Is there an acceptable surrogate for caries clinical trials? Evidence from a systematic review of primary studies

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Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

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Competing interests

The authors declare that they have no competing interests

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Authors' contributions

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Abstract

Background: There is currently a lack of evidence supporting the use of valid surrogates in caries clinical trials. This study aimed to examine the validity of two surrogate outcomes used in randomized clinical trials for caries prevention, pit and fissure sealants and fluoridated dentifrices, according to the Prentice criteria.

Methods: A systematic review was conducted in MEDLINE (PubMed), LILACS, and Scopus databases up to October 05, 2022. The grey literature and the list of eligible studies' references were also screened. The search was conducted, selecting randomized clinical trials focussed on dental caries prevention using pit and fissure sealants or fluoridated dentifrices and with at least one surrogate endpoint for cavitated caries lesions. The risk for each surrogate endpoint and for the occurrence of cavitated caries lesions was calculated and compared. The association between each surrogate and the presence of cavitation was quantified, and each outcome was assessed graphically for validity according to the Prentice criteria.

Results: For pit and fissure sealants, from 1696 potentially eligible studies, 51 were included; while for fluoridated dentifrices, of 3,887 potentially eligible studies, four were included. Possible surrogates assessed were retention of sealants, presence of white spot lesions, presence of plaque or marginal discoloration around the sealants, oral hygiene index, radiographic and fluorescence caries lesion assessments. However, only the retention of sealants and the presence of white spot lesions could be evaluated for their validity according to the Prentice criteria.

Conclusion: Loss of retention of sealants and the presence of white spot lesions do not fulfill all of the Prentice criteria. Therefore, they cannot be considered valid surrogates for caries prevention.

Keywords: Biomarkers. Outcome Assessment, Health Care. Dental caries.

Introduction

Randomized clinical trials (RCTs) are fundamental to increasing the strength of the evidence on treatments indicated for common oral diseases in clinical practice. This importance includes dental caries, the most prevalent oral health problem affecting the population [1]. However, clinical trials on dental caries should ideally consider cavitated lesions as the endpoint since this condition is regarded as a clinically relevant outcome [2]. Nevertheless, the limitations of RCTs in this field are that cavities can take a long time to appear [3], which acts to increase the number of participants required [2] and the follow-up time. This leads to a greater cost to carry out RCTs. Therefore, different surrogate endpoints have been used to overcome these difficulties and reduce the costs of the RCTs.

Surrogate endpoints are intermediate biomarkers in disease pathways that can be observed and assessed earlier and are often easier to measure [2, 4]. This means that surrogate endpoints are criteria that can be evaluated in place of more clinically relevant outcomes, with the supposed intention of predicting them. Regarding dental caries, several possibilities have been used as surrogate outcomes for cavitation, such as white spots, lesion activity, radiographic images, fluorescence emitted by the lesions, presence of dental plaque, microorganisms count, and retention of or discolorations around sealants [2]. However, surrogates should only be considered if they are valid. For this, analyses should be performed to verify the compliance of the surrogate endpoint to the Prentice criteria [5]. The surrogate variable has to 'capture' any relationship between the treatment and the actual endpoint. To date, retention of glass ionomer cement (GIC) and resin sealants in permanent molars are the only two measures investigated on its validity as a surrogate endpoint [6]. However, there may be other possible surrogate outcomes (that have been used in dental caries trials) for caries cavitation.

The present study aimed to examine the validity of commonly used surrogates in caries clinical trials according to the Prentice criteria. A qualitative assessment was carried out in cases where it was not possible to evaluate the variables according to this criterion. For this purpose, two methods for caries prevention were considered - fluoridated toothpaste and pit and fissure sealants – as both have been used in multiple clinical trials and strong effectiveness evidence is available [7, 8].

Methods

The review was registered in PROSPERO (International Prospective Register of Systematic Reviews) on January 4th, 2019, with registration number CRD42019115205. The aim of the review was to list the possible surrogate endpoints used in clinical trials to prevent dental caries using sealants or fluoridated dentifrices and perform a series of analyses to assess the surrogate's validity.

Eligibility criteria and Study selection

Titles and abstracts were evaluated by two independent reviewers based on the following inclusion criteria: (1) a randomized clinical trial on dental caries; (2) evaluated fluoride toothpaste of standard concentration (1,000 or 1,100 ppm of fluoride) compared to a control group (placebo or low F concentration) OR the use of pit and fissure sealants. Articles that meet the inclusion criteria were reviewed. Those that met at least one of the following exclusion criteria were considered ineligible: (1) non-computable data considering the absence of information on follow-up time, number of teeth treated, or which teeth developed cavitated caries lesions); (2) did not assess any surrogate endpoint for cavitation. Possible surrogates were white spots lesions, caries lesions activity, radiographic lesions, lesions measured by quantitative diagnostic methods, microorganisms count, dental plaque index, retention of the sealants or discoloration around; (3) written in a language other than English. If more than one study was conducted on the same sample, the study with the most prolonged follow-up outcome was included.

Information sources

Systematic searches were performed in MEDLINE (PubMed), LILACS, and Scopus. Unpublished documents were searched through OpenGREY. All studies published in those databases until October 05, 2022 (no start date restriction) were screened. The reference lists of any systematic reviews were manually checked for additional references not covered by the search. If eligible studies were not accessible via electronic databases, authors were contacted.

Search

The search strategies were developed based on two previously published systematic reviews [7, 9] for the MEDLINE/Pubmed database (Figure 1). Duplicates were eliminated through cross-checking using MS Excel software.

Data collection process and data items

The selected studies' data were collected and annotated independently by two reviewers in an excel spreadsheet. The following variables were extracted: first author; journal; year of publication; database where it was retrieved; the surrogate outcome that was used; duration of the follow-up; the number of teeth under each intervention group (n); the number of teeth that underwent treatment and presented the surrogate endpoint (nS); the number of teeth that underwent treatment and presented cavitation (nC).

Only one dataset per surrogate endpoint per study was collected. For studies that presented results for more than one follow-up period, only the longest follow-up point was included.

Summary measures and synthesis

First, inter-examiner agreement was performed in 10% of retrieved papers. The risk of having the surrogate endpoint (RS=nS/n) and the risk of caries cavitation occurrence (RC=nC/N) was calculated for each surrogate.

All analyses were performed for data from permanent and primary teeth together (global analysis) and, following this, separately (subgroup analysis). Linear regression analysis was performed to quantify the association between each surrogate and the presence of cavitation (RStudio Team, 2015). Log transformation was conducted to meet linearity assumptions by computing the natural logarithm of the risks (lnRS and lnRC). The natural logarithm of RC was set as the dependent variable and lnRS as the independent variable. If nS or nC were equal to zero, 0.5 was added before transformation to allow statistical analyses.

Surrogate outcomes were assessed graphically regarding their validity according to the Prentice criteria [5] and in line with the methodology described by Baker and Kramer [10]. A scatter plot with an intercept equal to zero was used, and straight lines were calculated using both treatments' risk values (RC and RS). The validity of each surrogate was visually assessed by comparing the two treatments' lines that must have been

coincident in the graph [10]. The mean RS and the mean RC was also calculated and plotted.

Divergences observed graphically between both lines were additionally assessed by computing an RS/RC rate for each dataset (RCS), then mean RCS (SD), and comparing the mean lnRCSs of the two treatments, using the t-test (MedCalc Software version 12.1, Ostend, Belgium).

A surrogate endpoint can be considered valid if it shows association with cavitation occurrence, does not show differences between treatments regarding lnRCSs, and demonstrates coincident regression lines of both treatments in the Baker-Kramer graphic. Statistical significance was set at $p < 0.05$ for all analyses.

Additional analyses

Sensitivity analysis was not performed given that only one dataset of each type of sealant from each randomized clinical trial (the one with the most extended follow-up result) was included, and only data about cavitated caries lesions assessed by visual inspection and separate from the other components of DMFT. Although both of these strategies meant that the review included a reduced sample, under or overestimation of results was avoided.

For the surrogates that was not possible to use this analytical approach, a descriptive analysis was carried out to observe qualitatively if the surrogates showed the same trends observed with cavitated lesions.

Results

Study selection and study characteristics

Regarding strategy for sealants, PubMed, Lilacs, and Scopus search yielded 1,696 papers. No additional records were identified through manual search and OpenGrey. After the removal of duplicates, 1,265 unique studies were screened. Then, 51 studies were included after eligibility criteria were applied (reasons for exclusions are detailed in Appendix Figure 1a).

The publication year of the included studies on pit and fissure sealants ranged from 1976 to 2022, with follow-up periods varying from 3 to 84 months. Forty-five studies evaluated

the retention of sealants in permanent teeth, and five studies considered retention in primary teeth. Other surrogates used in the studies on sealants were: radiographic images (one study), white spots (five studies), plaque fluorescence (one study), dental plaque index (one study), and marginal discoloration (two studies). More details on the study characteristics of the RCTs on pit and fissure sealants can be found in the online supplemental material. The individual characteristics of each included study are presented in Appendix Table 1.

For fluoridated dentifrices, PubMed, Lilacs, and Scopus searches yielded 3,887 papers. Ten additional records were identified through manual search and OpenGrey. After the removal of duplicates, 2,741 unique studies were screened. Then, four studies were included after eligibility criteria were applied (reasons for exclusions are detailed in Appendix Figure 1b).

The publication year of RCTs on fluoridated dentifrices varied from 1981 to 2009, with follow-ups from 3 to 48 months. The surrogates evaluated were the frequency of white spots (two studies), lesions detected by Fiber-optic transillumination and white spot lesions (one study), and caries lesions detected through radiography (one study). More details are presented in the online appendix and Appendix table 2.

Synthesis of results

Inter-examiner agreement for screening was 0.9 for both systematic reviews. Values for RC and RS for individual studies of pit and fissure sealants are shown in Appendix Table 2, and for fluoridated dentifrices in Appendix Table 3.

Regarding the sealants RCTs, it was only possible to analyze the validity of retention as a surrogate for cavitated caries lesions in all types of teeth, permanent and primary teeth. Other surrogates found in the studies did not present sufficient data for statistical analyses. The results of the regression analysis are shown in Table 1. The adjusted R^2 was low, thus indicating that a minor proportion of the variation in the presence of cavitation was explained by the loss of retention independent of the type of teeth. However, there was a linear association between the variables involved in the retention of resin sealants in global analysis and for the permanent teeth (ln(RS) p-value<0.05). The other regressions

did not present any statistical association. The mean RCS values for both teeth types were 18.5 (SD=31.8) for GIC sealants and 7.2 (SD=13.1) for resin sealants.

Similarly, only for permanent teeth, the mean RCS values were 15.7 (SD=30.3) for GIC sealants and 6.3 (SD=12.7) for resin sealants. The difference was statistically significant ($p<0.01$) in both cases. The results show that the ratio was treatment-dependent, indicating no compliance with the Prentice criterion for global analysis and permanent teeth. Regarding mean RCS for primary teeth, this was 45.1 (SD=46.5) for GIC sealants and 18.8 (SD=15.0) for resin sealants. The difference was not statistically significant ($p=0.50$). The results show that the ratio was treatment-independent, thus indicating compliance with the Prentice criterion.

Regarding Baker-Kramer plots for both types of teeth (Figure 2a) and permanent teeth only (Figure 2b), the mean risk of loss of retention (RS) was 0.5 (SD=0.3 and 0.3, respectively) for GIC sealants and 0.2 (SD=0.2) and 0.2 (SD=0.2) for resin, respectively, signaling more than double the risk for loss of GIC sealants. The mean risk of cavitation occurrence (RC) is 0.1 (all teeth) and 0.1 (permanent teeth) (SD =0.1/0.1) for both types of sealants, implying an equal risk of cavitation. The visual assessments show no coincidence of both regression lines, thus indicating no compliance with the Prentice criterion.

Similarly, the Baker-Kramer plot for the primary teeth (Figure 2c) indicates no compliance with the Prentice criterion. The mean risk of loss of retention (RS) was 0.6 (SD=0.5) for GIC sealants and 0.3 (SD=0.2) for resin, signaling more risk for loss of GIC sealants again. The mean risk of cavitation occurrence (RC) was 0.1 (SD =0.0) for GIC and 0.1 (SD =0.0) for resin sealants implying a similar risk of cavitation.

It was only possible to analyze white spot lesions' validity as a surrogate for cavitated caries lesions regarding fluoridated dentifrices trials. Other surrogates found did not present sufficient data for statistical analyses. The results of the regression analysis can be seen in Table 1. The adjusted R^2 was high, indicating that white spot lesions explained a large proportion of cavitation occurrence variation. However, there was no indication of a linear association between the variables involved (ln(RS) p-value=0.06).

The mean RCS values were 46.4 (SD=77.6) for conventional dentifrices and 24.5 (SD=39.4) for control treatments. The difference was not statistically significant

(p=0.92). The results show that the ratio was treatment-independent, thus indicating compliance with the Prentice criterion.

Regarding the Baker-Kramer plot (Figure 2d), the mean risk of the presence of white spot lesions (RS) was 0.3 (SD=0.0) for conventional dentifrices and 0.3 (SD=0.1) for control treatments, signaling a similar risk for both treatments. The mean risk of cavitation occurrence (RC) was 0.2 (SD =0.2) for dentifrice and 0.2 (SD = 0.3) for control, also implying a similar risk. Both regression lines in the visual assessment were not coincident, indicating no compliance with the Prentice criterion.

Qualitative analysis of additional surrogates

In two studies, there was a tendency for the presence of caries assessed through radiography to have a greater proportion of events compared with the non-events than that found by the clinical presence of a cavity. Moreover, the statistical significance between the experimental groups in the studies [11, 12] was similar for both the surrogate and clinically relevant outcome (Table 2).

The presence of plaque through Quantitative Light-induced Fluorescence (QLF) evaluation showed a much greater proportion of events than that observed with a cavity presence. Although more than 10% of the sealants presented plaque assessed by the QLF, no sample presented cavitation after 12 months [13] (Table 2). Regarding the level of oral hygiene assessed by one study, only five patients were classified as having poor oral hygiene, but 17 presented cavitation at follow-up, demonstrating a smaller proportion of surrogate presence [14] (Table 2).

Only two studies used the presence of marginal discoloration of the sealant as a surrogate, but in a short follow-up period (3 and 12 months). It was not observed any sealants with discoloration, nor the presence of cavities [15, 16] (Table 2). Finally, the evaluation of the presence of caries lesions through Fiber-optic transillumination (FOTI) showed a number similar to that found by the evaluation of the presence of the cavity, but higher. Only one study used this method as a surrogate, and there was a significant difference between the groups for both outcomes [17] (Table 2).

Discussion

Different surrogates have been used in many RCTs on dental caries to reduce the number of participants, duration, and consequently, costs of the trials. However, it is still being determined how valid these surrogates are in translating results that would be obtained with clinically relevant outcomes. To the best of our knowledge, the present study is the first systematic review that assessed which possible surrogate endpoints have been used in dental caries trials and analyzed their validity. This study found seven potential surrogate outcomes for dental caries trials. However, no variable presented significant validity in replacing clinically relevant outcomes for dental caries.

The most used surrogates were the retention of sealants and initial caries lesions (white spots). Both outcomes were analyzed regarding their validity. Due to a lack of data, the analyses of surrogate validity were not possible for other variables. For the first potential surrogate, the retention of sealants in permanent and primary teeth, the present study found that the criteria did not adhere to all requirements to be considered a valid surrogate. This finding corroborates a previous study that observed the same pattern for permanent teeth [6]. Given that permanent and primary teeth characteristics and behavior can be different, the present study evaluated the validity of surrogate endpoints for all teeth together and separately for primary and permanent teeth. In main and subgroup analyses, there was no compliance with the Prentice criterion considering resin and GIC sealants.

Although using pit and fissure sealants effectively prevents caries incidence, mainly due to the physical barrier against the biofilm, other pathways are involved in dental caries control [6]. Moreover, newly erupted teeth are more prone to develop dental caries [18]. Therefore, the presence of the sealant could be more necessary during the eruption period before they reach the functional occlusion, and the loss of the sealant after this period would not significantly influence caries development.

Another point is related to GIC sealants. It has been discussed above that the association between the loss of retention of resin sealants and not for GIC sealants with the occurrence of cavitation may be because GIC might be microscopically retained at the bottom of the pits and fissures. Therefore, continuously serving as reservoirs for fluoride release and provide a more efficient caries-preventive effect [19]. Therefore, sealant retention, on the basis of this explanation, would be an inaccurate surrogate.

Concerning the validity of white spots' presence as a surrogate outcome, most requirements to be considered a valid surrogate were also not observed. However, a

possible limitation is that the number of datasets included in the analysis was relatively small. Indeed, the detection of initial caries lesions has been performed by clinicians in daily clinical practice. However, it is already known that not all lesions progress to cavitation [20]. Studies have shown a low incidence of progression of white spots to cavitated stages, with about 10% of the surfaces with initial caries lesions progressing for worse conditions after two years in primary [21] and permanent teeth [3].

For the other outcomes where there were too few studies to analyze, it was observed that radiographic and FOTI methods presented more events than the occurrence of cavitations which, in turn, could act to reduce the minimum sample size for clinical trials. Moreover, both surrogates presented the same pattern of lesion progression when using the presence of cavitation as outcome. The statistical analyzes performed showed the same differences between the control and intervention groups when the outcome was evaluated using the surrogate method (FOTI and radiographic methods) or the presence of cavitation.. However, more studies would be required to validate these variables as possible surrogates.

Another alternative to be used as an outcome in substitution of clinically relevant endpoints are patient-reported outcome measures (PROMs) [3]. These are even more important than the clinically centered outcomes since they reflect the patients' feelings and opinions about the treatment received [3]. However, this type of outcome has rarely been used as primary outcome in dentistry [22]. It was recently found that changes in children's oral health-related quality of life (by parental proxy) was related to the primary endpoint, a clinically centered measure (number of new operative interventions during the follow-up) [23]. Findings such as this may indicate that PROMs in RCTs for dental caries should be considered as surrogates in future studies.

There are a number of limitations with the present study. First, non-English language papers were excluded (11 and 14 for sealants and dentifrices, respectively). Second, many articles were not accessible via electronic databases; although authors were contacted, few requests were returned.

In conclusion, the current systematic review found that the loss of retention of sealants and the presence of white spot lesions do not fulfill all of Prentice's criteria. Therefore, they cannot be considered valid surrogates for caries prevention. Future research is

303 needed to test different surrogate endpoints, including data about the frequency of both
304 surrogate endpoints and cavitated caries lesions.

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Legends

Figure 1. Search Strategy

Figure 2. Baker-Kramer plot for graphical investigation of Prentice criterion compliance for (a) sealants in all type of teeth; (b) sealants in permanent teeth; (c) sealants in primary teeth and (d) fluoride dentifrices vs control group.

Table 1. Linear regression analysis to examine the association between each surrogate and the presence of cavitation

			Intercept		Risk of having the Surrogate endpoint	
Type of Intervention	**N of studies**	**Adj R^2**	**Estimate**	**95%CI**	**Estimate**	**95%CI**
				Global analysis for retention		
GIC sealant	21	0.1	0.1	0.0;0.3	2.0	0.9;4.7
Resin sealant	38	0.1	0.1	0.1;2.0	1.5	1.1;2.0
				Sub-group analysis for retention		
GIC sealant - Permanent tooth	19	0.1	0.1	0.0;0.3	1.8	0.8;4.3
Resin sealant - Permanent tooth	35	0.2	0.1	0.1;0.3	1.5	1.1;2.0
GIC sealant - Primary tooth	3	1	0.1	0.0;0.3	11.0	3.7;24.5
Resin sealant - Primary tooth	3	0	0.2	0.0; >100	5.0	0.0; >100
				White spot lesion		
Dentifrice (1000-1100ppmF)	3	1	0.0	0.0;>100	0.0	0.0;>100
Control	3	0.4	200.3	0.0; >100	445.9	0.0; >100

Legend: Adj = Adjusted; CI = Confidence interval; GIC = glass ionomer cement; N = number.

Table 2. Summary of qualitative approach of surrogates (brackets contain percentages of events). Number of events indicates how many teeth exhibited cavitation or lesion progression, assessed by the surrogate method.

Study (Author and Date)	Surrogate endpoint	Intervention	Type of tooth	Follow-up (months)	Surrogate	Cavitation
					Number of events (%)	
Joshi et al., 2019 **	marginal discoloration	GIC sealant	primary	12	0 (0)	0 (0)
Prabakar et al., 2018 **	marginal discoloration	resin sealant	permanent	3	0 (0)	0 (0)
Chadwick et al., 2005 **	oral hygiene	GIC sealant	primary	30	5 (2.3)	17 (7.7)
Amaechi et al., 2019 **	plaque QLF	resin sealant	permanent	12	15 (11.5)	0 (0)
Poulsen et al., 2006	radiography	GIC sealant	permanent	30	34 (9.3)	23 (6.3)
	radiography	resin sealant	permanent	30	19 (5.2)	10 (2.7)
Winter et al., 1989	radiography	dentifrice	primary	36	178 (41.6)	397 (37.0)
	radiography	control	primary	36	231 (48.4)*	459 (41.6)*
Curnow et al., 2002	FOTI	dentifrice	primary	24	28 (11.7)	27 (11.3)
	FOTI	control	primary	24	35 (16.7)*	35 (15.8)*

* Statistically significant differences ($p < 0.05$) between experimental and control group for that specific outcome.

** These studies do not have a control group

Legend: FOTI = Fibre-optic transillumination; GIC = glass ionomer cement; QLF = Quantitative Light Fluorescence.

Supplemental File

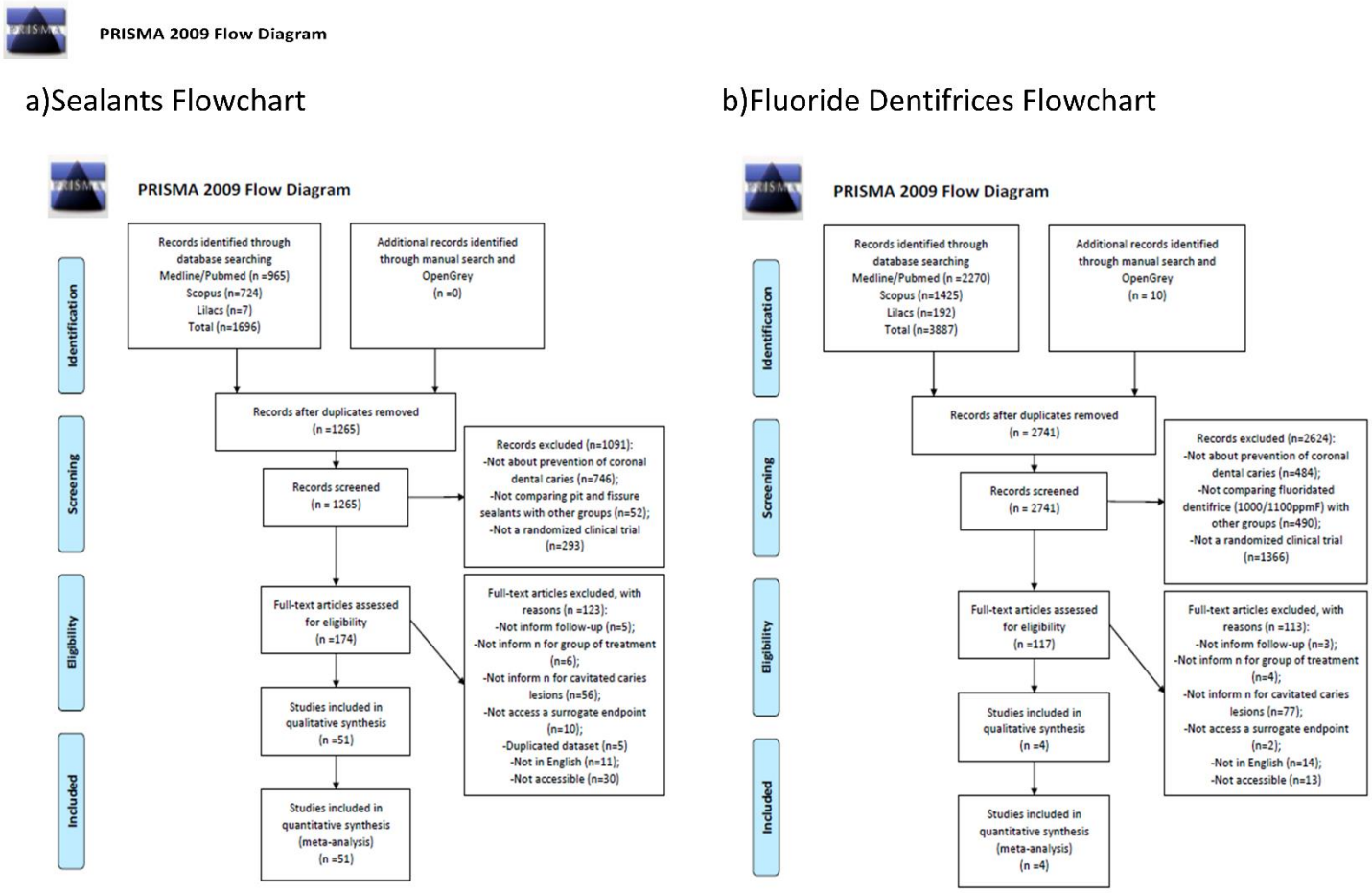
Study Selection

Regarding strategy for sealants, PubMed, Lilacs and Scopus searches yielded 1,696 papers. No additional records were identified through manual search and

OpenGrey. After removal of duplicates, 1,265 unique studies were screened. Then, 51 studies were included after eligibility criteria were applied (reasons of exclusions are detailed in Appendix Figure 1a).

On the other hand, concerning fluoridated dentifrices, PubMed, Lilacs and Scopus searches yielded 3,887 papers. Ten additional records were identified through manual search and OpenGrey. After removal of duplicates, 2,741 unique studies were screened. Then, 4 studies were included after eligibility criteria were applied (reasons of exclusions are detailed in Appendix Figure 1b).

Appendix Figure 1. Flow diagram with the information through the phases of studies selection.



Study Characteristics for sealants trials

Publication year of included studies ranged from 1976 to 2022 and follow-up periods ranged from 3 to 84 months. Forty-five studies evaluated retention of sealants in permanent teeth (Al-Jobair et al. 2017; Althomali et al. 2022; Alvesalo et al. 1977; Amaechi et al. 2019; Amin 2008; Arrow and Riordan 1995; Baca et al. 2007; Beiruti et al. 2006; Bravo et al. 1996; Burbridge et al. 2006; Cabral et al. 2018; Chen and Liu 2013; Chestnutt et al. 2017; Cons et al. 1976; de Oliveira and Cunha 2013; Elkwatehy and Bukhari 2019; Ercan et al. 2009; Forss and Halme 1998; Haricharan et al. 2019; Haricharan et al. 2022; Horowitz et al. 1976; Houpt and Sheykholeslam 1978; Khatri et al. 2019; Liu et al. 2014; Mascarenhas et al. 2008; Mertz-Fairhurst et al. 1982; Mohanraj et al. 2019; Monse et al. 2012; Nazar et al. 2013; Ntaoutidou et al. 2018; Pardi et al. 2003; Poulsen et al. 2001; Prabakar et al. 2018; Prathibha et al. 2019; Raadal et al. 1991; Reis et al. 2019; Rock 1977; Schill et al. 2022; Stiles et al. 1976; Ulusu et al. 2012; Whitehurst and Soni 1976; Williams et al. 1978; Williams et al. 1986; Williams and Winter 1976; Yildiz et al. 2004), five studies also assessed retention but in primary teeth (Chabadel et al. 2021; Chadwick et al. 2005; Honkala et al. 2015; Joshi et al. 2019; Ying Lam et al. 2021), and one assessed the presence of dental caries through radiography in permanent teeth (Poulsen et al. 2006). In addition to retention data, five studies collected the presence of white spot lesions in permanent (Burbridge et al. 2006; Khatri et al. 2019; Ntaoutidou et al. 2018) and primary (Honkala et al. 2015; Joshi et al. 2019) tooth; one verified presence of plaque using Quantitative Light-induced Fluorescence (QLF™)(Amaechi et al. 2019); one used index of oral hygiene (Chadwick et al. 2005) and two assessed presence of marginal discoloration in permanent (Prabakar et al. 2018) and primary (Joshi et al. 2019) teeth. We collected a total of 75 datasets, being only one dataset per surrogate per sealant type for each study. Twenty-six datasets presented data for glass-ionomer sealants (GIC) and 49 datasets for resin sealants. Characteristics of each included study are provided in Appendix Tables 1 and 2.

Appendix Table 1. Summary of general characteristics of included studies regarding sealants trials

Title	authors	database	Surrogate endpoint	type of sealant	tooth	Follow-up (months)	n of teeth per group
Dawn of a New Age Fissure Sealant? A Study Evaluating the Clinical Performance of Embrace WetBond and ART Sealants: Results from a Randomized Controlled Clinical Trial.	Haricharan PB et al., 2019	pubmed	retention	gic	permanent	12	90
			retention	resin	permanent	12	90
Comparative Efficacy in Preventing Plaque Formation around Pit and Fissure Sealants: A Clinical Trial.	Amaechi BT et al., 2019	pubmed	plaque QLF	resin	permanent	12	131
			retention	resin	permanent	12	131
The Efficacy of Different Sealant Modalities for Prevention of Pits and Fissures Caries: A Randomized Clinical Trial.	Elkwatehy WMA & Bukhari OM., 2019	pubmed	retention	gic	permanent	24	41
			retention	resin	permanent	24	41
Sealants revisited: An efficacy battle between the two major types of sealants - A randomized controlled clinical trial.	Prathibha B et al., 2019	pubmed	retention	gic	permanent	12	111
			retention	resin	permanent	12	111
Retention of moisture-tolerant fluoride-releasing sealant and amorphous calcium phosphate-containing sealant in 6-9-year-old children: A randomized controlled trial.	Khatri SG et al., 2019	pubmed	white spot	resin	permanent	12	32
			retention	resin	permanent	12	32
Split-mouth Randomised Clinical Trial on the Efficacy of GIC Sealant on Occlusal Surfaces of Primary Second Molar.	Joshi S et al., 2019	pubmed	marginal discolouration	gic	primary	12	172
			white spot	gic	primary	12	172
			retention	gic	primary	12	172
Retention rates and caries-preventive effects of two different sealant materials: a randomised clinical trial.	Cabral RN et al., 2018	pubmed	retention	gic	permanent	24	92
Clinical evaluation of a surface pre-reacted glass (S-PRG) filler-containing dental sealant placed with a self-etching primer/adhesive.	Ntaoutidou S et al., 2018	pubmed	white spot	resin	permanent	18	89
			retention	resin	permanent	18	89

Comparative Evaluation of Retention, Cariostatic Effect and Discoloration of Conventional and Hydrophilic Sealants - A Single Blinded Randomized Split Mouth Clinical Trial.	Prabakar J et al., 2018	pubmed	discoloration	resin	permanent	3	30
			retention	resin	permanent	3	60
Retention and caries-preventive effect of glass ionomer and resin-based sealants: An 18-month-randomized clinical trial.	Al-Jobair A et al., 2017	pubmed	retention	resin	permanent	18	70
			retention	gic	permanent	18	70
Fissure Seal or Fluoride Varnish? A Randomized Trial of Relative Effectiveness.	Chestnutt IG et al., 2017	pubmed	retention	resin	permanent	36	1609
Sealant versus Fluoride in Primary Molars of Kindergarten Children Regularly Receiving Fluoride Varnish: One-Year Randomized Clinical Trial Follow-Up.	Honkala S et al., 2015	pubmed	white spot	resin	primary	12	267
			retention	resin	primary	12	345
Glass ionomer ART sealant and fluoride-releasing resin sealant in fissure caries prevention--results from a randomized clinical trial.	Liu BY et al., 2014	pubmed	retention	gic	permanent	24	179
			retention	resin	permanent	24	178
Comparison of the caries-preventive effect of a glass ionomer sealant and fluoride varnish on newly erupted first permanent molars of children with and without dental caries experience.	de Oliveira DC & Cunha RF., 2013	pubmed	retention	gic	permanent	18	151
Clinical comparison of Fuji VII and a resin sealant in children at high and low risk of caries.	Chen Xx & Liu Xg., 2013	pubmed	retention	resin	permanent	24	75
			retention	gic	permanent	24	75
Effectiveness of fissure sealant retention and caries prevention with and without primer and bond.	Nazar H et al., 2013	pubmed	retention	resin	permanent	60	240
Caries preventive efficacy of silver diammine fluoride (SDF) and ART sealants in a school-based daily fluoride toothbrushing program in the Philippines.	Monse B et al., 2012	pubmed	retention	gic	permanent	18	768
	Ulusu T et al., 2012	pubmed	retention	gic	permanent	24	139

The success rates of a glass ionomer cement and a resin-based fissure sealant placed by fifth-year undergraduate dental students.			retention	resin	permanent	24	137
Clinical and antibacterial effectiveness of three different sealant materials.	Amin HE., 2008	pubmed	retention	resin	permanent	24	26
Effectiveness of primer and bond in sealant retention and caries prevention.	Mascarenhas AK et al., 2008	pubmed	retention	resin	permanent	24	156
Retention of three fissure sealants and a dentin bonding system used as fissure sealant in caries prevention: 12-month follow-up results.	Baca P et al., 2007	pubmed	retention	resin	permanent	12	81
A randomized controlled trial of the effectiveness of a one-step conditioning agent in sealant placement: 6-month results.	Burbridge L et al., 2006	pubmed	retention	resin	permanent	6	28
			white spot	resin	permanent	6	28
A field trial of resin-based and glass-ionomer fissure sealants: clinical and radiographic assessment of caries.	Poulsen S et al., 2006	pubmed	radiography	gic	permanent	30	364
			radiography	resin	permanent	30	364
Caries-preventive effect of a one-time application of composite resin and glass ionomer sealants after 5 years.	Beiruti N et al., 2006	pubmed	retention	resin	permanent	60	115
			retention	gic	permanent	60	139
A randomised controlled trial to determine the effectiveness of glass ionomer sealants in pre-school children.	Chadwick BL et al., 2005	pubmed	retention	gic	primary	30	221
			oral higyene	gic	primary	30	221
A 5-year evaluation of two glass-ionomer cements used as fissure sealants.	Pardi V et al., 2003	pubmed	retention	gic	permanent	60	128
A comparison of retention and the effect on caries of fissure sealing with a glass-ionomer and a resin-based sealant.	Poulsen S et al., 2001	pubmed	retention	gic	permanent	36	103
			retention	resin	permanent	36	103
		pubmed	retention	resin	permanent	84	97

Retention of a glass ionomer cement and a resin-based fissure sealant and effect on carious outcome after 7 years.	Forss H & Halme E., 1998		retention	gic	permanent	84	97
Effectiveness of visible light fissure sealant (Delton) versus fluoride varnish (Duraphat): 24-month clinical trial.	Bravo M et al., 1996	pubmed	retention	resin	permanent	24	238
Retention and caries preventive effects of a GIC and a resin-based fissure sealant.	Arrow P & Riordan PJ., 1995	pubmed	retention	resin	permanent	36	412
			retention	gic	permanent	36	412
A two-year clinical trial comparing the retention of two fissure sealants.	Raadal M et al., 1991	pubmed	retention	resin	permanent	24	117
A two-year clinical trial comparing different resin systems used as fissure sealants.	Williams B et al., 1986	pubmed	retention	resin	permanent	24	60
Fissure sealants. A 2-year clinical trial.	Williams B et al., 1978	pubmed	retention	gic	permanent	24	633
			retention	resin	permanent	24	707
The clinical effectiveness of Delton fissure sealant after one year.	Houpt M et al., 1978	pubmed	retention	resin	permanent	11	185
Fissure sealants. Results of a 3-year clinical trial using an ultra-violet sensitive resin.	Rock WP., 1977	pubmed	retention	resin	permanent	36	161
On the use of fissure sealants in caries prevention. A clinical study.	Alvesalo L et al., 1977	pubmed	retention	resin	permanent	24	120
			retention	resin	primary	24	29
Fissure sealants. A 2-year clinical trial.	Williams B & Winter GB., 1976	pubmed	retention	gic	permanent	24	166
Adhesive sealant clinical trial: comparative results of application by a dentist or dental auxiliaries.	Stiles HM et al., 1976	pubmed	retention	resin	primary	12	283
			retention	resin	permanent	12	1373
Adhesive sealant clinical trial: an overview of results after four years in Kalispell, Montana.	Horowitz HS et al., 1976	pubmed	retention	resin	permanent	48	927
Adhesive sealant clinical trial: results eighteen months after one application.	Whitehurst V & Soni NN., 1976	pubmed	retention	resin	permanent	18	249

Adhesive sealant clinical trial: results of a three-year study in a fluoridated area.	Cons NC et al., 1976	pubmed	retention	resin	permanent	36	3581
Comparative Evaluation of Hydrophobic and Hydrophilic Resin-based Sealants: A Clinical Study	Mohanraj, M et al., 2019	scopus	retention	resin	permanent	12	50
Alternative of lower-cost glass-ionomer sealant in the prevention of caries lesions in brazilian children	Reis, J.T.A. et al., 2019	scopus	retention	gic	permanent	8	114
Anticaries effect of atraumatic restorative treatment with fissure sealants in suburban districts of Turkey	Ercan, E. et al., 2009	scopus	retention	gic	permanent	24	156
A comparative study of two fissure sealants: A 2-year clinical follow-up	Yildiz, E. et al., 2004	scopus	retention	resin	permanent	24	61
A comparative clinical study of two pit and fissure sealants: six-year results in Augusta, Ga.	Mertz-Fairhurst, E.J. et al., 1982	scopus	retention	resin	permanent	84	102
Retention Evaluation of Fissure Sealants Applied Using Self-Etch and Conventional Acid-Etch Techniques: A Randomized Control Trial Among Schoolchildren	Althomali et al., 2022	Pubmed	retention	resin	permanent	24	66
Effectiveness of pit and fissure sealants on primary molars: A 2-yr split-mouth randomized clinical trial	Chabadel et al., 2021	Pubmed	retention	resin	primary	24	128
An Efficacy Study between High Viscosity Glass Ionomers and Resin Sealants in Fissure Caries Prevention: A 2-Year Split Mouth Randomized Controlled Trial	Haricharan et al., 2022	Pubmed	retention	resin	permanent	24	180
Glass Ionomer Sealant versus Fluoride Varnish Application to Prevent Occlusal Caries in Primary Second Molars among Preschool Children: A Randomized Controlled Trial	Ying Lam et al., 2021	pubmed	retention	gic	primary	12	514

3-Year Clinical Performance of a New Pit and Fissure Sealant	Schill et al., 2022	pubmed	retention	resin	permanent	36	70

Appendix Table 2 – Summary of outcome characteristics of included studies regarding sealants trials

authors	Surrogate endpoint	type of sealant	tooth	n of teeth per group	nSurrogate	nCavitated	RS	logRS	RC	logRC	RS/RC
Haricharan PB et al., 2019	retention	gic	permanent	90	28	28	0.3	-1.2	0.3	-1.2	1.0
	retention	resin	permanent	90	19	28	0.2	-1.6	0.3	-1.2	0.7
Amaechi BT et al., 2019	plaque QLF	resin	permanent	131	15	0,5	0.1	-2.2	0.0	-5.6	30.0
	retention	resin	permanent	131	25	0,5	0.2	-1.7	0.0	-5.6	50.0
Elkwatehy WMA & Bukhari OM., 2019	retention	gic	permanent	41	36	0,5	0.9	-0.1	0.0	-4.4	72.0
	retention	resin	permanent	41	28	0,5	0.7	-0.4	0.0	-4.4	56.0
Prathibha B et al., 2019	retention	gic	permanent	111	37	10	0.3	-1.1	0.1	-2.4	3.7
	retention	resin	permanent	111	11	6	0.1	-2.3	0.1	-2.9	1.8
Khatri SG et al., 2019	white spot	resin	permanent	32	4	0,5	0.1	-2.1	0.0	-4.2	8.0
	retention	resin	permanent	32	4	0,5	0.1	-2.1	0.0	-4.2	8.0
Joshi S et al., 2019	marginal discolouration	gic	primary	172	0,5	0,5	0.0	-5.8	0.0	-5.8	1.0
	white spot	gic	primary	172	0,5	0,5	0.0	-5.8	0.0	-5.8	1.0
	retention	gic	primary	172	39	0,5	0.2	-1.5	0.0	-5.8	78.0
Cabral RN et al., 2018	retention	gic	permanent	92	28	2	0.3	-1.2	0.0	-3.8	14.0
Ntaoutidou S et al., 2018	white spot	resin	permanent	89	1	0,5	0.0	-4.5	0.0	-5.2	2.0
	retention	resin	permanent	89	5	0,5	0.1	-2.9	0.0	-5.2	10.0
	discoloration	resin	permanent	30	0,5	0,5	0.0	-4.1	0.0	-4.1	1.0

Prabakar J et al., 2018	retention	resin	permanent	60	0,5	0,5	0.0	-4.8	0.0	-4.8	1.0
Al-Jobair A et al., 2017	retention	resin	permanent	70	13	19	0.2	-1.7	0.3	-1.3	0.7
	retention	gic	permanent	70	14	22	0.2	-1.6	0.3	-1.2	0.6
Chestnutt IG et al., 2017	retention	resin	permanent	1609	21	120	0.0	-4.3	0.1	-2.6	0.2
Honkala S et al., 2015	white spot	resin	primary	267	8	2	0.0	-3.5	0.0	-4.9	4.0
	retention	resin	primary	345	41	2	0.1	-2.1	0.0	-5.2	20.5
Liu BY et al., 2014	retention	gic	permanent	179	80	13	0.5	-0.8	0.1	-2.6	6.2
	retention	resin	permanent	178	38	7	0.2	-1.5	0.0	-3.2	5.4
de Oliveira DC & Cunha RF., 2013	retention	gic	permanent	151	42	15	0.3	-1.3	0.1	-2.3	2.8
Chen Xx & Liu Xg., 2013	retention	resin	permanent	75	0,5	6	0.0	-5.0	0.1	-2.5	0.1
	retention	gic	permanent	75	12	6	0.2	-1.8	0.1	-2.5	2.0
Nazar H et al., 2013	retention	resin	permanent	240	166	119	0.7	-0.4	0.5	-0.7	1.4
Monse B et al., 2012	retention	gic	permanent	768	322	32	0.4	-0.9	0.0	-3.2	10.1
Ulusu T et al., 2012	retention	gic	permanent	139	46	5	0.3	-1.1	0.0	-3.3	9.2
	retention	resin	permanent	137	24	7	0.2	-1.7	0.1	-3.0	3.4
Amin HE., 2008	retention	resin	permanent	26	3	1	0.1	-2.2	0.0	-3.3	3.0
Mascarenhas AK et al., 2008	retention	resin	permanent	156	20	37	0.1	-2.1	0.2	-1.4	0.5
Baca P et al., 2007	retention	resin	permanent	81	13	2	0.2	-1.8	0.0	-3.7	6.5

Burbridge L et	retention	resin	permanent	28	0,5	0,5	0.0	-4.0	0.0	-4.0	1.0
al., 2006	white spot	resin	permanent	28	0,5	0,5	0.0	-4.0	0.0	-4.0	1.0
Poulsen S et	radiography	gic	permanent	364	34	23	0.1	-2.4	0.1	-2.8	1.5
al., 2006	radiography	resin	permanent	364	19	10	0.1	-3.0	0.0	-3.6	1.9
Beiruti N et	retention	resin	permanent	115	99	6	0.9	-0.2	0.1	-3.0	16.5
al., 2006	retention	gic	permanent	139	122	1	0.9	-0.1	0.0	-4.9	122.0
Chadwick BL	retention	gic	primary	221	208	17	0.9	-0.1	0.1	-2.6	12.2
et al., 2005	oral higyene	gic	primary	221	5	17	0.0	-3.8	0.1	-2.6	0.3
Pardi V et al., 2003	retention	gic	permanent	128	114	26	0.9	-0.1	0.2	-1.6	4.4
Poulsen S et	retention	gic	permanent	103	92	44	0.9	-0.1	0.4	-0.9	2.1
al., 2001	retention	resin	permanent	103	10	13	0.1	-2.3	0.1	-2.1	0.8
Forss H &	retention	resin	permanent	97	6	8	0.1	-2.8	0.1	-2.5	0.8
Halme E., 1998	retention	gic	permanent	97	40	15	0.4	-0.9	0.2	-1.9	2.7
Bravo M et al., 1996	retention	resin	permanent	238	21	25	0.1	-2.4	0.1	-2.3	0.8
Arrow P &	retention	resin	permanent	412	40	28	0.1	-2.3	0.1	-2.7	1.4
Riordan PJ., 1995	retention	gic	permanent	412	71	3	0.2	-1.8	0.0	-4.9	23.7
Raadal M et al., 1991	retention	resin	permanent	117	0,5	0,5	0.0	-5.5	0.0	-5.5	1.0
Williams B et al., 1986	retention	resin	permanent	60	41	20	0.7	-0.4	0.3	-1.1	2.1
Williams B et	retention	gic	permanent	633	335	81	0.5	-0.6	0.1	-2.1	4.1
al., 1978	retention	resin	permanent	707	31	19	0.0	-3.1	0.0	-3.6	1.6

Houpt M et al., 1978	retention	resin	permanent	185	1	5	0.0	-5.2	0.0	-3.6	0.2
Rock WP., 1977	retention	resin	permanent	161	17	11	0.1	-2.3	0.1	-2.7	1.6
Alvesalo L et al., 1977	retention	resin	permanent	120	24	48	0.2	-1.6	0.4	-0.9	0.5
	retention	resin	primary	29	12	4	0.4	-0.9	0.1	-2.0	3.0
Williams B & Winter GB., 1976	retention	gic	permanent	166	131	19	0.8	-0.2	0.1	-2.2	6.9
Stiles HM et al., 1976	retention	resin	primary	283	131	4	0.5	-0.8	0.0	-4.3	32.8
	retention	resin	permanent	1373	726	75	0.5	-0.6	0.1	-2.9	9.7
Horowitz HS et al., 1976	retention	resin	permanent	927	313	184	0.3	-1.1	0.2	-1.6	1.7
Whitehurst V & Soni NN., 1976	retention	resin	permanent	249	23	41	0.1	-2.4	0.2	-1.8	0.6
Cons NC et al., 1976	retention	resin	permanent	3581	1806	540	0.5	-0.7	0.2	-1.9	3.3
Mohanraj, M et al., 2019	retention	resin	permanent	50	29	14	0.6	-0.5	0.3	-1.3	2.1
Reis, J.T.A. et al., 2019	retention	gic	permanent	114	4	0,5	0.0	-3.4	0.0	-5.4	8.0
Ercan, E. et al., 2009	retention	gic	permanent	156	78	27	0.5	-0.7	0.2	-1.8	2.9
Yildiz, E. et al., 2004	retention	resin	permanent	61	11	0,5	0.2	-1.7	0.0	-4.8	22.0

Mertz-Fairhurst, E.J. et al., 1982	retention	resin	permanent	102	20	32	0.2	-1.6	0.3	-1.2	0.6
Althomali et al., 2022	retention	resin	permanent	66	7	0.5	0.1	-2.2	0.0	-4.9	14.0
Chabadel et al., 2021	retention	resin	primary	128	41	21	0.3	-1.1	0.2	-1.8	2.0
Haricharan et al., 2022	retention	resin	permanent	180	55	12	0.3	-1.2	0.1	-2.7	4.6
Ying Lam et al., 2021	retention	gic	primary	514	446	41	0.9	-0.1	0.1	-2.5	10.9
Schill et al., 2022	retention	resin	permanent	70	0.5	0.5	0.0	-4.9	0.0	-4.9	1.0

Study Characteristics for fluoridated dentifrices trials

Publication year of included studies ranged from 1981 to 2009 and follow-up periods ranged from 12 weeks to 48 months. Two studies evaluated only the frequency of white spot lesions as surrogate (Bailey et al. 2009; Powell et al. 1981), one study used both Fiber-optic transillumination (FOTI) and white spot lesions as surrogates (Curnow et al. 2002) and one assessed the presence of dental caries through radiography (Winter et al. 1989). Characteristics of each included study are provided in Appendix Table 3.

Appendix Table 3. Summary ofcharacteristics of included studies regarding fluoridated dentifrices trials

Title	authors	Surrogate endpoint	treatment	Follow-up	n of participants group1	nSurrogate	n of participants group2	nCavitated	RS	logRS	RC	logRC	RS/RC
Regression of post-orthodontic lesions by a remineralizing cream.	Bailey DL et al., 2009	white spot	dentifrice	12 weeks	201	68		0,5	0.3	-1.1	0.0	-6.0	136.0
			control	12 weeks	207	35		0,5	0.2	-1.8	0.0	-6.0	70.0
A randomised controlled trial of the efficacy of supervised toothbrushing in high-caries-risk children.	Curnow MM et al., 2002	FOTI	dentifrice	24 months	239	28		27	0.1	-2.1	0.1	-2.2	1.0
			control	24 months	222	37		35	0.2	-1.8	0.2	-1.9	1.1
		white spot	dentifrice	24 months	239	69		27	0.3	-1.2	0.1	-2.2	2.6
			control	24 months	222	80		27	0.4	-1.0	0.1	-2.1	3.0
Clinical trial of a low-fluoride toothpaste for young children.	Winter GB et al, 1989	rx	dentifrice	36 months	428	178	1073	397	0.4	-0.9	0.4	-1.0	1.1
			control	36 months	477	231	1104	459	0.5	-0.7	0.4	-0.9	1.2
Effect of stannous fluoride treatments on the progression of initial lesions in approximal surfaces of permanent posterior teeth.	Powell KR et al., 1981	white spot	dentifrice	48 months	129	36		63	0.3	-1.3	0.5	-0.7	0.6
			control	48 months	198	57		116	0.3	-1.3	0.6	-0.5	0.5

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