Concise Review

Nonrestorative Caries Treatment: A Systematic Review Update

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ABSTRACT

Caries is the most prevalent chronic noncommunicable disease. Strategies to prevent its onset and early interventions to arrest the progression of early lesions have been emphasised throughout recent decades to avoid or delay the restorative spiral of the tooth. More individuals are retaining their natural teeth into old age, thereby necessitating ongoing restorative dentistry intervention for their maintenance. The aim of this systematic review was to update the state of the art regarding clinical studies reporting the effectiveness of different nonrestorative caries treatment options in the 5-year period from 2017 to 2022. Relevant articles were retrieved from 2 electronic databases, including randomised clinical trials (RCTs) published from January 2017 until April 2022, assessing effectiveness and secondary effects of at least one nonrestorative caries treatment option, carried out with adults and/or children with noncavitated or cavitated carious lesions on either primary or permanent teeth and diagnosed by radiographs or visual/tactile assessment. All 35 included articles presented the results of RCTs with a follow-up period ranging from 6 to 84 months. Most of these studies were considered high-quality articles with a low risk of bias. Sealants and fluoride gels and varnishes were mentioned in 12 studies as effective strategies to prevent the onset of caries lesions and to arrest them in the early stages. Resin infiltration reported high caries arresting rates in noncavitated proximal lesions in 10 publications. Silver diammine fluoride presented high caries-arresting rates in open dentin lesions, both in primary and permanent dentitions as well as in root caries lesions that were accessible for cleansing. New evidence has been published between 2017 and 2022 as the result of numerous clinical studies providing further evidence of the effectiveness of nonrestorative caries treatment options.

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Introduction

Despite a better understanding of its etiopathogenesis and all the efforts undertaken over the last few decades to control it, dental caries is still the most prevalent chronic noncommunicable disease in the world.[1] As defined in a recent consensus paper, caries is a biofilm-mediated, multifactorial, dynamic disease driven by frequent intake of fermentable carbohydrates and characterised by phasic demineralisation and remineralisation of dental hard tissues. Carious lesions are caused via oral bacteria breaking down ingested carbohydrates and producing organic acids and other enzymes that induce demineralisation of tooth structures, eventually leading to cavitation or further destruction of the affected tooth structures.[2]

Preventive actions are focussed on minimising risk factors. At the tooth (host) level, the application of fluorides and the use of sealants constituted one of the main strategies to increase the resistance of tooth structures to carious attack.[3] In line with these actions, the current trend in the treatment of carious lesions seeks to preserve tooth

NONRESTORATIVE CARIES TREATMENT

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structures as much as possible and stimulate repair by activating biological responses from the tooth and surrounding environment, that is, minimally invasive treatments.[4,5] In addition, occasionally where an ultraconservative restorative intervention is needed, for example, removal of biofilm is impossible, this should be combined with the use of remineralising agents to enhance the lifespan of a restoration, which also reduces the overall cost burden on the patient or public health programmes.[6] Recovering decayed structures instead of removing them could be then considered to achieve every aspect of the concept of minimal-intervention dentistry.

As more individuals are retaining their natural teeth into old age, thereby necessitating ongoing restorative dentistry input for their maintenance, it is essential that less invasive interventions are developed to avoid or delay the death spiral of a tooth. Therefore, nonrestorative treatment options have been highlighted as promising resources to reduce the need for a surgical intervention of lesions as well as to maximise the outcome benefits of very conservative surgical interventions. This is achieved by reducing the loss of dental tissues by recovering their biological and physical properties through different remineralisation processes such as the use of sodium fluoride (NaF), stannous fluoride containing toothpastes or gels, acidulated phosphate fluoride gels, difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, amorphous calcium phosphate (ACP), casein phosphopeptide (CPP)-ACP/CPP-amorphous calcium fluoro phosphate (ACFP), 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.[4-7]

A recent systematic review collected and synthesised the best available evidence on the effectiveness 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.[8] However, after the publication of this review, 2 key facts put nonrestorative caries treatment resources into the spotlight again. The first one is the inclusion in 2021 of fluoride-containing materials such as glass ionomer cements and SDF in the World Health Organization's (WHO) Model List of Essential Medicines (EML)[9] and Model List of Essential Medicines for Children (EMLc),[10] given their indication for dental caries, as these products may help to reduce the burden of dental caries. Second, new findings on the use of these products, as well as other nonrestorative innovations, are particularly relevant in a pandemic context (which also occurred after the publication of the mentioned review article), where reducing aerosol exposure from dental procedures has gained greater importance with respect to personal risk management in the dental setting.

Therefore, the present study aims to update this review to identify clinical studies that may provide new scientific evidence for recommendations of use, the effectiveness of treatments, and their potential adverse effects.

Methods

To proceed with the systematic review, the guidance from the PRISMA Checklist[11] was followed (Appendix 1). This review was registered at the PROSPERO platform with the assigned #CRD42022337588. Criteria for the inclusion of studies in this review were related to the type of studies, the participants, the interventions, and treatment outcomes.

The Population, Intervention, Comparator, Outcome (PICO) strategy was followed to answer the research question: "What is the currently available scientific evidence of clinical trials that evaluated effectiveness and adverse effects of nonrestorative caries treatment options?" According to the PICO/PICOS statement, the comparison was carried out by using the terms: "nonrestorative cavity control," "restorative dental procedure on tooth," and "topical application of fluoride – tooth."

The search strategy was carried out between March 8 and April 1, 2022, in collaboration with a panel of dental experts (GFM, AB, and BC) and a health science librarian (TC), retrieving studies that matched the inclusion criteria from 3 electronic databases (Lilacs, Medline, and PubMed). The Cochrane Database was consulted for potential cross references. Medical Subject Headings (MeSH) terms used in the search strategy are described in Appendix 2.

Type of studies

The inclusion criteria defined suitable randomised clinical studies (RCTs) that compared one treatment vs another treatment method, placebo treatment, or no treatment published between June 2017 and March 2022 with at least 6 months' follow-up, either with a parallel or split-mouth design.

Type of participants

Adults and children with noncavitated or cavitated carious lesions, either on primary or permanent teeth, diagnosed by radiographs or visual/tactile assessment were included in this review. The International Caries Detection and Assessment System (ICDAS)[12] was used to visually identify the involvement of dental structures in the caries lesion, but other assessment tools such as DIAGNOdent and quantitative light-induced fluorescence-digital (QLF-D) were excluded when these were the only diagnostic tools to evaluate the progression of the lesions. Location of the lesions and/or where treatments were targeted were disclosed as occlusal, proximal, smooth, or root surfaces.

Type of interventions

The effectiveness of the following professional applied or prescribed products considered as active interventions (compared to other interventions or to non-intervention/placebo) was searched:

- NaF toothpaste or gel
- Stannous fluoride (SnF) toothpaste or gel
- Acidulated phosphate fluoride
- Difluorsilane
- Ammonium fluoride

- Polyols
- Chlorhexidine
- Calcium phosphate
- ACP
- CPP/ACP and CPP/ACFP
- Nanohydroxyapatite
- Tricalcium phosphate
- Prebiotics and/or 1.5% arginine
- Probiotics
- SDF
- Silver nitrate
- Lasers
- Resin infiltration
- Sealants
- Sodium bicarbonate
- Calcium hydroxide
- Carbamide peroxide

Types of outcome measures

Effectiveness was measured by means of the primary outcomes of the studies regarding arrest or reversal of existing noncavitated and cavitated caries lesions. Adverse effects were included as secondary outcomes.

Data collection and analysis

Selection of primary data and relevant studies

References, titles, and abstracts were initially retrieved in duplicate by 2 reviewers (BC and GFM) to identify potentially included studies, discussing eligibility until agreement was achieved by consensus. A preliminary list of full-text articles was screened, and a cross search was also carried out by seeking relevant references from the primary selected articles and from 2 systematic reviews retrieved from the Cochrane Database.

Data regarding country, study design, demography of patient population, type of dentition, tooth surface, type of lesions (cavitated or noncavitated) and their location (occlusal, approximal, buccal, or lingual), risk factors, follow-up times, interventions, outcomes of the interventions, adverse events, conflicts of interest, and funding sources were extracted from the articles independently and in duplicate and recorded into an Excel spreadsheet.

Assessment of risk of bias in included studies

Two review authors (BC and GFM) independently assessed the risk of bias of included studies using the Cochrane Collaboration tool,[13] and disagreements were resolved by consensus. Each study was judged as low, moderate, high, or unclear risk of bias. Unclear risk of bias was assigned to indicate lack of information or uncertainty about the potential for bias.

Reliability of the evidence was also assessed using established criteria (Grading of Recommendations Assessment, Development, and Evaluation [GRADE] approach)[14] (Appendix 3).

Analysis of data

Data were grouped according to the treatment described by the authors to assess the relative effectiveness of each intervention on the primary outcome by combining direct and indirect evidence using a random-effects model that assumed a common between-study heterogeneity. If studies reported dissimilar follow-up times or lacked a common comparator or if pairwise meta-analysis was not possible, these studies were categorised as unpooled data and prioritised the calculation and reporting of relative risks and mean differences (and 95% confidence intervals) at an individual-study level. If these measures of association were still not obtained, these data were also considered as unpooled and the results were reported as described by the primary study authors.

Descriptive statistics were used in terms of frequencies for qualitative analysis. Quantitative analysis was performed by Review Manager 5.3 software. No comparisons or meta-analysis were considered feasible due to the heterogeneity of the types of outcomes and the low number of strategies suitable for comparisons.

Results

Results of the search are displayed in the PRISMA flowchart (Figure) and described in Tables 1, 2, and 3.

After retrieving 74 titles/abstracts that potentially met the inclusion criteria, a consensus was reached that 43 papers were suitable for their selection to continue with the analysis of the full text. One extra article was considered suitable for analysis after a hand search from a review article, totaling 44 articles for full-text analysis. Reasons for the exclusion of the remaining 31 were as follows: 11 articles were published before 2017, 9 were not clinical studies (in vitro/in situ), 6 articles did not meet the criteria for the design of the study (mainly review articles), and 5 studies assessed the outcomes of restorative treatments only or the treatment of noncarious lesions.

After reading the articles, a further 9 were excluded for the following reasons: (1) 2 presented follow-up results of less than 6 months; (2) 2 were in vitro/in situ studies; (3) 4 utilised DIAGNOdent or QLF-D to assess and follow up the lesions, and (4) 1 article was unable to be retrieved.

Types of study

All 35 included articles presented the results of RCTs, of which 4 were double-blinded and 16 had a split-mouth design. The length of the follow-ups reported varied from 6 months (5 studies) to 84 months (1 study), but most of the studies reported the results obtained between 12 and 18 months (14 studies), followed by 24- to 30-month reports (10 studies), 36-month reports (4 studies), and 1 report of a 48-month follow-up.

Types of participants

Children and young and adult participants received nonrestorative interventions: 11 studies included children within an

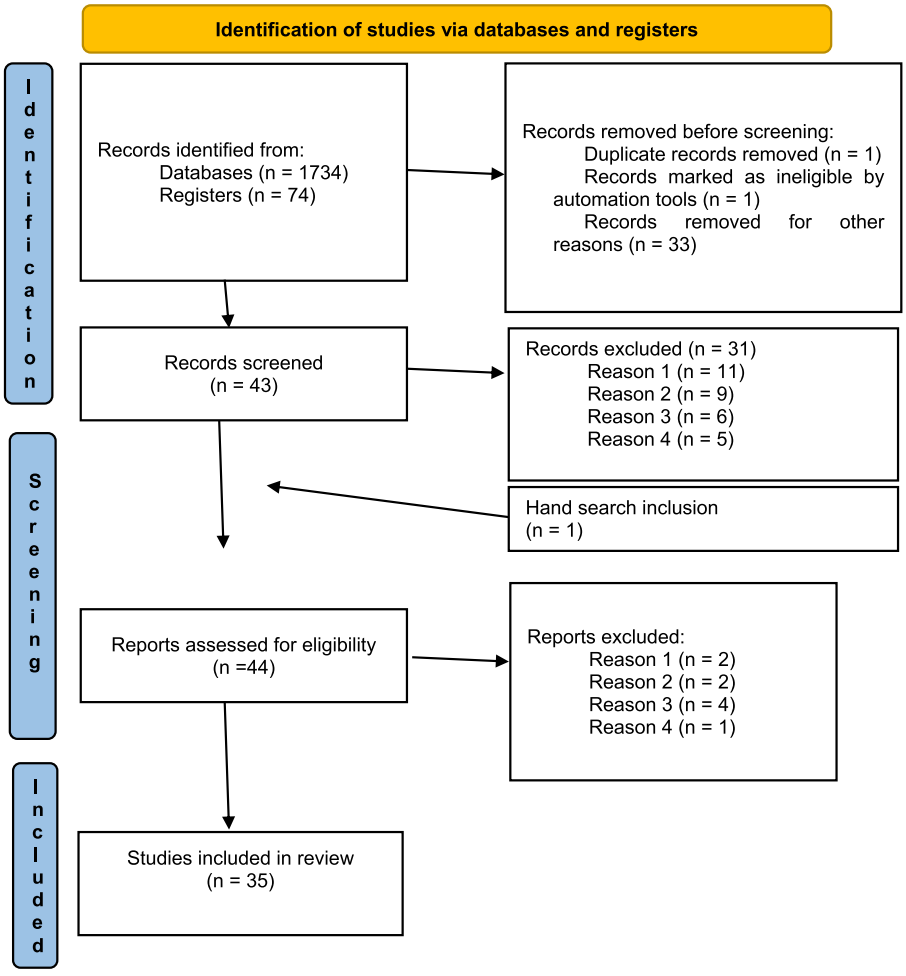

Fig – PRISMA flowchart of articles included in the study.
Source: Page et al.[11]

age range of 1 to 6 years; 12 studies included children from 6 to 13 years, and 11 studies included participants 13 years and older. In 12 of the 35 studies, interventions targeted primary teeth, whereas the other 22 focussed on the permanent dentition. Targeted interventions were located to occlusal surfaces in 19 studies; 9 articles evaluated interventions on proximal surfaces; 5 on smooth surfaces, mostly related to white spot lesions; and 2 papers described the outcomes of nonrestorative treatment options of root surfaces.

Type of interventions

Different nonrestorative treatment options were assessed, either comparing one alternative to another or to placebo control groups. In publications between January 2017 and March 2022 that met the inclusion criteria for this review, the treatment options that were most frequently evaluated were pit and fissure sealants of different types (atraumatic restorative technique, glass ionomer cement, and resin-based sealants) and the use of fluoride varnishes; these strategies were addressed in 12 out of 35 studies (34.3%); followed by resin infiltration with 10 of 35 studies (28.6%). Effectiveness of SDF was usually compared to fluoride varnishes and/or the remineralising effect of highly concentrated fluoride toothpastes, being assessed in 4 articles of the 35 (11.4%).

The effect of CPP/ACP and CPP/ACFP was frequently assessed using DIAGNOdent or QLF-D and, therefore, these publications were excluded from this analysis. Only 2 articles evaluated these calcium-based remineralising agents by means of visual assessment, recording the results using ICDAS codes.[15,16]

Although other promising resources such as the use of ozone, probiotics, nano-hydroxyapatite gels, or self-assembly peptides have been evaluated in different studies, a low number of clinical studies for each strategy (1 or 2 = 2.9% to 5.8%) and short evaluation periods were still insufficient to provide good evidence for recommending their use.[17-20]

Effectiveness of the interventions

Regarding the primary outcomes that responded to the research question about effectiveness of nonrestorative carious lesion treatments, the caries arrest rate (CAR) demonstrated that SDF can arrest active dentin caries lesions in significant percentages when compared to no intervention or regular oral hygiene as the intervention. Reported outcomes in active dentin lesions of primary and permanent dentitions

Table 1 – Titles and abstracts included after consensus and excluded after reading the full text with the reasons for their exclusion and summary of relevant outcomes.

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
Ahmed et al 2019: Effect of different remineralizing agents on the initial carious lesions - a comparative study. *Saudi Dental Journal*. doi:10.1016/j.sdentj.2019.11.001	Randomised comparative clinical trial	Adults 20-40 y	Occlusal and smooth surfaces ICDAS 1-2	NaF varnish, tri-calcium phosphate, and Nano-hydroxy-apatite gel	4 wk	Significant differences between baseline and follow-up for the 3 groups. Nano-hydroxy-apatite gel was significantly better than TCP and fluoride varnish for pits and fissures caries prevention		Excluded (<6 months to follow-up)
Chen et al 2020: Randomized clinical trial on sodium fluoride with tricalcium phosphate. *Journal of Dental Research*. 2021;100(1):66−73.	RCT double-blind parallel design	356/408 3-year-old children	1607/1831 active dentin caries in primary teeth	Semiannual 25% $AgN0_3$ + 5% NaF varnish semiannual 25% $AgNO_3$ + 5% NaF varnish + TCP	24 mo	CAR = 57% vs 42%; significantly higher caries arrest with the addition of TCP ($p = 0.656$)		Included
Duangthip el at 2017: Caries arrest by topical fluorides in preschool children: 30-month results. *Journal of Dentistry*. doi:10.1016/j.jdent.2017.12.013	RCT	309/371 3- to 4-year-old children; 2526 ICDAS 3-6 teeth	At least 1 active dentin caries in primary teeth ICDAS 3-6	30% SDF 3 applications once a year; 30% SDF weekly applications during 3 weeks; 5% NaF varnish weekly applications during 3 weeks	30 mo	CAR = 48% vs 34% and 33% in ICDAS 5-6 lesions	No adverse effects were detected	Included
Ballikaya et al 2021: Management of initial carious lesions of hypomineralised molars (MIH) with silver diamine fuoride or silver−modifed atraumatic restorative treatment (SMART): 1−year results of a prospective, randomized clinical trial. *Clinical Oral Investigations*. doi:10.1007/s00784-021-04236-5	RCT split-mouth design	48 6- to 13-year-old children	112 MIH first molars ICDAS 1-2	SDF SMART	12 mo	Hypersensitivity and survival of the sealants were assessed. No statistical differences were found between the 2 treatments	Marginal discolouration caused by SDF and increased with application of a curing source	Included
Gao et al 2019: Randomized trial of silver nitrate with sodium fluoride for caries arrest. *JDR Clinical and Translational Research*. doi:10.1177/2380084418818482	RCT noninferiority, double-blind	1070 3-year-old children	Active dentin caries lesions in primary teeth	Semiannual 25% $AgNO_3$ + 5% NaF semiannual 38% SDF + placebo coat	18 mo	CAR = 64.1% vs 62.4%. No statistical differences between the 2 treatments	Black staining of the arrested lesions	Included
Hesse et al 2020: Atraumatic restorative treatment-sealed versus nonsealed first permanent molars: a 3-year split-mouth clinical trial. *Caries Research*. doi:10.1159/000506466	RCT split-mouth design	187 6- to 8-year-old children	748 first permanent molars fully erupted	ART sealants vs non-sealed pits and fissures	36 mo	90% vs 90.8% survival (avoidance) of dentin caries development		Included

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Table 1 (*Continued*)

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
Mathew et al 2019: One-year clinical evaluation of retention ability and anticaries effect of a glass ionomer-based and a resin-based fissure sealant on permanent first molars: an in vivo study. *International Journal of Clinical Pediatric Dentistry*. doi:10.5005/jp-journals-10005-1702	Clinical trial split-mouth design	50 6- to 8-year-old children	100 sound first lower permanent molars	Resin-based sealants vs glass ionomer sealants	12 mo	100% vs 98% caries preventive effect. No statistical differences between the 2 treatments		Included
Jaafar et al 2020: Performance of fissure sealants on fully erupted permanent molars with incipient carious lesions: a glass-ionomer-based versus a resin-based sealant. *Journal of Dental Research Dental Clinics Dental Prospects*. 2020;14 (1):61-67. doi:10.34172/ joddd.2020.009	RCT split-mouth design	45 8- to 12-year-old children	90 fully erupted first permanent molars ICDAS 1-4	Resin-based sealants vs glass ionomer sealants	6 mo	93.3% vs 66.7% caries preventive effect. Resin-based sealants had statistically better performance		Included
Jorge et al 2019: Randomized controlled clinical trial of resin infiltration in primary molars: 2 years follow-up. *Journal of Dentistry*. doi:10.1016/j. jdent.2019.103184	RCT	29/50 6- to 9-year-old children	At least 2 primary molars with E2/D1 proximal lesions	Resin infiltration + flossing and only flossing	24 mo	31.1% absolute effectiveness of resin infiltration		Included
Magabanhru et al 2020: A randomized clinical trial to arrest dentin caries in young children using silver diamine fluoride. *Journal of Dentistry*. doi:10.1016/j. jdent.2020.103375	RCT	153 and 149 1- to 3-year-old children	At least 1 active dentin caries in primary teeth	Semiannual 38% SDF; semiannual 5% NaF varnish	12 mo	CAR = 35.7% vs 20.9%		Included
Piwat et al 2020: Efficacy of probiotic milk for caries regression in preschool children: a multicenter randomized controlled trial. *Caries Research*. doi:10.1159/ 000509926	RCT, multicentre, double-blind	487 2- to 4-year-old children from 8 child-care centres	≤4 decayed teeth	Daily consumption of probiotic milk; triweekly consumption of probiotic milk; placebo (milk without probiotics)	12 mo	Probiotic milk demonstrated significantly higher caries regression rates and a reduction in caries progression compared to the placebo group		Included
Turska-Szybka et al 2021: Clinical effect of two fluoride varnishes in caries-active preschool children: a randomized controlled trial. *Caries Research*. 2021;55:137 –143.	RCT	Children between 36 and 71 mo of age	All primary teeth erupted	1.5% ammonium fluoride varnish; 5% NaF varnish; professional tooth-cleaning	12 mo	The 2 fluoride varnishes demonstrated an equal capacity to reduce the incidence of caries in caries-active children		Included

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Table 1 (*Continued*)

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
Ying Lam et al 2021: Glass ionomer sealant versus fluoride varnish application to prevent occlusal caries in primary second molars among preschool children: a randomized controlled trial. *Caries Research*. 2021;55:322–332.	RCT	Children aged 3 to 4 y	Occlusal caries	Glass ionomer sealant 5%; NaF varnish	12 mo	NaF varnish 7.8% vs GIC sealants 8.0%. No significant difference was found		Included
Peters et al 2019: Efficacy of proximal resin infiltration on caries inhibition: results from a 3-year randomized controlled clinical trial. *Journal of Dental Research*. doi:10.1177/0022034519876853	RCT	Young adults (does not specify age)	Proximal surfaces	Resin infiltration vs mock infiltration	36 mo	86% vs 52% caries preventive effect. CAR = 100% successful in arresting caries progression in inner enamel lesions and 64% in outer dentin lesions		Included
Arslan et al 2020: The effect of resin infiltration on the progression of proximal caries lesions: a randomized clinical trial. *Medical Principles and Practice*. 2020;29:238–243.	RCT split-mouth design	15 and 33 years	Proximal surfaces	Resin infiltration + fluoridated toothpaste +flossing vs fluoridated toothpaste + flossing	12 mo	2.2% vs 20% of progression. Progression was significantly greater in control group		Included
Arthur et al 2017: Proximal carious lesions infiltration—a 3-year follow-up study of a randomized controlled clinical trial. *Clinical Oral Investigations*. doi:10.1007/s00784-017-2135-x	RCT split-mouth design	16- to 41-year-old patients	Proximal surfaces	Resin infiltration	36 mo	7.4% vs 18.5% of progression		Included
Chabadel et al 2020: Effectiveness of pit and fissure sealants on primary molars: a 2-yr split-mouth randomized clinical trial. *European Journal of Oral Sciences*. 2021;129:e12758.	RCT split-mouth design	3- to 7-year-old children	Occlusal caries (pit and fissure caries)	Resin-based sealants	24 mo	The caries increment was not significantly different between the sealed and the unsealed molars		Included
Al Jobair et al 2017: Retention and caries-preventive effect of glass ionomer and resin-based sealants: an 18-month-randomized clinical trial. *Dental Materials Journal*. 2017;36(5):654–661.	RCT split-mouth design	6- to 9-year-old children	Occlusal	Glass ionomer sealants vs. resin-based sealants	18 mo	There were no statistically significant differences in the survival of partially and fully retained sealants or in the survival of caries-free pits and fissures between glass ionomer– and resin-based sealants		Included
Kasemkhun et al 2021: The efficacy of dental sealant used with bonding agent on occlusal caries (ICDAS 2-4): a 24-month	RCT	7.3- to 9.9-year-old children	Occlusal caries	Bonded sealants vs non-bonded sealants	24 mo	Bonded sealants had a higher retention rate (83.3%) than nonbonded sealants (53.7%). The difference in the caries		Excluded (authors could not retrieve the article)

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Table 1 (*Continued*)

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
randomized clinical trial. *International Journal of Paediatric Dentistry*. 2021;31(6):760–766.						transition rate was not significant		
Muller-Bolla et al 2018: Effectiveness of resin-based sealants with and without fluoride placed in a high caries risk population: multicentric 2-year randomized clinical trial. *Caries Research*. 2018;52:312–322.	RCT split-mouth design	5- to 15-year-old children	Occlusal caries	Resin-based sealants with fluoride vs resin-based sealants without fluoride	24 mo	The effect of the sealant was similar regardless of whether it contained fluoride or not		Included
Giray et al 2018: Resin infiltration technique and fluoride varnish on white spot lesions in children: preliminary findings of a randomized clinical trial. *Nigerian Journal of Clinical Practice*. 2018;21:1564–1569.	RCT	8- to 14-year-old children	Anterior white spot lesions	Resin infiltration vs NaF varnish	6 mo	Resin infiltration and fluoride varnish are clinically feasible and efficacious methods for the treatment of anterior WSLs		Included
Peters et al 2018: Resin infiltration: an effective adjunct strategy for managing high caries risk—a within-person randomized controlled clinical trial. *Journal of Dentistry*. doi:10.1016/j.jdent.2018.09.005	RCT placebo-controlled split-mouth design	18- to 24-year-old adults	Proximal lesions	Resin infiltration vs mock infiltration	24 mo	97% vs 74% resin infiltration is highly efficacious		Included
Al-Batayneh et al 2019:- Assessment of the effects of a fluoride dentifrice and GC Tooth Mousse on early caries lesions in primary anterior teeth using quantitative light–induced fluorescence: a randomised clinical trial. *European Archives of Paediatric Dentistry*. doi:10.1007/s40368-019-00451-7	RCT	4- to 5-year-old children	Primary anterior teeth	Fluoride dentifrice (500 ppm) CPP-ACP cream (10% w/v) vs fluoride dentifrice followed by CPP-ACP cream	6 mo	Differences between treatment groups were not statistically significant. The combination of the 2 did not give additive benefits		Excluded (quantitative light-induced fluorescence was used to diagnose the lesions)
Alabdullah et al 2017: Effect of fluoride-releasing resin composite in white spot lesions prevention: a single-centre, split-mouth, randomized controlled trial. *European Journal of Orthodontics*. doi:10.1093/ejo/cjx010	RCT split-mouth design	13- to 25-year-old patients	White spot lesion during orthodontic treatment	Fluoride-releasing resin composite	12 mo	Fluoride-containing resin adhesive does not have the desired preventive effect to prevent demineralisation and WSL formation during orthodontic treatment		Included
Alkilzy et al 2017: Self-assembling peptide P11-4 and fluoride for regenerating enamel. *Journal of*	RCT single-blind study	>5-year-old children	Early caries on erupting permanent molars	P11-4 + fluoride varnish vs fluoride varnish alone	6 mo	P11-4 in combination with fluoride is superior to the fluoride alone		Included

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Table 1 (*Continued*)

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
Dental Research. doi:10.1177/ 0022034517730531								
Alsabek et al 2019: Retention and remineralization effect of moisture tolerant resin-based sealant and glass ionomer sealant on non-cavitated pit and fissure caries: randomized controlled clinical trial. *Journal of Dentistry*. 2019;86:69–74.	RCT single-blind split-mouth design	6- to 9-year-old children	Occlusal surfaces	Resin-based sealant vs glass ionomer sealant	6 mo	85% vs 62.5% of retention 5% vs 17.5% of loss. There were not statistically significant differences in remineralisation effect		Included
Ammari et al 2017: Efficacy of resin infiltration of proximal caries in primary molars: 1-year follow-up of a split-mouth randomized controlled clinical Trial. *Clinical Oral Investigations*. doi:10.1007/ s00784-017-2227-7	RCT split-mouth design	5- to 9-year-old children	Proximal caries	Fluoridated toothpaste + flossing + infiltration vs fluoridated toothpaste + flossing	12 mo	11.9% vs 33.3% reduction in caries progression		Included
Bhongsatiern et al 2019: Adjunctive use of fluoride rinsing and brush-on gel increased incipient caries-like lesion remineralization compared with fluoride toothpaste alone in situ. *Acta Odontologica Scandinavica*. doi:10.1080/ 00016357.2019.1582796	In situ study	20- to 23-year-old adults	Orthodontic brackets with artificial demineralised enamel slabs	NaF mouth rinse vs NaF brush-on gel	Three 30-day sessions	NaF brush-on gel yielded the greatest mean depth of remineralisation (168 mm vs 144 mm)		Excluded (in situ study, <6 mo follow-up)
Bröseler et al 2019: Randomised clinical trial investigating self-assembling peptide P11-4 in the treatment of early caries. *Clinical Oral Investigations*. doi:10.1007/ s00784-019-02901-4	RCT split-mouth design	13- to 36-year-old patients	Early buccal carious lesions	Self-assembling peptide P11-4 vs NaF varnish	12 mo	The size of early carious lesions treated with P11-4 was significantly reduced		Included
Creeth et al 2018: A randomized in situ clinical study of fluoride dentifrices on enamel remineralization and resistance to demineralization: effects of zinc. *Caries Research*. 2018;52:129–138.	A randomised in situ clinical study	18- to 64-year-old adults				In situ study		Excluded (in situ study)
Grocholewicz et al 2020: Efect of nano–hydroxyapatite and ozone on approximal initial caries: a randomized clinical trial.	RCT	20- to 30-year-old adults	Initial approximal enamel lesions	Nano-hydroxyapatite gel and gaseous ozone therapy separately vs nano-	24 mo	The combination of both methods produces the best effect compared to nano-hydroxyapatite or ozone therapy applied alone		Included

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Table 1 (*Continued*)

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
Scientific Reports. doi:10.1038/ s41598-020-67885-8				hydroxyapatite gel + ozone				
Kim et al 2018: Cutoff fluorescence loss for the recovery of incipient carious lesions after fluoride application in primary teeth: a clinical study. *Photodiagnosis and Photodynamic Therapy*. doi:10.1016/j.pdpdt.2018.08.007	Clinical study	4- to 10-year-old children	Incipient enamel lesions on primary teeth	Fluoride treatment + light-induced fluorescence-digital	4 wk	Fluorescence loss cutoff value can be determined for pretending the effects of remineralisation after fluoride application		Excluded (<6 months follow-up and light-induced fluorescence was used)
León et al 2019: High fluoride dentifrice for preventing and arresting root caries in community-dwelling older adults: a randomized controlled clinical trial. *Journal of Dentistry*. 2019;86:110–117.	RCT	≥60-year-old adults	Root carious lesions	Toothbrushing with 5000 ppm vs 1450 ppm fluoridated dentifrice	24 mo	5000 ppm dentifrice is more effective than conventional dentifrices		Included
Meyer-Lueckel et al 2021: Proximal caries infiltration – pragmatic RCT with 4 years of follow-up. *Journal of Dentistry*. doi:10.1016/j.jdent.2021.103733	RCT split-mouth design	13- to 40-year-old patients	Proximal caries lesions	Resin infiltrationvs mock infiltration	48 mo	18% vs 48% reduction in the progression of the lesions		Included
Paris et al 2020: Seven-year-efficacy of proximal caries infiltration – randomized clinical trial. *Journal of Dentistry*. doi:10.1016/j.jdent.2020.103277	RCT split-mouth design	18- to 35-year-old adults	Interproximal non-cavitated caries lesions	Resin infiltrationvs mock infiltration	84 mo	The relative risk reduction was 80%. Resin infiltration of proximal caries lesions extending radiographically around the enamel dentin junction is efficacious to reduce lesion progression		Included
Rechmann et al 2018: MI Varnish and MI Paste Plus in a caries prevention and remineralization study: a randomized controlled trial. *Clinical Oral Investigations*. doi:10.1007/s00784-017-2314-9	RCT	≥11-year-old children	Buccal surfaces	Twice-daily 1100 ppm fluoride toothpaste + daily MI Paste Plus + quarterly MI Varnish vs twice-daily 1100 ppm fluoride toothpaste + fluoride rinse	12 mo	Daily MI Paste Plus and quarterly MI Varnish applications do not appear to significantly reduce WSLs		Included
Schwendicke et al 2018: Cost-effectiveness of managing cavitated primary molar caries lesions: a randomized trial in Germany. *Journal of Dentistry*. doi:10.1016/j.jdent.2018.05.022	Randomised trial	3- to 8-year-old children	Cavitated caries lesions in primary molars	Hall Technique (HT), nonrestorative cavity control (NRCC), and conventional carious tissue	30 mo	HT was more cost-effective than CR or NRCC for managing cavitated caries lesions in primary molars		Included

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Table 1 (*Continued*)

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
				removal and restoration (CR)				
Sleibi et al 2021: Reversal of root caries with casein phosphopeptide-amorphous calcium phosphate and fluoride varnish in xerostomia. *Caries Research*. doi:10.1159/000516176	Clinical trial	45- to 92-year-old adults	Primary root caries in xerostomic patients	Varnish containing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and fluoride 5% vs fluoride varnish 5%	12 mo	The differences were insignificant in Severity Index (SI) after 12 months: 89.6% vs 81.7%	Change colour from lighter to darker colour in both treatments	Included
Youssef et al 2020: Improving oral health: a short-term split-mouth randomized clinical trial revealing the superiority of resin infiltration over remineralization of white spot lesions. *Quintessence International*. 2020;51(9):696–709.	RCT split-mouth design	15- to 30-year-old patients	Labial WSL	Resin-infiltrated with Icon (RI) vs Remin Pro (RP) vs Teeth brushed with Complete Care toothpaste (CC)	7 d	RI vs RP ($P = .029$), RI vs CC ($P < .001$), and RP vs CC ($P = .001$). Resin infiltration is considered a time-effective treatment option for aesthetically camouflaging WSLs		Excluded (<6 months' follow-up)
Olgen et al 2022: Effects of different remineralization agents on MIH defects: a randomized clinical study. *Clinical Oral Investigations*. 2022;26(3):3227–3238.	RCT	49/69 6- to 9-year-old children	90/120 teeth with MIH diagnosed ICDAS 1-2	Control with regular oral hygiene vs NaF varnish vs CPP/ACP vs CPP/ACPF	24 mo	No statistical differences but higher remineralisation using CPP/ACP and CPP/ACPF		Included
Esparza-Villalpando V et al 2021: Clinical efficacy of two topical agents for the remineralization of enamel white spot lesions in primary teeth. *Pediatric Dentistry*. 2021;43(2):95–101.	RCT double-blinded Excluded (uses DIAGNOdent for the evaluation/<6 months' follow-up)	3- to 7-year-old children	At least 1 primary anterior tooth with MIH diagnosed ICDAS 1-2 but followed up with DIAGNOdent			Fluoride + hydroxyapatite (ReminPro) vs CPP/ACPF (MI Paste Plus) vs NaF paste (Colgate Total)	21 d	ReminPro and MI Paste Plus achieved more remineralisation compared to Colgate Total
Mekky et al 2021: Casein phosphopeptide amorphous calcium phosphate fluoride varnish in remineralization of early carious lesions in primary dentition: randomized clinical trial. *Pediatric Dentistry*.2021;43(1):17–23.	RCT	44 3- to 5-year-old children	At least 4 WSLs in primary anterior teeth ICDAS 1-2	NaF varnish (Duraphat) vs CPP/ACP varnish (MI Varnish)	30 wk	MI Varnish significantly decreased number of active lesions and increased mineralisation (DIAGNOdent)		Excluded (uses DIAGNOdent for the evaluation)
Chestnutt et al 2017: Seal or varnish? A randomized controlled	RCT allocation-		At least 1 first permanent molar		36 mo			Included

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Table 1 (Continued)

Titles/abstracts included after consensus or excluded after reading the full-text article						Outcomes		Articles included/ excluded
Author(s)/title/year/journal	Study design	Participants	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Tested intervention	Follow-ups	Primary: (a) preventive effect (survival of sealants or DMFT or ICDAS variations) and (b) arrest or reversal (CAR)	Secondary: adverse effects	
trial to determine the relative cost and effectiveness of pit and fissure sealant and fluoride varnish in preventing dental decay. *Health Technology Assessment*. 2017;21(21):1–256.	blinded, 2-arm, parallel-group trial	835/920 6- to 7-year-old children	with no caries into dentin ICDAS 1-3	Resin sealants (Delton) vs NaF varnish (Duraphat)		No significant differences in caries-preventive effect (>80%)		
Hilgert et al 2017: 3-year survival rates of retained composite resin and ART sealants using two assessment criteria. *Brazilian Oral Research*. 31:1–13.	Cluster RCT	123 6- to 7-year-old children with high caries risk	Fully erupted first permanent molars ICDAS 1-3	Resin vs GIC/ART sealants	36 mo	Higher retention for resin sealants but no statistical differences in caries prevention		Included

ACP, amorphous calcium phosphate; ACPF, amorphous calcium phosphate plus fluoride; ART, atraumatic restorative treatment; CAR, caries arrest rate; CPP, casein phosphopeptide; DMFT, decayed, missing, and filled teeth; GIC, glass ionomer cement; ICDAS, International Caries Detection and Assessment System; NaF, sodium fluoride;; RCT, randomised controlled trial; SDF, silver diamine fluoride; TCP, tri-calcium phosphate; WSL, white spot lesion.

showed that CAR percentages varied from 37.5% to 64.1% at 12-month follow-up,[21] 42% to 57% after 24 months,[22] and 48% at 30-month follow-up.[23]

Outcomes of the SMART technique (Silver Modified Atraumatic Restorative Treatment), described as a combination of the application of SDF and a restorative glass ionomer cement, were reported to successfully reduce hypersensitivity and increase mineralisation in permanent molars of patients with hypomineralised molars[24] as well as the use of remineralising agents such as fluoride varnishes and CPP/ACP compounds.[25]

Resin infiltration appeared to be the most effective method in this review, not only because it led the number of studies that reported outcomes of RCTs between 2017 and 2022 but also because it demonstrated a high efficacy to arrest proximal lesions even after long intervals, both in the primary and permanent dentitions.[26,27] Its caries-arresting potential could be disclosed by observing the progression rate of lesions after 12 (2.8% permanent–12% primary), 24 (3%), 36 (7.4%–11%), 48 (18%), and 84 (20%) months of follow-up when compared to no treatment or flossing only.[28-33]

Resin infiltration showed good results to mask white spot lesions on smooth surfaces,[34] although no significant differences were observed when the effectiveness for arresting these lesions was compared to the use of remineralising agents such as 5% fluoride varnish or CPP/ACP with and without additional fluoride at 6 months.[25]

Results of RCTs retrieved for this study confirmed previous findings regarding the caries-preventive efficacy of pit and fissure sealants but found no differences in favour of type of sealant material, namely resin- or glass ionomer–based.[35-42]

Furthermore, neither material showed a statistical difference between sealants and the use of fluoride varnishes to prevent caries lesions on occlusal surfaces of permanent first molars.[43,44] Fluoride varnishes were also reported as effective compounds to prevent the development of early caries lesions in both primary and permanent teeth.[43-47] The caries-arresting potential of these varnishes, however, were mainly restricted to ICDAS 1-3 lesions rather than to active dentin lesions, where SDF achieves higher CAR percentages.

Although other technologies were reported in clinical trials, the frequency was usually restricted to one article, which therefore made it impossible to provide sound conclusions of treatment efficacy due to a lack of comparator studies. The use of ozone combined with a nano-hydroxyapatite gel showed promising outcomes in arresting approximal lesions in permanent molars.[20] Probiotic milk was demonstrated to be an effective resource to prevent the development of caries in high-risk children in another clinical study.[19,20]

No adverse effects were reported in these studies, although the staining caused by application of SDF when the lesions are arrested was mentioned as a potential drawback of the method.

Assessment of bias risk

The risk of bias of the articles that were analysed after reading the full text was mainly related either to the short period of follow-up, low sample size, high dropout rate, or a combination of these factors. Nevertheless, 22 out of 35 articles

Table 2 – Titles and abstracts excluded after consensus with the reasons for their exclusion.

Titles/abstracts excluded after consensus			
Author(s)/title/year/journal	Study design	Location (occlusal, approximal, buccal, lingual, cervical/ root)	Reason(s) for exclusion
Francois et al 2020: Commercially available fluoride-releasing restorative materials: a review and a proposal for classification. *Materials*.	Review		Review
Ahovuo-Saloranta et al 2016: Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents (review). *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD003067.pub4	Systematic review	Occlusal surfaces	Review published before 2017
Ahovuo-Saloranta et al 2017: Pit and fissure sealants for preventing dental decay in permanent teeth (Review). *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD001830.pub5	Updated review	Occlusal surfaces of premolar	Review
Amoedo Campos Velo et al 2019: Root caries lesions inhibition and repair using commercial high-fluoride toothpastes with or without tri-calcium phosphate and conventional toothpastes containing or not 1.5% arginine CaCO3: an in-situ investigation. *Clinical Oral Investigations*. doi:10.1007/s00784-019-03084-8	In situ study	Root caries-like	In situ studies
Antonson et al 2012: 24-month follow-up of sealants. *Journal of the American Dental Association*. 2012;143(2):115–122.		Partially erupted first permanent molars	Published before 2017
Jardim et al 2020: Restorations after selective caries removal: 5-Year randomized trial. *J Dent*.. doi:10.1016/j.jdent.2020.103416	Randomised controlled clinical trial	Occlusal or proximal deep caries lesions	Not the topic
Kalnina et al 2016: Prevention of occlusal caries using a ozone, sealant and fluoride varnish in Children. *Stomatologija, Baltic Dental and Maxillofacial Journal*. 2016;18:26–31.	Clinical trial	Occlusal caries in permanent premolars	Published before 2017
Kashbour et al 2020: Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents. *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD003067.pub58	Systematic review	Occlusal surfaces	Review
Souza et al 2013: Comparing the efficacy of a dentifrice containing 1.5% arginine and 1450 ppm fluoride to a dentifrice containing 1450 ppm fluoride alone in the management of primary root caries. *Journal of Dentistry*.		Root caries	Published before 2017
Walsh et al 2015: Chlorhexidine treatment for the prevention of dental caries in children and adolescents (review). *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD008457.pub2	Systematic review	Dental caries	Published before 2017
Yengopal et al 2009: Caries-preventive effect of glass ionomer and resin-based fissure sealants on permanent teeth: a meta analysis. *Journal of Oral Science*. 2009;51(3):373–382.	Meta analysis	Occlusal caries	Published before 2017
Honkala et al 2015: Sealant versus fluoride in primary molars of kindergarten children regularly receiving fluoride varnish: one-year randomized clinical trial follow-up. *Caries Research*. doi:10.1159/000431038	Randomised clinical trial	Occlusal surfaces	Published before 2017
Liu et al 2014: Glass ionomer ART sealant and fluoride-releasing resin sealant in fissure caries prevention—results from a randomized clinical trial. *BMC Oral Health*. doi:10.1186/1472-6831-14-54	Randomised clinical trial	Occlusal fissures	Published before 2017
Mattos Silveira et al 2014: New proposal of silver diamine fluoride use in arresting approximal caries: study protocol for a randomized controlled trial. *Trials Journal*. doi: 10.1186/1745-6215-15-448	Randomised clinical trial	Approximal surfaces	Published before 2017
Senestraro et al 2013: Minimally invasive resin infiltration of arrested white-spot lesions: a randomized clinical trial. *Journal of the American Dental Association*. 2013;144(9):997–1005.	Randomised clinical trial	White spot lesions	Published before 2017
Zhang et al 2014: Do light cured ART conventional high-viscosity glass-ionomer sealants perform better than resin-composite sealants: a 4-year randomized clinical trial. *Dent Mater*.. doi: 10.1016/j.dental.2014.01.016	Randomised clinical trial	Occlusal surfaces	Published before 2017
Araujo et al 2020: Atraumatic restorative treatment compared to the Hall technique for occluso-proximal carious lesions in primary molars; 36-month follow-up of a randomised control trial in a school setting. *BMC Oral Health*doi:10.1186/s12903-020-01298-x	Randomised control trial	Occluso-proximal carious lesions	Not the topic
Arrow et al 2016: Minimal intervention dentistry for early childhood caries and child dental anxiety: a randomised control trial. *Australian Dental Journal*. doi:10.1111/adj.12492	Randomised controlled trial	Early dental caries	Published before 2017
Canali et al 2018: One-year clinical evaluation of bulk-fill flowable vs. regular nanofilled composite in non-carious cervical lesions. *Clinical Oral Investigations*. doi:10.1007/s00784-018-2509-8	Randomised trial	Noncarious cervical lesions	Not the topic
Danelon et al 2019: Effect of fluoride toothpaste containing nano-sized sodium hexametaphosphate on enamel remineralization: an in situ study. *Caries Research*. 2019;53:260–267.	In situ study	Artificial caries lesions	In situ study
Da Silva et al 2019: Impact of different restorative treatments for deep caries lesion in primary teeth (CEPECO 1)—study protocol for a noninferiority randomized clinical trial. *BMC Oral Health*. doi:10.1186/s12903-018-0703-3	Randomised clinical trial	Deep cavitated caries lesions	Not the topic
Fernando et al 2019: Self-assembly of dental surface nanofilaments and remineralisation by SnF2 and CPP-ACP nanocomplexes. *Scientific Reports*. doi:10.1038/s41598-018-37580-w	In vitro, randomised, and in situ clinical trial	Tooth surface	In vitro and in situ studies
Kitasako et al 2018: Remineralization capacity of carious and non-carious white spot lesions: clinical evaluation using ICDAS and SS-OCT. *Clinical Oral Investigations*. doi:10.1007/s00784-018-2503-1	Quasi-experimental design	White spot lesions	Experimental study

(*continued*)

Table 2 (*Continued*)

Titles/abstracts excluded after consensus			
Author(s)/title/year/journal	Study design	Location (occlusal, approximal, buccal, lingual, cervical/root)	Reason(s) for exclusion
Leal et al 2020: Dose-response effect of fluoride dentifrices on de-/remineralization of root dentine in situ. *Caries Research*. doi:10.1159/000510535	Randomised, double-blind, crossover, and split-mouth in situ experimental study	Root dentine	In situ experimental study
Said et al 2016: Effect of different fluoride varnishes on remineralization of artificial enamel carious lesions. *International Journal of Pediatric Dentistry*. doi:10.1111/ipd.12243	In vitro study	Artificial enamel caries	In vitro study
Oliveira et al 2020: Effect of CPP-ACP on remineralization of artificial caries-like lesion: an in situ study. *Original Research Cariology*.doi:10.1590/1807-3107bor-2020.vol34.0061	Double-blind, randomised, crossover in situ study	Enamel lesions	In situ study
Parkinson et al 2018: Effect of phytate and zinc ions on fluoride toothpaste-efficacy using an in situ caries model. *Journal of Dentistry*.doi:10.1016/j.jdent.2018.03.013	Single-centre, randomised, blinded (examiner/laboratory analyst), 6-treatment, 4-period crossover, in situ study	Tooth surface	In situ study
Schlee et al 2017: Clinical performance of self-assembling peptide P11-4 in the treatment of initial proximal carious lesions: a practice-based case series. *Conservative Dentistry*. doi:10.1111/jicd.12286	Practice-based, uncontrolled, prospective case series	Proximal carious lesions	Practice-based and uncontrolled study
Shen et al 2017: Polyols and remineralisation of enamel subsurface lesions. *Journal of Dentistry*. doi:10.1016/j.jdent.2017.08.008	In vitro study	Enamel subsurface lesions	In vitro study
Yazdanfar et al 2020: Combination effects of diode laser and resin-modified tricalcium silicate on direct pulp capping treatment of caries exposures in permanent teeth: a randomized clinical trial. *Laser in Medical Sciences*. doi:10.1007/s10103-020-03052-9	Randomised clinical trial	Pulp caries exposures	Not the topic
Yazicioglu et al 2017: Quantitative evaluation of the enamel caries which were treated with casein phosphopeptide-amorphous calcium fluoride phosphate. *Nigerian Journal*. doi:10.4103/1119-3077.180073	In vivo study	Enamel caries on smooth and occlusal surfaces	In vivo study; uncontrolled sample
Yu et al 2017: Effects of rinsing with arginine bicarbonate and urea solutions on initial enamel lesions in situ. *Oral Diseases.doi: 10.1111/odi.12618*.	In situ study	Enamel lesions	In situ study
Amaechi et al 2021: Anti-caries evaluation of a nano-hydroxyapatite dental lotion for use after toothbrushing: an in situ study. doi:10.1016/j.jdent.2021.103863	In situ study	Tooth surface	In situ study

(62.9%) were considered to present a low risk of bias based on the consort list for the Cochrane Collaboration tool[13] and were ranked with high quality of evidence according to the GRADE criteria.[14] One study presented the results obtained after 24 and 36 months with a relatively high dropout rate, although it was stated that the occurrence of this event had been taken into account for the power analysis of the results when the calculation of the sample size was carried out. In this case, the 2 articles were coded as having an "unclear" risk of bias.

Only one study presented a high dropout rate at the 2-year follow-up, which was likely to increase its risk of bias. The remaining 10 articles presented a moderate to low risk of bias. Risk of bias and quality of the evidence are displayed in Table 3.

Discussion

Minimally invasive strategies for the management of caries lesions have experienced an outburst after the onset of the COVID-19 pandemic, when a focus was placed on the reduction of aerosol-generating procedures aimed to minimise the risk of cross-infection amongst oral health care workers and patients attending dental clinics. For this reason, it had been expected that this update would have included a number of articles reporting the results of studies that assessed such resources. However, as a side effect of this global phenomenon, clinical studies have been delayed or even discarded due to the uncertainty of safe and sustainable conditions depending on the current, ever-changing epidemiologic situation worldwide. This unexpected low number of articles retrieved and the heterogeneity of the results were the reasons that a meta-analysis was not employed.

Overall, the results of this review have confirmed that sealants are a valuable strategy to prevent the development of caries lesions in pits and fissures of permanent molars.[48] However, the dichotomy of selecting a resin-based or glass ionomer–based sealant remains, as no concluding evidence has been produced for final recommendations further than the good results achieved for both materials.[49] Moreover, SDF and fluoride varnish have also been added to the list of strategies to prevent occlusal lesions, although more clinical studies that compare these four resources are needed to rank their effectiveness and their best clinical indication.[50]

Clinical studies to back up a generalised use of SDF for treating caries lesions in the permanent dentition are still needed to provide strong scientific evidence. Although its effectiveness for arresting dentin caries has been demonstrated, especially in primary teeth, aspects related to standardised protocols for its application and the patients' perspectives or level of satisfaction with the outcomes,

Table 3 – Risk of bias (Cochrane Collaboration tool) and quality of the evidence (GRADE) of the included articles.

Articles included		Trial registration	Risk of bias	Quality of the evidence
Author(s)/title/year/journal	Tested intervention			
Chen et al 2020: Randomized clinical trial on sodium fluoride with tricalcium phosphate. *Journal of Dental Research*. 2021;100(1):66–73.	Semiannual 25% $AgNO_3$ + 5% NaF varnish vs. semiannual 25% $AgNO_3$ + 5% NaF varnish + TCP	Hong Kong, ClinicalTrials.gov #NCT03423797	Low	High
Duangthip el at 2017: Caries arrest by topical fluorides in preschool children: 30-month results. *Journal of Dentistry*. doi:10.1016/j.jdent.2017.12.013	30% SDF 3 applications once a year vs 30% SDF weekly applications during 3 weeks, vs. 5% NaF varnish weekly applications during 3 weeks	Hong Kong, ClinicalTrials.gov #NCT02426619	Low	High
Ballikaya et al 2021: Management of initial carious lesions of hypomineralized molars (MIH) with silver diamine fuoride or silver–modifed atraumatic restorative treatment (SMART): 1–year results of a prospective, randomized clinical trial. *Clinical Oral Investigations*. doi:10.1007/s00784-021-04236-5	SDF SMART	Turkey, ClinicalTrials.gov #NCT03862014	Low	Moderate
Gao et al 2019: Randomized trial of silver nitrate with sodium fluoride for caries arrest. *JDR Clinical and Translational Research*. doi:10.1177/2380084418818482	Semiannual 25% $AgNO_3$ + 5% NaF vs. semiannual 38% SDF + placebo coat	Hong Kong, ClinicalTrials.gov #NCT02019160	Low	High
Hesse et al 2020: Atraumatic restorative treatment-sealed versus nonsealed first permanent molars: a 3-year split-mouth clinical trial. *Caries Research*. doi:10.1159/000506466	ART sealants vs. nonsealed pits and fissures	Brazil, ClinicalTrials.gov #NCT03667768	Low	High
Mathew et al 2019: One-year clinical evaluation of retention ability and anticaries effect of a glass ionomer-based and a resin-based fissure sealant on permanent first molars: an in vivo study. *International Journal of Clinical Pediatric Dentistry*. doi:10.5005/jp-journals-10005-1702	Resin-based sealants vs. glass-ionomer sealants	Approval from the Institutional Ethics Committee, Government Medical College, Kozhikode, India	Moderate	Low
Jaafar et al 2020: Performance of fissure sealants on fully erupted permanent molars with incipient carious lesions: a glass-ionomer-based versus a resin-based sealant. *Journal of Dental Research Dental Clinics Dental Prospects*. 2020;14(1):61–67.	Resin-based sealants vs glass-ionomer sealants	Ethics and Research Committee and Beirut Arab University, Lebanon (code: 2018H-0058-D-P-0258)	Moderate	Moderate
Jorge et al 2019: Randomized controlled clinical trial of resin infiltration in primary molars: 2 years follow-up. *Journal of Dentistry*. doi:10.1016/j.jdent.2019.103184	Resin infiltration + flossing vs only flossing	Brazil, ClinicalTrials.gov #NCT01726179	High	Low
Magabanhru et al 2020: A randomized clinical trial to arrest dentin caries in young children using silver diamine fluoride. *Journal of Dentistry*. doi:10.1016/j.jdent.2020.103375	Semiannual 38% SDF vs semiannual 5% NaF varnish	Thai Clinical Trials Registry TCTR #20180624001	Low	High
Piwat et al 2020: Efficacy of probiotic milk for caries regression in preschool children: a multicenter randomized controlled trial. *Caries Research*. doi:10.1159/000509926	Daily consumption of probiotic milk vs triweekly consumption of probiotic milk placebo (milk without probiotics)	Thai Clinical Trial Registry TCTR #20170511002	Low	High
Turska-Szybka et al 2021: Clinical effect of two fluoride varnishes in caries-active preschool children: a randomized controlled trial. *Caries Research*. 2021;55:137–143.	1.5% ammonium fluoride vs varnish 5% NaF varnish for professional tooth-cleaning	Poland, ClinicalTrials.gov #NCT02027922	Low	High
Ying Lam et al 2021: Glass ionomer sealant versus fluoride varnish application to prevent occlusal caries in primary second molars among preschool children: a randomized controlled trial. *Caries Research*. 2021;55:322–332.	Glass ionomer sealant vs 5% NaF varnish	Hong Kong, ClinicalTrials.gov #NCT04163354	Low	High
Peters et al 2019: Efficacy of proximal resin infiltration on caries inhibition: results from a 3-year randomized controlled clinical trial. *Journal of Dental Research*. doi:10.1177/0022034519876853	Resin infiltration vs mock infiltration	Review board, University of Michigan (IRBMED HUM00019821) and Keller Army Community Hospital (KACH-IRB 12/006–IRBNet 373988).	Unclear	Moderate
Arslan et al 2020: The effect of resin infiltration on the progression of proximal caries lesions: a randomized clinical trial. *Medical Principles and Practice*. 2020;29:238–243.	Resin infiltration + fluoridated toothpaste + flossing vs fluoridated toothpaste + flossing	Thai Clinical Trial Registry TCTR #20190406001	Low	High
Arthur et al 2017: Proximal carious lesions infiltration—a 3-year follow-up study of a randomized controlled clinical trial. *Clinical Oral Investigations*. doi:10.1007/s00784-017-2135-x	Resin infiltration	Ethics Committee of the Federal University of Rio Grande do Sul and Federal University of Santa Maria, Brazil (CAAE 35534914.3.0000.5347 and 0347.0.243.000-10)	Low	High
Chabadel et al 2020: Effectiveness of pit and fissure sealants on primary molars: a 2-yr split-mouth randomized clinical trial. *European Journal of Oral Sciences*. 2021;129:e12758.	Resin-based sealants	France, ClinicalTrials.gov #NCT02896088	Low	High
Al Jobair et al 2017: Retention and caries-preventive effect of glass ionomer and resin-based sealants: an 18-month-randomized clinical trial. *Dental Materials Journal*. 2017;36(5):654–661.	Resin-based sealants vs glass ionomer sealants	Human Ethical Committee at the College of Dentistry Research Center (CDRC) at King Saud University (NF2260)	Low	Moderate
Muller-Bolla et al 2018: Effectiveness of resin-based sealants with and without fluoride placed in a high caries risk population: multicentric 2-year randomized clinical trial. *Caries Research*. 2018;52:312–322.	Resin-based sealants with fluoride vs resin-based sealants without fluoride	France, ClinicalTrials.gov #NCT00674869	Moderate	Moderate

(*continued*)

Table 3 (*Continued*)

Articles included		Trial registration	Risk of bias	Quality of the evidence
Author(s)/title/year/journal	Tested intervention			
Giray et al 2018: Resin infiltration technique and fluoride varnish on white spot lesions in children: preliminary findings of a randomized clinical trial. *Nigerian Journal of Clinical Practice*. 2018;21:1564–1569.	Resin infiltration vs NaF varnish	Turkey, Clinical Research Ethics Committee of Medical School (protocol number: C–02)	Low	Moderate
Peters et al 2018: Resin infiltration: an effective adjunct strategy for managing high caries risk—a within-person randomized controlled clinical trial. *Journal of Dentistry*. doi:10.1016/j.jdent.2018.09.005	Resin infiltration vs mock infiltration	USA, ClinicalTrials.gov #NCT01584024	Unclear	Moderate
Alabdullah et al 2017: Effect of fluoride-releasing resin composite in white spot lesions prevention: a single-centre, split-mouth, randomized controlled trial. *European Journal of Orthodontics*. doi:10.1093/ejo/cjx010	Fluoride-releasing resin composite	Not registered	Low	Moderate
Alkilzy et al 2017: Self-assembling peptide P11-4 and fluoride for regenerating enamel. *Journal of Dental Research*. doi:10.1177/0022034517730531	Self-assembly P11-4 + fluoride varnish vs fluoride varnish alone	Germany, ClinicalTrials.gov #NCT02724592	Moderate	Moderate
Alsabek et al 2019: Retention and remineralization effect of moisture tolerant resin-based sealant and glass ionomer sealant on non-cavitated pit and fissure caries: randomized controlled clinical trial. *Journal of Dentistry*. 2019;86:69–74.	Resin sealant glass ionomer sealant	Syria, Clinical Trials Registry (Trial Id:		
ACTRN12618001940268)	Moderate	Moderate		
Ammari et al 2017: Efficacy of resin infiltration of proximal caries in primary molars: 1-year follow-up of a split-mouth randomized controlled clinical trial. *Clinical Oral Investigations*. doi:10.1007/s00784-017-2227-7	Fluoridated toothpaste + flossing + Resin infiltration vs fluoridated toothpaste + flossing	Brazil, ClinicalTrials.gov #NCT01726179	Low	Moderate
Bröseler et al 2019: Randomised clinical trial investigating self-assembling peptide P11-4 in the treatment of early caries. *Clinical Oral Investigations*. doi:10.1007/s00784-019-02901-4	Self-assembling peptide P11-4 NaF varnish	German Registry for Clinical Studies (DRKS00012941)	Low	High
Grocholewicz et at 2020: Effect of nano–hydroxyapatite and ozone on approximal initial caries: a randomized clinical trial. *Scientific Reports*. doi:10.1038/s41598-020-67885-8	Nano-hydroxyapatite gel and gaseous ozone therapy separately vs nano-hydroxyapatite gel + ozone	Poland, ClinicalTrials.gov #NCT04147091	Low	High
León et al 2019: High fluoride dentifrice for preventing and arresting root caries in community-dwelling older adults: a randomized controlled clinical trial. *Journal of Dentistry*. 2019;86:110–117.	Toothbrushing with 5000 ppm vs 1450 ppm fluoridated dentifrice	Chile, ClinicalTrials.gov #NCT02647203	Moderate	Moderate
Meyer-Lueckel et al 2021: Proximal caries infiltration – pragmatic RCT with 4 years of follow-up. *Journal of Dentistry*. doi:10.1016/j.jdent.2021.103733	Resin infiltration vs mock infiltration	Local institutional board at Christian-Albrechts-Universitat¨ zu Kiel (A 122/10)	Moderate	Moderate
Paris et al 2020: Seven-year-efficacy of proximal caries infiltration – randomized clinical trial. *Journal of Dentistry*. doi:10.1016/j.jdent.2020.103277	Resin infiltration vs mock infiltration	Not registered	Low	High
Rechmann et al 2018: MI Varnish and MI Paste Plus in a caries prevention and remineralization study: a randomized controlled trial. *Clinical Oral Investigations*. doi:10.1007/s00784-017-2314-9	Twice-daily 1100 ppm fluoride toothpaste + daily MI Paste Plus + quarterly MI varnish vs twice-daily 1100 ppm fluoride toothpaste + fluoride rinse	USA, ClinicalTrials.gov #NCT02424097	Low	High
Schwendicke et al 2018: Cost-effectiveness of managing cavitated primary molar caries lesions: a randomized trial in Germany. *Journal of Dentistry*. doi:10.1016/j.jdent.2018.05.022	Hall technique (HT) nonrestorative cavity control (NRCC) vs conventional carious tissue removal and restoration (CR)	Germany, ClinicalTrials.gov #NCT01797458	Low	Moderate
Sleibi et al 2021: Reversal of root caries with casein phosphopeptide-amorphous calcium phosphate and fluoride varnish in xerostomia. *Caries Research*. doi:10.1159/000516176	Varnish containing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and fluoride 5% vs fluoride varnish 5%	UK, Office for Research Ethics Committees (ORECNI, 16/NI/0101)	Low	High
Olgen et al 2022: Effects of different remineralization agents on MIH defects: a randomized clinical study. Clinical Oral Investigations. 2022;26(3):3227–3238.	Control with regular oral hygiene vs NaF Varnish vs CPP/ACP vs CPP/ACPF	Turkey	Moderate	Moderate
Chestnutt et al 2017: Seal or varnish? A randomized controlled trial to determine the relative cost and effectiveness of pit and fissure sealant and fluoride varnish in preventing dental decay. *Health Technology Assessment* 2017;21(21):1–256.	Resin sealants (Delton) vs NaF varnish (Duraphat)	UK, Medicine and Healthcare products Regulatory agency, Protocol #SPON766-09	Low	High
Hilgert et al 2017: 3-year survival rates of retained composite resin and ART sealants using two assessment criteria. *Brazilian Oral Research*. doi:10.1590/1807-3107BOR-2017	Resin vs GIC/ART sealants	The Netherlands Trial Register (reference number 1699)	Moderate	Moderate

ART, atraumatic restorative treatment; GIC, glass ionomer cement; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NaF, sodium fluoride; SDF, silver diamine fluoride; SMART, Silver Modified Atraumatic Restorative Treatment; TCP, tri-calcium phosphate.

mainly related to the dark staining of tooth structures, need to be further disclosed.

Resin infiltration appears to be effective to stop the progression of caries lesions when applied to affected enamel on approximal surfaces or even in noncavitated dentin caries. Although a relatively high number of articles were retrieved on this topic, most of these publications were distributed amongst a limited number of research teams, revolving around the same clinical studies at different stages of their follow-up.

As regards resin infiltration to mask white spot lesions on buccal surfaces, good optical results have been described. However, reversal of initial enamel lesions on smooth surfaces has been addressed mainly by using self-assembly

peptides or CPP-ACP (with and without the incorporation of fluoride) successfully. No such remineralising effects had been observed by using fluoride toothpastes alone in an in vitro study.[51] It is fair to say that many studies that were excluded from the analysis of the present review evaluated the changes that occur in enamel surfaces either after resin infiltration, CPP/ACP, self-assembly peptides, or fluoride varnishes using more accurate diagnostic tools such as DIAGNOdent or QLF-D. In these studies, significant changes were detected in shorter intervals than the minimum 6-month follow-up period that had been set as one criterion for the inclusion of articles.[52-57]

A few new developments have been introduced in clinical studies, such as the use of ozone combined with a nanohydroxyapatite for proximal lesions or the shift to probiotic milk to prevent the development of caries in high-risk children. These promising strategies may still need to be tested in further clinical studies to gain their place in the armamentarium of nonrestorative strategies. Although a decade has passed since early publications on the subject, no evidence from clinical studies has yet been retrieved regarding functional remineralisation using polymer-induced liquid precursors, which has been addressed as another potential resource for reversing the progression of caries lesions by means of chemical interactions between the product and the remaining structures of the tooth (intrafibrillar mineralisation of caries affected dentin collagen).[58,59]

Limitations of the present review are related to the broad scope of nonrestorative options that may target a variety of situations, ranging from early intervention of caries lesions to arresting advanced dentin cavities. Therefore, the heterogeneity of outcomes and the low number of publications with similar measurements did not allow comparative statistics to be used across this range of studies. It is clear that more well controlled studies based on subject pool size, age, tooth location, and perhaps lesion size are needed to make sound comparisons amongst the materials analysed in this review.

Conclusions

More evidence has been gathered on the clinical efficacy of different nonrestorative treatment options in the 5-year period from 2017 to 2022. Sealants and fluoride gels and varnishes have made a contribution not only to prevent the onset of caries lesions but also to arrest them at early stages. Such features have also been demonstrated in noncavitated proximal lesions in long-term follow-up trials using resin infiltration, whereas CPP/ACF(+F) showed equal effectiveness in smooth surfaces. SDF is still the selected material to arrest open dentin and root caries lesions that are accessible for cleansing. Few innovations have been introduced in clinical studies for further recommendations.

Declaration of interests

None disclosed.

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Author contributions

María Belén Cabalén, Gustavo Fabián Molina, and Alejandra Bono contributed to the conception and design of the study. Gustavo Fabián Molina and María Belén Cabalén retrieved and selected the articles and, together with Alejandra Bono and Michael Burrow, analysed the data. Gustavo Fabián Molina and María Belén Cabalén drafted the manuscript. All authors participated in the discussion of the manuscript until its last version and final approval was provided to be accountable for all aspects of the work.

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Supplementary materials

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