty due to serious issues of risk of bias and imprecision.

Comparison to Other Reviews

Several pairwise comparison systematic reviews provide similar conclusions. Authors of a 2015 Cochrane systematic review found moderate certainty evidence that sealants and resin infiltration could be more effective than other noninvasive treatments (i.e., 5% NaF varnish) at arresting or reversing noncavitated carious lesions on approximal surfaces (Dorri et al. 2015). A 2016 ADA–AAPD systematic review found moderate certainty evidence supporting the effectiveness of pit-and-fissure sealants in managing noncavitated carious lesions on occlusal surfaces of primary and permanent teeth (Wright et al. 2016). A 2017 systematic review concluded that 30% SDF solution and 38% SDF solution could be more effective than other interventions (i.e., 5% NaF varnish) in arresting dentinal caries in the primary dentition (Contreras et al. 2017). While the authors of this review noted that SDF may darken lesions and create aesthetic concerns, their search date limited the inclusion of 1 study included in this review, and they were not able to determine that an application frequency of twice a year was more effective than once a year.

Although clinicians may be aware of the use of 5% NaF varnish to reduce caries incidence (i.e., prevention), we wanted to explore the effectiveness of 5% NaF in arresting or reversing existing noncavitated carious lesions. Authors of a 2016 systematic review concluded that 5% NaF varnish was effective in reversing noncavitated carious lesions in primary and permanent teeth when compared with 1.23% APF gel or no treatment (Lenzi et al. 2016). The authors also compared their conclusions with those of other reviews and suggested that sealants may be more effective than 5% NaF varnish in managing lesions on more susceptible occlusal surfaces (Ahovuo-Saloranta et al. 2016; Lenzi et al. 2016). Overall, this review supported our conclusion that, when used in combination with more superior nonrestorative treatments for noncavitated carious lesions (e.g., sealants or resin infiltration), 5% NaF provided an added benefit (Ahovuo-Saloranta et al. 2016; Lenzi et al. 2016).

Strengths and Limitations

Strengths of this systematic review include the rigor of its methodology, as informed by the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks et al. 2017) and the assessment of the certainty in the evidence with GRADE for NMA (Puhan et al. 2014; Brignardello-Petersen, Bonner, et al. 2018). We chose to use NMA in this review to enhance decision making because this statistical method allows us to compare several treatments at a time with 1 common comparator and obtain more precise estimates. To our knowledge, this is the first NMA conducted to inform the effect of nonrestorative treatments for arresting or reversing carious lesions.

Limitations of this systematic review include 1) the paucity of randomized controlled trials meeting our inclusion criteria for several interventions of interest and 2) the inability to create a funnel plot to complement the publication bias assessment, owing to the limited number of included studies per tooth surface/lesion type. In addition, the review was not registered in PROSPERO (International Prospective Register of Systematic Reviews). Our decision of pooling studies regardless of potential differences in treatment nodes, as well as small differences in follow-up times, were appropriately informed by experts who determined that we may be able to expect consistency in this review. Also, there was variability in how studies measured and defined arrest or reversal. We assumed that measurements/descriptions were similar enough to pool these results in our review (Appendix Methods). Finally, when an NMA is conducted, assumptions of homogeneity, transitivity, and consistency are made. We used a frequentist approach and assumed a common between-study heterogeneity because our networks were suspected to be sparse. This may result in spuriously wide confidence intervals for the network estimates, but this was not the case in our networks (Brignardello-Petersen, Murad, et al. 2018).

Implications for Research

It may be useful to clinical trialists if experts could establish a core set of outcomes informing benefits and harms of nonrestorative treatments for caries management and definitions of these outcomes. This would subsequently help systematic review developers define and pool outcomes in their reviews. Additionally, although we were interested in the effect of SDF for noncavitated carious lesions on approximal surfaces, we did not identify any published RCTs. However, we did identify a protocol for an RCT evaluating this indication for SDF scheduled for completion in October 2018 (Mattos-Silveira et al. 2014). Lastly, future trialists should aim to increase the overall quality of their research by providing a more detailed report of their methods and reducing risk of bias by implementing acceptable methods for allocation concealment and randomization.

Author Contributions

O. Urquhart, M.P. Tampi, L. Pilcher, A. Carrasco-Labra, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; R.L. Slayton, contributed to conception, design, and data interpretation, drafted and critically revised the manuscript; M.W.B. Araujo, M. Fontana, S. Guzmán-Armstrong, M.M. Nascimento, B.B. Nový, N. Tinanoff, R.J. Weyant, M.S. Wolff, D.A. Young, D.T. Zero, contributed to conception, design, and data interpretation, critically revised the manuscript; R. Brignardello-Petersen, contributed to conception, design, and data analysis, drafted and critically revised the manuscript; L. Banfield, contributed to conception and design, drafted and critically revised the manuscript; A. Parikh, G. Joshi, contributed to conception, design, and data acquisition, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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The authors declare no further potential conflicts of interest with respect to the authorship and/or publication of this article.

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