Review Article

Caries Research

Caries Res 2019;53:502–513
DOI: 10.1159/000499639

Received: November 14, 2018
Accepted: December 6, 2018
Published online: June 20, 2019

Fluoride Varnish and Dental Caries in Preschoolers: A Systematic Review and Meta-Analysis

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Keywords
Dental caries · Cariostatic agents · Topical fluorides · Preschool children · Meta-analysis

Abstract
The aim of this study was to assess the effectiveness of fluoride varnish (FV) in reducing dentine caries at the patient, tooth, and surface levels as well as caries-related hospitalizations in preschoolers. We performed a systematic review of clinical trials of FV, alone or associated with an oral health program, compared with placebo, usual care, or no intervention. Bibliographical search included electronic searches of seven databases, registers of ongoing trials, and meeting abstracts, as well as hand searching. We performed random-effects meta-analyses and calculated confidence and prediction intervals. The search yielded 2,441 records; 20 trials were included in the review and 17 in at least one meta-analysis. Only one study had low risk of bias in all domains. We found no study reporting on caries-related hospitalizations. At the individual level, the pooled relative risk was 0.88 (95% confidence interval [CI] 0.81, 0.95); this means that in a population of preschool children with 50% caries incidence, we need to apply fluoride varnish in 17 children to avoid new caries in one child. At the tooth level, the pooled weighted mean difference was –0.30 (95% CI –0.69, 0.09) and at the surface level –0.77 (95% CI –1.23, –0.31). Considering the prediction intervals, none of the pooled estimates were statistically significant. We conclude that FV showed a modest and uncertain anticaries effect in preschoolers. Cost-effectiveness analyses are needed to assess whether FV should be adopted or abandoned by dental services.

Introduction

Fluoride varnish (FV) is considered safe [Dos Santos et al., 2016; Garcia et al., 2017], well accepted by children [Oliveira et al., 2014], and easily delivered by health practitioners [Rozier et al., 2003]. These features, coupled with its assumed anticaries benefits, have contributed to

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it being widely recommended as the main professional fluoride therapy for dental caries prevention in preschoolers [European Academy of Paediatric Dentistry, 2009; Weyant et al., 2013; American Academy of Pediatric Dentistry, 2017].

In some countries, dentists often treat children with severe early childhood caries in hospitals under general anesthesia, and there are claims that FV substantially reduces the incidence of caries to the point that it may even reduce caries-related hospitalizations and use of medical services. Indeed, at least two randomized controlled trial protocols published their intention to assess these claims [Lawrence et al., 2008; Quissell et al., 2014].

Empirical evidence on the effectiveness of FV from experimental studies is equivocal. Some systematic reviews on the subject have important limitations, especially regarding the comprehensiveness of their bibliographical searches [Rozier, 2001; Strohmenger and Brambilla, 2001; Petersson et al., 2004; Azarpazhooh and Main, 2008; Carvalho et al., 2010; Chou et al., 2013; Twetman and Dhar, 2015; Gao et al., 2016; Mishra et al., 2017] and the lack of assessment of the risk of bias in the primary studies included [Weyant et al., 2013; Lenzi et al., 2016]. Another systematic review needs updating [Marinho et al., 2013].

Usually, FV applications are targeted at children with high risk of caries, as FV is currently considered complementary to other forms of fluoride use, such as fluoridated water and toothpaste [Weyant et al., 2013]. However, more recent clinical trials on the subject, in low [Jiang et al., 2014; Tickle et al., 2017] and high caries risk populations [Agouropoulos et al., 2014; Oliveira et al., 2014; Anderson et al., 2016; Braun et al., 2016; Muñoz-Millán et al., 2018], have failed to show a protective effect of FV applications.

The aims of this study were to assess the effectiveness of FV in reducing the risk of developing new dentine caries lesions and caries-related hospitalizations in preschoolers and to assess whether its effectiveness is influenced by baseline caries levels.

Materials and Methods

Protocol Registration and Review Reporting

The protocol of this review has been registered at Prospero (CRD42016048599). We reported this review according to the PRISMA guidelines [Liberati et al., 2009].

Study Design

We performed systematic review and meta-analyses of individual or cluster randomized or quasi-randomized controlled trials with a follow-up of at least 1 year.

Eligibility Criteria

Participants were children up to 71 months of age (preschoolers). The interventions included FV – alone or associated with an oral health program – compared to placebo, usual care, or no intervention. Outcomes were caries at dentine level in the primary dentition assessed by any caries index and/or measurement of disease occurrence and hospitalizations due to caries. Short-term (allergy, itch, discomfort) and long-term (dental fluorosis) adverse effects were considered.

Search Strategy

For the electronic search, the databases consulted were the Cochrane Central Register of Controlled Trials, MEDLINE via PubMed, Web of Science, EMBASE, SCOPUS, LILACS, and BBO. Sources of grey literature included meeting abstracts of the International Association for Dental Research (2001–2018) and the European Organisation for Caries Research (1998–2018), Open Grey, EThOS, the New York Academy of Medicine (GreyLit Report), and Banco de Teses CAPES. The following registers of ongoing trials were searched: Current Controlled Trials, ClinicalTrials.gov, EU Clinical Trials Register, Australia New Zealand Clinical Trials Registry, and Registro Brasileiro de Ensaios Clínicos. The search strategy was developed for MEDLINE via PubMed and adapted for the other databases and included controlled vocabulary and free terms (online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000499639). References of eligible trials and systematic and narrative reviews on the subject were checked in order to detect potential studies. There were no idiom restraints. Hand searching was performed in nine dental journals and two medical journals (online suppl. Appendix 2) starting from the date of last update available at the Cochrane Master List of Journals Being Searched. All electronic and hand searches were last updated in July and August 2018, respectively.

Data Collection and Analysis

Two reviewers (A.P.P.S. and F.S.O.S.) independently extracted data regarding characteristics of study design, participants, interventions, outcomes, length of follow-up, adverse effects, and risk of bias. A third reviewer (B.H.O.) solved disagreements. We used the Cochrane risk of bias tool and the assessment included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, baseline balance, and diagnosis reliability.

Our outcomes were the proportion of children who developed new dentine caries lesions and caries-related hospitalizations (individual level), and the number of primary teeth and tooth surfaces that developed dentine caries lesions. These outcomes at the tooth and surface levels were measured using the indexes decayed, missing, and filled teeth (dmft) and decayed, missing, and filled surfaces (dmfs). Meta-analyses at the individual level were performed using relative risk (RR), and at the tooth and surface levels prevented fraction (PF) and weighted mean difference (WMD). The number needed to treat (NNT) for an additional beneficial outcome was derived from the pooled RR and the median caries incidence in the control groups [Schünemann et al., 2011].

Due to the heterogeneity observed, we performed meta-analyses using a random-effects model and estimated prediction intervals [Borenstein et al., 2009]. We used the Fieller method to calculate the 95% confidence intervals (CIs) for the PFs [Abrams et al.,

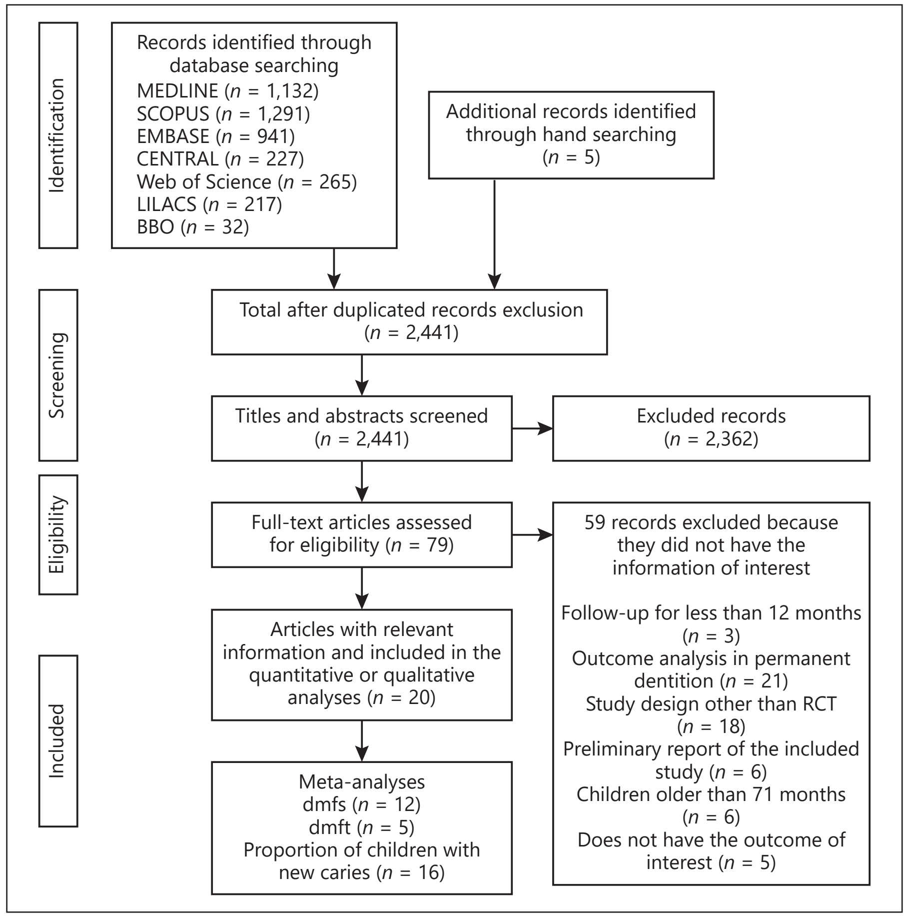

Fig. 1. Flow diagram showing the process of identifying, screening, assessing for eligibility, excluding, and including studies. CENTRAL, Cochrane Central Register of Controlled Trials; dmfs, decayed, missing, and filled surfaces; dmft, decayed, missing, and filled teeth; RCT, randomized controlled trial.

1972]. For the meta-analyses of the WMD we used either the final dmfs/dmft or the net increment, depending on the data reported in the included studies [Deeks et al., 2011]. In two studies [Weintraub et al., 2006; Yang et al., 2008] there were two FV intervention groups, so we combined them according to Higgins and Deeks [2011]. In order to assess whether baseline caries levels could influence the effectiveness of FV, we performed a meta-regression using the RR as the outcome variable and the mean baseline dmfs as the potential effect modifier. Publication bias was investigated using funnel plot and Egger's regression. All analyses were carried out in STATA 13.1 (StataCorp LP, College Station, TX, USA).

Results

After excluding duplicates, 2,441 records were retrieved from electronic and hand searches; 79 were considered relevant and the full-text articles were obtained. Fifty-nine full-text articles were excluded, and 20 studies were included: 19 in the qualitative analysis and 17 in at least one meta-analysis (online suppl. Appendix 3). Figure 1 shows the flow diagram of all reports that were identified, screened, assessed for eligibility, excluded, and included in this review.

The studies in this review were conducted in 13 different countries: Australia, Brazil, Canada, Chile, China, Germany, Greece, Iran, Ireland, Poland, Scotland, Sweden, and the USA. Randomization was performed at the individual level in 14 studies [Holm, 1979; Frostell et al., 1991; Chu et al., 2002; Borutta et al., 2006; Weintraub et al., 2006; Yang et al., 2008; Agouropoulos et al., 2014; Jiang et al., 2014; Oliveira et al., 2014; Memarpour et al., 2015, 2016; Tickle et al., 2017; Muñoz-Millán et al., 2018; McMahon et al., 2018] and at the cluster level in six studies [Grodzka et al., 1982; Petersson et al., 1998; Lawrence et al., 2008; Slade et al., 2011; Anderson et al., 2016; Braun et al., 2016]. The total number of children randomized was 16,877, and 13,658 were included in the analyses. The proportion of caries-free children at baseline varied from 0% [Chu et al., 2002] to 100% [Weintraub et al., 2006; Memarpour et al., 2015, 2016; Tickle et al., 2017; Muñoz-Millán et al., 2018]. Mean baseline dmfs and dmft varied from 0 [Weintraub et al., 2006; Tickle et al., 2017] to 22.8

Table 1. Characteristics of the interventions and exposure to other sources of fluoride in the included studies

First author, country	Year	Test group		Control group	Follow-up	Other sources of fluoride exposure in test and control groups
		fluoride varnish	application interval			
Agouropoulos, Greece	2014	Fluor Protector (0.9% difluorosilane) + oral health education + supervised toothbrushing	6 months	biannual application of placebo varnish + oral health education + supervised toothbrushing	24 months	1,000 ppm fluoride toothpaste
Anderson, Sweden	2016	Duraphat (5% sodium fluoride) + oral health education + dietary counseling	6 months	usual care + oral health education + dietary counseling	24 months	1,000–1,450 ppm fluoride toothpaste
Borutta, Germany	2006	group A: Fluoridin N5 (5% sodium fluoride) + oral health education; group B: Duraphat (5% sodium fluoride) + oral health education	6 months	no intervention + oral health education	24 months	500 ppm fluoride toothpaste
Braun, USA	2016	3M ESPE Vanish (5% sodium fluoride) + oral health education	3 months	usual care	36 months	1,100 ppm fluoride toothpaste
Chu, China	2002	Duraphat (5% sodium fluoride) + oral health education	3 months	water as a placebo + oral health education	30 months	fluoride toothpaste
Frostell, Sweden	1991	Duraphat (5% sodium fluoride)	6 months	not mentioned	24 months	fluoride toothpaste
Grodzka, Poland	1982	Duraphat (5% sodium fluoride)	6 months	no intervention	24 months	very low exposure to fluoride from sources other than Duraphat
Holm, Sweden	1979	Duraphat (5% sodium fluoride) + oral health education for caries-free children only	6 months	no intervention + oral health education for caries-free children only	24 months	fluoride toothpaste used by most children; fluoride tablets used by some children
Jiang, China	2014	Clinpro White Varnish (5% sodium fluoride) + oral health education + supervised toothbrushing	6 months	toothpaste without fluoride as a placebo + oral health education + supervised toothbrushing	24 months	fluoridated drinking water; 500 ppm fluoride toothpaste
Lawrence, Canada	2008	Duraflor (5% sodium fluoride) + oral health education	6 months	no intervention + oral health education	24 months	not mentioned
McMahon, Scotland	2018	Duraphat (5% sodium fluoride)	6 months	usual care	24 months	fluoride toothpaste
Memarpour, Iran	2015	DuraShield (5% sodium fluoride) + oral health education + dietary counseling	4 months	placebo water-based colored solution + oral health education + dietary counseling	12 months	water fluoridation level <0.7 ppm
Memarpour, Iran	2016	DuraShield (5% sodium fluoride) + oral health education + supervised toothbrushing + dietary counseling	6 months	water-based colored solution as a placebo + oral health education + supervised toothbrushing + dietary counseling	12 months	water fluoridation level <0.7 ppm
Muñoz-Millán, Chile	2018	Profluorid Varnish (5% sodium fluoride)	6 months	placebo varnish	24 months	500 ppm fluoride toothpaste
Oliveira, Brazil	2014	Duraphat (5% sodium fluoride)	6 months	placebo varnish	24 months	fluoridated drinking water; 1,450 ppm fluoride toothpaste

Table 1 (continued)

First author, country	Year	Test group		Control group	Follow-up	Other sources of fluoride exposure in test and control groups
		fluoride varnish	application interval			
Petersson, Sweden	1998	Fluor Protector (0.1% difluorosilane) + oral health education + dietary counseling	6 months	oral health education + dietary counseling; fluoride tablets were recommended for children in the control group determined to be at risk or with previous caries	24 months	low fluoride levels (0.1 ppm) in drinking water; fluoride toothpaste
Slade, Australia	2011	Duraphat (5% sodium fluoride) + oral health education + dietary counseling + 500 ppm fluoride toothpaste	6 months	no intervention	24 months	most children had <0.6 ppm fluoride in drinking water
Tickle, Ireland	2017	Duraphat (5% sodium fluoride) + oral health education + dietary counseling + 1,450 ppm fluoride toothpaste	6 months	oral health education + dietary counseling	36 months	not mentioned
Weintraub, USA	2006	Duraphat (5% sodium fluoride)	6 months	individualized oral health education	24 months	fluoridated drinking water (~1 ppm)
Yang, China	2008	Fluor Protector 0.1% (difluorosilane); Fluor Protector 0.5% (difluorosilane)	6 months	deionized water	24 months	not mentioned

surfaces [Braun et al., 2016] and from 0 [Memarpour et al., 2016; Muñoz-Millán et al., 2018] to 6.57 teeth [Grodzka et al., 1982], respectively. Participants' age at the beginning of the study ranged from 6 months [Lawrence et al., 2008] to 5 years [Petersson et al., 1998; Lawrence et al., 2008; Agouropoulos et al., 2014; Braun et al., 2016]. The characteristics of the interventions in the included studies are detailed in Table 1.

The risk of bias in the studies is shown in Figure 2. Only one study [Jiang et al., 2014] had low risk of bias in all domains assessed. The older studies had a poorer performance, especially regarding selection bias. They also had more domains assessed as unclear risk of bias, which emphasizes a poorer reporting of these studies. Studies published in the last 10 years tended to have more domains assessed as low risk of bias. We could not assess the risk of bias of one of the studies included in a meta-analysis because we only had access to the abstract; the authors were contacted, but they were not able to provide the necessary information [McMahon et al., 2018].

We found no study reporting on caries-related hospitalizations. Figure 3 shows a forest plot which includes all 16 studies that reported the proportion of children who developed new dentine caries lesions. There are five different comparisons: FV versus placebo, usual care, or no intervention and two comparisons where FV was associated with an oral health program and distribution of toothpaste. When FV was compared to usual care (RR = 0.84; 95% CI 0.72, 0.98) or no intervention (RR = 0.85; 95% CI 0.73, 0.98), the results favored FV. However, this effect was not observed among the other comparisons, including the comparison between FV and placebo (RR = 0.86; 95% CI 0.72, 1.03). We obtained a pooled RR of 0.88 (95% CI 0.81, 0.95), which means an overall FV protection of 12%. The results of all comparisons, including the overall pooled estimate, were not statistically significant when we considered the prediction intervals. The prediction interval for the pooled RR was 0.68 to 1.14, which means that given the current data, the RR of a future study may be as low as 0.68 and as high as 1.14. The NNT was 17 (95% CI 11, 40), in populations where 50% of children developed new dentine caries.

We obtained pooled PFs of 24.15% (95% CI 12.91, 35.38) and 31.13% (95% CI 21.08, 41.18) for dmfs and dmft data, respectively. Meta-analyses using the WMD for dmfs and dmft resulted in pooled estimates of –0.77 (95% CI –1.23, –0.31) and –0.30 (95% CI –0.69, 0.09), respectively. Results regarding subgroup analyses are depicted in Table 2.

Online supplementary Appendix 4 shows the adverse events associated with FV applications reported in 13 studies. These included vomiting, unpleasant smell, burning sensation, and dissatisfaction with tooth appearance after varnish application. Only one study actively investigated long-term adverse events. The participants of this study were recruited 5 years after the trial ended in order to assess dental fluorosis incidence; there was no significant difference between those who had received FV and those who had received placebo varnish [Oliveira et al., 2014; Dos Santos et al., 2016].

The results of the meta-regression showed that the increase in one unit of mean baseline dmfs led to a 1% increase in RR (95% CI 0.99, 1.02), which was not statistically significant. Adjusted R^2 showed that baseline caries levels explained 25.87% of between-study variance (online suppl. Appendix 5).

The funnel plot showed asymmetry among the studies (online suppl. Appendix 6), and Egger's regression coefficient was –1.60 (95% CI –2.44, –0.75). The *p* value for the null hypothesis test of no small-study effects was 0.001.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Baseline balance (selection bias)	Diagnosis reliability (misclassification bias)
Agouropoulos, 2014	+	+	+	+	+	?	+	+
Anderson, 2016	+	?	–	–	?	?	+	+
Borutta, 2006	?	?	?	+	–	?	–	?
Braun, 2016	+	?	–	+	+	–	+	+
Chu, 2002	–	–	+	+	?	?	+	+
Frostell, 1991	?	?	–	?	?	?	?	?
Grodzka, 1982	?	?	?	?	?	?	+	?
Holm, 1979	–	–	–	+	+	?	+	?
Jiang, 2014	+	+	+	+	+	+	+	+
Lawrence, 2008	+	?	–	+	+	–	+	+
Memarpour, 2015	+	?	+	+	–	?	?	+
Memarpour, 2016	+	+	+	–	?	?	+	+
Muñoz-Millán, 2018	+	+	+	+	–	?	+	+
Oliveira, 2014	+	+	+	+	+	?	+	+
Petersson, 1998	+	?	–	?	–	?	+	?
Slade, 2011	+	+	–	–	+	?	–	+
Tickle, 2017	+	+	–	+	+	+	+	+
Weintraub, 2006	+	+	–	+	–	?	?	+
Yang, 2008	?	?	+	+	+	?	?	+

Fig. 2. Assessment of the risk of bias in the included studies.

Discussion and Conclusion

This systematic review assessed FV effectiveness in preschoolers using qualitative and quantitative syntheses. At the surface level, the results showed a statistically significant difference favoring FV. Overall, the lower increment of caries in the varnish group was of one surface per child or less. This difference is possibly clinically irrelevant. At the tooth level, no significant difference was observed between children who received FV and those who did not. Finally, at the individual level, the meta-analysis showed that the risk of developing new dentine caries lesions was reduced by 12% among the children who received FV when compared to those who did not. This was a rather modest benefit as a large number of the children developed new dentine caries lesions, regardless of FV use.

The PF is usually the preferred method to compute dmfs and dmft data in meta-analyses assessing dental caries as the outcome, as its interpretation is presumably easy and it enables the combination of different ways of caries measurement (dmfs, dfs, ds, dmft, dft, dt). However, as it is a relative measure, the PF fails to show the true differences in caries increment observed between the groups, and apparent substantial PFs may in fact be clinically irrelevant in terms of actual caries reductions. In addition, PF calculations are very unstable when there are studies with caries increment close to zero. For example, the study by Jiang et al. [2014] had an increment of 0.1 dmft in the control group and 0.2 in the FV group, and these increments led to a PF of –100 with a 95% confidence interval from –1.056 to 55. This enormous confidence interval gave the Jiang et al. [2014] study a nearly zero weight in the PF dmft meta-analysis, while in the WMD dmft meta-analysis its weight was the largest of the five

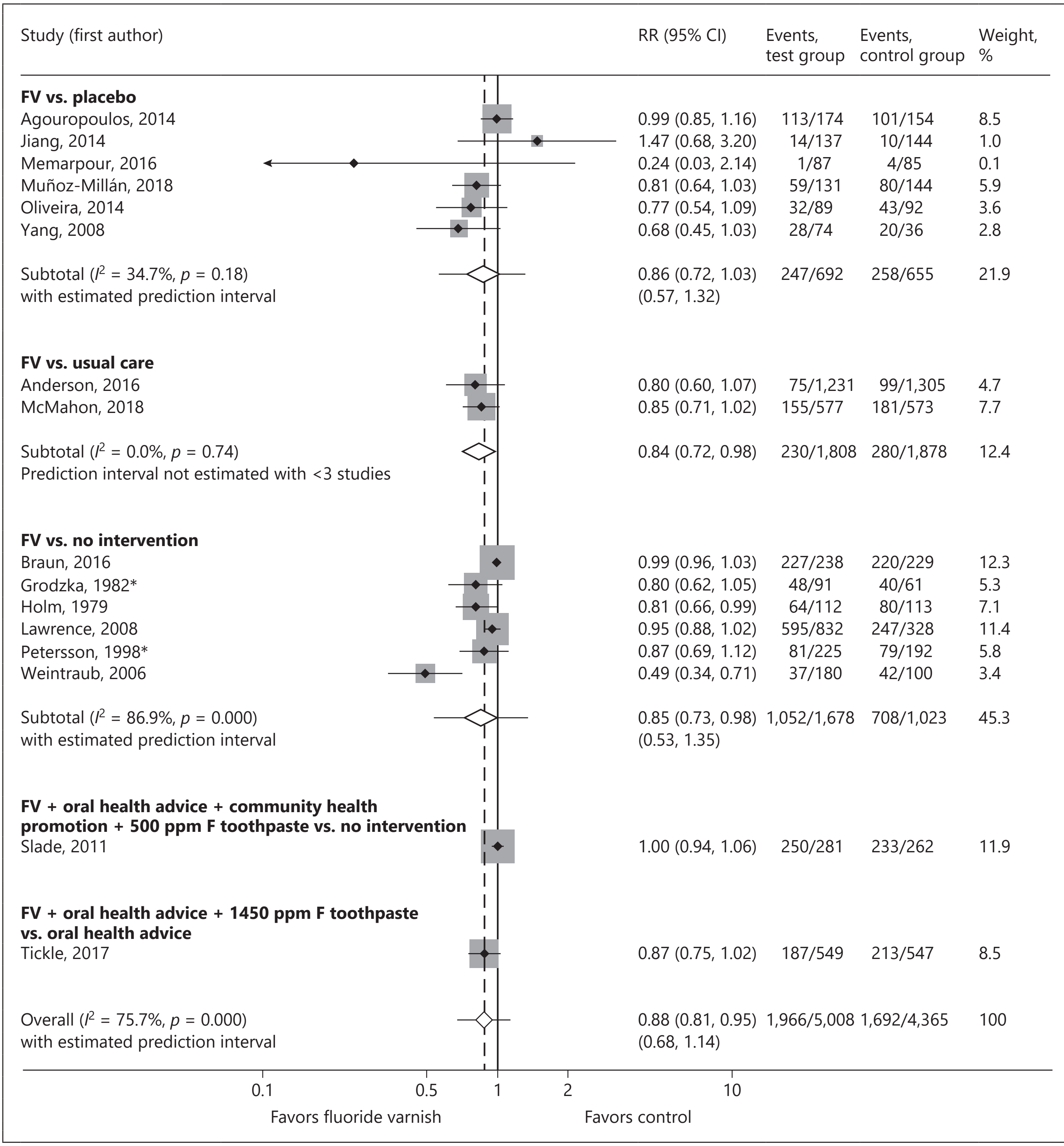

Fig. 3. Meta-analysis of the global RR and according to the comparisons in each subgroup. Weights are from random-effects analysis. * Effective sample size. CI, confidence interval; FV, fluoride varnish; RR, relative risk.

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DOI: 10.1159/000499639

Table 2. Mean number and SD of baseline and final dmfs and dmft; pooled PFs and WMDs and their 95% CIs and PIs

First author, year	Test group				Control group				PF, % (95% CI)	WMD (95% CI)
	n	mean (SD) baseline	mean (SD) final	mean (SD) increment	*n*	mean (SD) baseline	mean (SD) final	mean (SD) increment		
dmfs data[1]										
FV vs. placebo										
Agouropoulos, 2014	174	3.1 (7.1)		2.9 (5.3)	154	2.5 (5.6)		3.0 (5.2)	3.33 (–44.04, 35.04)	–0.10 (–1.24, 1.04)
Chu, 2002	61	4.71 (3.50)	–	0.7 (0.94)	62	4.36 (2.81)	–	1.58 (1.97)	55.7 (29.11, 72.84)	–0.88 (–1.42, –0.34)
Oliveira, 2014	89	0.6 (1.6)	–	1.8 (3.9)	92	1.0 (2.1)	–	2.5 (4.0)	28 (–23.87, 62.64)	–0.70 (–1.85, 0.45)
Yang, 2008	74	1.55 (0.79)	2.19 (1.25)	–	36	1.54 (0.61)	2.85 (1.88)	–	23.16 (–0.74, 39.57)	–0.67 (–1.34, 0.01)
Subtotal									30.49 (8.01, 52.96) (95% PI –58.21, 119.19)	–0.71 (–1.09, –0.33) (95% PI –1.53, 0.11)
FV vs. usual care										
Anderson, 2016	1,231	–	–	0.4 (2.2)	1,305	–	–	0.3 (1.6)	–33.33 (–105.56, 14.52)	0.10 (–0.05, 0.25)
FV vs. no intervention										
Braun, 2016	238	19.9 (21.05)	28.5 (21.1)	–	229	22.8 (24.71)	31.2 (21.3)	–	8.65 (–3.93, 19.79)	–2.70 (–6.55, 1.15)
Grodzka, 1982	90	9.32 (7.51)	–	6.35 (4.98)	61	9.96 (7.08)	–	6.71 (5.22)	5.37 (–23.15, 26.38)	–0.36 (–2.03, 1.31)
Holm, 1979	112	1.05 (2.34)		2.10 (2.75)	113	0.71 (1.62)		3.74 (4.62)	43.85 (21.35, 60.21)	–1.64 (–2.63, –0.65)
Lawrence, 2008	832	12.89 (16.01)	–	11 (14.99)	328	11.80 (16.29)	–	13.48 (15.03)	18.40 (4.63, 29.76)	–2.48 (–4.40, –0.56)
Petersson, 1998	225	1.13 (2.36)	1.30 (2.46)	–	192	1.18 (3.20)	1.39 (2.66)	–	6.47 (–37.30, 35.46)	–0.09 (–0.58, 0.40)
Weintraub, 2006	180	0	0.7 (1.95)	–	100	0	1.7 (3.1)	–	58.82 (28.16, 77.42)	–1.00 (–1.67, –0.33)
Subtotal									23.70 (7.86, 39.55) (95% PI –27.46, 74.87)	–1.01 (–1.77, –0.25) (95% PI –3.21, 1.19)
FV + oral health advice + community health promotion + 500 ppm F toothpaste vs. no intervention										
Slade, 2011	344	4.9 (6.62)	–	7.3 (10.4)	322	4.6 (5.95)	–	9.6 (10.07)	23.96 (8.42, 37.47)	–2.30 (–3.86, –0.74)
Pooled estimate									24.15 (12.91, 35.38) (95% PI –12.02, 60.31)	–0.77 (–1.23, –0.31) (95% PI –2.25, 0.71)
dmft data										
FV vs. placebo										
Jiang, 2014	137	–	–	0.2 (0.9)	144	–	–	0.1 (0.5)	–100 (–1,056.11, 55.10)	0.10 (–0.07, 0.27)
Muñoz-Millán, 2018	131	0	1.6 (2.04)	–	144	0	2.1 (2.76)	–	23.81 (–4.02, 44.31)	–0.50 (–1.07, 0.07)
Yang, 2008	74	0.91 (0.41)	1.19 (0.64)	–	36	0.92 (0.37)	1.87 (0.83)	–	36.36 (22.71, 47.28)	–0.68 (–0.99, –0.37)
Subtotal									33.73 (22.78, 44.68) (95% PI –37.25, 104.72)	–0.34 (–0.93, 0.25) (95% PI –7.57, 6.89)
FV vs. no intervention										
Grodzka, 1982	90	6.33 (3.66)	–	2.04 (1.98)	61	6.57 (3.65)	–	2.46 (2.13)	17.07 (–12.49, 38.42)	–0.42 (–1.09, 0.25)
FV + oral health advice vs. oral health advice										
Memarpour, 2015	29	0	0.30 (0.90)	–	31	0	0.42 (0.99)	–	28.57 (–365.42, 106.77)	–0.12 (–0.60, 0.36)
Pooled estimate									31.13 (21.08, 41.18) (95% PI 14.81, 47.44)	–0.30 (–0.70, 0.09) (95% PI –1.69, 1.09)

CI, confidence interval; dmfs, decayed, missing, and filled surfaces; dmft, decayed, missing, and filled teeth; FV, fluoride varnish; *n*, numbers of participants included in the analysis; PF, prevented fraction; PI, prediction interval; SD, standard deviation; WMD, weighted mean difference. [1] We excluded Tickle 2017 from this analysis as they calculated and reported the mean dmfs increment only in children who developed caries (subgroup analysis).

included studies. This PF instability may also explain the discrepancy between the statistical significance of the PF and WMD results at tooth level. These are the reasons why the PF results in the present meta-analyses should not be emphasized and instead we should focus on the dmfs and dmft meta-analyses that used WMD.

Due to the high clinical and statistical heterogeneity observed among the studies, we used a random-effects model and estimated prediction intervals. While the confidence interval quantifies the accuracy of the point estimate, the prediction interval addresses the actual dispersion of effect sizes. These are two distinct and not interchangeable issues. Therefore, whenever we use a random-effects model, we should also estimate the prediction interval in order to allow inferences that are more informative in the meta-analyses [Borenstein et al., 2009; IntHout et al., 2016]. Based on the prediction intervals, only the pooled PF at tooth level attained statistical significance.

Of particular interest is the difference between the results of the studies that used placebo, showing no beneficial effect of FV, and those that did not, with a small beneficial effect. Without a placebo we cannot be confident that the attention and treatment overall were equal in the FV and in the control groups. When children in the control group received no intervention, questions remained as whether the fewer caries lesions in the FV group were due to the varnish itself or due to other influences of the overall care and attention offered only to the test group.

The results of our meta-regression showed that baseline caries levels explained a small percentage of between-study variance, which means that other factors besides baseline caries levels led to heterogeneous treatment effects among the trials included in our review, which contradicts the current recommendations to apply FV in high-risk children. In addition, the high-risk preventive strategy faces important challenges [Rose, 1985]. Past caries experience is still the best single predictor of future caries increment, but even this best predictor does not accurately identify those children who are at high and low risk of developing new caries [Hausen and Baelum, 2015]. In addition, even if we were able to accurately identify children at high risk, they would have to adhere to preventive visiting schedules. This is often unrealistic, as illustrated by the large number of losses to follow-up in programs with this type of risk-based protocols [Featherstone and Chaffee, 2018]. Finally, taking the perspective of the whole population, most new caries usually affects the low-risk children because the high-risk children are a minority in the population [Batchelor and Sheiham, 2006].

In contrast with some previous systematic reviews on this subject [Rozier, 2001; Strohmenger and Brambilla, 2001; Petersson et al., 2004; Azarpazhooh and Main, 2008; Carvalho et al., 2010; Chou et al., 2013; Weyant et al., 2013; Twetman and Dhar, 2015; Gao et al., 2016; Lenzi et al., 2016; Mishra et al., 2017], we performed an exhaustive bibliographical search and a thorough assessment of the risk of bias in the included studies. In addition, we identified 10 new clinical trials that were not included in the 2013 Cochrane review on FV [Agouropoulos et al., 2014; Jiang et al., 2014; Oliveira et al., 2014; Memarpour et al., 2015; Anderson et al., 2016; Braun et al., 2016; Memarpour et al., 2016; Tickle et al., 2017; McMahon et al., 2018; Muñoz-Millán et al., 2018].

Medical and dental associations suggest that FV may reduce hospitalizations due to caries. The protocols of two clinical trials [Lawrence et al., 2008; Quissell et al., 2014] planned to assess this outcome, but the results related specifically to this outcome have not been reported in their publications. In any case, it seems rather implausible that the questionable modest caries-preventive effect of FV revealed by clinical trials could lead to fewer caries-related hospitalizations.

Despite the uncertainty around the size of the effect estimates and the small effect size, FV could still be a cost-effective alternative in certain circumstances. However, there is a lack of cost-effectiveness evidence regarding FV applications in the primary dentition. FV applications during the first 3 years of life did not save money, but seemed to approach cost savings by 4 years of age [Quiñonez et al., 2006]. However, as pointed out by these authors, limited data were available to derive the probabilities and costs used in this cost-effectiveness analysis, and FV effectiveness was calculated using data from a single study [Holm, 1979] carried out in the seventies. One of the included studies in our review showed that the costs of providing biannual FV applications, oral health advice, and distribution of toothbrushes and 1,450 ppm F toothpaste outweighed savings in treatment over a period of 3 years [O'Neill et al., 2017; Tickle et al., 2017]. A more recent study updated the Cochrane evidence to obtain more recent FV effectiveness data and applied it to different caries risk scenarios considering 12-year-olds in Germany [Schwendicke et al., 2018]. The authors concluded that applying FV in the dental office is probably not cost-effective in low-caries-risk populations, suggesting that it should be restricted to high-caries-risk populations or provided in nonclinical settings. However, these results refer to the permanent and not to the primary dentition. More cost-effectiveness analyses should be carried out in different populations and application settings using updated FV effectiveness estimates. Our results reinforced the need for FV cost-effectiveness analyses before its adoption by dental services. In a population where 50% of preschool children develop new caries (the median incidence in the control groups in the present review) we would need to treat 17 children with FV in order to avoid new caries in one child. Is avoiding caries in 1,000 children worth the cost of applying varnish in 17,000 children, considering all the direct and indirect savings of avoiding caries and all the direct and indirect costs of unnecessary FV applications?

Despite all the efforts we made, it was not possible to obtain the full-text articles of three potentially eligible abstracts we found through hand searching [Zhu, 2005; Mascarenhas et al., 2009; Rong et al., 2016] and one protocol registered at ClinicalTrials.gov (NCT00475618) and checked as completed trial status [Cadavid, 2012]. Also, although we developed very sensitive electronic search strategies, we cannot guarantee that we were able to identify all studies that would meet our eligibility criteria. If missing studies were a random sample of all relevant studies, this would only affect the precision of our effect estimates. However, according to our publication bias analyses, we cannot rule out the possibility of publication bias in this review. Despite the heterogeneity, which can affect the validity of publication bias analyses, funnel plot and Egger's regression suggest that we may have missed small studies with nonsignificant results. Had these studies been included, our effect estimates would have been even smaller and provided stronger evidence against FV.

Our results showed that FV effectiveness is lower in more recent trials than in older trials. Maybe this is due to the higher risk of bias in the older studies, especially selection bias, which can overestimate the effect of the treatments [Schulz et al., 1995]. One could argue that in the past children were exposed to fewer sources of fluoride, which could make the effect of FV more prominent. However, it appears that the majority of the children in the included studies brushed their teeth with fluoride toothpaste.

Regarding FV safety, few unimportant short-term adverse effects of a local dental nature have been reported [Agouropoulos et al., 2014; Oliveira et al., 2014; Anderson et al., 2016]. The only long-term dental adverse effect investigated was dental fluorosis, which was not associated with FV applications during early childhood [Dos Santos et al., 2016]. Despite the widespread exposure to fluoride, the burden and the prevalence of dental caries have remained relatively stable between 1990 and 2015 [Kassebaum et al., 2017]. In the present review, a large number of the children developed new dentine caries lesions, regardless of FV use. The cause of dental caries, and of the increase in caries with age, is the excessive exposure to sugar, not the lack of fluoride exposure [Sheiham and James, 2015; Simón-Soro and Mira, 2015]. Sugar reduction is urgently needed as fluoride does not halt caries when sugar intake is high (≥10%) [Sheiham and James, 2014, 2015]. Our study highlighted that increasing the exposure to professionally applied fluoride through varnish made hardly any difference for the risk of developing new caries in children.

Acknowledgments

The authors thank the undergraduate dental students Patricia Filizzola Dias and Paulo Rogério Nunes Barbosa for their valuable contribution in the hand searching for the primary studies and in the critical reading and evaluation of the previously published FV reviews.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brasil (CAPES), finance code 001. P. Nadanovsky receives financial support from the Brazilian National Research Council (CNPq grant number 306740/2015-0).

Author Contributions

F.S.O. Sousa, A.P.P. Santos, P. Nadanovsky, and B.H. Oliveira contributed to the conception and design of the study. All authors contributed to the acquisition, analysis, and interpretation of data, and drafting of the manuscript. All authors critically revised the manuscript for important intellectual content, gave final approval, and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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