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REVIEW

The additional benefit of professional fluoride application for children as an adjunct to regular fluoride toothpaste: a systematic review and meta-analysis

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Abstract

Objective To assess whether professional fluoride application (PFA) used in addition to regular fluoride toothpaste (RFT, ≥ 1,000 ppm) is more effective than RFT alone in children.

Materials and methods A systematic search was conducted using the PubMed, Embase, Google Scholar and CENTRAL databases. Randomized controlled trials (RCTs) comparing the effectiveness of RFT + PFA and RFT alone were included. Meta-analyses with random-effects models were performed. The certainty of evidence was assessed using the GRADE approach.

Results A total of 2,729 records were identified from electronic and manual searches, which were screened by two reviewers independently and in duplicate. Six RCTs (5,034 participants) were included, of which four had high risk of bias and two had unclear risk of bias. The PFA used in all these trials was fluoride varnish (FV). In meta-analyses, no significant difference was observed between participants receiving FV + RFT and RFT alone of d(m/e)fs increment (mean difference (MD) − 0.17, 95% confidence interval (CI) − 0.60 to 0.26, $P = 0.43$, $I^2 = 38\%$; 6 trials, 5,034 participants, moderate certainty evidence), incidence of caries (risk ratio (RR) 0.91, 95% CI 0.80 to 1.05, $P = 0.21$, $I^2 = 41\%$; 4 trials, 4,487 participants, moderate certainty evidence) or changes in prevalence of caries (RR 0.89, 95% CI 0.78 to 1.01, $P = 0.07$, $I^2 = 0\%$, 4 trials, 4,189 participants, low certainty evidence).

Conclusions Low to moderate certainty evidence suggests that FV does not have significant additional caries-preventive benefit for children (under 8 years old) when provided as an adjunct to daily tooth brushing with RFT (≥ 1,000 ppm). There is insufficient evidence regarding the additional benefit of other PFA interventions.

Clinical relevance The decision to apply FV to children needs to be made in light of their actual usage of RFT.

Trial registration PROSPERO (CRD42020165270)

Keywords Caries · Fluoride · Toothpaste · Professional fluoride application · Children · Fluoride varnish

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Introduction

Fluoride is a key element in successful caries prevention [1–4]. The anti-caries effect of fluoride has been investigated extensively over the past 50 years [5, 6]. Various modalities and modes of fluoride use have been studied, each with its own recommended concentration, frequency of use, and dosage schedule [5]. Numerous evidence-based reviews have confirmed that fluoride is both safe and highly effective for the prevention and control of caries [7, 8]. The use of fluoride through toothpaste, varnishes, gels, mouthwashes and water is common in caries prevention programmes [9, 10].

Regular fluoride toothpaste (RFT) is the most common non-professional intervention in caries prevention [11]. The typical strength of regular toothpaste is approximately 1,000 to 1,500 parts per million (ppm) fluoride [12]. Systematic reviews have shown that only toothpaste with fluoride of 1,000 ppm or above can prevent caries effectively [8]. Many professional societies have recommended that all children use toothpaste with at least 1,000 ppm fluoride, regardless of their ages [1, 8].

Professional fluoride application (PFA) is usually carried out by dental professionals and is often advocated for children, especially those at high risk of caries [12–15]. PFA, which includes the use of fluorinated gels, varnishes, foams and pastes, can be implemented in clinics, as well as in schools or other institutions as part of caries prevention programmes [1, 16]. The American Dental Association stated that children should receive 2.25% fluoride varnish (FV) twice a year [17]. However, whether additional PFA is still necessary when children have already used RFT is unclear to dentists [18, 19]. Some recent randomized controlled trials (RCTs) have shown that after daily use of fluoride toothpaste (≥ 1,000 ppm), extra PFA did not reduce caries [20–22]. Recent systematic reviews and meta-analyses have investigated the role of PFA or RFT in the prevention of dental caries in children [5, 11, 23, 24]. However, almost all these systematic reviews focused on using a specific type of fluorides alone. Only one systematic review in 2004 [5] investigated the effectiveness of the combination of toothpaste and PFA, but this review did not consider the concentration of fluoride in toothpaste, and its evidence remains to be updated.

The objective of this study was to assess whether the combined use of PFA and RFT has additional benefit than using RFT alone for children under 16.

Materials and methods

Protocol and methods

This systematic review was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020165270) and written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. The protocol has been reviewed and published [26], with no important discrepancies between the protocol and this final report.

Search strategy

We used PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase and Google Scholar to search for potentially eligible articles. The search strategy was developed for PubMed and adapted for other databases (see Electronic Appendix Table 1**)**, without any language or time restraints. In addition, the reference lists of eligible trials, as well as relevant systematic and narrative reviews, were examined. Manual searching was performed for ten relevant dental journals (see Electronic Appendix Table 2). All electronic and manual searches were last updated in February and March 2020, respectively.

Eligibility criteria

Two reviewers (L.Y. and X.Y.) screened the titles and abstracts of all retrieved records independently and in duplicate, based on the following Population, Intervention, Comparison, Outcome and Study design (PICOS) framework. All disagreements were resolved by discussion with two experts (G.S. and F.H.).

- Population (P): For consistency with existing Cochrane systematic reviews on topical fluorides, the participants of interest in this review were children aged 16 or younger at baseline (including children with deciduous, mixed or permanent dentition) [27, 28].
- Intervention (I): The invention of interest was the combined use of PFA (with fluoride in any form or concentration) and RFT (≥ 1,000 ppm).
- Comparison (C): The control of interest was self-applied RFT alone, with a fluoride concentration of 1,000 ppm or above.
- Outcome measures (O):

  The primary outcomes of this review were [29]:

(1) Increment of decayed (missing/extraction indicated) and filled surfaces/teeth (D(M/E)FS or D(M/E)FT in permanent teeth and d(m/e)fs or d(m/e)ft in deciduous teeth, continuous outcome) and/or

(2) Incidence of caries (percentage of children who developed new caries, including both those of caries-free and already with caries at baseline, dichotomous outcome) and/or

(3) Changes in prevalence of caries (caries prevalence rate at follow-up minus caries prevalence rate at baseline, dichotomous outcome).

Caries was defined as being recorded at the dentine level of diagnosis. If caries data only reported caries at both dentine and enamel levels, then the data were also used in the analysis.

Secondary outcomes were the progression of caries lesions through enamel or into dentine and caries arrest (that were assessed by the International Caries Detection and Assessment System (ICDAS), ICDAS II or DIAGNOdent, with continuous outcome and measured at least 6 months after application), patient-reported outcomes (e.g., ease of use/quality of life) and fluoride-related adverse effects (e.g., dental fluorosis, allergic reactions and tooth staining).

- Study design (S): RCTs with a follow-up of at least 6 months.

Data extraction

Two reviewers (L.Y. and X.Y.) extracted relevant data independently and in duplicate using piloted forms. Any disagreements were discussed, and a third reviewer was consulted when necessary. We contacted the first or corresponding authors of the included studies for missing information. For each trial, the extracted data consisted of six components: general information, study characteristics, patient characteristics, intervention, outcome measures and results.

(1) General information: title, publication year, countries where the studies were carried out, journal information and author information.
(2) Study characteristics: sample size, date and duration of the study, method for random selection, allocation concealment and blinding.
(3) Patient characteristics: age range, sex, dentition (permanent, mixed or deciduous dentition), caries risk, clinical features (e.g., location of the lesions) and demographic features of the individuals at baseline.
(4) Intervention: the type of intervention and type of control, the application interval, the fluoride content of toothpaste, other sources of fluoride and other measures to prevent caries.
(5) Outcomes: the instrument or scale for measurement and the detailed description of the outcomes of interest.
(6) Results: the number of patients, point estimates and measures of variability for continuous variables, frequency counts for dichotomous variables.

Data synthesis

We summarized dichotomous data with risk ratios (RRs) and continuous data with mean differences (MDs), together with the corresponding 95% confidence intervals (CIs) [30, 31]. Data synthesis was conducted using Review Manager software (RevMan 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). A random-effects model was applied to analyse pooled data, as the CI of mean effect size was wider than that obtained from a fixed effects model and consequently led to a more conservative interpretation [32]. The number needed to treat (NNT) was calculated when the difference was statistically significant in the overall pooled effect [33].

Subgroup analyses and investigation of heterogeneity

We carried out three subgroup analyses for d(m/e)fs or D(M/E)FS increment-related outcomes according to our protocol:

(1) Primary dentition at baseline versus mixed dentition at baseline versus permanent dentition;
(2) Different follow-up length (12 months versus 24 months versus 36 months);
(3) High caries risk at baseline versus low caries risk at baseline.

We assessed statistically the presence of heterogeneity within each comparison using a chi^2 test, where a P value < 0.1 was considered statistically significant. Degree of heterogeneity was assessed with I^2 statistic to avoid random error.

Risk of bias (ROB) assessment

The Cochrane risk of bias tool (V 1.0) was used to assess the ROB among included studies [33]. The tool addresses seven key domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of assessment, incomplete outcome data, selective reporting and other biases. Two reviewers (L.Y. and X.Y.) assessed all studies independently and in duplicate, with each domain assessed as having a "high", "low" or "unclear" risk of bias. All discrepancies were resolved by discussion with two experts (G.S. and F.H.).

Sensitivity analyses

For the main meta-analysis of d(m/e)fs or D(M/E)FS increment, we proposed two forms of sensitivity analysis: removing studies with the shortest observed follow-up period (12 months) and removing studies where we imputed missing

standard deviations. We performed these meta-analyses using random-effects models.

Assessment of publication bias

Possible publication bias would be assessed through a funnel plot and Egger's test when at least 10 studies were included in the meta-analysis [33].

Certainty of evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) framework was used to assess the certainty of evidence for every primary outcome [30, 31]. Six criteria for GRADE were study design, risk of bias, precision, consistency, publication bias and other considerations. RCTs started with high certainty evidence. Thereafter, five factors (risk of bias, imprecision, inconsistency, indirectness and publication bias) might downgrade the certainty of evidence, and three factors (large effect, dose-response and all plausible confounding would reduce a demonstrated effect) may upgrade the certainty of evidence. Based on these criteria, four grades of supporting evidence (high, moderate, low or very low) were evaluated for each outcome.

Results

Study selection

We used the MEDLINE (via PubMed), CENTRAL, and Embase databases and retrieved 1442, 1103, and 1184 records, respectively. Three additional records were identified through manual searching. After removing duplicates, 2729 unique records were left. We screened the titles and abstracts of these records and found 116 to be potentially eligible. After examination of their full texts, only 6 studies were deemed eligible and included in this review (Fig. 1).

Characteristics of the included studies

Trial design and participants

All six included RCTs were published between 2007 and 2017, and five of them were published in 2014 or later. The included studies were conducted in five different countries: Brazil, Sweden, the UK, Greece and the USA. Randomization was performed at individual level in three studies [34–36] and at cluster level in the other three studies [20, 22, 37]. In five of the six included studies [20, 22, 34–36], all participants were no more than 5 years old at baseline and with primary dentition. While in the other study [37], participants were with mixed dentition. The children at baseline were caries-free in two studies [22, 34], while those in the other four studies with the caries prevalence of 24 [36] to 88% [22].

Interventions and comparisons

The characteristics of the interventions used in the included studies are detailed in Table 1. In all trials, the fluoride concentration in the toothpaste was similar, three of which were 1450 ppm, one 1100 ppm, one 1000 ppm and one ranging from 1000 to 1450 ppm. In two of the trials [35, 36], toothbrushing was performed under supervision (see Electronic Appendix Table 3). Two studies [35, 37] reported a clear source of other fluorides, such as fluoridated milk or water. All PFA used in the study groups was FV. Five of the trials used FV with 5% sodium fluoride, and the other [35] used FV with 0.9% difluorosilane. All the professional fluoride was applied every 6 months.

Outcome measures

All the six studies reported caries increment data (or the data could be derived) with d(m/e)fs. Most studies evaluated dental caries using the d(m/e)fs index, according to the World Health Organization. One study [22] determined caries surfaces using the ICDAS. One study [37] used a caries diagnostic system of three levels from superficial (level 1) to profound (level 3): level 1 constituted small enamel lesions; level 2 were large enamel lesions; level 3 consisted of profound caries involving dentine lesions.

Other dental caries data included incidence of caries (reported in four trials [22, 34, 36, 37]) and changes in prevalence of caries (reported in four trials [20, 22, 34, 35]). The children at baseline in two studies [22, 34] were caries-free, which means the value of incidence of caries is equivalent to that changes in prevalence of caries in these studies.

Risk of bias

The risk of bias in the six studies is shown in Fig. 2. We accessed all the full texts so we could assess the risk of bias of all studies included in this systematic review. Based on the assessment by two reviewers, the agreement was good for the seven domains of six studies. We assessed four studies [20, 22, 34, 37] at high risk of bias for at least one domain, and therefore at high risk of bias overall. The other two studies [35, 36] were assessed as unclear overall risk of bias. These two studies had one domain judged to be at unclear risk of bias, but no domain judged to be at high risk of bias. None of the studies fulfilled all criteria across all domains to permit a judgement of low risk of bias. In the overall rating of bias risk, all six studies had good performance regarding selection

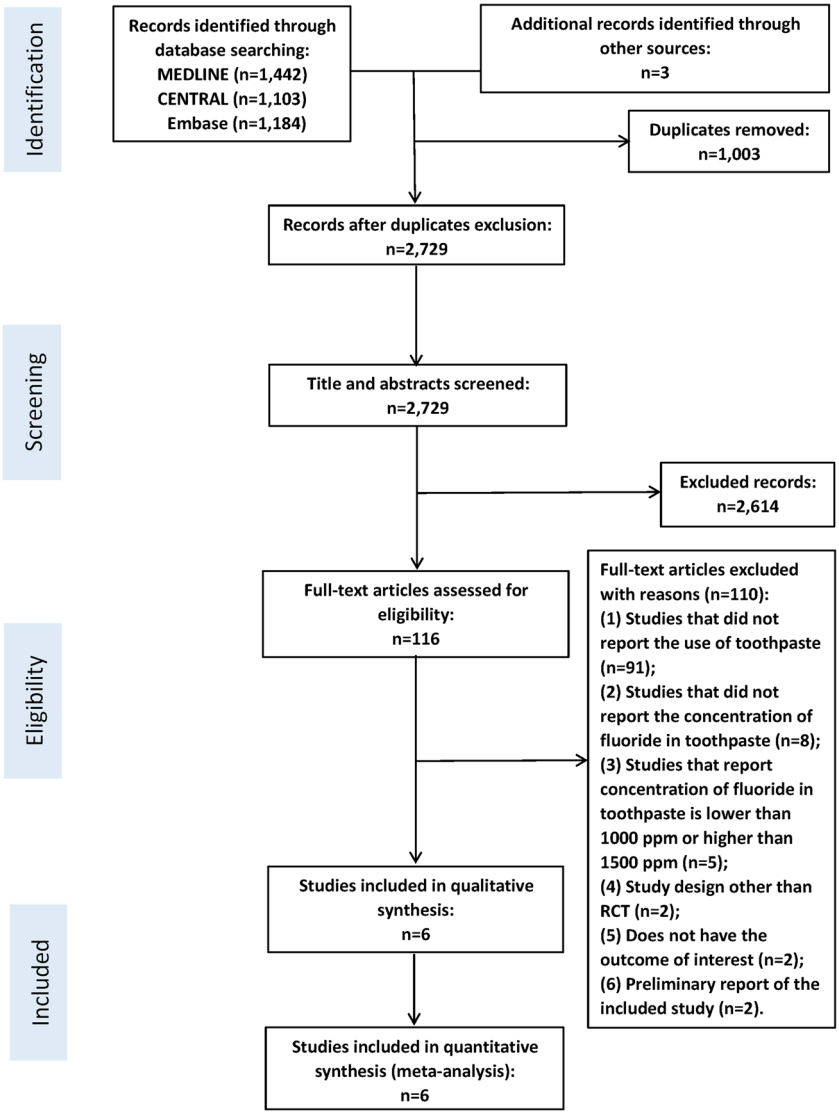

Fig. 1 Flow diagram of study selection

bias. Half of the studies [34–36] had only one domain rated as unclear or high risk of bias (see Electronic Appendix Table 4).

Publication bias was not evaluated, as only six studies were included in this synthesis. Funnel plots could not be presented either. Based on the GRADE assessment, the certainty of evidence for meta-analysis using the d(m/e)fs increment and incidence of caries was assessed to be moderate certainty, while the certainty of evidence for changes in prevalence of caries was found to be low (see Table 2).

Effects of interventions

The effects of additional FV on dental caries increments were reported in a variety of ways in the included studies. Where appropriate and possible, these have been combined to produce pooled estimates, as described in the Protocol and methods section. The results are reported separately here for (1) d(m/e)fs increment, (2) incidence of caries and (3) changes in prevalence of caries.

d(m/e)fs increment

Figure 3 shows that d(m/e)fs increment pooled estimate of all six trials from the random-effects meta-analysis was − 0.17 (95% CI − 0.60 to 0.26; P = 0.43), which suggests a non-significant effect in favour of the additional use of FV. Heterogeneity of the outcome was not statistically significant (chi^2 = 8.07 on 5 degrees of freedom, P = 0.15, I^2 = 38%). The detailed information about d(m/e)fs at baseline and final examination as well as the caries increment are showed in Electronic Appendix Table 5.

Table 1 Characteristics of included studies

First author (year)	Country	Participants			Follow-up time	Test group	Interval of FV	Control group	F concentration in toothpaste	Other source of fluoride
		Age range	*N*	Dentition						
Tickle (2017)	UK	2~3 years	1096	Primary dentition	36 months	Duraphat (5% sodium fluoride) + oral health education + dietary counseling	6 months	Oral health education + dietary counseling	1450 ppm	Unreported
Agouropoulos (2014)	Greece	2~5 years	328	Primary dentition	12 months, 24 months	Fluor Protector (0.9% difluorosilane) + oral health education + supervised toothbrushing	6 months	Biannual application of placebo varnish + oral health education + supervised toothbrushing	1000 ppm	Unreported
Oliveira (2014)	Brazil.	1~4 years	181	Primary dentition	24 months	Duraphat (5% sodium fluoride) + supervised toothbrushing + oral health counseling	6 months	Placebo varnish + supervised toothbrushing + oral health counseling	1450 ppm	Fluoridated drinking water*
Anderson (2016)	Sweden	1 year	2536	Primary dentition	36 months	Duraphat (5% sodium fluoride) + oral health education + dietary counseling	6 months	Usual care + oral health education + dietary counseling	1000–1450 ppm	Unreported
Hardman (2007)	UK	6–8 years	664	Mixed dentition	24 months	Duraphat (5% sodium fluoride) +usual care	6 months	Usual care	1450 ppm	Fluoride milk**
Braun (2016)	USA	3~5 years	229	Primary dentition	12 months, 24 months, 36 months	3M espe vanish (5% sodium fluoride) + oral health education	6 months	Usual care	1100 ppm	Unreported

*Brazilian public water supply system, with an usual fluoride concentration of 0.6–0.8 ppm

**For pupils who paid for the milk, low uptake and short length of consumption time

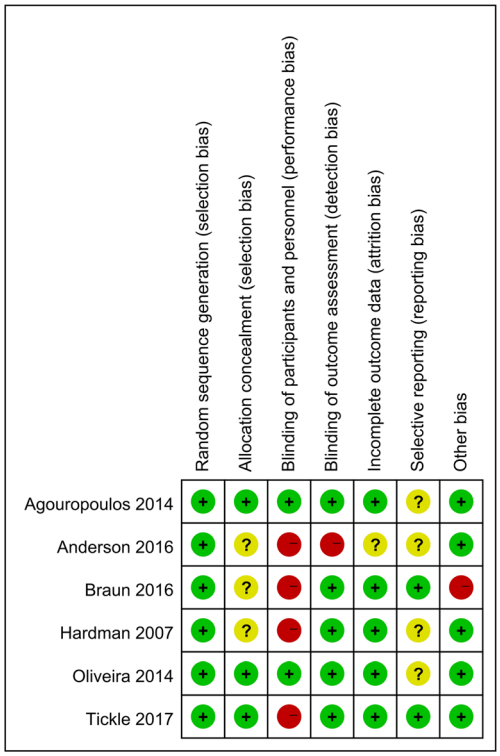

Fig. 2 Risk of bias summary graph: review authors' judgements about each risk of bias item for each included study

Incidence of caries

As shown in Fig. 4a, the pooled RR (random-effects meta-analysis) of the incidence of caries was 0.91 (95% CI 0.80 to 1.05), which suggests a non-significant effect ($P = 0.21$) that is slightly in favour of additional use of FV. Heterogeneity was moderate in these results ($P = 0.17$; $I^2 = 41\%$).

Changes in prevalence of caries

Figure 4b shows that the pooled RR (random-effects meta-analysis) of changes in prevalence of caries was 0.89 (95% CI 0.78 to 1.01; $P = 0.07$), which suggests a non-significant effect that is slightly in favour of additional FV. Heterogeneity was not detected in these results ($P = 0.74$; $I^2 = 0\%$). Using alternative methods to measure this effect yielded similar results (OR 0.85, 95% CI 0.71 to 1.01).

Other outcome measures

No study reported caries-related hospitalizations. There was no significant difference regarding the proportion of children dropping out from trials (Electronic Appendix Figure 1). Electronic Appendix Table 6 shows the adverse events associated with the combined use of FV and RFT.

Table 2 Summary of findings for the main comparison. RFT + FV compared to RFT alone for preventing caries in children

RFT + FV compared with RFT alone for preventing caries in children
Patient or population: children under 16 years old at the start of the study
Setting: professional fluoride application and/or home use
Intervention: combining FV and RFT
Comparison: regular fluoride toothpaste alone

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	RFT alone	RFT + FV	Difference			
Incidence of caries	22.6%	20.6% (181 to 238)	2.0% fewer (from 4.5% fewer to 1.1% more)	RR 0.91 (0.80 to 1.05)	4477 (4 studies)	⊕⊕⊕⊖moderate[a]
Changes in prevalence of caries	17.0%	15.1% (132 to 171)	1.9% fewer (from 3.7% fewer to 0.2% more)	RR 0.89 (0.78 to 1.01)	4189 (4 studies)	⊕⊕⊖⊖low[ab]
d(m/e)fs increment			The mean in the intervention groups was 0.17 lower (0.6 lower to 0.26 higher)	MD − 0.17 (− 0.60 to 0.26)	5034 (6 studies)	⊕⊕⊕⊖moderate[c]

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI*, confidence interval; *RR*, risk ratio; *MD*, mean difference; *FV*, fluoride varnish; *RFT*, regular fluoride toothpaste, the typical strength of regular toothpaste is around 1000 to 1500 parts per million (ppm) fluoride. GRADE Working Group grades of evidence: High certainty: Further research is very unlikely to change our confidence in the estimate of effect. Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low certainty: We are very uncertain about the estimate. [a] Downgraded 1 level for imprecision (95% confidence interval around the pooled estimate of effect included both: no effect and appreciable benefit.) [b] Downgraded 1 level due to single study at unclear risk of bias (Braun 2016). [c] Downgraded 1 level for imprecision (there were insufficient number of participants in single study leads to a wide confidence interval (Braun 2016))

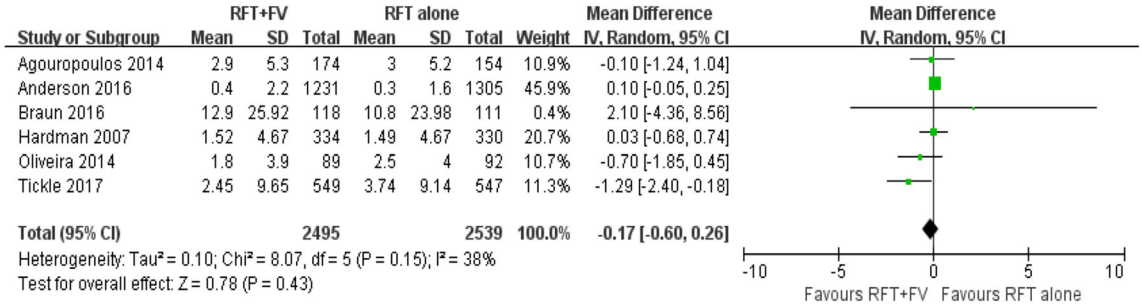

Fig. 3 Comparison of regular fluoride toothpaste (RFT) plus fluoride varnish (FV) versus RFT alone by outcome: d(m/e)fs increment

Subgroup analyses

As depicted in Electronic Appendix Figures 2, 3 and 4, no significant differences were found between the RFT + FV group and RFT-alone group in all seven results of the three subgroup meta-analyses. No evidence suggested that primary dentition or mixed dentition, low or high caries risks at baseline and different follow-up lengths could affect the caries prevention effect of additional use of FV.

Discussion

The main question addressed by this review is, based on the currently available evidence, how effective the combined use of RFT and PFA is for the prevention of caries in children when compared to RFT alone. In this systematic review, no significant difference was observed between participants receiving FV + RFT and RFT alone in d(m/e)fs increment, incidence of caries or changes in prevalence of caries. Over 5000 children were included, and for all of them, the professional fluoride regimen used in all included studies was FV.

The outcome was reported at different levels of surfaces, individuals and populations. Caries could be presented at the surface or tooth level as d(m/e)fs or D(M/E)FS as well as d(m/e)ft or D(M/E)FT. Indicators of d(m/e)fs or D(M/E)FS are the most commonly used indices in meta-analyses on caries prevention [5, 11, 27, 38–42]. All six included studies reported caries increment data at tooth level with d(m/e)fs and contributed to the overall pooled estimate. The indicators of incidence of caries at the individual level and changes in caries prevalence rate at the population level are not always strictly distinguished in previous studies [40]. The incidence of caries presents the proportion of children who develop new carious lesions within a stated period of time [43], while changes in prevalence of caries present the increase or decrease in caries prevalence rate within a stated period of time. The former includes those who already have had caries at baseline, while that of the latter does not. The value of the changes in prevalence of caries is equivalent to that of incidence of caries only when the children at baseline are caries-free. No significant differences were observed at all three

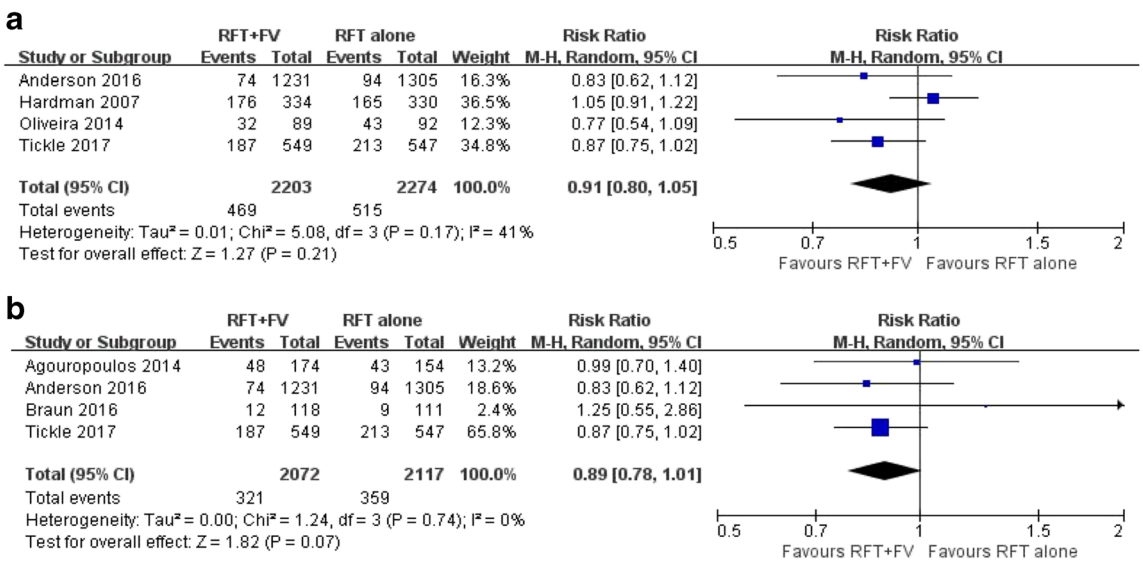

Fig. 4 Comparison of regular fluoride toothpaste (RFT) plus fluoride varnish (FV) versus RFT alone by outcome. **a** Incidence of caries. **b** Changes in prevalence of caries

levels between children who received additional FV and those who did not.

Fluoride toothpaste is by far the most widely used form of fluoride. According to a previous review, the decline in caries prevalence in developed countries is mainly due to the increased use of fluoride toothpaste [44]. The consensus among researchers and public health authorities is to use RFT (≥ 1,000 ppm) as the main method of preventing caries for children above 6 years old, but there is an argument about the concentration of fluoride in toothpaste for children under 6. Stronger fluoride toothpaste may offer greater protection against decay but also increase the risk of fluorosis in developing teeth, while a fluoride toothpaste containing less than 1000 ppm F may lose its anti-caries effect [45]. The latest guidelines suggest that children of all age groups should use fluoride toothpaste (≥ 1,000 ppm) but with variable amounts [1]. All the participants in our included studies received free RFT, and some of them received health education or even brushed teeth under supervision to ensure the effectiveness of toothbrushing. A more probable explanation for our failure to demonstrate effectiveness was that the impact of additional FV was obscured by the effectiveness of RFT, carried out in health programmes or under supervision. However, in daily life, children may not brush their teeth as carefully as those involved in clinical trials and strictly control their sugar consumption. The decision to apply FV to children needs to be made in light of their actual usage of RFT.

An increasing number of reviews suggest that PFA is capable of reducing caries [5, 27, 38, 40]. Actually, these reviews, which confirmed the caries prevention effect of PFA, hardly consider the basic caries prevention effect of RFT. When fluoride is used with other fluorine-containing vehicles, the cumulative fluoride exposure of children under 6 years of age must be considered [8]. Care must be taken to ensure a balance between the maximum prevention of dental caries and the minimal risk of dental fluorosis. Only one systematic review [5] published in 2004 concentrated on a combined use of topical fluorides versus single topical fluoride for preventing dental caries in children and adolescents. The evidence showed that the combined use of fluorides could produce an additional anti-caries effect, but the pooled effect size was small (10%).

However, we were unable to detect a clear difference from all seven available subgroup comparisons. It appears that most evidence suggests that children with a high risk of caries should use RFT (≥ 1000 ppm) or receive FV twice a year [8]. The caries risk assessment is so complex and comprehensive to accurately identify outcomes [46]. Nevertheless, past caries experience is the best single predictor for future caries increment [40]. Therefore, we performed a subgroup analysis of caries risk based on past caries experience, and the result indicates that there may be little cariostatic effect of adding FV to fluoride toothpaste even for children with a high risk of caries. Measured by the proportion of drop-outs, no significant difference was found in the acceptance between RFT alone and RFT+FV. Within the corresponding body of evidence, the additional cariostatic effects of FV may not be significant.

Our review has several limitations. First, due to a limited number of relevant RCTs, there is insufficient evidence for other types of PFA except for FV. In addition, we could not analyse the publication bias by creating funnel plots because the number of included studies was less than ten. We found little useful information about the effects of combination of RFT and FV on other clinically important outcomes, such as d(m/e)ft in the deciduous dentition and D(M/E)FS and D(M/E)FT in the permanent dentition. All the participants included in our reviews were no more than 8 years old. More trials are highly recommended to use indicators such as D(M/E)FS or D(M/E)FT of permanent teeth to evaluate the efficacy of FV in addition to RFT. We also found no useful information on adverse effects such as dental fluorosis, allergic reactions or tooth staining. Due to the lack of evidence of adverse effects, it is more difficult for clinicians and policymakers to weigh the benefit of combining FV and RFT. However, we performed this systematic review and subgroup analysis following our protocol, which has already been registered on PROSPERO to avoid any unreasonable deviations, and we also followed the GRADE approach to evaluate the certainty of evidence. More importantly, only RCTs were included to ensure the validity of any results and conclusions.

Conclusion

Low to moderate certainty evidence suggests that FV does not have significant additional caries-preventive benefit for children (under 8 years old) when provided as an adjunct to daily tooth brushing with RFT (≥ 1000 ppm). There is insufficient evidence regarding the additional benefit of other PFA interventions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-021-03909-5.

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Declarations

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, informed consent is not required.

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