

Cochrane reviews of randomized trials of fluoride therapies for preventing dental caries

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Abstract

AIM: To present the evidence summarized in the Cochrane fluoride reviews. **STUDY DESIGN:** An overview of the results of selected systematic reviews. **METHODS:** Relevant systematic reviews published in the Cochrane Database of Systematic Reviews (CDSR) were identified by searching 'The Cochrane Library issue 4, 2008', using the terms 'Fluoride' and 'Caries'. Complete Cochrane reviews assessing the effectiveness of any fluoride-based intervention for preventing caries were selected, and their main features and findings were reviewed. **RESULTS:** 14 papers were identified of which 11 were relevant full-text reviews. The results were assessed of 7 reviews published from 2002 to 2004 concerning the relative effectiveness of 4 topical fluoride treatments (toothpastes, gels, varnishes and mouthrinses) in preventing caries in children and adolescents. Comparisons in these reviews were made against non-fluoride controls, against each other, and against different combinations. Findings from 4 reviews published between 2004 and 2006, assessing other fluoride modalities (slow release devices, milk), specific comparison/site (fluoride varnishes versus sealants in occlusal surfaces), and particular population and caries outcome (fluorides for white spot lesions in orthodontic patients) were also assessed. The 7 reviews confirm a clear and similar effectiveness of topical fluoride toothpastes, mouthrinses, gels and varnishes for preventing caries, and show that additional caries reduction can be expected when another topical fluoride is combined with fluoride toothpaste. Evidence is insufficient to confirm the effectiveness of slow release fluoride devices and fluoridated milk. The comparative effectiveness of other modes of delivering fluoride, such as to orthodontic patients is also as yet unclear. Fissure sealants appear more effective than fluoride varnish for preventing occlusal caries but the size of the difference is unclear. **CONCLUSIONS:** The benefits of topical fluorides are firmly established based on a sizeable body of evidence from randomized controlled trials. The size of the reductions in caries increment in both the permanent and the primary dentitions emphasizes the importance of including topical fluoride delivered through toothpastes, rinses, gels or varnishes in any caries preventive program. However, trials to discern potential adverse effects are required, and data on acceptability. Better quality research is needed to reach clearer conclusions on the effects of slow release fluoride devices, milk fluoridation, seal-

ants in comparison with fluoride varnishes, and of different modes of delivering fluoride to orthodontic patients.

Introduction

Fluoride (F) based caries preventive interventions, especially in the form of toothpaste, are the most significant and widespread form of caries control used globally. F-toothpaste is the single factor most commonly linked to reported decline in caries prevalence seen in many countries since the 1970s, and is used by more than 500 million people worldwide. However, its cost prohibits its more widespread use in many low- and middle-income countries. One of WHO's policies is to support the widespread use of affordable F-toothpaste in developing countries [WHO, 2008].

In addition, F has been the subject of basic and clinical research for well over half a century and a very large number of formal studies are available. These attempt to address uncertainties about the effects of the many forms of F interventions, making its use the most vigorously evaluated approach to reduce dental caries. This can be illustrated by the results of a simple search performed in CENTRAL (The Cochrane Central Register of Controlled Trials), the most comprehensive source of reports of trials available). In the last 6 decades more trial reports have been published on fluorides than on any other caries preventive intervention (Table 1).

Systematic reviews are increasingly common in the dental literature and are often the most robust type of research evidence to inform decisions about health care interventions.

Such reviews, include a large body of experimental evidence of good quality from randomised trials (RCTs). Large well-designed RCTs, are placed at the top of the hierarchy of research evidence about effectiveness used by guideline development organisations worldwide. This is because the strongest scientific evidence on effectiveness will come from such quantitative study designs that are likely to provide the best means of minimizing bias and the effects of confounding. They also have a large enough number of observations compiled together to control for random errors (or chance effects).

Many systematic reviews of the evidence on the effects of F in its various forms for caries prevention have become available, compiling hundreds of reports of randomized con-

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trolled trials published since the 1950s (for F toothpastes, mouthrinses, gels and varnishes), as well as other types of studies (non-randomized evidence for F-water). Recommendations systematically developed for the appropriate use of F for caries are increasingly being made in clinical practice guidelines. These are based largely on the results of the systematic reviews published through the last decade [van Rijkom et al., 1998; McDonagh et al., 2000; Bartizek et al., 2001; Strohmenger and Brambilla, 2001; Chaves and Vieira da Silva, 2002; Marinho et al., 2002a,b, 2003a,b,c, 2004a,b; Ammari et al., 2003; Twetman et al., 2003; Benson et al., 2004; Petersson et al., 2004; Steiner et al., 2004; Twetman et al., 2004; Yeung et al., 2005; Bonner et al., 2006; Hiiri et al., 2006].

Cochrane reviews are systematic reviews that employ rigorous research methods, and have been shown to be of higher methodological quality than other systematic reviews [Jadad et al., 1998; Glenny et al., 2003; Jørgensen et al., 2008]. They focus primarily, but not solely, on synthesizing evidence from randomized trials. The Cochrane Collaboration was established in the early 1990s, and the growth in systematic reviews through the last decade is in part due to its work. All Cochrane reviews have the same structure, are prepared according to standard guidelines, and are supported by the use of standard software. They are published in full in The Cochrane Library following an editorial process which is common to all reviews, and they are maintained / updated regularly. The reviews encompass all areas of health care, with one of the 52 Cochrane Review Groups available in different specialties taking editorial responsibility for each review.

Cochrane reviews are not intended to provide recommendations for practice in any particular clinical context. However, all Cochrane reviews include an Authors' Conclusions section. The latter is divided into the Implications for Practice and the Implications for Research, which are rich sources of information for anyone making decisions and recommendations about health care practice and future research [Clarke, 2008]. The degree of certainty they provide, however, depends on the quality of the evidence that has been identified and included in the review, where the level of quality of evidence will not only depend on the risk of bias (methodological quality) and the directness of the evidence, but also on the heterogeneity/consistency and precision of the findings, amongst other factors [Schünemann et al., 2008].

The aim of this paper was to identify all available Cochrane reviews assessing the effectiveness of F-based interventions for the prevention of dental caries in children/adolescents and to review their main methodological features and findings, facilitating their subsequent interpretation and use for the development of practice recommendations.

Materials and Methods

The Cochrane Database of Systematic Reviews (CDSR), in Issue 4, 2008 of The Cochrane Library, was searched for relevant systematic Cochrane reviews using the terms 'Fluoride' and 'Caries'. All records electronically identified were scanned by title, and all reviews assessing primarily the effectiveness of any F-based intervention for caries were selected. Reports of ongoing Cochrane reviews in the form of protocols were not considered. The main methodological features of the complete reviews are described followed by a qualitative compilation (overview) of the reviews' findings. These are presented mainly in terms of the caries-preventive effectiveness of the various F modalities assessed. Where reported, the factors influencing their effectiveness were assessed, their comparative effectiveness and effectiveness when used in combination, as well as their safety (and acceptability), in an attempt to account for any assessment of beneficial and undesirable (adverse) effects. The findings are summarised in Table 1.

Table 1. Number of reports according to different approaches for dental caries control, 1950-2008 (results from a search of CENTRAL, The Cochrane Library, Issue 4, 2008)

Study Modality	Number of papers
Fluorides + caries	948
Fissure sealants + caries	226
Chlohexidine + caries	138
Xylitol + caries	85
(Diet, sugar) + caries	165
(Oral hygiene, flossing) + caries	188
Oral health education + caries	55

Results

The search identified 14 papers, all reporting on Cochrane reviews of controlled trials produced under the auspices of the Cochrane Oral Health Group (COHG). One of these reports, a review that is outside the scope of this paper (Ozone therapy for treating caries), and two others were reports of relevant reviews under development, in the form of protocols. These were not considered further (Salt-F for preventing dental caries, and topical-F for treating dental caries). There were 11 complete Cochrane systematic reviews on the effects of F interventions identified in the search and assessed further (Table 2).

A series of 7 Cochrane systematic reviews published from 2002 to 2004 are considered herein. They bring together and summarise the large body of knowledge from the available experimental evidence on the main modalities of self-applied and professionally-applied topical Ftherapies (TFT) currently used for the prevention of dental caries in children and adolescents (F toothpastes, mouthrinses, gels and varnishes)

[Marinho et al., 2002a,b, 2003a,b,c, 2004a,b]. Examined individually were 4 reviews published subsequently (2004 to 2006), assessing other F interventions and comparisons, and more specific populations and caries outcome measures. They assess the caries preventive effect of slow release F devices [Bonner et al., 2006], F milk [Yeung et al., 2005], sealants versus F varnishes [Hiiri et al., 2006] and F for white spot lesions during orthodontic treatment [Benson et al., 2004].

Cochrane reviews of topical fluorides. The first four reviews [Marinho et al., 2002a,b, 2003a,b,c, 2004a,b] in this series investigated the effectiveness of F gels, varnishes, rinses, or toothpastes using placebo or no-treatment controls and examined factors potentially influencing effectiveness. The fifth review was a summary of the first 4 reviews, with additional investigations of differences in effectiveness between F modalities based on meta-regression analyses using the treatments as covariates. The sixth review collated trials of head-to-head comparisons among the 4 treatments; and the 7th review also involved direct comparisons of these 4 treatments used in combination versus one form used alone (primarily any topical F plus F toothpaste versus F toothpaste alone).

The reviews were based upon the same comprehensive searches of published and unpublished evidence, with no language restrictions, and collated and critiqued the included trials using similar methodology and measures of effect. One of the advantages of the publication of a series of reviews in this manner, beyond the ability to bring all the evidence together in a consistent way, is that sensible comparisons between the different topical F treatments could be made, and results were not interpreted in isolation.

The main outcome used in all reviews was caries increment, as measured by the change in decayed, missing and filled permanent tooth surfaces (DMFS). To compare DMFS increment in two groups, an effect measure commonly used in caries trials was chosen, the prevented fraction (PF), that is the difference in mean caries increments between the treatment and control groups divided by the mean increment in the control group. Decisions about whether trials were included, quality assessment and data extraction were duplicated in a random sample of one third of the studies.

Major issues considered in the series of topical F reviews were firstly the potential benefits to be expected from topical F (in terms of the size of the reduction in caries increments that may be obtained from the single use of the various interventions). Secondly, how the benefits of topical F therapy may vary according to the influence of potentially important effective modifiers in terms of the possible dependence of the caries preventive effect of topical F on background exposure to F sources other than the study options. This would be on baseline (initial) caries levels, and on intervention features, such as F content and frequency of use. Finally,

whether the benefits differ among the various interventions and when these are used in combination. Potential adverse effects, such as dental fluorosis, oral allergies, tooth staining or symptoms of acute toxicity were also considered in the reviews.

The main findings from the series of topical F reviews were:

Effect on caries increment in permanent tooth surfaces- placebo/no-treatment comparisons. The first question addressed by the reviews was how effective was the use of topical F as toothpaste, mouthrinse, gel and varnishes for the prevention of caries in children and adolescents compared with placebo or no-treatment. Table 3 shows the results for placebo and no-treatment comparisons from each of the 4 individual reviews on F gel, varnish, mouthrinse and toothpaste, alongside the results for placebo comparisons only, from the summary review. All 4 topical F were found to be effective. The average D(M)FS prevented ranged from 24% (95% CI, 21% to 28%) for F toothpaste, to 46% (95% CI, 30% to 63%) for F varnishes. In terms of absolute caries reductions per year, in populations with caries increments of around 2 D(M)FS per year, these ranged from 0.46 for F gels to 0.74 for F varnishes (mouthrinses 0.56, toothpaste 0.62). However, conclusions on treatment effects were made on a clearer basis in placebo controlled trials, as caries reductions are overestimated in no-treatment control topical F trials, which are not double-blind and are likely to be of lower methodological quality. This was clearly shown by the results of the 5th review, which compiled and analyzed results of the 4 individual reviews together, and in the F gel review. The pooled D(M)FS prevented for F gel was 21% (95% CI, 14% to 28%), based exclusively on 13 placebo-controlled studies (one trial originally included in the gel review was excluded from the analysis in the summary review because it had a poor estimate of PF). This was significantly different from the 38% (95% CI, 0.23% to 0.53%) D(M)FS PF for the 9 studies that compared the gel with a no-treatment control group.

Effect on caries increment on primary tooth surfaces- placebo/no-treatment comparisons. These results are presented in Table 4 stratified by type of control group and TFT type. The conclusion that F varnish is effective for caries prevention in primary teeth had not been advanced in previous reviews. The average d(e/m)fs PF of 33% (95% CI, 19% to 48%) obtained for varnishes was based on 3 trials, 2 of which used no-treatment controls. Two placebo-controlled studies in the F gel review that tested self-applications of gel with a toothbrush assessed caries prevention on primary teeth. But these data were not pooled in that review due to missing statistics. One trial showed no difference in effect (a defs PF of -0.0055), while the other reported a sizeable effect favouring gels (a defs PF of 0.39). In addition, a large F toothpaste trial involving 2008 children (6 to 9 years) reporting on the number of new decayed or filled primary teeth per 100 ('df-rate'), showed a similarly large reduction in caries increment (37%, p. 0.001) favouring toothpastes. Pooled

Table 2. Cochrane Fluoride Reviews in the CDSR (The Cochrane Library, Issue 4, 2008).

Citation	Title
Series of 7 topical fluoride reviews	
Marinho et al., 2002a	(1st) Fluoride gels for preventing dental caries in children and adolescents
Marinho et al., 2002b	(2nd) Fluoride mouthrinses for preventing dental caries in children and adolescents
Marinho et al., 2003a	(3rd) Fluoride toothpastes for preventing dental caries in children and adolescents
Marinho et al., 2003b	(4th) Fluoride varnishes for preventing dental caries in children and adolescents
Marinho et al., 2003c	(5th) Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents
Marinho et al., 2004a	(6th) One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents
Marinho et al., 2004b	(7th) Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents
Other independent reviews	
Benson et al., 2004	Fluorides for the prevention of white spots on teeth during fixed brace treatment
Yeung et al., 2005	Fluoridated milk for preventing dental caries
Bonner et al., 2006	Slow-release fluoride devices for the control of dental decay
Hiiri et al., 2006	Pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents

Table 3. D(M)FS pooled estimates of topical fluoride treatment effects (measured as prevented fractions).

TFT type**	Prevented fraction	95% CI	TFT type***	Prevented fraction	95% CI
Varnish (7)	46%	30–63%	Varnish (3)	40%	09–72%
Gel (23)	28%	19–37%	Gel (13)	21%	14–28%
Rinse (34)	26%	23–30%	Rinse (30)	26%	22–29%
Toothpaste (70)*	24%	21–28%	Toothpaste (70)	24%	21–28%
All 4 TFTs (133)	26%	24–29%	All 4 TFTs (116)	24%	22–27%

CI = confidence interval; **number of placebo/no treatment comparisons; *** number of placebo comparisons.

Table 4. Primary teeth d(e/m)fs (pooled) estimates of treatment effects (all measured as prevented fractions).

TFT type**	Effect measure	95% CI	TFT type***	Effect measure	95% CI
Varnish (3)	33% PF	19–48%	Varnish (1)	20% PF	2–38%
Gel (2)	26% PF	-11–63%	Gel (2)	26% PF	-11–63%
Overall (5)	33% PF	22–44%	Overall (3)	27% PF	8–48%

CI = confidence interval; **number of placebo/no treatment comparisons; *** number of placebo comparisons.

Table 5. Factors potentially influencing effectiveness in the Cochrane fluoride toothpaste review (results from random effects meta-regression analyses of D(M)FS prevented fractions (PFs)).

Characteristic/factor (number of studies) Estimate (95% CI)	Interpretation
Mean initial caries (67) 0.7% (0.07 to 1.3%)	Increase in PF per unit increase in mean initial level of caries
Background fluorides (56) 0.6% (-6 to 8%)	Higher PF in presence of any back-ground fluoride (e.g. water F)
Fluoride content (69) 8.3% (1 to 16%)	Increase in PF per 1,000 ppm F
Frequency of tooth brushing (70) 14% (6 to 22%)	Increase in PF moving from once to twice a day
Supervision (70) -11% (-18 to -4%)	Lower PF with unsupervised tooth brushing

Table 6. D(M)FS (pooled) estimates of treatment effects (as PF) for direct comparisons between fluoride gels, varnishes, rinses, and toothpastes (results from the 2 final reviews in the series evaluating the single and combined use of topical fluorides).

TFT types in the comparisons (number of studies)	Prevented fraction	95% CI
Varnish versus gel (1)	14%	-12 to 40%
Varnish versus mouthrinse (4)	10%	-12 to 32%
Gel vs mouthrinse (1)	-14%	-40 to 12%
Toothpaste vs gel (3)	0	-21 to 21%
Toothpaste vs mouthrinse (6)	0	-18 to 19%
Toothpaste versus any TFT*	1%	-13 to 14%
Toothpaste+varnish vs toothpaste alone (1)	48%	12 to 84%
Toothpaste+gel vs toothpaste alone (3)	14%	-9 to 38%
Toothpaste+mouthrinse vs toothpaste alone (5)	7%	0 to 13%
Toothpaste+any TFT vs toothpaste alone (9)	10%	2 to 17%

CI = confidence interval; *3 gel trials and 6 mouthrinse trials, no varnish trial;

estimates of d(m/e)fs PF were however calculated in the 5th (summary) review combining the varnish and gel data, and suggested that the use of topical F applications was associated on average with a 33% (95% CI, 22% to 44%) reduction in carious surfaces in the primary dentition.

Factors influencing the effectiveness of topical fluorides. Another important question addressed in the Cochrane reviews is whether the caries preventive effect is influenced by initial level of caries, background exposure to other F sources, use under supervision, F concentration and frequency of use (and intensity of use), and the type of topical F used.

Most of the factors were formally examined in the individual reviews, but the largest number of studies reporting relevant data in the toothpaste review made this analysis more reliable in this particular review, which included 70 placebo-controlled trials in the meta-analysis (and 133 trials in the summary review).

As shown in table 5, in the F toothpaste review, higher PF were significantly associated with higher initial levels of caries, higher F concentration and supervised brushing. However, no association between treatment effect and exposure to F from other sources was found in this and in the other reviews. Estimates of topical F treatment effect were similar between trials conducted in F and non-F water areas. There was also evidence that higher frequency of use and/or higher F concentration were associated with a greater treatment effect with F toothpaste (and gel, mouthrinse, in each review).

Analysis in the fifth review in the series also showed a significant influence of initial level of caries, frequency and intensity of topical F application, supervision of self-applied topical F use, and modality of topical F on the prevented fraction. For the influence of F modalities, results suggested no significant differences in treatment effects among F gel, mouthrinse, and toothpaste, but significantly lower D(M)FS prevented fractions for F gel, mouthrinse, or toothpaste in comparison with F varnish. However, in these adjusted indirect comparisons of all four F modalities, it is difficult to rule out the possibility of an overestimation of the size of the differential effect in favour of F varnish (DMFS PFs were on average 14% (95% CI, 2% to 26%) higher in F varnish trials), since relatively few varnish trials were included and few among these were placebo-controlled trials.

Comparative effect on caries increment between topical fluorides – direct (head to head) comparisons. The question of the effectiveness of one type of topical F compared with another was also addressed by direct head-to-head comparisons between F modalities, in the 6th review in the series. The results, from comparisons of one F modality versus another, are summarized in Table 6. The 15 studies included in the meta-analyses in this review covered nearly all the range of direct comparisons of possible practical value between F toothpastes, mouthrinses, gels and varnishes. There was, however, a relatively small number of trials for each com-

parison and a general lack of statistical significance of the results for virtually all analyses. The results from the 9 trials comparing F toothpaste with either gel or mouthrinse were consistent with no evidence of an important differential effect, the pooled DMFS PF was 1% (95% CI, -13% to 14%). Relevant comparisons with useable data of F toothpaste and varnish were lacking.

Comparative effect on caries increment between combined and single topical fluoride use – direct comparisons. The final review investigated the simultaneous use of topical F therapies compared with one topical F used alone. The results from the comparisons involving the combined use of different fluoride modalities with toothpaste versus toothpaste used alone are also summarized in Table 6. There was an indication of a greater caries inhibiting effect with the combined use of topical F in the permanent dentition for most of the relevant comparisons. But with a general lack of randomized trial evidence for most comparisons, a modest treatment effect may have been missed. There was, however, evidence from 9 trials clearly showing that the simultaneous use of a topical F treatment with F toothpaste results in an enhanced caries inhibiting effect compared with the use of toothpaste alone; on average, an additional 10% (95% CI, 2% to 17%) reduction in D(M)FS can be expected. To what extent the statistically significant caries reductions in the order of 10% should be considered important is a decision that requires consideration of other relevant aspects. It should be noted, however, that where two methods of applying topical F are already in use, additional benefits might be small, especially when the measures act identically or by similar mechanisms.

Effect on other outcomes. While robust evidence on effectiveness was available, the reviews were generally unable to examine the safety of the various topical F interventions, as the trials rarely provided information on fluorosis and other adverse effects. Regarding acceptance, an interesting finding from the review comparing the 4 topical F modalities against each other was that if children were allocated to F toothpaste groups they appeared to be more likely to stay in the study than if they were given alternative forms of TFT. Thus, the pooled estimate of the relative risk of dropping out from the F toothpaste group as opposed to the other TFT arm in the 6 trials assessed was 0.88 (95% CI, 0.78 to 1.00, p=0.05) in favour of toothpaste. Furthermore, in the summary review, the lack of significant differences in dropouts between the F intervention and no-treatment control arms in the 10 trials reporting this outcome suggests that treatment with topical F agents can be considered acceptable.

The four fluoride reviews published from 2004 to 2006.

The main features and the results of the 4 Cochrane F reviews published subsequently to the series of reviews described previously are shown in Table 7. Of the 2 reviews assessing other F modalities, slow release devices and milk,

Table 7. Summary of Cochrane fluoride reviews published from 2004 to 2006.

Review	Inclusion criteria	Methods	Findings
Fluoride for white spot lesions during orthodontic treatment [Benson et al., 2004]	Study design: RCT's/ quasi-randomised trials Intervention: Any fluoride-containing product (topical fluorides or glass ionomer cements, or fluoride releasing resin/devices) compared with no -fluoride control Outcome measure: presence/absence of new white spot lesions (enamel demineralisation) Participants: patients of any age using fixed braces	Multiple databases/ sources were searched without language restrictions; trialists were contacted for unpublished data; data were extracted and quality assessed independently and in duplicate.	15 trials, with 723 participants, provided data. No studies fulfilled all of the methodological quality assessment criteria, and no meta-analyses were undertaken (scarce data for each comparison). There is some evidence that a daily NaF mouthrinse reduces the severity of enamel decay surrounding a fixed brace (weighted mean difference for lesion depth -70.0; 95% CI -118.2 to -21.8) and that the use of a glass ionomer cement for bracket bonding reduces the prevalence (OR 0.35; 95% CI 0.15 to 0.84) and severity of white spots (weighted mean difference for mineral loss -645 vol%µm; 95% CI -915 to -375) compared with composite resins.
Fluoridated milk for preventing dental caries [Yeung et al., 2005]	Study design: RCT's/ quasi-randomised trials with an intervention or follow-up period of at least 3 years. Intervention: fluoridated milk compared with non-fluoridated milk Outcome measure: changes in caries experience (DMFT/DMFS) in permanent teeth or in primary teeth (dmft/dmfs), Participants: children or adults	Multiple databases/ sources were searched without language restrictions; trialists were contacted for unpublished data; data were extracted and quality assessed independently and in duplicate.	2 trials involving 353 children included. For permanent teeth, a significant reduction in the DMFT (78.4%, $P \sim 0.05$) between the test and control groups was shown in one trial after 3 years. The other showed a reduction after four (35.5%, $P \sim 0.02$) and five (31.2%, $P \sim 0.05$) years. For primary teeth, again, a reduction in the dmft (31.3%, $P \sim 0.05$) was shown after 3 years in one study, but not in the other. The results could not be pooled because of the difference in concentration of F in the milk.
Slow release fluoride devices for the control of dental caries [Bonner et al., 2006]	Study design: RCT's/ quasi-randomised trials Intervention: slow-release fluoride devices compared with an alternative fluoride treatment, placebo, or no intervention Outcome measure: changes in caries (DMFT/DMFS) in permanent teeth or in primary teeth (dmft/dmfs), and progression of lesions through enamel and into dentine Participants: children or adults	Multiple databases/ sources were searched without language restrictions; trial authors were contacted for unpublished data; data were extracted and quality assessed independently and in duplicate.	Only 1 trial involving 174 children provided data. Although 132 children were still included in the trial at the 2-year completion point, examination and statistical analysis was performed on the 63 children who had retained the beads (31 in the intervention and 32 in the control group). Amongst these, caries increment was reported to be statistically significantly lower in the intervention group than in the placebo group (mean difference: -0.72 DMFT, 95% confidence interval -1.23 to -0.21 and -1.52 DMFS, 95% confidence interval -2.68 to -0.36).
Sealants versus fluoride varnishes for preventing dental caries [Hiiri et al., 2006]	Study design: RCT's/ quasi-randomised trials Intervention: sealants versus fluoride varnish or sealants and fluoride varnish combination versus fluoride varnish alone Outcome measure: changes in the number of occlusal caries (DMFS/DMFT) in permanent teeth. Participants: children/ young adults (under 20 years of age)	Multiple databases/ sources were searched without language restrictions; trialists were contacted for unpublished data; data were extracted and quality assessed independently and in duplicate.	4 trials were included. No meta-analyses were undertaken due to the clinical and methodological diversity between study designs/methods. The effectiveness of sealants was statistically significantly higher than varnish in preventing caries at 23 months (RR 0.74, 95% CI 0.58 to 0.95) and at 9 years follow up (RR 0.48, 95% CI 0.29 to 0.79). One small study failed to find a statistically significant difference between sealants and fluoride varnishes. A statistically significant difference in favour of the sealants and fluoride varnish combination compared with varnish at 24 months follow up (RR 0.36 (95% CI 0.21 to 0.61)) was found.

one addresses a particular comparison in a specific tooth site (F varnishes versus fissure sealants in occlusal surfaces), and the other addresses a particular population and caries outcome measure (F for white spot lesions in orthodontic patients). The main clinical findings from each review are summarized below.

Fluoride for white spot lesions during orthodontic treatment. Reviewed by Benson et al., [2004], there is some evidence that the use of topical F, or F-containing bonding materials during orthodontic treatment reduces the occurrence and severity of white spot lesions. However there is little evidence as to which F modality or combination of F is the most effective (although 15 trials involving 723 participants were included in the review, there were scarce data for each comparison).

Slow release fluoride devices for the control of dental caries. Reviewed by Bonner et al., [2006], there is weak evidence from one trial involving 174 children of a caries-inhibiting effect of slow-release F glass beads, because the trial results were from participants selected on the basis of bead retention, which excluded 52% of available participants, whose beads had become dislodged.

Fluoridated milk for preventing dental caries. Reviewed by Yeung et al., [2005]. Data from 2 trials involving 353 children provided some evidence that F milk was beneficial to school children. After 3 years there was a significant reduction in DMFT for both permanent and primary teeth, in one trial, but not in the other.

Sealants versus fluoride varnishes. Reviewed by Hiiri et al., [2006] data from 4 trials provided some evidence of the superiority of pit and fissure sealants over F varnish application in the prevention of occlusal caries, but it is not clear how large the difference is.

Discussion

The series of 7 Cochrane reviews of topical fluorides. The research involving more than 65,000 children and adolescents in over 130 controlled trials compiled in the Cochrane topical reviews shows that the evidence on the beneficial effects of F toothpaste, mouthrinse, gel and varnish is consistent and strongly based on a sizeable body of evidence from randomized controlled trials. The size of the reductions in caries increment in both the permanent and the primary dentition emphasizes the importance of including topical F delivered through toothpastes, rinses, gels or varnishes in any caries preventive program.

The published research also shows that topical F treatments can reduce dental caries irrespective of F-water or other sources of F exposure, that the caries preventive effect of F toothpaste increases with higher initial levels of D(M)FS and when higher F concentration is used, and that supervising a child's use of the F (toothpaste or mouthrinse) leads to greater benefits. It should be pointed out however that, although the analyses, including indirect evidence from 130

trials, should have sufficient power to detect such relationship, more robust investigations of many of these aspects also require direct evidence from head-to-head comparisons. With this regard, a new Cochrane review is underway to evaluate the optimum F concentration in F toothpastes for the prevention of caries in young children, which will assess both direct and indirect evidence simultaneously, addressing a relevant question not formally examined in the previous series of Cochrane topical F reviews.

In this series of reviews, however, the caries-preventive effect of competing topical F interventions was examined using both indirect and direct evidence. Taking the available results into account, and those of a further investigation of the relative effectiveness of the 4 topical F modalities employing a simultaneous analysis of both types of comparisons (multiple treatment meta-analysis), no clear evidence was found that any modality is more effective than any other [Salanti et al., 2009]. It was also shown by direct evidence that F toothpaste, the most readily available form of F can protect children and adolescents against dental caries as much as other topical F. Also that young people are more likely to persist with using toothpaste than with using F mouthrinses, or having gels or varnishes applied. The greater acceptability of toothpaste makes its regular use more likely, thereby improving effectiveness. This is an additional indication for the major role of F toothpaste as an effective and acceptable public health approach for the prevention of dental caries.

The evidence from the Cochrane topical F reviews also shows that children and adolescents using another form of topical F with F toothpaste will experience additional reductions in dental caries, compared with children using F toothpaste only. The size of the caries preventive effect may not be substantial though. Moreover, because other important outcomes were not addressed in the trials, such as adverse effects from the combined use of topical F and toothpaste, it can be difficult to derive clear recommendations on the benefits of using another topical F in addition to toothpaste. Nevertheless, current clinical practice usually includes an additional TFT (over toothpaste) for children at higher risk of developing dental caries. As increased effectiveness of topical F is to be expected in children with higher initial D(M)FS scores, this practice may be considered in populations with a caries increment of around 2 D(M)FS per year or more, based on the trial data analysed in the reviews.

The Cochrane topical F reviews are now being updated, and as evidence from new trials is being incorporated into the existing reviews, the precision of the estimated effects are likely to increase. This is especially so in the case for F varnishes, with 5 additional trials on the effect of varnishes on primary teeth being included in the review [Autio-Gold and Courts, 2001; Chu et al., 2002; Weintraub et al., 2006; Hardman et al., 2007; Lawrence et al., 2008], as well as a F varnish trial assessing the effect on permanent teeth [Moberg Sköld et al., 2005].

Other Cochrane fluoride reviews. This overview does not collate a great deal of trial data from the 4 Cochrane reviews on slow release F devices, F milk, F varnishes versus fissure sealants, and F for white spot lesions in orthodontic patients. Due to the general lack of randomized evidence addressing the questions posed in each of these 4 reviews, a common conclusion from all of them is that more research, and of better methodological quality, is needed.

Conclusions

Dentists and recipients of dental care could benefit from thorough evaluations of any of these topical F interventions, comparisons, and outcomes within large, simple and well designed randomized trials, which should be reported according to the guidelines in the Consolidated Standards of Reporting Trials (CONSORT) statement (<http://www.consort-statement.org>). A general observation, which would apply to all the Cochrane Fluoride reviews, is that the general lack of information across the reviews on relevant outcomes other than caries makes it more important that further experimental research on topical fluorides include assessments of potential benefits as well as harms. This would improve the future identification and quantification of all the effects of topical fluorides.

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