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Fluoride mouthrinses for preventing dental caries in children and adolescents (Review)

Marinho VCC, Chong LY, Worthington HV, Walsh T

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[Intervention Review]

Fluoride mouthrinses for preventing dental caries in children and adolescents

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ABSTRACT

Background

Fluoride mouthrinses have been used extensively as a caries-preventive intervention in school-based programmes and by individuals at home. This is an update of the Cochrane review of fluoride mouthrinses for preventing dental caries in children and adolescents that was first published in 2003.

Objectives

The primary objective is to determine the effectiveness and safety of fluoride mouthrinses in preventing dental caries in the child and adolescent population.

The secondary objective is to examine whether the effect of fluoride rinses is influenced by:

- initial level of caries severity;
- background exposure to fluoride in water (or salt), toothpastes or reported fluoride sources other than the study option(s); or
- fluoride concentration (ppm F) or frequency of use (times per year).

Search methods

We searched the following electronic databases: Cochrane Oral Health's Trials Register (whole database, to 22 April 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2016, Issue 3), MEDLINE Ovid (1946 to 22 April 2016), Embase Ovid (1980 to 22 April 2016), CINAHL EBSCO (the Cumulative Index to Nursing and Allied Health Literature, 1937 to 22 April 2016), LILACS BIREME (Latin American and Caribbean Health Science Information Database, 1982 to 22 April 2016), BBO BIREME (Bibliografia Brasileira de Odontologia; from 1986 to 22 April 2016), Proquest Dissertations and Theses (1861 to 22 April 2016) and Web of Science Conference Proceedings (1990 to 22 April 2016). We undertook a search for ongoing trials on the US National Institutes of Health Trials Register (<http://clinicaltrials.gov>) and the World Health Organization International Clinical Trials Registry Platform. We placed no restrictions on language or date of publication when searching electronic databases. We also searched reference lists of articles and contacted selected authors and manufacturers.

Selection criteria

Randomised or quasi-randomised controlled trials where blind outcome assessment was stated or indicated, comparing fluoride mouthrinse with placebo or no treatment in children up to 16 years of age. Study duration had to be at least one year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces in permanent teeth (D(M)FS).

Data collection and analysis

At least two review authors independently performed study selection, data extraction and risk of bias assessment. We contacted study authors for additional information when required. The primary measure of effect was the prevented fraction (PF), that is, the difference in mean caries increments between treatment and control groups expressed as a percentage of the mean increment in the control group. We conducted random-effects meta-analyses where data could be pooled. We examined potential sources of heterogeneity in random-effects metaregression analyses. We collected adverse effects information from the included trials.

Main results

In this review, we included 37 trials involving 15,813 children and adolescents. All trials tested supervised use of fluoride mouthrinse in schools, with two studies also including home use. Almost all children received a fluoride rinse formulated with sodium fluoride (NaF), mostly on either a daily or weekly/fortnightly basis and at two main strengths, 230 or 900 ppm F, respectively. Most studies (28) were at high risk of bias, and nine were at unclear risk of bias.

From the 35 trials (15,305 participants) that contributed data on permanent tooth surface for meta-analysis, the D(M)FS pooled PF was 27% (95% confidence interval (CI), 23% to 30%; $I^2 = 42%$) (moderate quality evidence). We found no significant association between estimates of D(M)FS prevented fractions and baseline caries severity, background exposure to fluorides, rinsing frequency or fluoride concentration in metaregression analyses. A funnel plot of the 35 studies in the D(M)FS PF meta-analysis indicated no relationship between prevented fraction and study precision (no evidence of reporting bias). The pooled estimate of D(M)FT PF was 23% (95% CI, 18% to 29%; $I^2 = 54%$), from the 13 trials that contributed data for the permanent teeth meta-analysis (moderate quality evidence).

We found limited information concerning possible adverse effects or acceptability of the treatment regimen in the included trials. Three trials incompletely reported data on tooth staining, and one trial incompletely reported information on mucosal irritation/allergic reaction. None of the trials reported on acute adverse symptoms during treatment.

Authors' conclusions

This review found that supervised regular use of fluoride mouthrinse by children and adolescents is associated with a large reduction in caries increment in permanent teeth. We are moderately certain of the size of the effect. Most of the evidence evaluated use of fluoride mouthrinse supervised in a school setting, but the findings may be applicable to children in other settings with supervised or unsupervised rinsing, although the size of the caries-preventive effect is less clear. Any future research on fluoride mouthrinses should focus on head-to-head comparisons between different fluoride rinse features or fluoride rinses against other preventive strategies, and should evaluate adverse effects and acceptability.

PLAIN LANGUAGE SUMMARY

Fluoride mouthrinses for preventing dental caries in children and adolescents

Review question

How effective and safe is the use of fluoride mouthrinse for preventing tooth decay (dental caries) in children and adolescents compared with placebo (a mouthrinse without the active ingredient fluoride) or no treatment?

Background

Tooth decay is a health problem worldwide, affecting the vast majority of adults and children. Levels of tooth decay vary between and within countries, but children in lower socioeconomic groups (measured by income, education and employment) tend to have more tooth decay. Untreated tooth decay can cause progressive destruction of the tops of teeth (crowns), often accompanied by severe pain. Repair and replacement of decayed teeth is costly in terms of time and money and is a major drain on the resources of healthcare systems.

Preventing tooth decay in children and adolescents is regarded as a priority for dental services and is considered more cost-effective than treatment. Use of fluoride, a mineral that prevents tooth decay, is widespread. As well as occurring naturally, fluoride is added to the water supply in some areas, and is used in most toothpastes and in other products that are available to varying degrees worldwide. As an extra preventive measure, fluoride can be applied directly to teeth as mouthrinses, lozenges, varnishes and gels.

Fluoride mouthrinse has frequently been used under supervision in school-based programmes to prevent tooth decay. Supervised (depending on the age of the child) or unsupervised fluoride mouthrinse needs to be used regularly to have an effect. Recommended procedure involves rinsing the mouth one to two minutes per day with a less concentrated solution containing fluoride, or once a week or once every two weeks with a more concentrated solution. Because of the risk of swallowing too much fluoride, fluoride mouthrinses are not recommended for children younger than six years of age.

This review updates the Cochrane review of fluoride mouthrinses for preventing tooth decay in children and adolescents that was first published in 2003. We assessed existing research for [Cochrane Oral Health](#), and evidence is current up to 22 April 2016.

Study characteristics

We included 37 studies in which more than 15,000 children (aged six to 14 years) were treated with fluoride mouthrinse or placebo (a mouthrinse with no active ingredient) or received no treatment. All studies assessed supervised use of fluoride mouthrinse in school settings, with two studies also including home use. Most children received a sodium fluoride (NaF) solution, given at 230 parts per million of fluoride (ppm F) daily or a higher concentration of 900 ppm F weekly or fortnightly. Studies lasted from two to three years. Reports were published between 1965 and 2005, and studies took place in several countries.

Key results

This review update confirmed that supervised regular use of fluoride mouthrinse can reduce tooth decay in children and adolescents. Combined results of 35 trials showed that, on average, there is a 27% reduction in decayed, missing and filled tooth surfaces in permanent teeth with fluoride mouthrinse compared with placebo or no mouthrinse. This benefit is likely to be present even if children use fluoride toothpaste or live in water-fluoridated areas. Combined results of 13 trials found an average 23% reduction in decayed, missing and filled teeth (rather than tooth surfaces) in permanent teeth with fluoride mouthrinse compared with placebo or no mouthrinse. No trials have looked at the effect of fluoride rinse on baby teeth. We found little information about unwanted side effects or about how well children were able to cope with the use of mouthrinses.

Conclusion

Regular use of fluoride mouthrinse under supervision results in a large reduction in tooth decay in children's permanent teeth. We found little information about potential adverse effects and acceptability.

Quality of the evidence

Available evidence for permanent teeth is of moderate quality. This means we are moderately confident in the size of the effect. Very little evidence is available to assess adverse effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Fluoride mouthrinse compared with placebo or no treatment for preventing caries in children and adolescents						
Patient or population: children and adolescents Setting: community (schools) Intervention: fluoride mouthrinse (primarily supervised use in school setting) Comparison: placebo or no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment (assumed risk)	Risk with fluoride mouthrinse (corresponding risk)				
Changes in caries on the surfaces of permanent teeth measured by D(M)FS increment - nearest to 3 years	Mean increment ranged across control groups from 0.74 to 21.05, median 5.6	The corresponding mean increment in the intervention group is 3.80 (95%CI 3.64 to 4.00)	PF^a 0.27 (0.23 to 0.30)	15305 (35 RCTs)	⊕⊕⊕○ moderate^b	Large effect: D(M)FS PF 27% (23% to 30%)
Changes in caries on the permanent teeth measured by D(M)FT increment - nearest to 3 years	Mean increment ranged across control groups from 0.72 to 8.41, median 3.2	The corresponding mean increment in the intervention group is 2.46 (95%CI 2.27 to 2.62)	PF^a 0.23 (0.18 to 0.29)	5105 (13 RCTs)	⊕⊕⊕○ moderate^b	Moderate to large effect: D(M)FT PF 23% (18% to 29%)
Unacceptability of treatment as measured by leaving study early	149 per 1000	198 per 1000 (92 to 422)	RR 1.33 (0.62 to 2.83)	1700 (4 RCTs)	⊕○○○ very low^{b,c,d}	
Tooth staining	Study 1: "significant difference" in stain score (from the control) in the group using an amine fluoride mouthrinse: "non-significant differ-			Study 1: 525 Study 2: 743 Study 3: 726	⊕○○○ very low^e	We know little about the risk of tooth staining owing to incomplete reporting

	<p>ence” (from the control) in the group using sodium fluoride</p> <p>In 2 trials where stannous fluoride mouthrinsing was tested against placebo rinsing:</p> <p>Study 2: “approximately six children had tenacious staining that required a rubber cup prophylaxis carried out” - no indication as to which groups these children belonged</p> <p>Study 3: “some amount of yellow pigmentation, somewhat more noticeable in the children in the test group”</p>			
Signs of acute toxicity during application of treatment (such as nausea/gagging/vomiting)	Not reported in any studies			No data on signs of acute toxicity
Mucosal irritation/oral soft tissue allergic reaction	“no cases of mucosal hypersensitivity after periodical examinations of every subject” - reported in 1 study	434 (1 RCT)	⊕○○○ very low^e	We know very little about the risk of mucosal irritation/allergic reaction owing to lack of reporting

*The basis for the **assumed risk, the risk in the placebo or no treatment group**, was the range and median in the control groups of the studies included in the review. The **corresponding risk, the risk in the intervention group (and its 95% confidence interval)**, is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI = confidence interval; D(M)FS = decayed (missing) and filled permanent surfaces; D(M)FT = decayed (missing) and filled permanent teeth; PF = prevented fraction; RR = risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aPF = 1 - (mean increment in control group/mean increment in treatment group) (expressed as percentages). PF values between 1% and 10% are considered to be a small effect; between 10% and 20%, a moderate effect; above 20% a large or substantial effect.

^bAll studies were at unclear or high risk of bias. Trials had unclear or high risk of bias in sequence generation and allocation concealment. Most studies had supervised mouthrinsing conducted in the school setting - this was considered for indirectness but downgrading considered unnecessary.

^cWide confidence interval - small number of participants analysed.

^dHigh unexplained heterogeneity observed.

^eIncomplete information from one to three trials with unclear or high risk of bias. Outcome downgraded for concerns of risk of bias and serious imprecision.

BACKGROUND

Description of the condition

Dental caries is the most prevalent chronic disease, afflicting a significant proportion of the world population, including around 60% to 90% of school-aged children and the vast majority of adults (Marcenes 2013; Petersen 2004). Dental caries levels vary considerably between and within countries, but children in lower socioeconomic status (SES) groups have higher caries levels than those in upper SES groups, and in high-income countries the association between socioeconomic position and caries might be stronger (Chen 1995; Reisine 2001; Schwendicke 2015). Untreated caries causes progressive destruction of the crowns of the teeth, often accompanied by severe pain and suffering, especially in children, where it can result in poorer quality of life and general health (Sheiham 2005). Untreated caries in permanent teeth was the most prevalent condition among all those evaluated in the Global Burden of Disease (GBD) 2010 study, affecting 35% of the global population, or 2.4 billion people; untreated caries in deciduous teeth was the 10th most prevalent condition, affecting 9% of the population, or 621 million children worldwide (Kassebaum 2015). Repair and replacement of carious teeth is excessively time consuming and costly, representing a major drain of resources for healthcare systems. On a population basis, dental caries is the fourth most expensive chronic disease to treat according to the World Health Organization (Petersen 2008).

Dental caries occurs because of demineralisation of tooth structure by organic acids formed by oral bacteria present in dental plaque through the anaerobic metabolism of dietary sugars. The causal role of sugars in caries is well established (Sheiham 2001). Most caries lesions in children's permanent teeth progress relatively slowly, with an average lesion taking three years to progress through tooth enamel to dentine (Mejare 1998). The dental caries process is influenced by the susceptibility of the tooth surface, the bacterial profile, the quantity and quality of saliva and the presence of fluoride, which promotes remineralisation and inhibits demineralisation of the tooth structure.

Description of the intervention

Fluoride mouthrinses have been used extensively for the past 40 years to prevent dental caries in children. The use of rinses was especially widespread in school-based programmes in countries experiencing high caries prevalence in the 1970s and 1980s. Doubts about the effectiveness of fluoride mouthrinse as a population strategy began in the mid-1980s, in view of the decline in dental caries, and their presumed cost-effectiveness was challenged (Disney 1990; Stamm 1984). The current view is that fluoride mouthrinsing programmes are appropriate only for children at high risk of caries (FDI 2002). The fluoride compound most

commonly used in mouthrinse is sodium fluoride. Supervised, school-based, weekly rinsing programmes using 900 ppm fluoride (F) solutions of 0.2% sodium fluoride have been popular in the United States in non-fluoridated communities (Horowitz 1996). In Scandinavian countries and in several other countries, such programmes have been discontinued on the basis of the above-noted caries decline and widespread use of fluoride toothpastes (Seppa 1989; Twetman 2004). Mouthrinse solutions of 0.05% sodium fluoride, containing 230 ppm F, are available commercially for daily home use in some countries. Rinses containing 100 ppm F are also available for over-the-counter (OTC) sale and are recommended for twice-daily use. Fluoride mouthrinses have thus moved from being a tool mainly advocated in the public health setting; through the force of commercial marketing, they have gained greater prominence in the personal dental products market. By virtue of the widespread use of other oral mouthrinse products, from simple breath fresheners to products formulated to counter inflammatory periodontal (gum) diseases, it has been argued that the procedure could in fact be cost-effective if those already using non-fluoride mouthrinses convert to using fluoride rinses (Stamm 1993).

Although the procedure is not recommended for children younger than six years of age because of the risk of acute and chronic fluoride ingestion, data have implicated use of fluoride mouthrinse by preschool children as a risk factor for dental fluorosis (enamel defects caused by chronic ingestion of excessive amounts of fluoride during the period of tooth formation) because some young children might swallow substantial amounts (Ripa 1991; Stookey 1994). Accidental swallowing of the usual 10 mL rinse volume of a 0.05% (230 ppm F) NaF solution daily by a child of five or six years of age will result in ingestion of 2.3 mg of fluoride (the average dosage ingested would be twice the optimum level in a fluoridated area). Although this dose is far below the probable toxic dose (PTD) of fluoride, estimated to be 5 mg/kg body weight (Whitford 1992), or approximately 100 mg of fluoride for a child of five or six years (20 kg), this amount would be available in just 434 mL of the standard daily rinsing solution.

A large number of clinical trials have extensively investigated the effect of fluoride mouthrinses on the incidence of caries in children during the past five decades. Besides sodium fluoride solutions, mouthrinses containing other fluoride compounds in several concentrations and rinsing frequencies have been tested. Numerous articles and textbook chapters have reviewed evidence from these primary studies on the effectiveness of fluoride mouthrinses (Birkeland 1978; Bohannon 1985; Leverett 1989; Petersson 1993; Ripa 1991; Ripa 1992; Torell 1974). In one review article from the mid-1980s, review authors used a meta-analytical approach to synthesise the results of US fluoride mouthrinse studies carried out in fluoride-deficient communities (Stamm 1984). Two systematic reviews on the caries-inhibiting effect of fluoride mouthrinses have been published more recently (Twetman 2004; Weyant 2013). It is evident from these reviews and meta-analyses that fluoride

mouthrinses are caries-inhibitory treatments. However, the authors of these reviews failed to conduct a comprehensive search for individual trials or to formally evaluate the risk of bias in included trials, despite obvious drawbacks in the design and methods of the included trials.

How the intervention might work

The most important anti-caries effect of fluoride present in dental plaque and saliva is considered to result from its local action on the tooth/plaque interface, through promotion of remineralisation of early caries lesions and reduction in tooth enamel solubility (Featherstone 1988). Enamel demineralisation is markedly inhibited if fluoride is present at the time of the acid challenge because, as cariogenic bacteria metabolise carbohydrates and produce acid, fluoride diffuses with the acid from dental plaque into the enamel in response to lowered pH, and acts at the enamel crystal surface to reduce mineral loss. When pH rises following enamel demineralisation, released fluoride and fluoride present in the saliva can combine with dissolved calcium and phosphate ions to precipitate or grow fluorapatite-like crystalline material within the tooth, thereby establishing an improved enamel crystal structure. Thus, fluoride enhances this mineral gain and provides a material that is more resistant to subsequent acid attack (Ten Cate 1999). This occurs with all forms and concentrations of topical fluoride, although to a variable extent. With high-concentration topical fluoride vehicles (such as varnishes and gels), calcium fluoride is precipitated on the enamel surface and in the plaque. This calcium fluoride acts as a fluoride reservoir, which is released when the oral pH falls, and the amount of fluoride deposited in the subsurface lesion is greater after topical application with such high-concentration fluoride vehicles (Horowitz 1996; Ogaard 1994; Ogaard 2001). Regular use of fluoride toothpaste or mouthrinse results in sustained elevated fluoride concentrations in oral fluids during the demineralisation-remineralisation cycle, as small amounts are maintained constantly in the mouth (Clarkson 1996).

Why it is important to do this review

The Cochrane Oral Health Group undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles that were the most clinically important ones to maintain in *The Cochrane Library* (Worthington 2015). The paediatric expert panel identified this review as a priority title (Cochrane OHG priority review portfolio).

Prevention of dental caries in children and adolescents is generally regarded as a priority for dental services and is considered more cost-effective than treatment (Burt 1998). Fluoride therapy has been the centrepiece of caries-preventive strategies since water fluoridation schemes were introduced over six decades ago (Murray 1991), when caries was highly prevalent and severe, and

when even modest prevention activities led to considerable reduction in disease levels. Over the past 30 years, with the substantial decline in dental caries rates in many western countries, the increase in dental fluorosis levels in some countries and intensive research on the mechanism of action of fluoride highlighting the primary importance of its topical effect, greater attention has been paid to the appropriate use of other fluoride-based interventions (Featherstone 1988; Featherstone 1999; Glass 1982; Marthaler 1996; O'Mullane 1994; Ripa 1991).

Use of topically applied fluoride products in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades. By definition, the term 'topically applied fluoride' is used to describe those delivery systems that provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect, and therefore are not intended for ingestion. Fluoride-containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most commonly used at present, alone or in combination. Various products are marketed in different countries, and a variety of caries-preventive programmes based on these products have been implemented. Toothpastes are by far the most widespread form of fluoride usage (Murray 1991a; Ripa 1991); although reasons for the decline in prevalence of dental caries in children from different countries have been the topic of much debate (De Liefde 1998; Krasse 1996; Marthaler 1996; Marthaler 2004; Nadanovsky 1995), this event has been attributed mainly to the gradual increase in, and regular home use of, fluoride in toothpaste (Bratthall 1996; Glass 1982; Marthaler 1994; O'Mullane 1994; Ripa 1991; Rolla 1991).

At the same time, the lower caries prevalence in many countries now and the widespread availability of fluoride from multiple sources have raised the question of whether topically applied fluorides are still effective in reducing caries, and whether they are safe, mainly in terms of the potential risk of fluorosis (mottled enamel). This is particularly important, as nearly all child populations in high-income countries are exposed to some source of fluoride, notably in toothpaste, and adverse effects may be rare (such as acute fluoride toxicity) or more subtle (such as mild dental fluorosis) (Marthaler 2004; Murray 1991a).

Traditional narrative reviews have extensively reviewed evidence on the effects of topically applied fluoride products on prevention of dental caries in children. Several systematic reviews focusing on evaluation of specific fluoride active agents within specific delivery systems have used a quantitative meta-analytical approach to synthesise trial results (Ammari 2003; Bartizek 2001; Chaves 2002; Clark 1985; Helfenstein 1994; Johnson 1993; Petersson 2004; Stamm 1984; Stamm 1995; Steiner 2004; Strohmenger 2001; Twetman 2004; Van Rijkom 1998; Weyant 2013). However, no systematic investigation has been conducted to evaluate and compare effects of the main modalities of topically applied fluoride treatments and to examine formally the main factors that may influence their effectiveness.

This review, which is one in a series of Cochrane systematic reviews of topical fluoride interventions, assesses the effectiveness of fluoride rinses for prevention of dental caries in children (Marinho 2003a; Marinho 2003b; Marinho 2004; Marinho 2004a; Marinho 2013; Marinho 2015). This is an update of the review first published in 2003, which showed clear evidence of a caries-inhibiting effect of fluoride mouthrinse in the permanent teeth of children (Marinho 2003). It is generally recognised that blinding is particularly important when outcome measures require specific criteria to improve objectivity in measurement, as in assessment of dental caries. Of note in this series of topical fluoride reviews is that lack of blinding in the main outcome assessment (caries increment) or lack of any indication of blind outcome assessment remains an exclusion criterion - that is, we have excluded studies if open outcome assessment is reported, or if blind outcome assessment is not reported and is unlikely to have been used.

OBJECTIVES

The primary objective is to determine the effectiveness and safety of fluoride mouthrinses in preventing dental caries in the child/adolescent population.

The secondary objective is to examine whether the effect of fluoride rinses is influenced by:

- initial level of caries severity;
- background exposure to fluoride in water (or salt), toothpastes or reported fluoride sources other than the study option(s); or
- fluoride concentration (ppm F) or frequency of use (times per year).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised or quasi-randomised controlled trials where 'blind outcome assessment' was stated or indicated (e.g. caries examinations performed independently of previous results, radiographic examinations registered separately from clinical examinations/added later, examiners clearly not involved in giving treatment, use of placebo described), and in which the length of follow-up was at least one year/school year. We included cluster-randomised trials, except when only one cluster was assigned to each study group.

We excluded randomised or quasi-randomised controlled trials with open outcome assessment or no indication of blind assessment of outcome (blind assessment was considered unlikely if the following were not described: a caries examination performed independently of previous results, X-rays registered independently of clinical examination, examiners clearly not involved in giving treatment and use of placebo), or lasting less than one year/school year, or where random or quasi-random allocation was not used or indicated. We also excluded split-mouth studies as they are unsuitable for fluoride mouthrinse owing to unavoidable contamination.

Types of participants

Children or adolescents aged 16 or younger at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention was received or time when it started).

We excluded studies where participants were selected on the basis of special (general or oral) health conditions.

Types of interventions

Intervention: topical fluoride in the form of a mouthrinse that is swished and expectorated, not swallowed. We included fluoride mouthrinses irrespective of formulation, concentration (ppm F), volume, duration or frequency of application, or application technique of application.

Comparison: placebo or no treatment.

Therefore, the following comparison is of interest: fluoride mouthrinse versus placebo or no treatment.

We excluded studies where the intervention consisted of use of any other caries-preventive agent or procedure (e.g. other fluoride-based measures, chlorhexidine, sealants, oral hygiene interventions, xylitol chewing gums), in addition to fluoride rinse.

Types of outcome measures

The primary outcome measure in this review is caries increment, as measured by change from baseline in the number of decayed (missing) and filled permanent tooth surfaces (D(M)FS), or in the number of decayed (extracted/missing) and filled primary tooth surfaces (d(e/m)fs) or both (and change in the number of permanent or primary teeth (D(M)FT/d(e/m)ft). Dental caries is defined here as clinically and radiographically recorded at the dentin level of diagnosis. If caries data were reported only with dentin and enamel lesions combined, this was used in the analysis. (See [Data collection and analysis](#) for different ways of recording caries and reporting D(M)FT/S and d(m)ft/s scores in permanent and primary dentitions in clinical trials of caries preventive interventions, and for ways in which data were selected for analysis.)

We excluded studies reporting no dental caries data, reporting only on plaque/gingivitis/gingival bleeding, calculus, dentin hypersen-

sitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc).

Primary outcomes

- Caries increment in permanent tooth surfaces (D(M)FS), reported as change from baseline (and D(M)FT, whenever reported)
- Caries increment in primary tooth surfaces (d(e)fs), reported as change from baseline (and d(e)ft, whenever reported)

Secondary outcomes

- Development of new caries, reported as change in the proportion of children developing new caries
- Children not remaining caries-free, reported as a change in the proportion
- Tooth staining, measured as change in the proportion of children
- Signs of acute toxicity during application of treatment (such as nausea/gagging/vomiting)
- Mucosal irritation/oral soft tissue allergic reaction
- Dropouts or withdrawals during the trial (as an indirect measure of treatment acceptability)

Search methods for identification of studies

To identify trials for inclusion in this review, we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE Ovid but revised appropriately for each database. The search strategy used a combination of controlled vocabulary and free text terms and was linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in Box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (updated March 2011) (Higgins 2011). We have provided details of the current MEDLINE search strategy in Appendix 3. The search of Embase was linked to Cochrane Oral Health's filter for identifying RCTs.

Electronic searches

We searched the following electronic databases:

- Cochrane Oral Health's Trials Register (searched 22 April 2016) (see Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3) in the Cochrane Library (searched 22 April 2016) (see Appendix 2);
- MEDLINE Ovid (1946 to 22 April 2016) (see Appendix 3);
- Embase Ovid (1980 to 22 April 2016) (see Appendix 4);

- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 22 April 2016) (see Appendix 5);
- LILACS BIREME (Latin American Caribbean Health Sciences Literature; 1980 to 22 April 2016) (see Appendix 6);
- BBO BIREME (Brazilian Bibliography of Odontology; 1980 to 22 April 2016) (see Appendix 6);
- Proquest Dissertations and Theses (1861 to 22 April 2016) (see Appendix 7); and
- Web of Science Conference Proceedings (1990 to 22 April 2016) (see Appendix 8).

We placed no restrictions on the language or date of publication when searching electronic databases.

For ongoing trials, we searched the following trial registries (see Appendix 9 for details of search terms):

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (<http://clinicaltrials.gov/>; searched 22 April 2016);
- World Health Organization International Clinical Trials Registry Platform (<apps.who.int/trialsearch>; searched 22 April 2016).

Searching other resources

Reference searching

We scanned all eligible trial reports retrieved from the searches, meta-analytical reports and systematic reviews/review articles for relevant references. For the original version of this review, review authors had also checked reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions for relevant references (Ekstrand 1988; Fejerskov 1996; Murray 1991c).

Handsearching

Review authors carried out some handsearching for the original version of this review, using journals identified as having the highest yield of eligible RCTs and controlled clinical trials (CCTs). We handsearched the following journals:

- *Community Dentistry and Oral Epidemiology* (1990 to 2000);
- *British Dental Journal* (1999 to 2000);
- *Caries Research* (1999 to 2000);
- *Journal of the American Dental Association* (1999 to 2000);
- *Journal of Dental Research* (1999 to 2000);
- *Journal of Public Health Dentistry* (1999 to 2000); and
- *European Journal of Oral Sciences* (1999 to 2000).

For the update of this review, we did not undertake any handsearching.

Personal contact

For the original review, we contacted experts in the field of preventive dentistry to identify any unpublished trials or trial reports that may not have been indexed by the major databases. We sent a letter to the author(s) of each included study published during the 1980s and 1990s to request information on possible unpublished trials eligible for inclusion. All authors of trials who had been contacted to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished trials. In addition, on the basis of information extracted mainly from included trials, we created a list of manufacturers of fluoride rinses for locating unpublished trials, and we contacted six fluoride rinse manufacturers in October 2000. We requested information on any unpublished trials from GABA AG, Johnson & Johnson, Oral-B Laboratories, Colgate Oral Pharmaceuticals, Procter & Gamble and Warner Lambert. GABA provided a list of 409 records obtained through a search performed in GALILENT (Database of GABA Library in Dentistry) using the keyword 'amine fluoride'; we incorporated in this update the search results from this list of records from GABA.

Data collection and analysis

Selection of studies

At least two review authors performed screening for eligibility independently for all reports identified from all searches performed. We considered it essential to identify all reports related to the same study. When a trial report thought to be potentially relevant was written in a language not known to the review authors, it was translated and the inclusion criteria form completed by a review author with reference to the translator. We attempted to contact authors of trials that could not be classified to ascertain whether inclusion criteria were met. We noted trials not fulfilling the inclusion criteria and our reasons for excluding them in the [Characteristics of excluded studies](#) table.

Data extraction and management

At least two review authors extracted data from all included studies in duplicate using a predesigned pilot-tested data extraction form. We extracted numerical data presented only in graphs and figures whenever possible. We attempted to contact study authors by using an open-ended request to obtain missing information or for clarification when necessary.

We extracted information related to study methods, including study design, study duration (overall length of follow-up in years) and objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors).

We recorded information on sponsoring/funding institutions and manufacturers involved.

We extracted characteristics related to participants, including age (mean or range or both) at start, caries severity at start (average DMFS/dmfs, DFS/dfs or other caries increment measure, for sample analysed), background exposure to other fluoride sources (toothpaste, water, etc), year study began, location where study was conducted (country), setting where participants were recruited (and setting of treatment) and total sample randomised (at baseline) and analysed (at relevant final examination).

We extracted characteristics of the interventions, including mode of application (how the intervention was delivered/supervision), methods (technique/device) of application, before and after application, fluoride active agents and concentrations used (in ppm F), frequency and duration of application and amount applied. We recorded information on what the fluoride mouthrinse was compared with (no treatment or placebo), together with numbers for each group. We have described these data in the [Characteristics of included studies](#) table.

We recorded different ways of reporting caries increment (change from baseline as measured by the DMF index) separately and/or combined according to the components of the index chosen and units measured (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (primary/permanent teeth/surfaces, first molar teeth approximal surfaces, etc), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient enamel lesions or both), methods of examination adopted (clinical or radiographical, both or other), state of tooth eruption considered (teeth erupted at baseline and/or erupting teeth (or surface) during the trial) and approaches to account or not for reversals in caries increment adopted (in a net caries increment or observed/crude increment, respectively). In addition, we recorded caries increment data at all reported time periods (at various follow-ups).

As we were aware that caries increment would be recorded differently in different trials, we developed a set of a priori rules to choose the main outcome data (D(M)FS) for analysis from each study: DFS data would be chosen over DMFS data, and these would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted' only, and these over data for 'erupting' only; data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' only, and these over 'radiological' data only; data from 'clinical and FOTI examinations combined' would be chosen over data from 'clinical' examination only; data for dentinal/cavitated caries lesions would be chosen over combined data for dentinal/cavitated and for enamel/non-cavitated lesions, and these over enamel caries data only; net caries increment data would be chosen over crude (observed) increment data; and follow-up nearest to three years (often the one at the end of the treatment period) would be chosen over all other lengths of follow-up, unless otherwise stated. When no specification was pro-

vided with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth and types of tooth eruption recorded and approaches for reversals adopted, we assumed the primary choices described above.

The [Characteristics of included studies](#) table provides a description of all main outcome data reported from each study, with the chosen primary outcome measure featured at the top. When assessments of caries increments were made during a postintervention follow-up period, we noted the length of time over which outcomes were measured after the intervention ended. We also listed in this table all other relevant outcomes identified as assessed in the trials.

Assessment of risk of bias in included studies

At least two review authors independently undertook assessment of risk of bias in all included trials. We resolved disagreements by discussion or by involvement of another review author. This was carried out using the tool of The Cochrane Collaboration for assessing risk of bias, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), but according to predefined criteria that were adapted and refined for the Cochrane topical fluoride review updates. We assessed eight domains according to the tool, namely, sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, balance of baseline characteristics and freedom from contamination or co-intervention. Each domain included one or more specific entries in a 'Risk of bias' table. Within each entry, we described information reported in the study and assigned a judgement related to risk of bias for that entry. When the study clearly reported the methods used, we made a judgement of 'low risk of bias' or 'high risk of bias' as appropriate. Where trial methods were unclear, we judged a domain as at 'unclear risk of bias' until further information becomes available.

After taking into account additional information provided by trial authors, we assessed the overall risk of bias in included trials over all eight domains. We categorised studies as being at overall:

- low risk of bias (plausible bias unlikely to seriously alter the results: all eight domains assessed as at low risk of bias);
- unclear risk of bias (plausible bias that raises some doubt about the results: at least one domain assessed as at unclear risk of bias, but none at high risk of bias); or
- high risk of bias (plausible bias that seriously weakens confidence in the results: at least one domain assessed as at high risk of bias).

Measures of treatment effect

The chosen measure of treatment effect for the primary outcome, caries increment, was the prevented fraction (PF), that is, mean increment in control group minus mean increment in treated group, divided by mean increment in controls. For an outcome such as

caries increment, where discrete counts are considered to approximate to a continuous scale and are treated as continuous data, we considered this measure more appropriate than the mean difference or the standardised mean difference because it allows the combination of different ways of measuring caries increment and a meaningful investigation of heterogeneity between trials. It is also simple to interpret.

For outcomes other than caries increment, we planned that we would summarise continuous data as average mean differences (MDs) in treatment effects along with their 95% confidence intervals (95% CIs), or, if different scales were used to measure the same outcome in different trials, standardised mean differences (SMDs) and their 95% CIs. We analysed dichotomous outcome data by calculating risk ratios (RRs) or, for adverse effects of fluoride treatment, risk differences (RDs).

Unit of analysis issues

Trials with multiple treatment arms

In trials with more than one relevant intervention group and a common control group, such as those comparing different active fluoride agents or concentrations of fluoride ions against a placebo group, we combined summary statistics (the number of children analysed, mean caries increments and standard deviations) from all relevant experimental groups (and from any relevant control groups, if this was the case) to obtain a measure of treatment effect (the PF). This enabled the inclusion of all relevant data in the primary meta-analysis, although it might have slightly compromised the secondary investigations of dose response.

Cluster-randomised trials

When cluster-randomised trials did not report results adjusted for clustering present in the data, we performed an approximately correct analysis by estimating the design effect for such trials (Higgins 2011) by using:

- the intraclass correlation coefficient (ICC) if reported;
- an ICC value of 0.05 obtained from a similar study (Lawrence 2008; ICC = 0.045) to reduce the numbers in intervention and control groups to their 'effective sample size'; or
- an ICC value of 0.1 already used for the cluster trial in the original review to inflate the standard error of the PF by multiplying it by the square root of the design effect.

The design effect is $(1 + (M-1) * ICC)$ where M is the average cluster size.

Dealing with missing data

We decided that when missing standard deviations for caries increments could not be obtained by contacting the original researchers, we would impute these values through linear regression

of log standard deviations on log mean caries increments. This is a suitable approach for caries prevention trials because, as they follow an approximate Poisson distribution, caries increments are closely related (similar) to their standard deviations (Van Rijkom 1998).

Assessment of heterogeneity

We assessed heterogeneity by inspecting a graphical display of estimated treatment effects from trials along with their 95% CIs and by conducting formal tests of homogeneity undertaken before each meta-analysis (Thompson 1999). We quantified this by using the I^2 statistic and classified it according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A rough guide to interpretation follows: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% may indicate very substantial (“considerable”) heterogeneity.

Assessment of reporting biases

Reporting bias can be assessed as within-study outcomes reporting bias or as between-study publication bias.

Outcomes reporting bias (within-study reporting bias)

Within-study reporting bias (one of the eight ‘risk of bias’ domains listed above, as selective outcome reporting) would ideally be assessed by comparing outcomes reported in the published report against the study protocol. As this was not possible, we compared the outcomes listed in the Methods section with reported results. If results were mentioned but were not reported adequately in a way that allowed analysis (e.g. only mentioned whether or not the results were statistically significant), we sought information from the authors of study reports. Otherwise, this would be judged as “high risk” of bias. If information was insufficient to judge the risk of bias, we judged the risk as unclear (Higgins 2011).

Publication bias (between-study reporting bias)

We generated funnel plots (plots of effect estimates versus the inverse of their standard errors) when we identified sufficient trials (more than 10). Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, although this may also represent a true relationship between trial size and size of effect. We performed a formal investigation of the degree of asymmetry by using the method proposed by Egger 1997.

Data synthesis

We conducted meta-analyses for the PFs as inverse variance weighted averages in Review Manager 5.3 (RevMan 2014), where

the prevented fraction and standard error data [PF (SE)] were entered by using the generic inverse variance (GIV) method. We estimated variances using the formula presented in Dubey 1965, which was more suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable. Two previous reviews (Marinho 2013; Marinho 2015) noted that this formula was inappropriate for studies with small increments, and that the data from such studies were to be excluded from the analysis in this review. We used random-effects meta-analyses throughout and analysed primary and permanent teeth separately throughout. We used random-effects models to calculate a pooled estimate of effect for outcomes other than caries increment data.

Subgroup analysis and investigation of heterogeneity

We specified three potential sources of heterogeneity a priori, as these formed part of the primary objectives of this review. We hypothesised that the effect of fluoride mouthrinses on caries differs according to: (1) baseline levels of caries severity; (2) exposure to other fluoride sources (in water, in toothpastes, etc); and (3) frequency of application and fluoride concentration. We examined the association of these factors with estimated effects (D(M)FS PFs) by performing random-effects metaregression analyses in Stata version 12.0 (Stata Corporation, College Station, Texas, USA) using the ‘Metareg’ command (Sharp 1998).

To allow such investigation, we dealt with relevant data as follows. We calculated data on ‘baseline levels of caries’ from the study sample analysed (final sample) unless otherwise stated, and we averaged values among all relevant study groups. Data on ‘background exposure to other fluoride sources’ represented combined data on use of fluoride toothpaste and consumption of fluoridated water (or salt) and were grouped into two categories: one for studies that were based on samples provided with non-fluoride toothpaste and that were obtained from non-fluoridated areas (non-exposed), and another for studies based on samples using fluoride toothpaste or studies in fluoridated communities or both. We considered exposure to water fluoridation when fluoride levels in water were stated to be above 0.3 ppm F. Use of fluoride toothpaste reported for 30% or more of the study sample would indicate exposure to fluoridated toothpaste. When use or non-use of fluoride toothpaste was not clearly indicated in studies carried out in high-income countries, we assumed that fluoride toothpaste was widely used from the middle of the 1970s (Ripa 1989); we sought this information from study authors (or obtained it from other sources) when missing from studies carried out in other locations. When data on the year a study had begun were not provided, we calculated a ‘probable date’ by subtracting the duration of the study (in years) plus one extra year, from the publication date of the study. We have not categorised data on ‘frequency of application’ and ‘concentration applied’. We averaged concentrations in multiple-arm studies over fluoride mouthrinse groups. We dealt with incomplete data for frequency of mouthrinsing as follows: In studies of supervised daily rinse at school where participants were provided

with mouthrinse for home use, we assumed rinsing frequency of 365 times a year if not precisely reported. We assumed rinsing frequency of 320 times a year in studies of 'unsupervised' daily rinse at home (even if instructions to rinse more than once a day were given); we assumed frequency of 160 times (days) a year when it was not precisely reported in studies of supervised daily rinse at school where children were not provided with any rinse for home use; frequency of 30 times a year for weekly rinse at school and frequency of 17 times a year for fortnightly rinse at school.

We investigated further potential sources of heterogeneity by metaregression - for different types of control groups (placebo (PL) or no treatment (NT)), length of follow-up (years) and dropout rate (%). These 'post hoc' analyses were reported as such and findings should be treated with caution.

Sensitivity analysis

For the main meta-analysis of D(M)FS prevented fraction, we planned to undertake a sensitivity analysis including trials with an overall assessment of low risk of bias, but we found no trials satisfying this criterion. We undertook a sensitivity analysis excluding trials where we imputed missing standard deviations. We performed a sensitivity analysis to take account of additional uncertainty related to the cluster-randomised trial by [Ruiken 1987](#), and another excluding one trial ([Spets-Happonen 1991](#)) in which a non-fluoride active agent was present in both fluoride and control groups (the trial was different in this way from all others). We also undertook a sensitivity analysis excluding trials at high risk of bias for allocation concealment, and another excluding trials at high and unclear risk of bias for blinding of outcome assessment. We performed these meta-analyses using a random-effects model.

Presentation of main results - Summary of findings

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach (gdt.guidelinedevelopment.org) to rate the overall 'quality of evidence' for our primary outcome and the most important secondary outcomes in the main comparison. [Summary of findings for the](#)

[main comparison](#) provides outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined and the sum of available data on all outcomes that we rate as important to patient care and decision making.

The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and apply this in our interpretation of results. The four possible ratings are 'high', 'moderate', 'low' and 'very low'. A rating of 'high quality' of evidence implies that we are confident in our estimate of effect and believe that further research is very unlikely to change our confidence in the estimate of effect. A rating of 'very low quality' quality implies that any estimates of effect obtained are very uncertain.

The GRADE approach considers evidence from RCTs that do not have serious limitations as 'high' quality. However, the quality of evidence can be decreased by:

- study limitations (risk of bias);
- inconsistency;
- Indirectness of evidence;
- imprecision; and
- publication bias.

Depending on the seriousness of limitations, we downgraded the quality of evidence by one or two levels for each aspect.

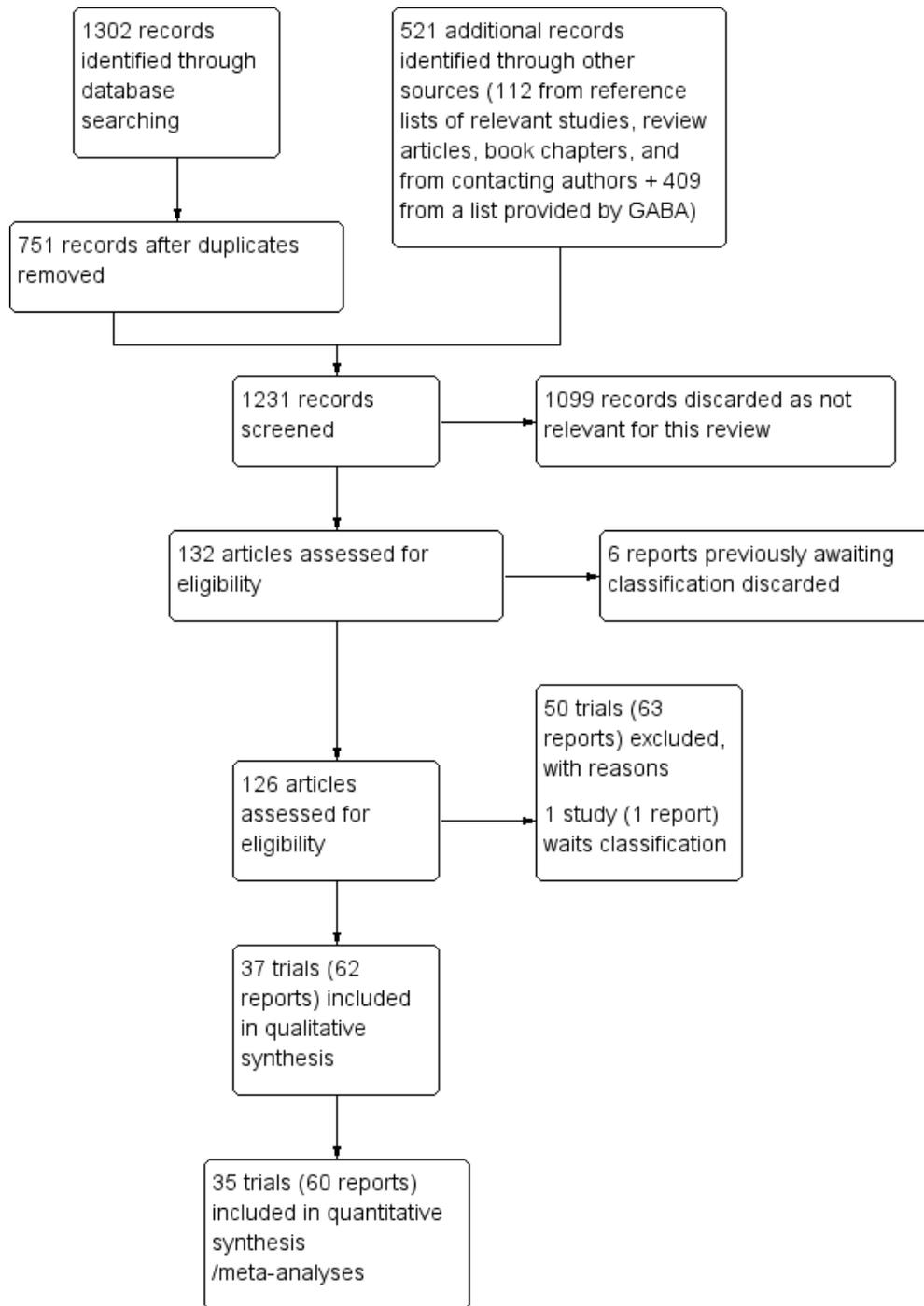
RESULTS

Description of studies

Results of the search

We have used the full search conducted on 22 April 2016 as described in [Search methods for identification of studies](#) to construct the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart shown in [Figure 1](#).

Figure 1. Study flow diagram from 2016 search



For this update, we identified 1823 records through searches (from electronic databases and other sources) and screened 1231 after removing duplicates and records already linked to the review in Archie. After discarding 1099 records as irrelevant, we assessed 132 full-text articles (including some available only as abstracts or summary reports) as potentially eligible, and considered 126 for inclusion in this review. Of these 126 reports:

- 62 reports were related to 37 included trials (including the 36 trials included in the original 2003 review);
- 63 reports were related to 50 excluded trials (including the 43 trials excluded in the original review); and
- one report was related to one study that awaits classification.

We found no reports of ongoing studies.

Included studies

See [Characteristics of included studies](#) table for details of each study.

We included 37 trials in the review. We treated the study conducted by Horowitz 1971 as two independent trials (Horowitz 1971 and Horowitz 1971a) because results for the two age groups in the study have been reported separately as distinct studies. Also, these completely distinct studies were published concomitantly by the same author: Koch 1967, Koch 1967a and Koch 1967b. All 62 study reports were published between 1965 and 2005. The 36 previously included trials were conducted between 1962 and 1994: 10 during the 1960s, 19 during the 1970s, six during the 1980s and one in the 1990s. The 2016 update of this review found another trial conducted in the early 2000s (Moberg Sköld 2005). Thirteen trials were conducted in the USA, four in the UK, six in Sweden, two in Denmark, two in Canada, two in New Zealand, three in Brazil and one in each of the following countries: Finland (Spets-Happonen 1991), The Netherlands (Ruiken 1987), South Africa (van Wyk 1986), Chile (Molina 1987) and Puerto Rico (Duany 1981). Fifteen studies had more than one publication, and one of these studies had seven published reports (Koch 1967). Eleven trials acknowledged assistance (e.g. product provision) and/or financial support from fluoride mouthrinse manufacturers; 13 trials acknowledged support from non-commercial sources, and 16 trials provided no information on sources of funding.

Design and methods

All included studies used a parallel-group design, and one was cluster randomised (Ruiken 1987). Sixteen studies had more than one fluoride mouthrinse treatment group compared with a control (multi-treatment studies); among these, one trial had two treatment groups and two placebo control groups (Ringelberg 1979). Six trials used a factorial design to investigate the effects of multiple topical fluoride interventions (Ashley 1977; Blinkhorn 1983;

DePaola 1980; Koch 1967; Ringelberg 1979; Torell 1965). With regard to type of control group used, five trials used a no treatment control group (Craig 1981; Moberg Sköld 2005; Moreira 1981; Ruiken 1987; Torell 1965), and the remaining 32 used a placebo control group, of which two used tap water as 'placebo solution' (Moreira 1972; Petersson 1998). Study duration (indicated by total length of follow-up as well as treatment duration) ranged from two to three years among included trials; only three trials lasted less than two years (1.6 years) (Horowitz 1971; Horowitz 1971a; Radike 1973).

Participants

Studies were large; only two trials allocated fewer than 100 children to relevant groups (Craig 1981; Spets-Happonen 1991). The total number of children participating in the 37 included trials (given by the sample analysed at the end of the trial periods) was 15,813, and ranged from 95 in the smallest trial (Spets-Happonen 1991) to 1238 in the largest trial (Ringelberg 1982), on average 427 participants per trial.

Investigators recruited all participants from school settings.

All included trials reported that participants were aged 14 or younger at the start, with similar numbers of males and females (where these data were reported). The age of children at the start of trials ranged from five to 14 years (where these data were reported); at least 18 trials included children who were 12 years old at the start, and at least five trials included six-year-olds (but reported no primary teeth caries data). Caries prevalence at baseline (decayed, missing and filled surfaces (D(M)FS)), reported in all but two studies, ranged from 0.94 (Horowitz 1971) to 14.6 D(M)FS (Koch 1967). With regard to 'background exposure to other fluoride sources', all but two studies reported whether or not participants were exposed to water fluoridation: Four studies were conducted in fluoridated communities (Driscoll 1982; Laswell 1975; Moreira 1981; Radike 1973), and 31 studies were not. Of the 31 studies conducted in non-fluoridated areas, researchers clearly reported no (or very low) background exposure to fluoride toothpaste or to other fluoride sources in eight studies, substantial exposure to fluoride toothpaste (over 95%) in seven studies and exposure to other fluoride sources - varnish (Moberg Sköld 2005) and tablets (Ruiken 1987) - in two studies; whether or not participants were exposed to fluoride toothpaste had to be assumed in 16 studies based on study location and year started, as described above.

Interventions

All included trials reported supervised use of fluoride mouthrinse in school programmes, and two trials also tested use of rinse at

home (Spets-Happonen 1991; Torell 1965). Rinsing with sodium fluoride (NaF) was tested in 33 trials, acidulated phosphate fluoride (APF) in four trials (Finn 1975; Heifetz 1973; Laswell 1975; Packer 1975), stannous fluoride (SnF₂) in two (McConchie 1977; Radike 1973) and sodium monofluorophosphate (SMFP), amine fluoride (AmF) and ammonium fluoride (NH₄F) each in a different study (Bastos 1989; Ringelberg 1979 and DePaola 1977, respectively). The fluoride concentration used in tested mouthrinses ranged from 100 ppm F (0.02% NaF) to 3000 ppm F (0.66% NaF), and frequency of application ranged from three to 330 times a year, but these were unusually low and high concentrations and frequencies. Eighteen studies used the concentration of 230 ppm F (180 and 250 ppm F in a few studies), and 20 studies the concentration of 900 ppm F (1000 ppm F in a few studies). It can be seen that when rinsing was performed once a week or once every two weeks, investigators employing 900 ppm F was usually used (17 trials). Conversely, when rinsing was performed once (or twice) a day, the fluoride concentration used was 230 ppm F, or around this concentration (13 trials). The only study (Duany 1981) where information on rinsing frequency was not available is likely to have used daily rinses for all three low concentrations of fluoride tested (this was one of the four studies testing 100 ppm F rinsing solutions). The most usual amounts of mouthrinse used per application was 5 or 10 mL, and usual rinsing time was one or two minutes (these amounts and rinsing times were reported in 21 studies). Four studies reported performance of some form of prior tooth prophylaxis (brushing without paste or with a non-fluoride paste before rinsing, which was not considered a separate intervention on its own but as a possible part of the rinsing procedure) (Ashley 1977; Blinkhorn 1983; Craig 1981; Spets-Happonen 1991).

Outcome measures

Caries increment data

All but two of the 37 trials (Brandt 1972; De Liefde 1989) reported caries increment data (or data from which these could be derived) at the tooth surface level (D(M)FS), and 13 trials reported caries increment at the tooth level (D(M)FT) for permanent dentition; no trial reported caries increment data for the primary dentition [d(e/m)fs/d data]. With regard to components of the DMFS index used (and types of teeth/surfaces assessed), 20 trials reported DMFS data (one trial for premolars and molars only, and 19 trials for all tooth surface types), and 17 trials reported DFS data (two trials for approximal surfaces of premolars and molars only, and 15 trials for all tooth surface types). No choice had to be made between DMFS or DFS data in any one trial. Sixteen trials presented D(M)FS data at more than one follow-up time (which ranged from 1.6 to three years); 27 trials reported follow-up of 2 or 3 years. Three trials also assessed D(M)FS increments during a postintervention follow-up period.

Two studies did not include a visual examination to detect caries (Moberg Sköld 2005; Petersson 1998) when caries was diagnosed by X-rays only. In five studies where a visual examination was employed, investigators did not report use of a probe including tactile criteria (Ashley 1977; Blinkhorn 1983; Brandt 1972; Rugg-Gunn 1973; Ruiken 1987). Twenty trials used X-rays in addition to visual examination for caries detection. Clinical (35 trials) and radiographic (22 trials) examinations provided the definition of different levels or grades of caries lesions, which have been grouped into two basic grades for each method of examination: NCA = non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor/walls) or showing frank cavitation; ER = any radiolucency in enamel/enamel-dentine junction; DR = radiolucency into dentine. Eighteen trials presented results using the dentine cavitation level of diagnosis for caries (CA/DR), and two trials presented results using the enamel level (NCA/ER) (Ashley 1977; Heifetz 1973). The 17 trials remaining did not report the diagnostic level/grade used for caries (14 trials), in which case CA/DR was assumed, or reported both levels of diagnosis (Moberg Sköld 2005; Petersson 1998; Ruiken 1987), in which case CA/DR was chosen where viable. Nineteen trials specified data on the state of tooth eruption considered: seven trials reported data for teeth erupted at baseline (although data were recorded on erupting and erupted teeth in some), and 12 trials reported combined data for erupting and erupted teeth.

Other outcome data

Five trials reporting caries increment also used other similar measures/indices - caries incidence/attack rate in permanent teeth/surfaces (Heidmann 1992; Koch 1967; Koch 1967a; Koch 1967b; Moreira 1981). Three trials reported data on the proportion of children developing new caries (Finn 1975; Heidmann 1992; Torell 1965). One trial also reported data on caries progression (Moberg Sköld 2005), but no trials have reported data on children not remaining caries-free.

A few trials reported assessment of data on adverse effects, but incompletely: stain score (Ringelberg 1979); proportion of children with tooth staining (McConchie 1977; Radike 1973), with incomplete data; signs of sensitivity (allergic reactions) in oral soft tissue (Rugg-Gunn 1973), with the following statement in the trial: "no cases of mucosal hypersensitivity after periodical examinations of every subject"; any side effects (Bastos 1989; DePaola 1977; McConchie 1977), with incomplete or no useable data and with the following statement in all three trials: "no adverse side effects observed". No trials reported adverse acute symptoms (nausea/vomiting during treatment).

Four of the five non-placebo (no-treatment) control trials provided data for unacceptability of the treatment regimen (as measured by dropouts/exclusions) (Craig 1981; Moberg Sköld 2005; Moreira

1981; Torell 1965).

Excluded studies

See [Characteristics of excluded studies](#) for a description of our reasons for rejecting each study.

We excluded 50 trials for a variety of reasons. We have categorised these as related to study design, intervention/comparison or outcome, as given below, on the basis of the main or most obvious reason(s) for exclusion.

Study design

- Not an RCT or quasi-RCT or unlikely to be so - 34 studies ([Arcieri 1981](#); [Badersten 1975](#); [Bohannan 1985a](#); [Boyd 1985](#); [Bristow 1975](#); [Chen 2010](#); [Chikte 1996](#); [Cichocka 1981](#); [Clark 1985a](#); [Corpus 1973](#); [De Canton 1983](#); [Disney 1989](#); [Esteve Canto 1991](#); [Fernandez 1979](#); [Hall 1964](#); [Irmisch 1974](#); [Ivanova 1990](#); [Kani 1973](#); [Kasakura 1966](#); [Kunzel 1978](#); [Louw 1995](#); [McCormick 1970](#); [Mendonca 1995](#); [Moungtin 1975](#); [Nenyei 1971](#); [Roberts 1948](#); [Rodriguez Miro 1983](#); [Shimada 1978](#); [Suntsov 1991](#); [Torell 1969](#); [Weisz 1960](#); [Widenheim 1989](#); [Wilson 1978](#); [Wycoff 1991](#)).

- Open assessment stated or blinded outcome assessment not stated or unlikely - 33 studies: four studies owing to lack of blinding in outcome assessment ([Brodeur 1989](#); [Castellanos 1983](#); [Mendonca 1995](#); [Ramos 1995](#)) and the other 29 studies owing to other features that met the exclusion criteria ([Arcieri 1981](#); [Axelsson 1976](#); [Badersten 1975](#); [Birkeland 1973](#); [Bohannan 1985a](#); [Chen 2010](#); [Chikte 1996](#); [Cichocka 1981](#);

[Corpus 1973](#); [DePaola 1967](#); [Disney 1989](#); [Esteve Canto 1991](#); [Fernandez 1979](#); [Hall 1964](#); [Irmisch 1974](#); [Ivanova 1990](#); [Kani 1973](#); [Kasakura 1966](#); [Kunzel 1978](#); [Louw 1995](#); [Morgan 1998](#); [Morozova 1983](#); [Moungtin 1975](#); [Nenyei 1971](#); [Shimada 1978](#); [Suntsov 1991](#); [Weisz 1960](#); [Widenheim 1989](#); [Wycoff 1991](#)).

Intervention/comparison

- Other intervention or active agent applied with fluoride mouthrinse - 16 studies: five studies owing to use of additional intervention ([Gray 1980](#); [Heifetz 1979](#); [Kitsugi 1978](#); [Luoma 1978](#); [Zickert 1982](#)) and the other 11 studies owing to other features that met the exclusion criteria ([Axelsson 1976](#); [Badersten 1975](#); [Boyd 1985](#); [Bristow 1975](#); [De Canton 1983](#); [DePaola 1967](#); [Disney 1989](#); [Irmisch 1974](#); [Morgan 1998](#); [Morozova 1983](#); [Rodriguez Miro 1983](#)).

- Fluoride rinse solution swallowed after rinsing - two studies ([Aasenden 1972](#); [Frankl 1972](#)).

Outcome

- Followed up for less than one year - we excluded three studies on this basis ([Birkeland 1973](#); [Boyd 1985](#); [Swerdlhoff 1969](#)), but only one study solely on this basis ([Swerdlhoff 1969](#)).

We excluded no studies or the reason that the children/adolescent population enrolled had been medically/dentally compromised.

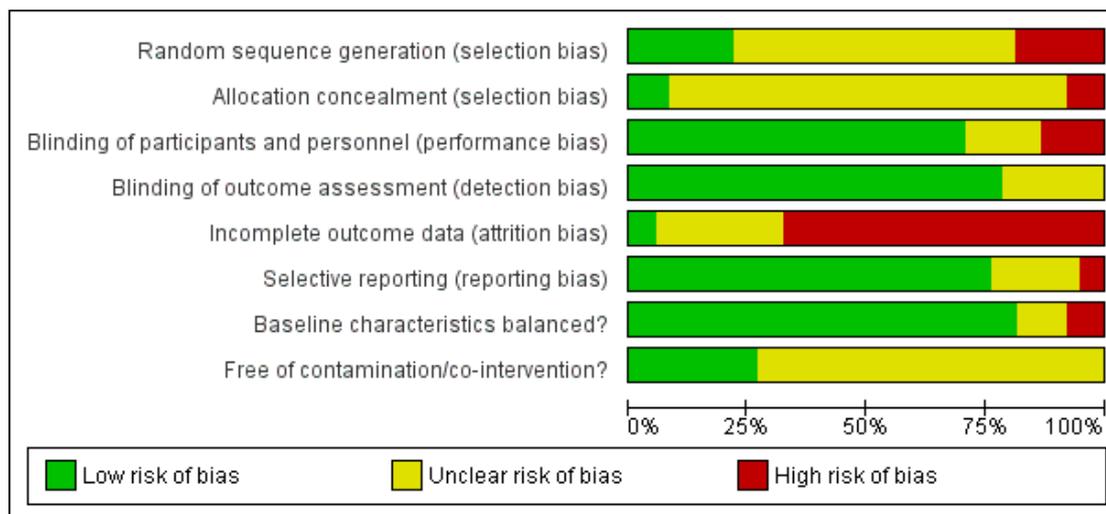
Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#) for a summary of the risk of bias of the 37 studies included in the review.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Baseline characteristics balanced?	Free of contamination/interention?
Ashley 1977	+	?	+	?	+	+	+	+
Bastos 1989	+	+	?	+	+	?	+	?
Blinkhorn 1983	?	?	+	+	?	+	+	?
Brandt 1972	?	?	+	+	+	+	+	?
Craig 1981	+	?	+	?	+	+	+	?
De Liefde 1989	?	?	+	+	+	+	+	?
DePaola 1977	?	?	+	+	+	?	+	?
DePaola 1980	?	?	+	+	+	?	?	?
Driscoll 1982	?	?	+	+	+	+	+	?
Duany 1981	?	?	+	+	+	+	+	?
Finn 1975	?	?	+	?	+	+	+	+
Gallagher 1974	?	?	+	+	?	+	+	?
Heldmann 1992	+	?	+	+	?	+	+	?
Heifetz 1973	?	?	+	+	+	+	+	?
Heifetz 1982	+	?	+	?	+	+	+	?
Horowitz 1971	?	?	+	+	+	+	+	?
Horowitz 1971a	?	?	+	+	+	+	+	?
Koch 1967	+	+	?	?	?	?	+	?
Koch 1967a	+	+	?	+	+	+	+	?
Koch 1967b	+	+	?	+	+	+	?	?
Laswell 1975	?	?	+	?	+	?	+	+
McConchie 1977	?	?	+	+	+	?	+	+
Moberg Sköld 2005	+	?	+	?	+	?	+	+
Molina 1987	+	?	+	+	+	+	+	?
Moreira 1972	+	+	?	+	+	+	+	?
Moreira 1981	+	+	?	?	+	+	+	?
Packer 1975	?	?	?	?	+	+	+	+
Petersson 1998	?	?	?	?	?	+	+	+
Poulsen 1984	?	?	+	+	+	+	+	?
Radike 1973	+	?	+	+	?	?	+	+
Ringelberg 1979	+	?	+	+	+	+	+	+
Ringelberg 1982	?	?	+	+	+	?	+	?
Rugg-Gunn 1973	?	?	+	+	?	+	?	?
Ruiken 1987	?	?	+	?	+	+	+	?
Spets-Happonen 1991	?	?	+	+	+	+	+	?
Torell 1965	+	?	+	?	?	+	+	?
van Vlyk 1988	?	?	+	+	+	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (a plot of the distribution of judgements (low risk of bias, unclear risk of bias and high risk of bias) across studies for each risk of bias item)



All included studies were published between one and four decades ago, and ratings considered the overall context of those papers and correspondence with study authors where available. We considered none of the included studies to be at low risk of bias overall. We considered nine studies to be at unclear risk of bias (Ashley 1977; Blinkhorn 1983; Gallagher 1974; Heidmann 1992; Heifetz 1982; Petersson 1998; Poulsen 1984; Radike 1973; Rugg-Gunn 1973) and the remaining 28 studies to be at high risk of bias.

Allocation

None of the studies were at low risk of selection bias overall, that is, low risk of bias for both sequence generation and allocation concealment. Most (23 studies) were at unclear risk of bias for sequence generation and allocation concealment. We rated three of the studies as having high risk of bias for both sequence generation and allocation concealment because researchers very likely used a quasi-randomisation method (Bastos 1989; Moreira 1972; Moreira 1981).

At least 20 studies had described attempting to do some form of stratification by sex, age, dental age, caries status, number of examiners, etc. Five of these (Bastos 1989; Gallagher 1974; Moreira 1972; Moreira 1981; Ruiken 1987) did not use participants as the unit of randomisation. Ruiken 1987 had stratified schools according to their socioeconomic status and used the schools as a unit of randomisation. Bastos 1989 had divided children “randomly”

between two examiners according to gender and age, and had arranged them in ascending order in terms of number of permanent teeth present and caries status (DMFS); investigators then formed these children into groups of four before assigning rinsing solutions “at random”. Moreira 1972 and Moreira 1981 had used a similar method, forming “homogeneous” groups of four and assigning interventions “randomly”. It seems very likely that investigators used a quasi-randomised method, and allocation concealment would not have been effective. Gallagher 1974 divided the children in each class into two “teams” on the basis of caries status and dental age, then used a flip of a coin to decide which team received the intervention.

We considered eight studies to be at low risk of bias related to random sequence generation (Ashley 1977; Craig 1981; Heidmann 1992; Heifetz 1982; Molina 1987; Radike 1973; Ringelberg 1979; Torell 1965), but the adequacy of allocation concealment was unclear. In addition to the three studies mentioned above (Bastos 1989; Moreira 1972; Moreira 1981), another four studies were likely to have used a quasi-randomised method for sequence generation. Three studies (Koch 1967; Koch 1967a; Koch 1967b) had separated girls and boys into classes, arranged their names in alphabetical order and then assigned them to treatment or control in alternation (quasi-randomisation). However, because all students

were involved in the trial and the order of students appearing in the class register cannot be changed, the risk of bias arising from lack of concealment is low. [Moberg Sköld 2005](#) had only described randomising participants and did not provide details, but overall descriptions in the report suggest that a quasi-randomised method very likely was used.

Blinding

Performance bias

We considered five studies as having high risk of performance bias, as a placebo group was not used ([Craig 1981](#); [Moberg Sköld 2005](#); [Moreira 1981](#); [Ruiken 1987](#); [Torell 1965](#)) - the control group did not use a mouthrinse (no treatment). Risk was unclear in another six studies ([Bastos 1989](#); [Koch 1967](#); [Koch 1967a](#); [Koch 1967b](#); [Moreira 1972](#); [Pettersson 1998](#)); we are unclear whether the “placebo” used was similar enough to maintain blinding. We considered the rest of the studies as having low risk of performance bias.

Detection bias

Only studies that indicated that outcomes assessors were blinded were included in this review. Of all studies included, it was uncertain if attempts to blind the examiners were adequate in eight studies: Five of these studies used no treatment as the control group ([Craig 1981](#); [Moberg Sköld 2005](#); [Moreira 1981](#); [Ruiken 1987](#); [Torell 1965](#)) and were at high risk of bias for participant/personnel blinding; three studies used a placebo control group ([Finn 1975](#); [Laswell 1975](#); [Packer 1975](#)) and indicated only blinding of outcome assessment (examinations were done independently, or X-rays were used). All studies described diagnostic methods used (clinical or radiographic), but not all studies reported thresholds/definitions used for caries and monitoring of diagnostic errors (see ‘Notes’ in the [Characteristics of included studies](#) table for methodological features assessed). We rated the remaining 29 studies as having low risk of bias for outcome assessment.

Incomplete outcome data

The risk of attrition bias was high for most of the included studies (25 trials). We considered only two out of 37 studies to be at low risk of attrition bias ([Craig 1981](#); [Poulsen 1984](#)). We considered another 10 studies to be at unclear risk of bias ([Ashley 1977](#); [Blinkhorn 1983](#); [Gallagher 1974](#); [Heidmann 1992](#); [Heifetz 1982](#); [Koch 1967](#); [Pettersson 1998](#); [Radike 1973](#); [Rugg-Gunn 1973](#); [Torell 1965](#)).

All the participants considered at the end of each study as a proportion of all the participants present at start was 65.3% (13,622 analysed out of 20,854 randomised); this excludes six studies with no data by group on participants randomised ([Ashley 1977](#);

[De Liefde 1989](#); [DePaola 1980](#); [Duany 1981](#); [Pettersson 1998](#); [Spets-Happonen 1991](#)). We could not obtain dropout rates for five of the 37 included studies ([De Liefde 1989](#); [DePaola 1980](#); [Duany 1981](#); [Pettersson 1998](#); [Spets-Happonen 1991](#)). We noted considerable variation in dropout rates, ranging from 8% at three years to 62% at 2.5 years. Reasons for exclusions (when given) included moving away, absence for follow-up examinations and refusal to participate or poor compliance. A few trials reported numbers excluded according to reason for attrition.

Selective reporting

Ideally, we would have compared outcomes listed in each study protocol against outcomes reported in the papers, but this was seldom possible. Most of the studies in this review were published before the year 2000 and provided very little information. We compared results reported in the studies against what was stated in the Methods section and used clinical judgement to consider whether studies had reported data as expected. We considered two studies to be at high risk of selective reporting bias ([Brandt 1972](#); [De Liefde 1989](#)). [Brandt 1972](#) reported only matched-pair analyses data (94 pairs; data from more than a quarter of available participants not analysed).. In our correspondence, the trial author explained that this was an attempt to correct the baseline imbalance observed, but unfortunately, the method of analysis broke the randomisation, precluding inclusion of data in the meta-analysis. [De Liefde 1989](#) reported only results of combined non-randomised and randomised groups (separate results for placebo group not available, data could not be included for meta-analysis). Seven other studies ([Bastos 1989](#); [DePaola 1977](#); [Koch 1967](#); [McConchic 1977](#); [Moberg Sköld 2005](#); [Radike 1973](#); [Ringelberg 1979](#)) had unclear risk of bias, most often because of inadequate reporting/non-reporting of adverse event data.

Other potential sources of bias

Baseline imbalance

We assessed whether imbalance of important prognostic factors (baseline caries level) was evident between the arms of included trials. We assessed 30 trials as having low risk of bias for this domain.

We considered three studies to be at high risk of bias from baseline imbalance. One trial did not report any baseline data ([De Liefde 1989](#)), whereas [Brandt 1972](#) had described baseline imbalance in caries level. [Duany 1981](#) also observed baseline imbalance in caries level.

We considered four studies to be at unclear risk of bias. [DePaola 1980](#) described baseline data as “balanced” (for which randomisation may have succeeded to produce nearly exact balance) but did not report any of the actual values for baseline characteristics (such as initial caries levels). A few trials reported some degree of

imbalance (for characteristics considered most influential, usually initial caries levels) and generally described this as not significant or indicated that adjustment had resulted in trivial differences in effect estimates (Koch 1967b; Laswell 1975; Rugg-Gunn 1973).

Contamination/co-intervention

We assessed 10 trials as having low risk of bias owing to freedom from contamination. These trials provided information suggesting no differences between groups in co-interventions that could have affected observed outcomes, such as toothbrushing practices, oral hygiene instructions, dental checkups/preventive treatments or rinsing procedures. In the other studies, risk of bias was unclear, as researchers provided no or not enough information.

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings - fluoride mouthrinse compared with placebo or no treatment for preventing caries in children and adolescents](#)

Fluoride mouthrinses versus placebo or no treatment

Effects of fluoride mouthrinses on dental caries increment

The included studies reported the effects of fluoride mouthrinses on dental caries increment (as measured by the DMF index) in a variety of ways. Where appropriate and possible, we have combined these to produce pooled estimates. We have reported the prevented fraction (PF) results separately here for:

- decayed (missing) and filled surface prevented fraction (D(M)FS PF) (Analysis 1.1; 35 trials); and
- decayed (missing) and filled teeth prevented fraction (D(M)FT PF) (Analysis 1.2; 13 trials).

We could not present in this review estimates of the effects of fluoride mouthrinse on caries increment in deciduous teeth/surfaces (as measured by the dmf index) as no study contributed data.

Two included studies (Brandt 1972; De Liefde 1989) did not contribute data suitable for meta-analysis, although we have retained them in the review as part of the qualitative data synthesis (we have described their characteristics in the [Characteristics of included studies](#) table). We have extracted data from the other trials as appropriate to produce the pooled estimates, as described in the [Methods](#) section.

Imputation of missing standard deviations

Standard deviations (SDs) of mean caries increment data were missing in 12 of the 35 studies reporting D(M)FS data (Bastos 1989; DePaola 1977; Driscoll 1982; Finn 1975; Gallagher 1974; Heidmann 1992; Laswell 1975; McConchie 1977; Moreira 1972;

Poulsen 1984; Ruiken 1987; van Wyk 1986). In the original version of this review, we estimated unreported SDs from analysis of the 179 available treatment arms for the series of topical fluoride reviews with complete information (as of October 1999). This resulted in a regression equation of $\log(\text{SD caries increment}) = 0.64 + 0.55 \cdot \log(\text{mean caries increment})$ ($R^2 = 77\%$). We used this equation to estimate missing SDs from mean D(M)FS increments for meta-analyses. Similarly, we used this same regression equation to estimate missing SD data for three of the 13 trials reporting D(M)FT data (Bastos 1989; Finn 1975; McConchie 1977).

Inflating standard errors for approximate analyses of cluster-randomised trials

One cluster-randomised trial did not account for clustering of the data in its reporting of results (Ruiken 1987). As we had already incorporated this in the original review, accounting for clustering through the inflated variance approach, we decided that the same approach would be used and we would conduct sensitivity analysis again to take account of additional uncertainty related to the cluster-randomised trial. We inflated the variance of the prevented fraction estimate by an amount equal to $(1 + (m-1) \cdot \text{ICC})$, where m is the average cluster size and ICC the intraclass correlation coefficient. A conservative value of 0.1 was used for the ICC because we could not find an ICC from this or a similar trial at the time.

Effects on tooth surfaces of permanent dentition: D(M)FS prevented fraction (PF)

For all 35 trials combined, the D(M)FS PF pooled estimate was 0.27 (95% confidence interval (CI), 0.23 to 0.30; P value < 0.0001), suggesting a large caries-preventive benefit from the use of fluoride mouthrinse. The CIs are relatively narrow, and although not substantial, heterogeneity in results could be observed statistically ($\text{Chi}^2 = 58.43$ on 34 degrees of freedom, P value = 0.006; $I^2 = 42\%$; Analysis 1.1).

Metaregression and sensitivity analyses: D(M)FS PF

Univariate metaregression suggested no significant association between estimates of D(M)FS prevented fractions and prespecified factors: baseline caries severity, background exposure to fluoridated water, background exposure to fluoride toothpaste, background exposure to any fluoride source, fluoride concentration and rinsing frequency. We noted an association of 'total intensity of application per year' (frequency times concentration) with the prevented fraction, but this became non-significant when we excluded from the analysis the trial of DePaola 1977, a study with high influence (an outlier).

Further univariate metaregression analyses on other characteristics not specified a priori showed no significant association between estimates of D(M)FS prevented fractions and type of control group

(placebo/no treatment), dropout rate or length of follow-up (duration of study in years). We have not investigated other potential effect modifiers (e.g. mode of mouthrinse use) because virtually all trials were conducted in school settings under supervision.

We have presented the results of random-effects meta-analyses of D(M)FS PFs (all trials) in Additional Table 1. We have provided metaregression results for all potential effect modifiers investigated in Additional Table 2. It should be noted that we omitted the influential study by DePaola 1977 from the analysis intensity of application with prevented fraction. These metaregression results must be interpreted with caution given the observational nature of the comparisons and the large number of comparisons made. To determine the potential influence of data imputation and approximation, we undertook a sensitivity analysis, restricting pooling of trials to those that were fully reported and suitable for analysis (23 trials). Results of this gave rise to a very similar D(M)FS PF value to the one obtained as a result of the full meta-analysis (PF = 0.28, 95% CI 0.24 to 0.31), although a large reduction in the indicator of heterogeneity ($I^2 = 19\%$) was evident. We also performed a sensitivity analysis for the main meta-analysis of D(M)FS prevented fraction to take account of additional uncertainty related to the cluster-randomised trial by Ruiken 1987 after accounting for clustering using the inflated variance approach. The D(M)FS PF pooled estimate was 0.26 (95% CI 0.23 to 0.30; P value < 0.0001). These results are nearly identical to results of the analysis ignoring the cluster-randomised design because the estimate for this trial is similar to the meta-analysis result, and altering its weight has minimal effect.

We also performed sensitivity analyses excluding the three trials at high risk of bias for allocation concealment (Bastos 1989; Moreira 1972; Moreira 1981) and excluding the eight trials at high or unclear risk of bias for blinding of outcome assessment (Craig 1981; Finn 1975; Laswell 1975; Moberg Sköld 2005; Moreira 1981; Packer 1975; Ruiken 1987; Torell 1965). For allocation concealment, results were equal to those of the full meta-analysis (PF = 0.27, 95% CI 0.23 to 0.30) with some increase in the indicator of heterogeneity (from 42% to 46%); for blind outcome assessment, results showed similar PF values (PF = 0.26, 95% CI 0.22 to 0.30) and a somewhat increased indicator of heterogeneity (from 42% to 48%).

We performed yet another sensitivity analysis by excluding one trial (Spets-Happonen 1991) in which a non-fluoride active agent was present in both fluoride and control groups, making the trial different in this way from all others that had been included. The D(M)FS PF pooled estimate resulting from exclusion of this trial was identical to the analysis that includes it (PF = 0.27, 95% CI 0.23 to 0.30). This is a small trial that carries little weight and had minimal effect in a meta-analysis that includes so many larger studies.

Funnel plot and test for funnel plot asymmetry: D(M)FS PF

A funnel plot of the 35 included trials reporting D(M)FS PFs does not look asymmetrical, and the weighted regression test for asymmetry (Egger 1997) was not statistically significant (asymmetry intercept: -0.69 (95% CI -1.89 to 0.50; P value = 0.24)). Therefore, we found no evidence of bias when this method was used.

Effects on whole teeth of permanent dentition: D(M)FT PF

Thirteen trials reported data that allowed calculation of the D(M)FT PF. We included all 13 studies in the analysis of D(M)FS PF. Results of this analysis are similar to those reported above (for D(M)FS PF).

The pooled estimate of D(M)FT PF was 0.23 (95% CI 0.18 to 0.29; P value < 0.0001), suggesting moderate to large benefit of fluoride mouthrinse within relatively narrow CIs. Heterogeneity between trials ($\text{Chi}^2 = 26.04$ on 12 degrees of freedom, P value = 0.01; $I^2 = 54\%$) was not substantial, although it was statistically significant.

We have also presented results of the random-effects meta-analysis of D(M)FT PFs (all 13 trials) in Additional Table 1.

Effects on primary tooth surfaces/teeth: d(e/m)fs/t PF

None of the included trials reported on caries increment in deciduous teeth/tooth surfaces (no data were available).

Effects of fluoride mouthrinse on other outcomes

A few trials report data for other relevant outcomes (see "Outcome measures" under Description of studies). Some of these are simply other measures/indices for dental caries increment in permanent teeth/surfaces and require no further consideration. Three trials reported on the proportion of children developing new caries. Results of meta-analyses for the proportion of children developing new caries are presented below. The few trials that reported on adverse effects give no useable (incomplete) data for analysis. Four of the non-placebo controlled trials reported data for unacceptability of treatment (as measured by dropouts in the no-treatment control trials). We have described below results of meta-analyses of these data.

Development of new caries: risk ratio

Three trials reported results on the proportion of children developing one or more new caries (Finn 1975; Heidmann 1992; Torell 1965). The pooled estimate (random-effects meta-analysis) of the risk ratio was 0.77 (95% CI 0.46 to 1.29), with considerable heterogeneity in the results ($\text{Chi}^2 = 54.59$ on 2 degrees of freedom, P value < 0.0001; $I^2 = 96\%$).

Not remaining caries-free

None of the trials reported data on the proportion of children not remaining caries-free.

Tooth staining

The only trial reporting average stain scores per individual within each group did not provide standard deviations (SDs), and data could not be summarised as average mean differences (MDs) in treatment effects with their 95% confidence intervals (Ringelberg 1979). Study authors reported a significant difference in stain score from control (n = 44; mean score = 1.05) in the group using an amine fluoride mouthrinse (n = 84; mean score = 3.57) and a non-significant difference from control (n = 52; mean score = 0.31) in the group using a sodium fluoride mouthrinse (n = 87; mean score = 0.97), concluding that use of amine fluoride mouthrinse resulted in the highest stain score.

Reporting on tooth staining was incomplete in two other trials, where stannous fluoride mouthrinsing was tested against placebo rinsing: In McConchie 1977, researchers stated that “some staining was observed in a very small number of children in the trial, where approximately six children had tenacious staining that required a rubber cup prophylaxis carried out”, but they did not indicate to which groups these children belonged. In Radike 1973, researchers stated that “most of the participants who exhibited poor oral hygiene had some amount of yellow pigmentation, somewhat more noticeable in the children in the test group”.

Mucosal irritation/oral allergic reaction

One trial reported incompletely on oral soft tissue irritation/signs of sensitivity (allergic reaction) to the rinse (Rugg-Gunn 1973); these researchers described “no cases of mucosal hypersensitivity after periodical examinations of every subject”.

Signs of acute toxicity

None of the studies reported adverse acute symptoms (nausea/vomiting during treatment).

Unacceptability of treatment (dropouts/exclusions)

The pooled estimate of the risk ratio of dropping out from the mouthrinse arm as opposed to the non-treatment arm in the four non-placebo-controlled trials that reported dropouts (Craig 1981; Moberg Sköld 2005; Moreira 1981; Torell 1965) was 1.33 (95% CI 0.62 to 2.83). Heterogeneity was evident in these results (Chi² = 14.15 on 3 degrees of freedom, P value = 0.003; I² = 79%).

DISCUSSION

Summary of main results

We have presented the key findings in [Summary of findings for the main comparison](#).

The main aim of this review was to estimate the effects on dental caries of using fluoride mouthrinse compared with placebo or no treatment in children. More than 15,800 children were included in the 37 trials comparing a fluoride mouthrinse against a placebo or no treatment. For almost all children, the fluoride rinse they received was a sodium fluoride (NaF) formulation, provided in supervised school-based mouthrinsing programmes, often on a daily or weekly/fortnightly basis. Fluoride mouthrinsing at these two rinse frequencies and two main different strengths (230 ppm F (fluoride concentration)/900 ppm F) has proved a versatile method of self applied topical fluoride use, and an effective method when used regularly over time under supervision.

An average caries reduction in terms of decayed, missing and filled tooth surfaces (DMFS) in permanent teeth of about 27% can be expected from use of this method. The meta-analysis of the 35 studies assessing the effect of fluoride mouthrinse on the permanent dentition suggests that this reduction falls within narrow confidence intervals (23% to 30%).

A secondary aim of this review was to determine whether we could find any relationship between the caries-preventive effectiveness of fluoride mouthrinse and a number of factors, including the initial level of caries severity, background exposure to fluoride and fluoride concentration and frequency of use. We were unable to detect a clear relationship between any of these factors and the magnitude of the treatment effect in the metaregression analysis performed in spite of substantial variation between trials in these factors. This result should, however, be interpreted with caution. Even a meta-analysis including 35 trials has limited power to detect such relationships and, like all analyses of observational data, is subject to the problem of potential confounding. In addition, some factors such as ‘background exposure to fluoride’ introduce the problem of potential misclassification due to the poor quality of reported data on exposure to fluoride other than in water. We were forced to make several assumptions, for instance, classifying ‘use of fluoride toothpaste’ for 16 of the studies on the basis of the year when the study was conducted and its location. We were also forced to treat this as a dichotomous variable (before/after mid 1970s), although it is likely that use of fluoridated toothpaste gradually increased during the 1960s, 1970s and 1980s. Similarly, we grouped exposure to fluoride in toothpaste and fluoride in water into a single dichotomous variable, which is likely to group studies whose participants had quite different levels of baseline exposure to fluoride sources. These problems may bias any estimates of effect towards the null hypothesis. Nevertheless, these results suggest that fluoride mouthrinse may still be of benefit after the advent of fluoride toothpaste, and in both fluoridated and non-fluoridated areas.

We did observe a significantly greater treatment effect with increased total intensity (frequency times concentration) of

mouthrinse application. Although plausible, this relationship was dependent on the inclusion of one study with particularly powerful effects (DePaola 1977). After exclusion of this study from the analysis, we noted no significant association with this factor. It should be noted that in most studies where mouthrinse was performed once a week (or once every two weeks), a rinse employing higher fluoride concentrations (usually 900 ppm F) was used (16 trials). Conversely, in most studies where rinsing was performed once (or twice) a day, a lower fluoride concentration (usually 230 ppm F) was used (13 trials). Moreover, in six multi-arm studies investigating both combinations of concentrations-frequencies (and in seven studies testing the two main fluoride concentrations), we averaged this intensity score over fluoride treatment groups to combine study results, a decision that may have slightly affected this particular investigation of heterogeneity (and that of dose response). Nevertheless, looking specifically at the effectiveness of the two most commonly used fluoride mouthrinse regimens indicates that few choices may be available when the weaker (low concentration) is used as a daily rinse and the stronger (high concentration) as a weekly or fortnightly rinse. This does not necessarily imply that when both concentrations are used daily, or both are used as weekly/fortnightly rinses, they will have a similar effect. A weaker solution may well yield poorer results when used less frequently. More robust investigations of these aspects of the intervention require direct, head-to-head comparisons of different fluoride concentrations, frequencies and intensities, which were not within the scope of this review.

Overall completeness and applicability of evidence

The evidence included in the review pertains to caries in children and adolescents, where all studies that met the review's inclusion criteria examined the caries-inhibiting effect of fluoride mouthrinse used in supervised school-based schemes on permanent teeth, with only two studies also looking at unsupervised home use of rinse, and none of the studies reporting data on the primary dentition. We found most of the evidence in the school setting where children were supervised when rinsing, although the evidence may be applicable to other settings where children use mouthrinsing under supervision or not.

Although there is clear evidence that fluoride mouthrinses have a caries-inhibiting effect, we found little information about the effects of fluoride mouthrinses on other outcomes such as the proportion of children developing new caries, or on the acceptability of a fluoride rinsing regimen. We found little useful information about possible adverse effects of the procedure, such as tooth staining or oral soft tissue irritation/allergic reactions, and none of the studies reported on signs of acute toxicity. This scarcity of direct evidence from clinical trials on relevant outcomes other than dental caries makes it more difficult for clinicians and policy makers to weigh the benefits of fluoride mouthrinse use in preventing caries

against possible shortcomings of the procedure, whether provided in community dental health programmes or in the home environment.

The trials included in this review used a variety of fluoride rinsing frequencies, agents and concentrations. In studies with more than one relevant intervention group and a common control group, such as those comparing different active fluoride agents or concentrations of fluoride ions, or rinsing frequencies, against a placebo group, we combined summary statistics from the studies (number of children analysed, mean caries increments, standard deviations) from all relevant intervention groups to obtain a measure of treatment effect. This enabled the inclusion of all relevant data in the primary meta-analyses assessing the caries-inhibiting effect of fluoride mouthrinsing on children's permanent tooth surfaces, but it has limited a secondary investigation of dose response.

The trials included in this review were conducted with participants who were at differing levels of caries risk, as evidenced by the variability of caries increments in the control groups, and who were based in different locations with variability in background exposure to other sources of fluoride.

The caries increment prevented fraction appeared to be consistent across different populations, levels of caries risk and exposure to other fluoride sources. The absolute benefit from fluoride mouthrinse will, of course, depend on the expected caries increment in the target population. When the expected caries increment is small, the absolute benefit of fluoride mouthrinse will be small. Moreover, the Cochrane review (Marinho 2003b) that evaluated the effects of all main topical fluoride interventions for preventing caries in children and adolescents found evidence that the relative effect of topical fluoride may be greater in those who have higher baseline levels of caries.

An important issue in this review is whether the body of evidence, which consists of older studies carried out in the 1960s and 1970s mainly with participants who were probably not exposed to fluoride toothpaste, is applicable today, when fluoridated toothpastes are widely available and level of use is generally high. Among the 31 studies conducted in non-fluoridated areas, seven studies reported substantial exposure to fluoride toothpaste (over 95%). In this update, we included only one new study (Moberg Sköld 2005), which was carried out in Sweden in the early 2000s. The prevented fractions (PFs) observed in this trial comparing various rinsing frequencies against a no-treatment control group where participants would have had lifetime use of fluoride toothpaste pointed out a large effect, greater than the overall pooled result. Again, the Cochrane review (Marinho 2003b) summarising all the evidence on the effects of the main topical fluoride interventions found no evidence that the effect of topical fluoride was dependent on background exposure to other fluoride sources.

We have found little information about the adverse effects of fluoride mouthrinse; only one randomised controlled trial (RCT) reported data on tooth staining, concluding that use of amine fluoride mouthrinse resulted in a high stain score. Substantial infor-

mation on a particular type of adverse effect (fluorosis) of topically applied fluoride treatments (especially toothpaste) can be found in a Cochrane review on topical fluoride and risk of fluorosis (Wong 2010).

Quality of the evidence

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach to assess the quality of evidence for fluoride mouth rinses versus placebo or no treatment.

In terms of methodological limitations of the studies, we assessed none of the trials included in this review as having low risk of bias; most (28) were at high risk of bias. The domain most commonly found to be at high risk of bias was incomplete outcome data (attrition bias), followed by random sequence generation and allocation concealment (selection bias), and blinding of participants and personnel (performance bias). Moreover, all but one of the included studies were published before the year 2000, most in the 1970s and 1980s, and most papers provided little information on topics considered important for assessment of bias. This meant that many of the trials included in the review were at 'unclear' risk of bias. Most studies conducted supervised mouthrinsing in the school setting - this was considered for indirectness, but downgrading was considered unnecessary because the evidence may be applicable to other settings where children use mouthrinsing under supervision or not.

For the primary outcome, we downgraded the quality of evidence on caries increment on permanent tooth surfaces (DMFS) to *moderate quality* because of limitations in study design across the 35 trials (15,813 participants) contributing data to this meta-analysis. The size of the treatment effect for the effectiveness outcomes (caries increment) was clinically important. For the same reason, the quality of evidence for the caries-preventive effect on permanent teeth (DMFT increment) based on 13 trials (5105 participants) was also moderate; we are moderately confident in the effect estimate - the true effect is likely to be close to the effect estimate, but there is a possibility that it could be different.

Only three studies reported on developing one or more new caries (1805 participants). It is unclear whether the other studies measured this outcome; therefore, we cannot rule out the possibility of reporting bias. We also downgraded the quality of evidence owing to high risk of bias in two of the three studies and owing to highly inconsistent findings across studies. Therefore quality of evidence for this outcome is very low. Our confidence in the effect estimate is very limited, and further research is very likely to have an important impact and is likely to change this estimate.

The quality of the evidence for dropping out from the mouthrinse as opposed to dropping out from the control condition (as an indirect measure of treatment acceptability) was also very low. The four studies (1700 participants) that contributed data to the pooled results have serious limitations in their methods; all are at

high risk of bias. We downgraded further for imprecision because of the small numbers of events and participants, which contributed to the wide confidence intervals. Serious, unresolved heterogeneity was also observed. Besides, it is unclear how this outcome is linked to participants' lack of acceptance of treatment.

The quality of the evidence on another two outcomes - risk of tooth staining (three trials) and oral mucosal irritation (one trial) - is very low, owing to very incomplete reporting and concerns about risk of bias. Too little information was provided for assessment of whether risk was increased with fluoridated mouthrinses.

Potential biases in the review process

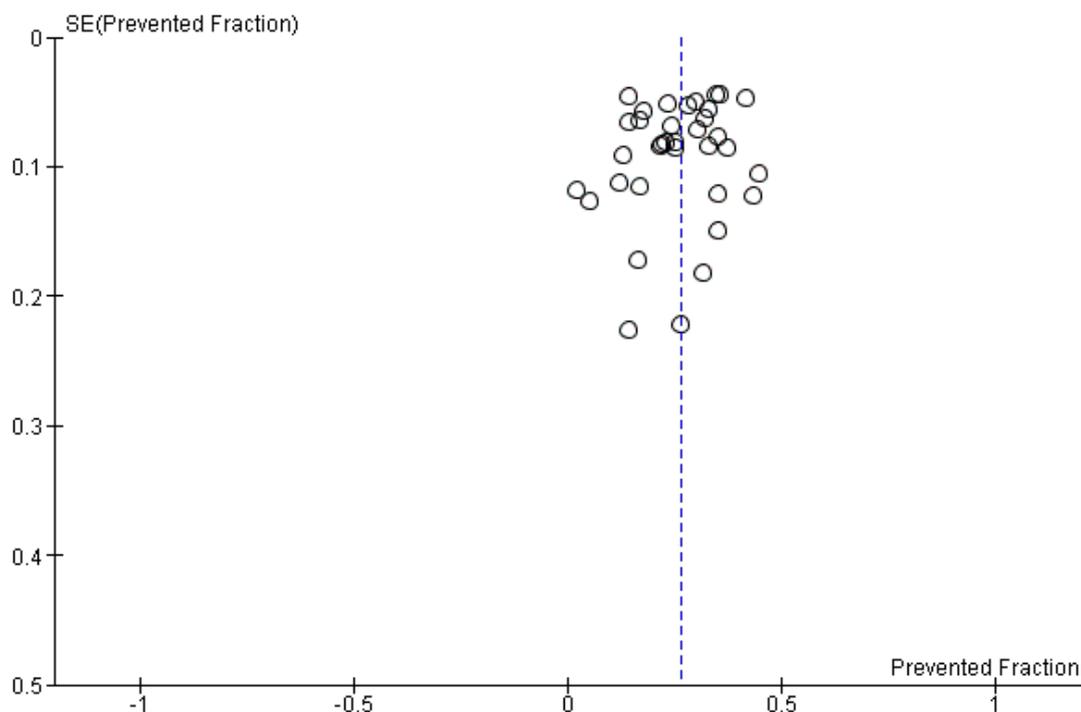
We used a sensitive search strategy to identify trials for inclusion in this review and placed no restrictions on publication status nor language. We translated many references to determine whether or not they included trials eligible for inclusion in this review.

We made a thorough attempt to investigate sources of heterogeneity in this review, examining factors related to participants and interventions, as discussed above (Summary of main results), and study methodological/design quality. None of the a priori specified factors discussed above (initial caries levels, background exposure to fluoride, frequency of use, fluoride concentration) was clearly related to heterogeneity. When we looked for any relationship between the caries-preventive effectiveness of fluoride rinse and a few other factors posed post hoc (length of follow-up, prior prophylaxis, dropout rate, type of control group), we found no significant associations. Even though the type of control group (placebo/no treatment) might represent a strong indicator of study quality and source of heterogeneity in the topical fluoride reviews (Marinho 2015), we did not observe a relationship between type of control group and prevented fraction in this review, possibly because only five non-placebo-controlled trials were included. Moreover, it should be pointed out that we observed a generally high attrition rate across fluoride rinse trials (mean of 32%). Overall only 65% of all participants at the start remained at the end of the studies, and results were often based on compliant participants who actually completed the study. Thus, the issue of longer-term compliance should not be disregarded when such a procedure is administered. We performed a sensitivity analysis for the main meta-analysis to take account of additional uncertainty we may have about the cluster-randomised trial by Ruiken 1987. This produced results (pooled DMFS PF) virtually identical to those of the analysis ignoring the cluster-randomised design because the estimate for this trial is similar to that for the meta-analysis result, and altering its weight has minimal effect. We also performed sensitivity analyses for the main meta-analysis to take into account the uncertainty that we had about imputations for missing standard deviations and for inclusion of trials at high risk of bias for allocation concealment and for blinding of outcome assessment. These sensitivity analyses showed results that were very similar, albeit with some variation in levels of heterogeneity, to those of the full DMFS PF

meta-analysis. The unchanged sensitivity analysis result obtained for the key domain of allocation concealment was possibly due to the fact that this process was generally poorly described in the included studies.

A degree of funnel plot asymmetry may be suggested by visual inspection (Figure 4), but the Egger test provided no evidence of a significant relationship between trial size and effect estimate.

Figure 4. Funnel plot of comparison: I Fluoride mouthrinse versus placebo or no treatment, outcome: I.I D(M)FS increment (PF) - nearest to 3 years (35 trials)



Agreements and disagreements with other studies or reviews

The general direction of findings presented is in keeping with those of other reviews (e.g. [Twetman 2004](#); [Weyant 2013](#)), which also found evidence for the effectiveness of fluoride mouthrinse.

The estimate of caries reduction in this review remains similar to that reported in the meta-analysis on the caries-preventive effect of fluoride mouthrinses in [Twetman 2004](#), which found a pooled D(M)FS PF estimate of 29% (95% confidence interval (CI) 14% to 53%) reduction in caries increment for children with no additional fluoride exposure, although trials including children with

no background fluoride exposure (pooled results combining both subsets not reported) found a PF of 6% (95% CI 0% to 30%). It is also similar to that reported in the most recently published meta-analysis ([Weyant 2013](#)), where treatment effects for 900 ppm F mouthrinse solutions only were presented as pooled D(M)FS standardised mean differences (SMDs), and a pooled estimate of -0.26 (95% CI -0.40 to -0.13) was obtained (owing to the character of D(M)FS data, mean caries increments are closely related to their standard deviations).

Nevertheless, there were substantial differences in selection criteria and methods between these reviews, and consequently in the

numbers and types of studies included. Of the 21 studies included in D(M)FS PF meta-analyses in the review by [Twetman 2004](#), we did not include five in this review. We identified and included 16 additional studies in this review, including one published after the [Twetman 2004](#) review ([Moberg Sköld 2005](#)).

As for the other review ([Weyant 2013](#)), of the eight studies included in its D(M)FS SMD meta-analysis of 900 ppm F mouthrinses, we included seven in this review; in the trial that did not meet the inclusion criteria for our review ([Chikte 1996](#)), we found no indication of random or quasi-random allocation, and blind outcome assessment, also not stated or indicated, was unlikely. We identified 10 additional studies testing 900 ppm F mouthrinses for inclusion in this review - all published before the [Weyant 2013](#) review.

This updated Cochrane review includes one additional RCT ([Moberg Sköld 2005](#)) compared with the previous version ([Marinho 2003](#)). This included trial is not included in the reviews mentioned above ([Twetman 2004](#); [Weyant 2013](#)).

The large body of evidence contained in this updated Cochrane review provides the best available evidence of the effectiveness of fluoride mouthrinses compared with placebo or no treatment (the comparative effectiveness of topical-fluoride interventions is addressed in another review in this series ([Marinho 2004](#))).

AUTHORS' CONCLUSIONS

Implications for practice

This review found that supervised regular use of fluoride mouthrinse by children and adolescents is associated with a large reduction in caries increment in permanent teeth (the quality of evidence is moderate). Compared with control groups, daily and weekly/fortnightly supervised rinse programmes result on average in 27% (95% CI 23% to 30% reduction) fewer decayed, missing or filled permanent tooth surfaces. Most of the evidence is from studies that evaluated use of fluoride mouthrinse supervised in a school setting, but the findings may be applicable to children in other settings with supervised/unsupervised rinsing, although the size of the caries preventive effect is less clear.

We found no evidence that this relative effect was dependent on baseline caries level nor exposure to other fluoride sources, fluoride concentration and mouthrinsing frequency, although this result should be interpreted with caution. A higher decayed (missing) and filled surface (D(M)FS) prevented fraction was shown with increased intensity of application (frequency times concentration). This relationship was dependent on the inclusion of one study with particularly powerful effects.

In line with the findings for permanent tooth surfaces, regular mouthrinsing with fluoride results on average in 23% (95% CI,

18% to 29%; $I^2 = 54%$) fewer decayed, missing or filled permanent teeth (moderate quality evidence).

Unfortunately, the review does not provide useful information on the likelihood of significant side effects with the use of fluoride mouthrinse, and information on acceptability is inconclusive.

The evidence seems applicable to current clinical practice. Although the evidence base for fluoride mouthrinse is derived mainly from studies conducted when fluoridated toothpaste was not widely available in the 1960s and 1970s, the eight trials from the 1980s and 1990s show no evidence of smaller treatment effects.

Implications for research

We have identified a large number of trials, but the reporting of the trials included in this review is relatively poor, with many lacking important methodological details. This is likely due in part to the fact that most are relatively old. Many characteristics considered crucial for excluding bias, such as clearly stated randomisation and allocation concealment, have been more emphasised only in recent years, after most of the mouthrinse trials were reported. However, given the clarity of study results, additional randomised comparisons of fluoride mouthrinse and placebo alone would be difficult to justify. Head-to-head comparisons of fluoride rinses and other preventive strategies, and of different fluoride rinse application features, may provide more useful information.

It is important that future trials include assessment of other relevant outcomes such as potential adverse effects and those related to acceptability of treatment. Planning and conducting an economic analysis alongside the clinical trial could be considered. In addition, evaluation of possible differences in effect associated with fluoride rinse application features, such as frequency/concentration of application, should be based on trials that directly compare such features. Future trials should be well-designed RCTs (adequate sequence generation and allocation concealment methods, blinding of participants and outcome assessors) reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (www.consort-statement.org). Researchers should use core outcomes on assessment of caries and the impact of caries, which may be available through the Core Outcome Measures in Effectiveness Trials (COMET) initiative (www.comet-initiative.org).

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ashley 1977

Methods	Study design: 4-arm parallel-group RCT (only 2 relevant arms used), placebo-controlled Study duration: 2 years	
Participants	Participants randomised (numbers for relevant groups NR) 488 children analysed at 2 years (available at final examination) Average age at start: 12 years Surfaces affected at start: 9.4 DFS Exposure to other fluoride: no Year study began: 1973 Location: UK Setting of recruitment and treatment: school	
Interventions	Comparison: FR + ptc vs PL + ptc FR group: 0.02 % NaF, 100 ppm F PL group: non-F rinse School use/supervised, daily (160 rinses/y), 20 mL applied for 1 minute Before application: Both groups had toothbrushing with non-fluoride toothpaste Postop instruction: NR	
Outcomes	2yNetDFS increment - (E+U)(NCA)cl+(ER)xr Reported at 2 years' follow-up PF-DFS MD-BL-DFS MD-DFS DFS (U)	
Declaration of Interest	No information provided	
Funding	Financial support for the study provided by the Warner Lambert Research Institute	
Notes	Clinical (V) caries assessment by 1 examiner (FOTI used); diagnostic threshold = NCA. Radiographic assessment (postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruptions included = E/U. Intraexaminer reproducibility checks for incremental caries data (ICC for clinical 0.95, for radiographic 0.8); reversal rate between 12% and 7% of observed DFS increment in study groups	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a table of random numbers, subjects were allocated within each school to one of four study groups"

Ashley 1977 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: “The study was organized on a double-blind basis...” “The placebo rinse preparation was identical to the active rinse, except that it did not contain any fluoride” Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “The study was organized on a double-blind basis...” Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 12% in 2 years (all groups) Dropout by group: not reported Reasons for losses: mainly due to moving from the area Comment: numbers lost not high, given length of follow-up; differential loss between groups not assessable. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at baseline and at final exams
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - (E+U)(NCA)cl+(ER)xr, reported at 2 years’ follow-up PF-DFS MD-BL-DFS MD-DFS DFS (U) Comment: trial protocol not available. All prespecified outcomes (in Methods) reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DFS: 9.10 (6.75) FD, 9.79 (7.28) PL DMFT: 5.71(3.44) FD, 6.06 (3.66) PL DMFS: 10.47 (7.36) FD, 11.05 (7.98) PL Age: 12.33 FD, 12.28 PL Comment: initial caries appears balanced between groups. Age also balanced
Free of contamination/co-intervention?	Low risk	Non-fluoride toothpaste provided to all for home use (no rinse provided)

Bastos 1989

Methods	<p>Study design: 4-arm parallel-group quasi-RCT (only 3 relevant arms used)**, “placebo”-controlled</p> <p>Study duration: 2.5 years</p>	
Participants	<p>Participants randomised: N = 766</p> <p>420 children analysed at 2.5 years (after exclusions, available at final examination)</p> <p>Age range at start: 9 to 12 years (average = 10)</p> <p>Surfaces affected at start: 10.5 DMFS (from sample randomised)</p> <p>Exposure to other fluoride: none assumed</p> <p>Year study began: 1977</p> <p>Location: Brazil</p> <p>Setting of recruitment and treatment: school</p>	
Interventions	<p>Comparison: FR (2 groups) vs PL</p> <p>FR group 1: 0.2% NaF, 900 ppm F</p> <p>FR group 2: 0.7% SMFP, 900 ppm F</p> <p>PL group: non-F rinse (aqueous 0.1% NaCl solution)</p> <p>School use/supervised, weekly (32 rinses/y), 10 mL applied for 1 minute</p> <p>Before application: NR</p> <p>Postop instruction: no rinsing, eating or drinking for 1 hour</p>	
Outcomes	<p>2.5yDMFS increment - (CA)(E)</p> <p>Reported at 1, 1.5 and 2.5 years’ follow-up</p> <p>DMFT (E/U)</p> <p>O-DFS</p> <p>BL-DFS</p> <p>MD-DFS</p> <p>DMFS (U)</p> <p>AntDMFS</p> <p>PostDMFS</p> <p>Side effects (incomplete data)</p> <p>Dropout</p>	
Declaration of Interest	No information provided	
Funding	Conselho Nacional de Desenvolvimento Cientifico e Tecnologico, Brazil	
Notes	<p>Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. State of tooth eruption included = E/U. Consistency of diagnosis assessed by duplicate examinations annually. Reversals < 5% of DMFS increments in all groups and equally common</p> <p>**Study group of sodium monofluorophosphate solution containing 4% of ethanol not considered</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

<p>Random sequence generation (selection bias)</p>	<p>High risk</p>	<p>Quotes from translation: “The children were 9-12 year olds and were divided between the two examiners in equal numbers according to gender and age but at random” “For each examiner, and for each gender, the children were ordered firstly in ascending order, according to the number of permanent teeth present, and secondly, according to the number of DMFS. To each group formed in this way, by lot, one of the following rinsing solutions were given...” “Then every set of four records (children) at random were distributed into four groups. In this way, comparability between the experimental groups was achieved. Then at random, each group was assigned to one of the four following rinsing solutions...” Comment: unclear how this method of randomisation could affect selection bias. Method of sequence generation not described - possibly a quasi method</p>
<p>Allocation concealment (selection bias)</p>	<p>High risk</p>	<p>Quotes from translation: “The children were 9-12 year olds and were divided between the two examiners in equal numbers according to gender and age but at random” “For each examiner, and for each gender, the children were ordered firstly in ascending order, according to the number of permanent teeth present, and secondly, according to the number of DMFS. To each group formed in this way, by lot, one of the following rinsing solutions were given...” “Then every set of four records (children) at random were distributed into four groups. In this way, comparability between the experimental groups was achieved. Then at random, each group was assigned to one of the four following rinsing solutions...” Comment: method of sequence generation not described - possibly a quasi-method</p>
<p>Blinding of participants and personnel (performance bias) All outcomes</p>	<p>Unclear risk</p>	<p>Quotes from translation: “Group D: aqueous solution of sodium chloride 0.1%(control)” “Through the school year, the mouthrinses, prepared weekly at the dental school laboratory, were put in plastic bottles, then accommodated in separate boxes, accord-</p>

		<p>ing to the different rinsing solutions, which were taken to the schools and given to the classroom teachers who had been trained to apply/supervise the procedures during the time of the study. The names of the children, who would use the bottles according to the groups to which they belonged, featured in the lid of the boxes”</p> <p>Comment: use of placebo described. Although blinding of participants indicated, study personnel (teachers carrying out the procedure in the schools) were not blind to group assignment</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quotes from translation: “Two dentists not involved in treatment conducted the exams”</p> <p>“The examiners were not aware of the study groups to which the children belonged” (in thesis dissertation)</p> <p>Comment: examiners likely to be unaware of treatment group assignment</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Overall dropout for length of follow-up: 45.17% in 2.5 years</p> <p>Dropout by group: 116/256 FR1, 116/256 FR2, 114/254 PL</p> <p>Reasons for losses: not reported, but exclusions based on ‘statistical reasons’ (made at random to keep groups of equal sizes)</p> <p>Comment: numbers lost unduly high for length of follow-up, and although no differential losses occurred, the reason for exclusion of data is unacceptable. Caries data used in analysis pertain to participants present at final examination (after exclusions were made)</p>
Selective reporting (reporting bias)	Unclear risk	<p>Outcomes reported</p> <p>DMFS increment - (CA)(E)</p> <p>Reported at 1, 1.5 and 2.5 years’ follow-up</p> <p>DMFT (E/U)</p> <p>O-DFS</p> <p>BL-DFS</p> <p>MD-DFS</p> <p>DMFS (U)</p> <p>AntDMFS</p> <p>PostDMFS</p>

Bastos 1989 (Continued)

		Side effects (incomplete data). Study reported that “no adverse effects were observed” but did not specify what adverse effects were assessed or how they were assessed Comment: trial protocol not available (thesis available). All prespecified outcomes (in Methods) were reported in the prespecified way, but we noted some discrepancy between outcomes actually reported and reporting in Methods
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 10.43 FR1, 10.51 FR2, 10.54 PL DMFT: 5.69 FR1, 5.67 FR2, 5.65 PL Dental age: 19.08 FR1, 19.01 FR2, 19.13 PL Comment: initial caries appears balanced between groups. Dental age also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Blinkhorn 1983

Methods	Study design: 4-arm parallel-group RCT (only 2 relevant arms used), placebo-controlled Study duration: 3 years
Participants	Participants randomised: N = 414 374 children analysed at 3 years (available at final examination) Age range at start: 11 to 12 years Surfaces affected at start: 8.6 DMFS Exposure to other fluoride: no Year study began: 1972 Location: UK Setting of recruitment and treatment: school
Interventions	Comparison: FR+ptc vs PL+ptc FR group: 0.05% NaF, 230 ppm F PL group: non-F rinse School use/supervised, daily (160 rinses/y), for half minutes Before application: toothbrushing with non-fluoride toothpaste in both groups Postop instruction: NR
Outcomes	3yNetDFS increment - (E+U)(CA)cl+(DR)xr Reported at 3 years' follow-up PF-DFS MD-BL-DFS MD-DFS

Blinkhorn 1983 (Continued)

	PostMD-DFS DMFT (E/U) Anterior DMFT Posterior DMFT DFS (U) Dropout	
Declaration of Interest	No information provided	
Funding	This study was supported by a grant from Colgate-Palmolive	
Notes	Clinical (V) caries assessment by 1 examiner, diagnostic threshold = CA. Radiographic assessment (1 postBW) by 1 examiner; diagnostic threshold = DR. State of tooth eruption included = E/U. Intraexaminer reproducibility checks for incremental clinical and radiographic caries data in 10% sample (ICC score 0.9)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were allocated to four groups by stratified random sampling at two levels: school and dental age..." Quote from correspondence: "The allocation to groups was random..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	Quote from correspondence: "The allocation to groups was random with complete concealment of treatment allocation" Comment: not enough information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The trial was organised on a double-blind basis, neither the children nor the examiner being aware of who was receiving test or control products" "Control subjects used the equivalent dentifrice and rinse without fluoride" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The trial was organised on a double-blind basis, neither the children nor the examiner being aware of who was receiving test or control products" Comment: blind outcome assessment and use of placebo described

Blinkhorn 1983 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 9.66% in 3 years Dropout by group: 19/209 FR, 21/205 PL Reasons for losses: left school (57), withdrawn by parents (12), absent at final exam (6) (for all 4 groups combined) Comment: numbers lost not high for length of follow-up, with no differential losses between groups. It is unclear whether reasons for losses are balanced between groups Caries data used in the analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - (E+U)(CA)cl+(DR)xr, reported at 3 years' follow-up PF-DFS MD-BL-DFS MD-DFS PostMD-DFS DMFT (E/U) Anterior DMFT Posterior DMFT DFS (U) Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 8.71(6.42) FR, 8.48(6.29) PL DMFT: 5.30(3.58) FR, 5.26(3.47) PL SAR: 93.00(19.75) FR, 93.61(20.43) PL Comment: initial caries appears balanced between groups (although DFS baseline data NR). SAR also seems balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Brandt 1972

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 2 years
Participants	Participants randomised: N = 314 246 children analysed at 2 years (after exclusions based on compliance, present at all examinations) Average age at start: 11.5 years

Brandt 1972 (Continued)

	<p>Surfaces affected at start: 7.9 DMFS (for sample present at all examinations) Exposure to other fluoride: none assumed Year study began: 1969 Location: UK Setting of recruitment and treatment: school</p>	
Interventions	<p>Comparison: FR vs PL FR group: 0.2% NaF (900 ppm F) PL group: non-F rinse School use/supervised, twice a week (60 rinses/y), 10 mL applied for 1 minute Prior to application: NR Postop instruction: NR</p>	
Outcomes	<p>2yDFS scores - (E+U) Reported at 2 years' follow-up DMFS* DMFT* PostMD-DMFS CFS CFT Dropout *Reported match-pair rather than randomised results - could not be included in meta-analysis. See ROB section</p>	
Declaration of Interest	No information provided	
Funding	The study authors thank the pharmacy department of The London Hospital	
Notes	Clinical caries assessment, diagnostic threshold NR. Radiographic assessment; diagnostic threshold = NR. State of tooth eruption included = E/U. Diagnostic errors NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...allocation to either study or control groups was done on a school house basis, allocation to a house being done by school administrative staff randomly" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The subjects rinsed with...NaF for one minute or similarly with...NaCl if they were in the control group" "The solutions were coloured ...and labelled as solution A and solution B...and

Brandt 1972 (Continued)

		the formula for each was unknown to the authors until the trial was completed” Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “The study was conducted as a 2 year CCT on a double-blind basis” Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 21.66% in 2 years Dropout by group: 28/153 (18.3%) FR, 40/161 (24.8%) PL Reasons for losses: exclusions based on compliance Reasons for attrition described with numbers by group: change of residence (18, 12), absent at final examination (5, 7); plus exclusions based on compliance, presence in all examinations and for statistical analysis; no differential group losses Comment: numbers lost not unduly high for length of follow-up, with no differential losses between groups. Reasons for dropout may not be acceptable or balanced between groups. Caries data used in analysis pertain to participants present at all examinations
Selective reporting (reporting bias)	High risk	Outcomes reported DFS scores* - (E+U), reported at 2 years’ follow-up DMFS* DMFT* PostMD-DMFS CFS CFT Comment: trial protocol not available *Only results of matched-pair analyses (94 pairs, rather than all participants) were reported - study author explained that this was due to baseline imbalance. No longer RCT data; could not be included in meta-analysis
Baseline characteristics balanced?	High risk	Prognostic factors reported DMFS: 7.10 FR, 8.65 PL Age: 11.5 FR, 11.5 PL Comment: initial caries with some imbalance between groups

Brandt 1972 (Continued)

Free of contamination/co-intervention?	Unclear risk	No information provided
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Craig 1981

Methods	<p>Study design: 3-arm parallel-group RCT (only 2 relevant arms used), non-placebo-controlled</p> <p>Study duration: 2 school years (21 months)</p>
Participants	<p>Participants randomised: N = 109 97 children analysed at 2 years (available at final examination)</p> <p>Age range at start: 11 to 12 years</p> <p>Surfaces affected at start: 10.6 DFS</p> <p>Exposure to other fluoride: toothpaste</p> <p>Year study began: 1977</p> <p>Location: New Zealand</p> <p>Setting of recruitment and treatment: school</p>
Interventions	<p>FR+ptc vs NT+ptc</p> <p>FR group: 0.2% NaF (900 ppm F)</p> <p>NT group: no intervention</p> <p>School use/supervised, fortnightly (17 rinses/y), 10 mL applied for 2 minutes</p> <p>Before application: prior professional prophylaxes with non-fluoride toothpaste in both groups (+oral hygiene instructions)</p> <p>Postop instruction: NR</p>
Outcomes	<p>2yDFS increment - (CA)</p> <p>Reported at 1 and 2 years' follow-up</p> <p>O-DFS</p> <p>MD-DFS</p> <p>BL-DFS</p> <p>Dropout</p>
Declaration of Interest	No information provided
Funding	The study authors thank the Director General of Health (NZ) for approval to publish the study report
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. State of tooth eruption included NR. Reproducibility checks for incremental clinical caries data in 15% sample at each examination (reversal rate < 4% for both examiners)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Low risk	Quote: "The children were then stratified according to sex, age and caries experience and allocated randomly to three groups" Quote from correspondence: "We are sure that a random number system was used to allocate the children into groups after stratification..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quotes: "one test group received professional prophylaxes and the other group prophylaxes + fluoride rinses" "...one of the examiners, ignorant of the group to which the child belonged" Comment: no placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...one of the examiners, ignorant of the group to which the child belonged" Comment: blind outcome assessment reported but no placebo described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall dropout for length of follow-up: 11.0% in 2 years Dropout by group: 6/54 FR, 7/55 NT Reasons for losses: leaving school (12 children) Comment: numbers lost not high, given length of follow-up. No differential losses between groups. Reason for losses acceptable and balanced between groups Caries data used in the analysis pertain to participants available at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - (CA), reported at 1 and 2 years' follow-up O-DFS MD-DFS BL-DFS Dropout Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DFS: 10.65(6.4) FR, 10.5(6.4) NT Dental age: 21.2(5.7) FR, 21.4(5.0) NT

Craig 1981 (Continued)

		Comment: initial caries appears balanced between groups. Dental age also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

De Liefde 1989

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 3 years	
Participants	Participants randomised: numbers NR 262 children analysed after 3 years (available at final examination) Age range at start: 7 to 10 years (average = 8) Surfaces affected at start: NR Exposure to other fluoride: toothpaste assumed Year study began: 1984 Location: New Zealand Setting of recruitment and treatment: school	
Interventions	Comparison: FR vs PL FR group: 0.2% NaF (900 ppm F) PL group: non-F rinse School use/supervised, fortnightly (17 rinses/y) Before application: NR Postop instruction: NR	
Outcomes	2yDMFS final scores* - (CA) Reported at 3 years' follow-up DMFT *Only results of combined non-randomised and randomised groups reported (separate results for placebo group not available, data could not be included in meta-analysis)	
Declaration of Interest	No information provided	
Funding	The study authors thank the permission of the Director General of Health (NZ) for approval to publish the paper	
Notes	Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included NR; diagnostic errors NR	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The high caries-risk children were randomly divided into two groups..." Comment: not enough information

De Liefde 1989 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "...the other used a placebo rinse.." "Mouth rinsing was conducted double-blind, with the supervisor, the dental nurses and the children being unaware of the composition of the mouth rinsing solution" "...after examination and tentative treatment planning by the dental nurses" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: as above Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: not reported Dropout by group: not assessable Reasons for losses: not reported Reasons for attrition NR: any differential group losses not assessable
Selective reporting (reporting bias)	High risk	Outcomes reported DMFS (final) - (CA), reported at 3 years' follow-up DMFT Comment: only results of combined non-randomised and randomised groups reported (separate results for placebo group not available, data could not be included for meta-analysis)
Baseline characteristics balanced?	High risk	Prognostic factors reported No baseline characteristics/values reported
Free of contamination/co-intervention?	Unclear risk	No information provided

DePaola 1977

Methods	Study design: 3-arm parallel group RCT, placebo-controlled Study duration: 2 years
Participants	Participants randomised: N = 614 (numbers randomised to each group NR) 475 children analysed at 2 years (available at final examination, who participated throughout) Age range at start: 10 to 12 years (average = 11.7) Surfaces affected at start: 6.1 DFS

	<p>Exposure to other fluoride: some assumed*** Year study began: assumed in/before 1974 Location: USA Setting of recruitment and treatment: schools in a non-fluoridated community ***History of prior exposure to systemic F was reported by nearly half of panel</p>	
Interventions	<p>Comparison: FR (2 groups) vs PL FR group 1 (n = 159): 0.2% NH₄F group = 1000 ppm F FR group 2 (n = 158): 0.22% NaF group = 1000 ppm F PL group (n = 158): distilled water, coloured and flavoured to simulate active agents School use/supervised, daily (140 rinses/y), 5 mL applied for 1 minute Before application: NR Postop instruction: NR</p>	
Outcomes	<p>2yNetDFS increment - (CA)cl+(ER)xr Reported at 2 years' follow-up DFS (U) Side effects (incomplete data)</p>	
Declaration of Interest	No information provided	
Funding	Supported by NIDR Contract Number NIH 71-2379	
Notes	Clinical (VT) caries assessment, diagnostic threshold = CA; state of tooth eruption included NR. Radiographic assessment (4 postBW); diagnostic threshold = ER; diagnostic errors NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After being randomly assigned to one of three treatment groups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "A double-blind clinical trial was conducted..." "The placebo agent consistent of distilled water colored and flavored to simulate the active agents" Comment: described as double-blinded. No descriptions on how personnel were blinded, but this was probably carried out. Use of placebo described

Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quotes: “A double-blind clinical trial was conducted...”</p> <p>“Subjects were examined clinically and by radiography after 12 and 24 months without reference to previous findings”</p> <p>Comment: described as double-blinded but method of blinding of outcome assessor not reported. Probably low risk because bitewing radiographs were used</p> <p>Blind outcome assessment and use of placebo described</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Overall dropout for length of follow-up: 22.64% in 2 years</p> <p>Dropout by group: not assessable</p> <p>Reasons for losses: “factors unrelated to the study”</p> <p>Comment: numbers lost not unduly high for length of follow-up. Differential losses not assessable. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present throughout the trial</p>
Selective reporting (reporting bias)	Unclear risk	<p>Outcomes reported</p> <p>DFS increment - (CA) cl+xr, reported at 2 years’ follow-up</p> <p>DFS (U)</p> <p>Side effects (incomplete data): Study reported that “no adverse effects were observed” but did not specify what adverse effects were assessed or how these were assessed</p> <p>Comment: trial protocol not available. Pre-specified outcomes (in Methods) were reported. However side effects data were incomplete</p>
Baseline characteristics balanced?	Low risk	<p>Prognostic factors reported</p> <p>DFS: 6.26(5.09) FR1, 5.46(4.54) FR2, 6.47(5.50) PL</p> <p>No prior exposure to systemic fluoride: 85/159 (53.5%) FR1, 92/158 (58.2%) 81/158 (51.3%) PL</p> <p>Comment: initial caries appears balanced between groups</p>

DePaola 1977 (Continued)

Free of contamination/co-intervention?	Unclear risk	No information provided
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DePaola 1980

Methods	<p>Study design: 4-arm parallel-group RCT (only 2 relevant arms used), placebo-controlled</p> <p>Study duration: 2 years</p>
Participants	<p>Participants randomised: numbers NR nor obtainable</p> <p>271 children analysed at 2 years (after exclusions, present for both examinations)</p> <p>Age range at start: 12 to 14 years (average = 13)</p> <p>Surfaces affected at start: NR</p> <p>Exposure to other fluoride: toothpaste assumed</p> <p>Year study began: assumed in/before 1977</p> <p>Location: USA</p> <p>Setting of recruitment and treatment: school</p>
Interventions	<p>Comparison: FR vs PL</p> <p>FR group: NaF 0.05% (230 ppm F)</p> <p>PL group: non-F rinse (disguised and colour coded)</p> <p>School use/supervised, daily (140 rinses/y), 10 mL applied for 1 minute</p> <p>Before application: no tooth cleaning performed</p> <p>Postop instruction: NR</p>
Outcomes	<p>2yNetDFS increment - (CA)cl+xr</p> <p>Reported at 1 and 2 years' follow-up (and 1 year post treatment)</p>
Declaration of Interest	No information provided
Funding	The study was supported by National Institute of Dental Research, Contract No. NOI-DE42445
Notes	Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold NR; diagnostic errors NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned to 1 examiner and 1 of 4 treatment groups at the time of the clinical examination" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided

DePaola 1980 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "A strict double-blind routine was maintained throughout the course of the investigation" "The placebo and active rinses were disguised and colour coding..." "Supervisors had typed lists indicating the agent code for each subject" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "A strict double-blind routine was maintained throughout the course of the investigation" "Subjects always seen by the same examiner and examined without reference to previous findings" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: not reported Dropout by group: not reported Reasons for losses: exclusions based on compliance and presence at all exams Comment: Reasons for missing outcome data may be unacceptable, and It is unclear whether these are balanced between groups
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - (CA) cl+xr, reported at 1 and 2 years' follow-up (and at 1 year post treatment) Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Unclear risk	Prognostic factors: DFS, dental age and age reported as "balanced" (values not reported)
Free of contamination/co-intervention?	Unclear risk	No information provided

Driscoll 1982

Methods	Study design: 4-arm parallel-group RCT (only 3 relevant arms used), placebo-controlled Study duration: 2.5 years	
Participants	Participants randomised: N = 966 524 children analysed at 2.5 years (present for entire trial period) Average age at start: 12.8 years Surfaces affected at start: 4.8 DMFS Exposure to other fluoride: water (and toothpaste assumed) Year study began: 1977 Location: USA Setting of recruitment and treatment: school	
Interventions	Comparison: FR (2 groups) vs PL NaF group 1: 230 ppm F, daily (160 rinses/y) NaF group 2: 900 ppm F, weekly (30 rinses/y) PL group: non-F rinse (0.1 NaCl) School use/supervised, 10 mL applied for 1 minute Before application: NR Postop instruction: NR	
Outcomes	2.5yNetDMFS increment Reported at 1.5 and 2.5 years' follow-up O-DMFS MD-DMFS BL-DMFS Dropout	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment by 2 examiners; diagnostic threshold NR. State of tooth eruption included NR; differences between examiner assessments NS (but reproducibility assessment NR). Results presented separately by examiner (combined results considered)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were assigned randomly, within each school, to one of three groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: “A control group of children followed the procedure once a week using a placebo mouthrinse” “Those in group C (controls) rinsed their mouths once every week in school with 10 ml of a placebo solution containing 0.1 percent sodium chloride” Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “The examiners were unaware of any child’s group assignment, and did not have access to records from the baseline examination” Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 45.75% in 2.5 years Dropout by group: 176/384 FR1, 133/298 FR2, 133/284 ‘PL’ Reasons for losses: moving out of the area/ school, voluntary withdrawal at request of child or parent Comment: Numbers lost were high, although no differential loss occurred between groups. It is unclear whether 1 of the reasons for missing outcome data (voluntary withdrawal) is acceptable and balanced. Caries data used in the analysis pertain to participants present throughout the trial
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment reported at 1.5 and 2.5 years’ follow-up O-DMFS MD-DMFS BL-DMFS Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 4.62 FR1, 4.76 FR2, 4.93 PL Comment: initial caries apparently balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Duany 1981

Methods	Study design: 4-arm parallel-group RCT, placebo-controlled Study duration: 3 years	
Participants	Participants randomised: numbers NR nor obtainable 936 children analysed at 3 years Age range at start: not obtainable Exposure to other fluoride: not obtainable Surfaces affected at start: 7 DMFS Year study began: assumed in/before 1977 Location: Puerto Rico Setting of recruitment and treatment: school	
Interventions	FR (3 groups) vs PL (NaF groups = 100 ppm F, 225 ppm F, 450 ppm F) FR group 1: 0.02% NaF = 100 ppm F FR group 2: 0.05% NaF = 225 ppm F FR group 3: 0.10% NaF = 450 ppm F PL group: non-F rinse Before application: NR Postop instruction: NR	
Outcomes	3yDMFS increment	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Other data NR nor obtainable	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were randomly assigned to one of four mouth rinse groups.." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...one of four mouthrinse groups (control, and three concentrations of sodium fluoride) and were followed double-blinded for three years..." Comment: Study described use of a control mouthrinse, the control is a mouthrinse group that did not rinse with F and it is a DB study

Duany 1981 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...one of four mouthrinse groups (control, and three concentrations of sodium fluoride) and were followed double-blinded for three years..." Comment: blind outcome assessment reported, although unclear what procedures were used, but use of placebo reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: not obtainable Dropout by group: not obtainable Reasons for losses: not obtainable
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	High risk	Prognostic factors reported DMFS: 7.39(8.52) FR1, 6.28(7.77) FR2, 6.79(7.07) FR3, 7.50(8.23) PL Comment: initial caries appears not balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Finn 1975

Methods	Study design: 3-arm parallel-group RCT, placebo-controlled Study duration: 2 years
Participants	Participants randomised: N = 820; numbers by group NR 453 children analysed at 2 years (present in all examinations) Age range at start: 8 to 13 years (average = 11.7) Surfaces affected at start: 6 DMFS Exposure to other fluoride: no Year study began: assumed in/before 1972 Location: USA Setting of recruitment and treatment: school
Interventions	FR (2 groups) vs PL FR group 1: 0.02% neutral NaF solution (100 ppm F) FR group 2: 0.04% neutral NaF solution (200 ppm F) PL group: non-F rinse School use/supervised, twice a day (330 rinses/y), 20 mL applied in 2 successive rinses of 30 seconds each Before application: NR

	Postop instruction: NR	
Outcomes	2yNetDFS increment - cl+xr Reported at 2 years' follow-up DMFS DMFT Proportion of children with new DFS	
Declaration of Interest	No information provided	
Funding	The study was supported by a grant from the Warner-Lambert Company	
Notes	Clinical (VT) caries assessment by 1 examiner, diagnostic threshold NR. Radiographic assessment (2-4 postBW+ 4 anterior) by 1 examiner; diagnostic threshold NR. State of tooth eruption included NR. Diagnostic errors NR. Reversals ranged between 6% and 16% of observed DMFS increment in study groups for combined clinical and x-ray findings, with rates higher in the test groups	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "On the basis of age and sex within individual classrooms in each of the three schools, the children were randomly assigned to one of three treatment regimen groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "Children in regimen group 3 used the placebo mouthwash which was fluoride free..." "...the children entered the room, announced their name and colour code, picked a colour-coded cup containing the assigned mouthwash..." Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quotes: "Children in regimen group 3 used the placebo mouthwash which was fluoride free..." "...the children entered the room, announced their name and colour code, picked a colour-coded cup containing the assigned mouthwash..."

		<p>“Radiographic findings were added later to the clinical findings” Comment: use of placebo described, but it is unclear whether examiner was blinded</p>
<p>Incomplete outcome data (attrition bias) All outcomes</p>	High risk	<p>Overall dropout for length of follow-up: 44.76% in 2 years Dropout by group: not assessable Reasons for dropout: children transferred to other schools, exclusion based on presence at all exams Comment: numbers lost unduly high for length of follow-up. Differential losses not assessable. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at all examinations</p>
<p>Selective reporting (reporting bias)</p>	Low risk	<p>Outcomes reported DFS increment - cl+xr, reported at 2 years’ follow-up DMFS DMFT Proportion of children with new DFS Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way</p>
<p>Baseline characteristics balanced?</p>	Low risk	<p>Prognostic factors reported DMFT: 3.67(2.81) FR1, 3.87(3.48) FR2, 3.60(2.90) PL DMFS: 5.82(5.18) FR1, 6.17(6.67) FR2, 6.02(6.21) PL Age: 11.8 FR1, 11.4 FR2, 11.8 PL Gender: 75M, 75F (FR1), 70M, 72F (FR2), 71M, 89F (PL) Comment: initial caries appears balanced (although DFS baseline data NR). Other characteristics also balanced</p>
<p>Free of contamination/co-intervention?</p>	Low risk	<p>Non-fluoride toothpaste and appropriate mouthrinse provided to all for home use</p>

Gallagher 1974

Methods	Study design: 2-arm parallel group (quasi) RCT, “placebo”-controlled Study duration: 3 years
Participants	Participants randomised: N = 809 594 children analysed at 2 years (available at final examination) Age range at start: 11 to 13 years Surfaces affected at start: 7.3 DMFS (from sample randomised) Exposure to other fluoride: none assumed Year study began: 1970 Location: Canada Dental treatment level (F/DMF): 42% Setting of recruitment and treatment: school
Interventions	FR vs PL FR group: NaF = 1800 ppm F. 0.4% neutral NaF PL group: sodium bicarbonate solution* School use/supervised, weekly (30 rinses/y), applied for 1 minute. Rinsing was performed once a week in the morning Before application: NR Postop instruction: Children were instructed not to swallow the solution and not to eat or drink for 30 minutes after rinsing *Test and control solutions look and taste similar
Outcomes	2yDMFS increment - (E+U) Reported at 2 years' follow-up DMFT DT DF Dropout
Declaration of Interest	No information provided
Funding	No information provided
Notes	Clinical (VT) caries assessment by 1 examiner, diagnostic threshold NR. State of tooth eruption included = E/U. Diagnostic errors NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quotes: “...all children in the same classrooms were divided into two teams. The criteria used for the division were DMFT and DMFS, dental age and score for OHI” “A flip of a coin decided which team would be experimental and which team would be controls” Comment: unclear how method of ran-

Gallagher 1974 (Continued)

		domination used affected selection bias. Coin flipping acceptable method of sequence generations but unclear how teams were formed
Allocation concealment (selection bias)	Unclear risk	Quote: "A flip of a coin decided which team would be experimental and which team will be controls" Comment: Allocation was done after teams were formed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The solutions were mixed by the dental staff. The solution used was 0.4% neutral sodium fluoride, with 0.18 % fluoride ion. The placebo consist of a solution of sodium bicarbonate. Both solutions were colourless and almost tasteless. Students act as the monitors who dispense the solution, collected the used cups, kept the time and reminded each other about brushing" Mouth rinsing was conducted in "teams" Comment: blinding likely maintained because both types of solutions look and taste similar
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In as much as a double-blind study was being accomplished, neither students nor examiner knew whether a student was a member of the controls or the experimental group" Comment: likely to be at low risk for outcome assessment blinding if blinding was maintained for participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 26.58% in 2 years Dropout by group: 108/414 FR, 107/395 PL Reasons for losses: exclusion of persistent swallowers, absence from school Comment: numbers lost not unduly high, given length of follow-up, with no differential losses between groups. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final exam

Gallagher 1974 (Continued)

Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment - (E+U), reported at 2 years' follow-up DMFT DT DF Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 7.19 FR, 7.37 PL DMFT: 4.50 FR, 4.59 PL DT: 2.36 FR, 2.49 PL FT: 1.90 FR, 1.85 PL Dental age: 18.53 FR, 18.64 PL OHI: 1.44 FR, 1.47 PL Comment: initial caries appears balanced between groups. Other characteristics also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Heidmann 1992

Methods	Study design: 2-arm parallel group RCT, placebo-controlled Study duration: 3 years
Participants	Number randomised: 1306 (numbers randomised to each group NR) Number analysed: 1083 children at 3 years (present at final examination) Age range at start: 6 to 12 years (average = 9) Surfaces affected at start: 1.4 DMFS Exposure to other fluoride: yes (toothpaste, "almost all sold toothpaste contains fluoride")** Year study began: 1983 Location: Denmark Setting of recruitment and treatment: school **Both groups had been using FR before the study started
Interventions	Comparison: FR vs PL FR group (n = 538): 0.2% NaF (900 ppm F) - peppermint flavoured PL group (n = 545): distilled water - peppermint flavoured School use/supervised, fortnightly (17 rinses/y) Before application: NR Postop instruction: NR

Heidmann 1992 (Continued)

Outcomes	3yCrude postDMFS increment - (CA)(E+U)cl DMFS (U) O-DMFS MD-DMFS BL-DMFS CIR - xr Proportion of children with new postMDDMFS	
Declaration of Interest	No information provided	
Funding	Danish Dental Association	
Notes	Clinical (VT) caries assessment by dentists at public dental service, diagnostic threshold = CA. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included = E/U. Reproducibility of diagnosis assessed by duplicate radiographic examination of 10% random sample (kappa value 0.72)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...children from kindergarten through 6th grade were stratified by school and grade and randomly distributed into two groups" Quote from correspondence: "The randomization was done using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "...the children were allocated to two groups: a fluoride group...and a water (placebo) group" " both solutions were slightly flavoured with peppermint. The solutions were centrally prepared and distributed to the schools in individual plastic cup labelled with the child's name and school class" Comment: use of placebo described. Both participants and personnel should be effectively blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "two bitewings radiographs taken using a standardised method" "The examiner was unaware of the the group to which the individual radiograph belonged"

Heidmann 1992 (Continued)

		Comment: objective method used, blinding stated. Blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 17.08% (223/1306) in 3 years Dropout by group: not reported Reasons for losses: not reported Comment: numbers lost not high for length of follow-up; differential losses between groups not assessable (study authors were unable to provide the numbers randomised to each group (personal correspondence)), but numbers analysed seem balanced across groups. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: postDMFS (CA) (E+U)cl, reported at 3 years' follow-up DMFS (U) O-DMFS MD-DMFS BL-DMFS CIR-xr Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 1.43 FR, 1.46 PL SAR: 27.7 FR, 28.6 PL Comment: initial caries appears balanced between groups. SAR also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Heifetz 1973

Methods	Study design: 3-arm parallel-group RCT; placebo-controlled Study duration: 2 years
Participants	Participants randomised: N = 947; numbers randomised to each group NR 413 children analysed at 2 years (after exclusions, present in all examinations) Age range at start: 10 to 12 years Surfaces affected at start: 10.8 DMFS

Heifetz 1973 (Continued)

	<p>Exposure to other fluoride: none assumed Year study began: 1969 Location: USA Setting of recruitment and treatment: school</p>	
Interventions	<p>FR (2 groups) vs PL FR group 1: APF 0.66% = 3000 ppm F FR group 2: NaF 0.66% = 3000 ppm F PL group: non-F rinse School use/supervised, weekly (25 rinses/y), 8 mL applied twice (16 mL) for 1 minute Before application: NR Postop instruction: NR</p>	
Outcomes	<p>2yNetDMFS increment - (E+U) cl+(ER)xr Reported at 1 and 2 years' follow-up</p>	
Declaration of Interest	<p>No information provided</p>	
Funding	<p>All mouthwash solutions used in the study were commercially prepared by the Lorvic Corp</p>	
Notes	<p>Clinical (VT) caries assessment by 2 examiners, diagnostic threshold NR. Radiographic assessment (5 postBW) by 2 examiners; diagnostic threshold = ER. State of tooth eruption included -E/U. Diagnostic errors NR (but examiners calibrated regularly). Reversals ranged between 5% and 10% of observed DMFS increment in study groups for combined clin+xr findings, with rates higher in the test groups</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The baseline records of the children were stratified according to sex, dental age... Within each stratum, each child was assigned randomly to one of three study groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "Group A rinsed their mouths in school once a week with a placebo solution" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "The examiner did not know the group to which any child was assigned" "Group A rinsed their mouths in school"

Heifetz 1973 (Continued)

		once a week with a placebo solution” Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 56.39% in 2 years Dropout by group: not reported Reasons for losses: high transience of the population, dissatisfaction with taste of the rinses. Exclusion due to poor compliance and lack of data for all examinations Comment: numbers lost unduly high, given length of follow-up. Differential losses not assessable. Reasons for missing outcome data (poor compliance) may be unacceptable, and it is unclear whether they are balanced between groups. Caries data used in the analysis pertain to participants present at baseline and final exams
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment (E+U) cl+(ER) xr, reported at 1 and 2 years’ follow-up Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 10.16(9.77) FR1, 11.38(10.60) FR2, 10.81(8.69) PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Heifetz 1982

Methods	Study design: 3-arm parallel-group RCT, placebo-controlled Study duration: 3 years
Participants	Participants randomised: N = 912; numbers by group NR 598 children analysed at 3 years (present for entire trial period) Age range at start: 10 to 12 years Surfaces affected at start: 6.2 DMFS Exposure to other fluoride: toothpaste Year study began: 1976 Location: USA Setting of recruitment and treatment: school

Interventions	FR (2 groups) vs PL FR group 1: 0.05% NaF 230 ppm F, daily (150 rinses/y) FR group 2: 0.2% NaF 900 ppm F, weekly (30 rinses/y) PL group: non-F rinse School use/supervised, 10 mL applied for 1 minute Before application: NR Postop instruction: NR
Outcomes	3yNetDMFS increment - (CA)(E)clin Reported at 1, 2 and 3 years' follow-up O-DMFS MD-DMFS BL-DMFS
Declaration of Interest	No information provided
Funding	No information provided
Notes	Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA (FOTI assessment - loss of translucency on transillumination - for approximal surfaces). State of tooth eruptions included = E; differences between examiner assessments NS (but reproducibility assessment NR). Results presented separately by examiner(combined results considered)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from correspondence: "Using a computer generated table of random numbers, the 912 subjects...were randomly assigned..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Group C (controls) rinsed once a week with a placebo solution" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "The examiners were unaware of any child's group assignment, and did not have access to records from the previous examinations" "Group C (controls) rinsed once a week with a placebo solution" Comment: blind outcome assessment and use of placebo described

Heifetz 1982 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 34.43% in 3 years Dropout by group: not assessable Reasons for losses: not assessable Comment: numbers lost unduly high, given length of follow-up. Differential losses between groups not assessable. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present throughout the trial
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment (CA)(E)clin, reported at 1, 2 and 3 years' follow-up O-DMFS MD-DMFS BL-DMFS Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 6.06(5.76) FR1, 5.98(5.70) FR2, 6.56(6.00) PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Horowitz 1971

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 1.6 years
Participants	Participants randomised: N = 493 256 children analysed at 1.6 years (present for entire trial period) Age range at start: 6 to 7 years Surfaces affected at start: 0.9 DMFS (sample available at end) Exposure to other fluoride: none assumed Year study began: 1967 Location: USA Setting of recruitment and treatment: school
Interventions	FR vs PL FR group 1: 0.2% neutral NaF solution (900 ppm F) PL group: non-F rinse solution School use/supervised, weekly (30 rinses/y), 10 mL applied for 1 minute

	Before application: NR Postop instruction: NR	
Outcomes	1.6yNetDMFS increment - (E+U) Reported at 1 and 1.6 years' follow-up DMFT (E/U) DMFS (U) Dropout	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold NR. State of tooth eruption included = E/U. Diagnostic errors NR	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...according to dental age...sex and previous caries experience of the children, they were randomly assigned to one of the two following study groups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The control group rinsed with a placebo" "A monthly rinsing for the controls seemed to be a reasonable compromise. Because the examiners for this study had no part in administering treatments, a double-blind method could be maintained strictly" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "The control group rinsed with a placebo" "A monthly rinsing for the controls seemed to be a reasonable compromise. Because the examiners for this study had no part in administering treatments, a double-blind method could be maintained strictly" Comment: blind outcome assessment and use of placebo described

Horowitz 1971 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 48.07% in 1.6 years Dropout by group: 114/247 FR, 123/246 PL Reasons for losses: transience of the schools' neighbourhoods, exclusion due to absence from any follow-up examination Comments: numbers lost unduly high, given length of follow-up, with no differential losses. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at all exams
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment - (E+U), reported at 1 and 1.6 years' follow-up DMFT (E/U) DMFS (U) Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 0.90 FR, 0.97 PL DMFT: 0.73 FR, 0.75 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Horowitz 1971a

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 1.6 years
Participants	Participants randomised: N = 381 208 children analysed at 1.6 years (present for entire trial period) Age range at start: 10 to 11 years Surfaces affected at start: 6.7 DMFS (sample available at end) Exposure to other fluoride: none assumed Year study began: 1967 Location: USA Setting of recruitment and treatment: school
Interventions	FR vs PL FR group 1: 0.2% neutral NaF solution (900 ppm F) PL group: non-F rinse solution

Horowitz 1971a (Continued)

	School use/supervised, weekly (30 rinses/y), 10 mL applied for 1 minute Before application: NR Postop instruction: NR	
Outcomes	1.6yNetDMFS increment - (E+U) Reported at 1 and 1.6 years' follow-up DMFT (E/U) DMFS (U) Dropout	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold NR. State of tooth eruption included = E/U. Diagnostic errors NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...according to dental age...sex and previous caries experience of the children, they were randomly assigned to one of the two following study groups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The control group rinsed with a placebo" "A monthly rinsing for the controls seemed to be a reasonable compromise. Because the examiners for this study had no part in administering treatments, a double-blind method could be maintained strictly" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "The control group rinsed with a placebo" "A monthly rinsing for the controls seemed to be a reasonable compromise. Because the examiners for this study had no part in administering treatments, a double-blind method could be maintained strictly" Comment: blind outcome assessment and use of placebo described

Horowitz 1971a (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 45.41% in 1.6 years Dropout by group: 93/191 FR, 80/190 PL Reasons for losses: transience of the schools' neighbourhoods. Exclusions due to absence from any follow-up examination Comments: numbers lost unduly high, given length of follow-up, with almost differential losses (51.31% FR, 42.11% PL) . It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at all exams
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment - (E+U), reported at 1 and 1.6 years' follow-up DMFT (E/U) DMFS (U) Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 6.97 FR, 6.48 PL DMFT: 3.59 FR, 3.44 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Koch 1967

Methods	Study design: 2-arm parallel-group RCT, "placebo"-controlled Study duration: 3 years
Participants	Participants randomised: N = 217 167 children analysed at 3 years (present for entire trial period) Age range at start: 9 to 11 years (average = 10) Surfaces affected at start: 14.5 DFS Exposure to other fluoride: no Year study began: 1962 Location: Sweden Setting of recruitment and treatment: school
Interventions	Comparison: FR vs 'PL' FR group: 0.5% NaF (2250 ppm F) 'PL' group: non-F rinse (distilled water)

	School use/supervised, fortnightly (17 rinses/y), 10 mL applied for 2 minutes Before application: NR Postop instruction: NR	
Outcomes	3yDFS increment - (CA)(E)cl Reported at 1 and 3 years' follow-up (and at 2 years post treatment) DFT O-DFS MD-DFS BL-DFS CAR (annual) Secondary caries Dropout	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E. Intraexaminer reproducibility checks for DFS in 10% sample (ICC over 0.98); reversals very small in both groups and equally common	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quotes: "The children were randomly assigned to test and control groups" "The children selected to be exposed to an experimental measure were divided into 2 groups by assigning every other child in the class register to one group; the remainder to the other group. In these alphabetical register the boys and the girls were entered separately. In this way, both groups comprised an equal number of boys and girls" Comment: not randomised. Alternation used to allocate into groups
Allocation concealment (selection bias)	Low risk	Comment: The non-random method (alternation) used for sequence generation would not allow for allocation concealment. However, because every child in the class was assigned according to the ordering in the class register (alphabetically), lack of allocation concealment could not influence assignment of participants

<p>Blinding of participants and personnel (performance bias) All outcomes</p>	<p>Unclear risk</p>	<p>Quotes: “In the present investigation, which was carried out with control groups, the double-blind method was used” “The examiner did not know to which group the children belonged” “...fluoride solution in test group and distilled water in control group” “The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the ‘yellow’ one and the ‘green’ one” Comment: Effectiveness of distilled water as a placebo is unclear. Moreover, participants were assigned in alternation, which makes it easier to guess</p>
<p>Blinding of outcome assessment (detection bias) All outcomes</p>	<p>Low risk</p>	<p>Quotes: “In the present investigation, which was carried out with control groups, the double-blind method was used” “The examiner did not know to which group the children belonged” “The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the ‘yellow’ one and the ‘green’ one” Radiographic examination conducted Comment: radiographic assessment used. Unclear whether examiners were effectively blinded but likely to be low risk</p>
<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>Unclear risk</p>	<p>Overall dropout for length of follow-up: 23.04% in 3 years Dropout by group: 24/109 (22%) FR, 26/108 (24%) PL Reasons for losses: not reported Comment: numbers lost not unduly high, given length of follow-up, and no differential loss evident between groups. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present throughout the trial</p>

Koch 1967 (Continued)

Selective reporting (reporting bias)	Unclear risk	Outcomes reported DFS increment - (CA) (E)cl, reported at 1 and 3 years' follow-up (and at 2 years post treatment) DFT O-DFS MD-DFS BL-DFS CAR (annual) Secondary caries Comment: trial protocol available. Pre-specified outcomes were reported. However side effects data were incomplete
Baseline characteristics balanced?	Low risk	Prognostic factors reported DFS: 14.36(7.47) FR, 14.93(8.47) PL DFT: 9.38(4.15) FR, 9.45(4.26) PL SAR: 67.82(19.82) FR, 64.30(16.85) PL TAR: 9.06(3.60) FR, 8.41(2.99) PL Comment: initial caries appears balanced between groups. Other baseline characteristics (SAR, TAR) also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Koch 1967a

Methods	Study design: 2-arm parallel-group RCT, "placebo"-controlled Study duration: 3 years
Participants	Participants randomised: N = 344 251 children analysed at 3 years (present for entire trial period) Age range at start: 6 to 8 years (average = 7) Surfaces affected at start: 5.6 DFS Exposure to other fluoride: none assumed Year study began: 1962 Location: Sweden Setting of recruitment and treatment: school
Interventions	Comparison: FR vs 'PL' FR group: 0.5% NaF (2250 ppm F) PL group: non-F rinse (distilled water) School clinic/supervised, 3 times a year (3 rinses/y), 10 mL applied for 2 minutes Before application: NR Postop instruction: NR

Outcomes	3yDFS increment - (CA)(E)cl Reported at 1 and 3 years' follow-up DFT CAR (annual) Secondary caries Dropout
Declaration of Interest	No information provided
Funding	No information provided
Notes	Clinical (VT) caries assessment by 4 examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E. Diagnostic errors NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quotes: "The children were randomly assigned to test and control groups" "The children selected to be exposed to an experimental measure were divided into 2 groups by assigning every other child in the class register to one group; the remainder to the other group. In these alphabetical register the boys and the girls were entered separately. In this way, both groups comprised an equal number of boys and girls" "The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the 'yellow' one and the 'green' one" Comment: not randomised. Alternation used to allocate into groups
Allocation concealment (selection bias)	Low risk	Comment: The non-random method (alternation) used for sequence generation would not allow for allocation concealment. However, because each child in the class was assigned according to the order in the class register (alphabetically), lack of allocation concealment could not influence assignment of participants

Koch 1967a (Continued)

<p>Blinding of participants and personnel (performance bias) All outcomes</p>	<p>Unclear risk</p>	<p>Quotes: “In the present investigation, which was carried out with control groups, the double-blind method was used” “The examiner did not know to which group the children belonged” “...fluoride solution in test group and distilled water in control group” “The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the ‘yellow’ one and the ‘green’ one” Comment: use of placebo described</p>
<p>Blinding of outcome assessment (detection bias) All outcomes</p>	<p>Low risk</p>	<p>Quotes: “In the present investigation, which was carried out with control groups, the double-blind method was used” “The examiner did not know to which group the children belonged” “The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the ‘yellow’ one and the ‘green’ one” Radiographic examination conducted Comment: radiographic assessment used. Unclear whether examiners were effectively blinded but likely to be low risk</p>
<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>High risk</p>	<p>Overall dropout for length of follow-up: 27.03% in 3 years Dropout by group: 55/172 (32%) FR, 38/172 (22%) PL Reasons for losses: not reported Comment: Numbers lost were not high, given length of follow-up, although differential losses evident between groups. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present throughout the trial</p>
<p>Selective reporting (reporting bias)</p>	<p>Low risk</p>	<p>Outcomes reported DFS increment - (CA)(E)cl, reported at 1 and 3 years’ follow-up DFT CAR (annual)</p>

Koch 1967a (Continued)

		Secondary caries Comment: trial protocol available. All pre-specified outcomes were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DFS: 5.52(3.14) FR, 5.63(3.12) PL DFT: 3.40(1.62) FR, 3.64(1.85) PL SAR: 32.45(10.39) FR, 33.34(11.23) PL TAR: 5.15(2.27) FR, 5.16(2.66) PL Comment: initial caries appears balanced between groups. Other baseline characteristics (SAR, TAR) also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Koch 1967b

Methods	Study design: 2-arm parallel-group RCT, “placebo”-controlled Study duration: 2 years
Participants	Participants randomised: N = 392 251 children analysed at 2 years (present for entire trial period) Age range at start: 7 to 11 years Surfaces affected at start: 7 DFS Exposure to other fluoride: none assumed Year study began: 1962 Location: Sweden Setting of recruitment and treatment: school
Interventions	Comparison: FR vs 'PL' FR group: 0.05% NaF (230 ppm F) PL group: non-F rinse (tap water) School clinic/supervised, 3 times a year (3 rinses/y), 10 mL applied for 2 minutes Before application: NR Postop instruction: NR
Outcomes	2yDFS increment - (CA)(E)cl Reported at 2 years' follow-up DFT CAR (annual) Secondary caries Dropout
Declaration of Interest	No information provided
Funding	No information provided

Notes	Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E. Diagnostic errors NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	<p>Quotes: "The children were randomly assigned to test and control groups"</p> <p>"The children selected to be exposed to an experimental measure were divided into 2 groups by assigning every other child in the class register to one group; the remainder to the other group. In these alphabetical register the boys and the girls were entered separately. In this way, both groups comprised an equal number of boys and girls"</p> <p>"The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the 'yellow' one and the 'green' one"</p> <p>Comment: not randomised. Alternation used to allocate into groups</p>
Allocation concealment (selection bias)	Low risk	<p>Comment: The non-random method (alternation) used for sequence generation would not allow for allocation concealment. However, because each child in the class was assigned according to ordering in the class register (alphabetically), lack of allocation concealment could not influence assignment of participants</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Quotes: "In the present investigation, which was carried out with control groups, the double-blind method was used"</p> <p>"The examiner did not know to which group the children belonged"</p> <p>"...fluoride solution for test group and tap water for control group"</p> <p>"The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the 'yellow' one and</p>

		the 'green' one" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "In the present investigation, which was carried out with control groups, the double-blind method was used" "The examiner did not know to which group the children belonged" "The terms test group and control group were never used, for it was not known until after the investigation which group was a test or a control group. The groups were therefore referred to as the 'yellow' one and the 'green' one" Radiographic examination conducted Comment: radiographic assessment used. Unclear whether examiners were effectively blinded but likely to be low risk
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 35.97% in 2 years Dropout by group: 82/196 (42%) FR, 59/196 (30%) PL Reasons for losses: not reported Comment: Numbers lost were high, given length of follow-up, and showed differential losses between groups. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present throughout the trial
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - (CA)(E)cl, reported at 2 years' follow-up DFT CAR (annual) Secondary caries Comment: trial protocol available. All pre-specified outcomes were reported in the prespecified way
Baseline characteristics balanced?	Unclear risk	Prognostic factors reported DFS: 6.89(3.10) FR, 7.01(3.63) PL DFT: 4.82(1.71) FR, 4.86(2.11) PL SAR: 51.75(13.88) FR, 53.20(16.04) PL TAR: 8.54(2.88) FR, 8.85(3.29) PL Comment: initial caries appears balanced between groups. Other baseline character-

Koch 1967b (Continued)

		istics (SAR, TAR) also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Laswell 1975

Methods	Study design: 3-arm parallel-group RCT, placebo-controlled Study duration: 2.4 years
Participants	Participants randomised: N = 575 343 children analysed at 2.4 years (after exclusions, present for entire trial period) Average age at start: 8.6 years Surfaces affected at start: 3 DMFS Exposure to other fluoride: water Year study began: assumed in/before 1971 Location: USA Setting of recruitment and treatment: school
Interventions	FR (2 groups) vs PL APF group 1: 200 ppm F, daily (160 rinses/y) APF group 2: 1000 ppm F, weekly (30 rinses/y) School use/supervised Before application: NR Postop instruction: NR
Outcomes	2.4yDFS increment - (E+U) Reported at 2.4 years' follow-up DMFS (U) Dropout
Declaration of Interest	No information provided
Funding	No information provided
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. State of tooth eruption included = E/U. Diagnostic errors NR (results from only 1 examiner reported)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were randomly assigned to three groups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided

Laswell 1975 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "One group received a daily placebo mouthwash..." Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quotes: "The examinations were accomplished by 2 examiners working independently" "One group received a daily placebo mouthwash..." Comment: use of placebo described, but It is unclear whether examiners were blinded, although examinations were done independently
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 40.35% in 2.4 years Dropout by group: 75/181 FR1, 84/204 FR2, 73/190 PL Reasons for losses: exclusions based on presence at exams and compliance Comment: numbers lost unduly high for length of follow-up with no differential loss between groups. It is unclear whether reasons for missing outcome data are balanced, and they may not be acceptable. Caries data used in the analysis pertain to participants present at all exams with more than 75% compliance
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - (E+U), reported at 2.4 years' follow-up DMFS (U) Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Unclear risk	Prognostic factors reported DMFS: 2.57 FR1, 3.25 FR2, 3.20 PL Age: 8.7 FR1, 8.6 FR2, 8.5 PL Comment: initial caries appears balanced between groups. Age also balanced
Free of contamination/co-intervention?	Low risk	Non-fluoride toothpaste provided to all for home use (no rinse provided)

McConchie 1977

Methods	Study design: 3-arm parallel-group RCT, placebo-controlled Study duration: 2 years (+ 1 year post-intervention period)
Participants	Participants randomised: N = 1202; numbers randomized to each group NR 743 children analysed at 2 years (available at final examination) Average age at start: 10 years Surfaces affected at start: 6.2 DFS Exposure to other fluoride: no Year study began: 1970 Location: Canada Setting of recruitment and treatment: school
Interventions	FR (2 groups) vs PL FR group 1: 0.08% SnF2 = 200 ppm F FR group 2: 0.04% SnF2 = 100 ppm F PL group: non-F rinse School use/supervised, daily (160 rinses/y), 20 mL applied in 2 successive rinses 30 seconds each Before application: NR Postop instruction: NR
Outcomes	2yNetDFS increment - (E+U)cl+xr Reported at 2 years' follow-up (and at 1 year post treatment) DMFS DMFT Increments standardised to 28 teeth and 122 surfaces (E/U) Children with tooth staining/pigmentation, lack of acceptance of the taste, side effects (incomplete data)
Declaration of Interest	No information provided
Funding	The study was supported by a grant from the Warner-Lambert Company
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold NR. Radiographic assessment (postBW) by 2 examiners; diagnostic threshold NR. State of tooth eruption included = E/U. Diagnostic errors NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They were divided by basis of random numbers into three groups selected in such a manner that the sex, age and previous caries experience of each group were closely similar" Comment: not enough information provided

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: “Two of the groups rinsed with the two strengths of the solution and the third rinsed with a placebo” “The three tablets...resembled each other in colour and taste” “The status of each group was not known to anyone actively involved in the study” Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: “Two of the groups rinsed with the two strengths of the solution and the third rinsed with a placebo” “The three tablets dissolved in cups...resembled each other in colour and taste” “The status of each group was not known to anyone actively involved in the study” Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 38.19% in 2 years Dropout by group: not assessable Reason for losses: movement out of the schools, administrative difficulties, absenteeism. Exclusions based on compliance Comment: numbers lost unduly high for length of follow-up. Differential losses not assessable. It is unclear whether reasons for losses are balanced, and they may not be acceptable. Caries data used in the analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Unclear risk	Outcomes reported DFS increment - (E+U)cl+xr, reported at 2 years' follow-up (and at 1 year post treatment) DMFS DMFT Increments standardised to 28 teeth and 122 surfaces (E/U) Children with tooth staining/pigmentation, lack of acceptance of the taste, side effects (incomplete data) Comment: trial protocol not available. Pre-specified outcomes were reported. However side effects data were incomplete

McConchie 1977 (Continued)

Baseline characteristics balanced?	Low risk	Prognostic factors reported DFS: 6.19 FR1, 6.39 FR2, 6.12 PL DMFT: 3.50 FR1, 3.67 FR2, 3.55 PL SAR: 63.59 FR1, 63.54 FR2, 62.73 PL TAR: 13.53 FR1, 13.45 FR2, 13.32 PL Comment: initial caries appears balanced. Other baseline characteristics (SAR, TAR, age) also balanced
Free of contamination/co-intervention?	Low risk	Non-fluoride toothpaste provided to all for home use (no rinse provided)

Moberg Sköld 2005

Methods	Study design: 5-arm parallel-group RCT (quasi), non-placebo-controlled Study duration: 3 years
Participants	Year study began: 1999 Location: Sweden, 1 city Setting of recruitment and treatment: school Numbers randomised: 788 children (“randomly selected”) Numbers analysed: 622 children at 3 years (after exclusions, present for both examinations) Age: all 13 years old Surfaces affected: 1.6 MD-DFS (SD = 2.8) Background exposure to other fluoride: yes (100% reported F toothpaste used twice a day, 100% reported F varnish applied annually at checkups, but no F in water - “0.1 ppm F”)
Interventions	Comparison: FR (4 groups) vs NT FR group 1: 0.2% NaF, 900 ppm F, 6 rinses/y (initial 3 school days every semester) FR group 2: 0.2% NaF, 900 ppm F, 12 rinses/y (initial 3 and last 3 school days every semester) FR group 3: 0.2% NaF, 900 ppm F, 27 rinses/y (3 consecutive school days every month) FR group 4: 0.2% NaF, 900 ppm F, 20 rinses/y (2 school days (fortnightly) during semesters) NT group: no intervention School use/supervised, 20 mL applied for 1 minute Before application: no toothbrushing before rinsing Postop instruction: Refrain from eating and drinking for 1 hour afterwards
Outcomes	3-year postMD-DFS incidence - (E)(DR/ER)xr Reported at 3 years’ follow-up DS FS Caries progression Dropout

Moberg Sköld 2005 (Continued)

Declaration of Interest	No information provided	
Funding	Supported by Swedish Patent Revenue Fund for Research in Preventive Dentistry and the Sigge Perssons & Alice Nybergs Foundation	
Notes	Radiographic caries assessment (4 postBW) by 2 examiners; diagnostic threshold = DR and ER; intraexaminer K statistics/kappa values - 0.94 and 0.88 for all scores and for carious surfaces scores only, respectively, interexaminer values NR. State of tooth eruption included = E	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "... Adolescents of five different secondary schools in Mölndal were randomised into five different groups (every school included had five classes within the age group)" Comment: method unclear, quasi-method likely
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Group 5 (control group) did not rinse" Comment: no placebo described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Two of the authors (E.B. and U. M.S.) read the radiographs simultaneously, using a light desk and a magnifying viewer. A consensus of each code was reached. The authors did not know to which group the adolescents belonged" Comment: blind outcome assessment reported, but no placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 166/788 (21%) in 3 years [but 88/788 (11%) in 3 years if no exclusions were performed based on compliance with intervention*] Dropout by group 46/173 (17%) FR1, 29/162 (18%) FR2, 30/184 (16%) FR3, 61/175 (35%) FR4, 0/94 NT Reasons for losses: excluded because of fewer rinses than stipulated, refused to

		<p>rinse, changed class, school, or moved out from area, missed radiograph or poor radiograph quality</p> <p>*78 participants were not included in the analysis, on a 'non-adherence' basis, because they rinsed less than stipulated = 62, or refused to rinse = 16); it is not clear if they had the 3-year follow-up examination</p> <p>Comment: numbers lost high for length of follow-up (FR 4), differential losses between NT and FR groups and among FR groups. Caries data used in analysis pertain to participants present at initial and final examinations</p>
Selective reporting (reporting bias)	Unclear risk	<p>Outcomes reported</p> <p>DFS incidence - (DR/ER)xr at 3 years' follow-up</p> <p>Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported; however, although caries prevalence data are fully reported by group (at varying levels of diagnosis) at baseline and at follow-up, not all caries incidence/increment data are fully reported/tabulated by group and diagnostic threshold</p>
Baseline characteristics balanced?	Low risk	<p>Prognostic factors reported</p> <p>Post MD-DFS (MD-DFSa+DeS) = 1.68 FR1, 1.44 FR2, 1.79 FR3, 1.75 FR4, 1.45 NT MD-DS, MD-FS</p> <p>Comment: initial caries appears balanced between groups</p>
Free of contamination/co-intervention?	Low risk	<p>Quote: "All participants attended dental clinics for regular check-ups once a year and they were given prophylactic treatment. .. It is custom in Sweden's dental clinics to treat all children and adolescents with F varnish at their yearly check-ups and it is standard to brush one's teeth with F toothpaste twice a day"</p> <p>Comment: no indication of inadvertent application of the intervention to people in the control group (no apparent contamination) or of any additional treatment given to 1 of the groups differentially (no risk of co-intervention)</p>

Molina 1987

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 2.5 years
Participants	Participants: N= 767 295 children analysed at 2.5 years (available at final examination) Age range at start: 5 to 13 years Surfaces affected at start: 4.3 DMFS Exposure to other fluoride: data not obtained for toothpaste or water Year study began: 1983 Location: Chile Setting of recruitment and treatment: school
Interventions	Comparison: FR vs PL FR group (n = 145): 0.2% NaF group = 900 ppm F PL group (n = 150): non-F rinse (no details described) School use/supervised, applied weekly (30 rinses/y) Before application: NR Postop instruction: NR
Outcomes	2.5yDMFS increment Reported at 2.5 years' follow-up DMFT Dropout
Declaration of Interest	No information provided
Funding	The investigation was financed by the Faculty of Dentistry University of Chile, Laboratorio Chile, Indus Lever and Manufacturas de Cepillos Duralon Ltd
Notes	Clinical (VT) caries assessment, diagnostic threshold NR. State of tooth eruption included NR. Consistency of diagnosis assessed by duplicate examinations annually. Diagnostic errors NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from translation: "In each school, children were divided at random by the statisticians..." Comment: A random method was likely used
Allocation concealment (selection bias)	Unclear risk	Method was not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes from translation: "The study was conducted double-blind" "..and placebo for the control group" Blind outcome assessment and use of

Molina 1987 (Continued)

		placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes from translation: “The study was conducted double-blind” “..and placebo for the control group” Blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 61.54% in 2.5 years Reasons for losses: moved away because of earthquake in the area (1985 Chilean earthquake) Comment: numbers lost very high, although no differential loss evident between groups (dropout by group: 225/370 FR, 247/397 PL). Caries data used in analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment, reported at 2.5 years’ follow-up DMFT Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 4.38 FR, 4.22 PL DMFT: 2.93 FR, 2.72 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Moreira 1972

Methods	Study design: 5-arm parallel-group quasi-RCT (only 4 relevant arms used, the NT control group not used), “placebo“-controlled Study duration: 2 years
Participants	Participants randomised (N = 330) 200 children analysed at 2 years (after exclusions, available at final examination) Age range at start: 6.5 to 7.5 years Surfaces affected at start: 4.6 DMFS (from sample randomised) Exposure to other fluoride: none assumed Year study began: 1968

	Location: Brazil Setting of recruitment and treatment: school	
Interventions	<p>Comparison: FR (3 groups) vs 'PL'</p> <p>FR group 1: 0.1% NaF, 450 ppm F, 3 times a week (80 rinses/y)</p> <p>FR group 2: 0.1% NaF, 450 ppm F, weekly (28 rinses/y)</p> <p>FR group 3: 0.1% NaF, 450 ppm F, fortnightly (14 rinses/y)</p> <p>'PL' group: tap water, 3 times a week (80 rinses/y)</p> <p>School use/supervised, 25 mL applied for 30 seconds</p> <p>Before application: Rinsing with water (tap = drinking water) was carried out first, in all 4 groups, for 30 seconds (followed by another rinse with water in the 'PL' group and rinse with F solution in the treatment groups, as described above)</p> <p>Postop instruction: NR</p>	
Outcomes	<p>2yDMFS increment</p> <p>Reported at 1 and 2 years' follow-up</p> <p>Dropout</p>	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment, diagnostic threshold NR. State of tooth eruption included NR. Diagnostic errors NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	<p>Quote from translation: "For this study, we constituted a control group and four experimental groups numbered 1 to 4, taking into consideration: approximate numbers of children of school age, previous experience of caries and permanent teeth erupted"</p> <p>Comment: not enough information provided</p> <p>Quote from correspondence: "In order to obtain 'homogeneous' groups, children were ordered and pre-stratified by gender, age, number of permanent teeth present, and by level of DMF, and in this way each one of the groups was formed"</p> <p>Comment: method unclear, quasi-method likely</p>

Allocation concealment (selection bias)	High risk	Comment: no concealment of allocation indicated/likely
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quotes: "Group V- children who rinsed with clean water, three times a week" "...study was conducted double-blind..." Comment: double-blinding and use of 'placebo' reported, but methods not described. It was unclear whether the 'placebo' could be distinguished from the active treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from correspondence: "The researcher/examiner did not know to which group the children belonged, and the children were also blind to group assignment" Comment: likely to be low risk because blind outcome assessment and use of 'placebo' described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 39.02% (130/330) in 2 years Dropout by group: 32/82 FR1, 35/85 FR2, 32/82 FR3, 31/81 PL Reasons for losses: exclusions based on 'statistical reasons' (made at random to keep groups of equal sizes) Comment: Numbers lost were high, given length of follow-up, and it is unclear whether differential losses were noted between groups (because the numbers above were produced after 'statistical' exclusions to keep groups of equal sizes). Reason for missing outcome data is unacceptable. Caries data used in analysis pertain to participants present at final examination (after exclusions)
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment, reported at 1 and 2 years' follow-up Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 4.58 FR1, 4.60 FR2, 4.62 FR3, 4.66 'PL' Age: 7 FR1, 7 FR2, 7 FR3, 7 'PL'

Moreira 1972 (Continued)

		Dental age: 8.1 FR1, 8.1 FR2, 8.3 FR3, 8.3 'PL' Comment: initial caries appears balanced between groups. Other baseline characteristics (dental age, age) also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Moreira 1981

Methods	Study design: 2-arm parallel-group RCT (quasi), non-placebo-controlled Study duration: 2.5 years	
Participants	Participants randomised: N = 230 164 children analysed at 2.5 years (available at final examination) Age range at start: 7 to 8 years Surfaces affected at start: 1.4 DMFS Exposure to other fluoride: water Year study began: 1974 Location: Brazil Setting of recruitment and treatment: school	
Interventions	Comparison: FR vs NT FR group: 0.2% NaF (900 ppm F) NT group: no intervention School use/supervised, weekly (30 rinses/y), 20 mL applied, for 30 seconds Before application: rinsing with drinking water for 30 seconds Postop instruction: no eating or drinking for 30 minutes	
Outcomes	2.5yDMFS increment Reported at 2.5 years' follow-up CAR Dropout	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment by 1 examiner, diagnostic threshold NR. State of tooth eruption included NR. Diagnostic errors NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote from translation: "...children were divided at random into 2 groups" Comment: not enough information pro-

		<p>vided</p> <p>Quote from correspondence: “In order to obtain ‘homogeneous’ groups, children were ordered and pre-stratified by gender, age, number of permanent teeth present, and by level of DMF, and then, they were distributed ‘at random’, to form each one of the groups”</p> <p>Comment: method unclear, quasi-method likely</p>
Allocation concealment (selection bias)	High risk	<p>Quote from correspondence: “In order to obtain ‘homogeneous’ groups, children were ordered and pre-stratified by gender, age, number of permanent teeth present, and by level of DMF, and then, they were distributed ‘at random’, to form each one of the groups”</p> <p>Comment: no concealment of allocation indicated/likely</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote from translation: “... received no treatment and served as control”</p> <p>Comment: no placebo used</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Quotes from translation: “... received no treatment and served as control”</p> <p>“The clinical examinations were performed by a single examiner without prior knowledge whether the child belonged to the experimental group or control”</p> <p>Comment: blind outcome assessment described, but no placebo used</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Overall dropout for length of follow-up: 28.7% (66/230) in 2.5 years</p> <p>Dropout by group: 42/115 FR, 24/115 NT</p> <p>Reasons for losses: not reported</p> <p>Comment: Numbers lost were not high for length of follow-up but showed differential loss between groups (36.52% FR, 20.87% NT). It is unclear whether reasons for missing data are acceptable. Caries data used in analysis pertain to participants present at final examinations</p>
Selective reporting (reporting bias)	Low risk	<p>Outcomes reported</p> <p>DMFS increment, reported at 2.5 years’ follow-up</p>

Moreira 1981 (Continued)

		CAR Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostics factors reported DMFS: 1.4(1.61) FR, 1.4(1.72) NT TAR: 8.3 FR, 8.3 NT Dental age: 9.6 FR, 9.5 NT Comment: initial caries appears balanced between groups. Dental age, TAR also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Packer 1975

Methods	Study design: 3-arm parallel-group RCT, placebo controlled Study duration: 2.4 years
Participants	Participants randomised: N = 464 285 children analysed at 2.4 years (after exclusions, present for entire trial period) Average age at start: 8.7 years Surfaces affected at start: 6.6 DMFS Exposure to other fluoride: no Year study began: assumed in/before 1971 Location: USA Setting of recruitment and treatment: school
Interventions	FR (2 groups) vs PL APF group 1: 200 ppm F, daily (160 rinses/y) APF group 2: 1000 ppm F, weekly (30 rinses/y) School use/supervised Before application: NR Postop instruction: NR
Outcomes	2.4yNetDMFS increment - (CA) (E+U) Reported at 2.4 years' follow-up DMFS (U) Dropout
Declaration of Interest	No information provided
Funding	No information provided
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. State of tooth eruption included = E/U. Diagnostic errors NR (results from only 1 examiner reported)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were randomly assigned into three groups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "One group received a daily placebo mouthwash..." Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quotes: "The examinations were accomplished by 2 examiners working independently" "One group received a daily placebo mouthwash..." Comment: use of placebo described, but It is unclear whether examiners were blinded, although examinations were done independently
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 38.58% in 2.4 years Dropout by group: 62/142 FR1, 56/164 FR2, 61/158 PL Reasons for losses: exclusion due to absence from more than 25% of examinations and compliance Comment: numbers lost unduly high for length of follow-up, with some differential loss between groups (43.66% FR1, 34.15% FR2, 38.61% PL). It is unclear whether reasons for missing outcome data are balanced, and they may not be acceptable. Caries data used in the analysis pertain to participants present at all exams with more than 75% compliance
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment - (E+U), reported at 2.4 years' follow-up DMFS (U) Comment: trial protocol not available. All prespecified outcomes (in Methods) were

Packer 1975 (Continued)

		reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 6.47(4.65) FR1, 6.80(4.60) FR2 6.48(4.98) PL Age: 8.7 FR1, 8.6 FR2, 8.6 PL Comment: initial caries appears balanced between groups. Age also balanced
Free of contamination/co-intervention?	Low risk	Non-fluoride toothpaste provided to all for home use (no rinse provided)

Petersson 1998

Methods	Study design: 2-arm parallel-group RCT, “placebo”-controlled Study duration: 3 years	
Participants	Participants randomised: numbers NR nor obtainable 139 children analysed at 3 years Average age at start: 13 years Mean surfaces affected at start: 1.3 DFS Background exposure to other fluoride: assumed yes (toothpaste) - The tap water contained a very low level of fluoride: 0.01 ppm F Year study began: assumed in/before 1994 Location: Sweden Setting of recruitment and treatment: school	
Interventions	Comparison: FR vs 'PL' FR group (n = 69): 0.045% NaF, 200 ppm F 'PL' group (n = 70): tap water (no F = 0.01 ppm F) School use/supervised, for 3 days every 6 months (6 rinses/y), 10 mL applied Before application: NR Postop instruction: NR	
Outcomes	3ypostMD-DFS increment - (DR/ER)xr Reported at 3 years' follow-up	
Declaration of Interest	No information provided	
Funding	The study was supported by the County Council of Halland, Sweden	
Notes	Radiographic assessment (4 postBW) by 1 examiner; diagnostic threshold = DR and ER. Diagnostic errors NR. State of tooth eruption included NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quotes: "A test group was randomly sampled..." "...school children were sampled into two groups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quotes: "...In the control group, the children rinsed with tap water..." "The study was designed so that the subjects did not know whether their rinsing solution contained fluoride or not" "The same prophylactic information was given to the teenagers during the rinsing procedures in both groups, and the same staff members.. organised the rinsing procedures in the test as well as control groups through the whole study periods" Comment: use of 'placebo' described (no description of whether the mouthrinse is identical in appearance or taste to tap water. Staff did not seem to be blinded)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the detection and recording of caries and filled surfaces from the bitewing radiographs were performed by one of the authors who was specially trained for the purposed and did not know the origin of the radiographs analysed" Comment: likely to be low risk because blind outcome assessment and use of 'placebo' described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers randomised not reported. Dropout rate NR nor obtainable. Reasons for attrition NR. Any differential group losses not assessable
Selective reporting (reporting bias)	Low risk	Outcomes reported PostMD-DFS, reported at 3 years' follow-up Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way

Petersson 1998 (Continued)

Baseline characteristics balanced?	Low risk	Prognostic factors reported PostMDDFS: 1.35 (1.58) FR, 1.16 (1.55) 'PL' Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "Similar preventive programs were applied to the two groups during the experimental period" Comment: sufficient indication of overall prevention of contamination/co-intervention

Poulsen 1984

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 3 years
Participants	Participants randomised: N = 398 Number analysed: 365 children analysed at 3 years (available at final examination) Age range at start: 7 to 10 years (average = 9) Surfaces affected at start: 3.6 DMFS Exposure to other fluoride: yes (toothpaste). Area has low fluoride content in water (0.5 ppm in most parts) Year study began: 1979 Location: Denmark Setting of recruitment and treatment: school
Interventions	Comparison: FR vs PL FR group (n = 207): 0.2% NaF(900 ppm F) PL group (n = 191): water, with flavouring solution added School use/supervised, fortnightly (19 rinses/y), 10 mL applied Before application: NR Postop instruction: NR
Outcomes	3yNetDMFS increment - (CA)(E)cl Reported at 3 years' follow-up DMFS (U) O-DMFS MD-DMFS BL-DMFS PostMDDMFS Dropout
Declaration of Interest	No information provided
Funding	Supported by a grant from Colgate Palmolive Inc., Copenhagen

Notes	Clinical (VT) caries assessment by dentists at public dental service, diagnostic threshold = CA. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = DR. State of tooth eruption included (E/U). Reproducibility of diagnosis assessed by duplicate radiographic examination of 10% random sample (kappa value 0.72)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were stratified according to school and age and subsequently randomly allocated to two groups" Quote from correspondence: "The method of randomisation is not mentioned in the protocol" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "...flavouring solution were added" "The children, the dental examiners and the dental assistants did not know which group the children belonged to" "Both placebo and fluoride solutions were poured into small plastic cups at the dental school and each cup labelled with the child's name, school and grade" Comment: adequate efforts to ensure that water was an effective placebo, and steps taken to ensure blinding; use of a placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "...the examiners did not know to which group the children belonged" "Caries was recorded on the radiographs when the lesion had reached the amelodentinal junction" Comment: Examiner did not know treatment assignment; definitions and objective outcome measures used (bitewing radiographs) Comment: blind outcome assessment and use of a placebo described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall dropout for length of follow-up: 8.29% in 3 years Dropout by group: 16/207 FR, 17/191 PL

Poulsen 1984 (Continued)

		Reasons for losses: not reported Comment: numbers lost not unduly high, given length of follow-up, with no differential losses between groups. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants who completed the trial
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment - (CA)(E)cl, reported at 3 years' follow-up DMFS (U) O-DMFS MD-DMFS BL-DMFS PostMDDMFS Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 3.56 (2.92) FR, 3.7 (2.49) PL Mean age (months): 106.66(10.52) FR, 108.43(10.70) PL Erupted surfaces: 56.86(17.66) FR, 57.34 (15.86) PL Comment: initial caries appears balanced between groups. Other baseline characteristics (erupted surfaces, age) also balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Radike 1973

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 2 school years (1.6 years)
Participants	Participants randomised: N = 890 726 children analysed at 1.6 years (available at final examination) Age range at start: 8 to 13 years (average = 10.4) Surfaces affected at start: 4.9 DMFS Exposure to other fluoride: water Year study began: assumed in/before 1970 Location: USA Setting of recruitment and treatment: school

Interventions	Comparison: FR vs PL FR group: 0.1% SnF2, 240 ppm F PL group: non-F rinse School use/supervised, daily (160 rinses/y), 60 mL applied in 3 successive rinses of 10, 30 and 30 seconds each Before application: NR Postop instruction: NR	
Outcomes	1.6yDMFS increment - cl+xr Reported at 8 months' and 1.6 years' follow-up DMFT Children with tooth staining/pigmentation (incomplete data) Dropout	
Declaration of Interest	No information provided	
Funding	Sponsors of the study were US Airforce School of Aerospace Medicine under contract no. F41609-68-C-0025, and Procter and Gamble Co	
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold NR. Radiographic assessment (4 postBW) by 2 examiners; diagnostic threshold NR. State of tooth eruption included NR. Diagnostic errors NR. Results of 1 examiner chosen (findings of both examiners consistent throughout)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At the time of the first examination, the children were grouped by sex, age... Within these groupings, adjacent subject entries were assigned to test or control groups by random permutations of two" Comment: block randomisation done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "Neither the participants nor the examiners were aware of the assignments throughout the test" "The test and the placebo mouthrinses were used by the children in school classrooms under direct supervision of the teachers" "the mouthrinses were simple in composition and similar in appearance and taste... SnF2 was added to the test rinse; nothing was added to the other rinse" "into red or green cups according to the

Radike 1973 (Continued)

		color assigned” “red-green coding used throughout the study” Comment: use of placebo reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: “Neither the participants nor the examiners were aware of the assignments throughout the test” “each child was sent to the two examiners in a random order for clinical VT examination, and radiographs were read at a later date by each examiner” Comment: blind outcome assessment and use of placebo reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 18.43% in 1.6 years Dropout by group: 92/440 FR, 72/450 PL Reasons for losses: not reported Comment: numbers lost not unduly high, given length of follow-up, with no differential losses evident between groups. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Unclear risk	Outcomes reported DMFS increment - cl+xr, reported at 8 months’ and 1.6 years’ follow-up DMFT Children with tooth staining/pigmentation (incomplete data) Comment: trial protocol not available. Pre-specified outcomes were reported. However side effects data were incomplete
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 4.90(4.03) FR, 4.80(4.51) PL DMFT: 3.22(2.18) FR, 3.06(2.47) PL Age: 10.38 FR, 10.39 PL Gender: 165 M 183 F (FR), 187 M, 191 F (PL) Comment: initial caries appears balanced between groups. Other baseline characteristics (age, gender) also balanced

Radike 1973 (Continued)

Free of contamination/co-intervention?	Low risk	Non-fluoride toothpaste provided to all for home use (no rinse provided)
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Ringelberg 1979

Methods	Study design: 6-arm parallel-group RCT (4 relevant arms used), placebo-controlled Study duration: 2.5 years	
Participants	Participants randomised: N = 878 527 children analysed at 2.5 years (available at final examination) Average age at start: 11 years Surfaces affected at start: 4.3 DMFS Exposure to other fluoride: no Year study began: 1973 Location: USA Setting of recruitment and treatment: school	
Interventions	FR (2 groups) vs PL (2 groups) FR group 1: AmF 250 ppm F FR group 2: NaF 250 ppm F PL group 1: non-F rinse PL group 2: non-F rinse School use/supervised, daily (150 rinses/y), 10 mL applied for 1 minute Before application: NR Postop instruction: NR	
Outcomes	2.5yNetDMFS increment - (CA)cl + (DR)xr Reported at 2.5 years' follow-up DMFT Stain score Dropout	
Declaration of Interest	No information provided	
Funding	Investigation supported by the US National Caries Program under contract no. N01-DE-32427 (product formulations by Procter and Gamble Co. and Menley and James Laboratories)	
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (5 BW) by 2 examiners; diagnostic threshold = DR. State of tooth eruption included NR. Reversal rate between 4% and 9% of observed caries increment in groups	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: “The baseline examinations were stratified by race and sex within each school, and ordered by increasing DMFT. Study group assignments were made by random permutations of seven within each stratum”
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “The placebo preparations were all fully formulated like their active fluoride ingredient, but did not have the specific active fluoride ingredient” Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: “A double-blind design was used; neither examiner nor subjects were aware of the type of treatment received” “The placebo preparations were all fully formulated like their active fluoride ingredient, but did not have the specific active fluoride ingredient” Comment: blinded outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 39.98% in 2.5 years Dropout by group: 131/293 FR1, 110/289 FR2, 92/147 PL1 94/149 PL2 Reasons for losses: not reported Comment: Numbers lost were high, given length of follow-up, with differential losses evident between groups: 44.71% FR1, 38.06% FR2, 37.42% PL1, 36.91% PL2 Reasons for missing outcome data are not reported. Caries data used in the analysis pertain to participants at final exam
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment - (CA) cl + (DR) xr, reported at 2.5 years’ follow-up DMFT Stain score Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way

Ringelberg 1979 (Continued)

Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 3.90(0.34) FR1, 4.30(0.41) PL1, 4.36(0.43) FR2, 4.95(0.54) PL2 DMFT: 2.30(0.17) FR1, 2.49(0.20) PL1, 2.36(0.20) FR2, 2.72(0.28) PL2 Comment: initial caries appears slightly imbalanced.
Free of contamination/co-intervention?	Low risk	Non-fluoride toothpaste provided to all for home use (no rinse provided)

Ringelberg 1982

Methods	Study design: 5-arm parallel-group RCT, placebo-controlled Study duration: 2 years
Participants	Participants randomised: N = 2014 1238 children analysed at 2 years (available at final examination) Average age at start: 12.5 years Surfaces affected at start: 4.7 DMFS Exposure to other fluoride: toothpaste assumed Year study began: in/before 1979 Location: USA Setting of recruitment and treatment: school
Interventions	FR (4 groups) vs PL NaF group 1: 230 ppm F, daily (160 rinses/y) NaF group 2: 900 ppm F, daily (160 rinses/y) NaF group 3: 230 ppm F, weekly (30 rinses/y) NaF group 4: 900 ppm F, weekly (30 rinses/y) School use/supervised, 10 mL applied for 1 minute Before application: NR Postop instruction: NR
Outcomes	2yNetDMFS increment Reported at 1.5 and 2.5 years' follow-up PostMD-DFS Dropout
Declaration of Interest	No information provided
Funding	No information provided
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold NR. Radiographic assessment by 2 examiners; diagnostic threshold NR. State of tooth eruption included NR. Diagnostic errors NR

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The participants were then allocated to study groups by random permutations of five after stratification by sex and race within each school..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "Group C rinsed weekly with a placebo solution containing 0.1% NaCl" "The examiners were not aware of group assignments and did not consult baseline findings during the incremental exam" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "Group C rinsed weekly with a placebo solution containing 0.1% NaCl" "The examiners were not aware of group assignments and did not consult baseline findings during the incremental exam" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 38.53% in 2 years Dropout by group: 186/421 FR1, 158/415 FR2, 153/397 FR3, 144/397 FR4, 135/384 PL Reasons for losses: "migratory" nature of community, changing schools Comment: Numbers lost were unduly high, given length of follow-up, with no differential loss evident between groups [44.18%(FR1), 38.01%(FR2), 38.53%(FR3), 36.27%(FR4), 35.16%(PL)]. Reasons for missing outcome data are acceptable. Caries data used in analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Unclear risk	Outcomes reported DMFS increment, reported at 1.5 and 2.5 years' follow-up PosMD-DFS

Ringelberg 1982 (Continued)

		Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 4.71 FR1, 5.17 FR2, 4.75 FR3, 4.11 FR4, 4.93 PL Comment: Initial caries shows some imbalance, but adjustment made no difference in results - "A covariance analysis utilizing baseline as the covariant, however failed to change the results of the tests"
Free of contamination/co-intervention?	Unclear risk	No information provided

Rugg-Gunn 1973

Methods	Study design: 2-arm parallel-group RCT, placebo-controlled Study duration: 2 school years (1.6 years)
Participants	Participants randomised: N = 491 434 children analysed at 3 years (available at final examination) Age range at start: 10 to 11 years Surfaces affected at start: 8.8 DMFS Exposure to other fluoride: no (only 14 children, 8 control, 6 test claimed dentifrice use) Year study began: assumed in/before 1969 Location: UK Setting of recruitment and treatment: school
Interventions	Comparison: FR vs PL FR group: 0.05% NaF (230 ppm F) PL group: non-F rinse School use/supervised, daily (160 rinses/y), 7.5 mL applied for 2 minutes Before application: NR Postop instruction: NR
Outcomes	3yNetDMFS increment - (E+U)(CA)cl+(DR)xr Reported at 1, 2 and 3 years' follow-up DMFT (E/U) PF-DMFS FS-DMFS AntMD-DMFS PostMD-DMFS DMFS (U) Signs of sensitivity in oral mucosa Dropout

Declaration of Interest	No information provided	
Funding	The project was financed by a grant from Colgate-Palmolive Ltd	
Notes	Clinical (V) caries assessment by 1 examiner, diagnostic threshold = CA/NCA. Radiographic assessment (2postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included = E/U. Intraexaminer reproducibility checks for incremental caries data in 10% sample (ICC score 0.9 for DMFS) Reversal rate 4% and 7% of observed DMFS increment in control and study groups, respectively	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quotes: "248 were allocated to the test and 243 to the control group" "Control and test subjects were arranged randomly within the same school classes" "The distribution of subjects into test and control groups was undertaken using stratified random sampling" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The trials was organised on a double-blind basis, neither the subjects nor the investigators being aware who was receiving test or control rinses" "...the control rinse was similar in taste and appearance to test rinse except for the omission of sodium fluoride" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "The trials was organised on a double-blind basis, neither the subjects nor the investigators being aware who was receiving test or control rinses" "...the control rinse was similar except for the omission of sodium fluoride" Comment: blinded outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 11.6% in 3 years Dropout by group: 26/248(10.5%) FR,

Rugg-Gunn 1973 (Continued)

		<p>31/243(12.7%) PL</p> <p>Reasons for losses: difficulty with rinsing (1), moved away from area or absent at final examination (56)</p> <p>Comment: numbers lost not high, given length of follow-up, with no differential loss evident between groups. It is unclear whether reasons for missing outcome data are balanced between groups. Caries data used in the analysis pertain to participants present at the final examination</p>
Selective reporting (reporting bias)	Low risk	<p>Outcomes reported</p> <p>DMFS increment (E+U)(CA)cl + (DR) xr, reported at 1, 2 and 3 years' follow-up</p> <p>DMFT (E/U)</p> <p>PF-DMFS</p> <p>FS-DMFS</p> <p>Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way</p>
Baseline characteristics balanced?	Unclear risk	<p>Prognostic factors reported</p> <p>DMFS: 8.74(5.49) FR, 8.88(5.44) PL</p> <p>DMFT: 5.55(3.04) FR, 5.58(3.06) PL</p> <p>Gender: 123 M, 99 F (FR), 121 M, 91 F (PL)</p> <p>Fluoride dentifrice use: 6 FR, 8 PL</p> <p>Comment: initial caries appears balanced between groups. Other baseline characteristics (gender, exposure to fluoride toothpaste) also balanced</p>
Free of contamination/co-intervention?	Unclear risk	No information provided

Ruiken 1987

Methods	<p>Study design: 2-arm cluster-randomised trial, non-placebo-controlled</p> <p>Study duration: 3 years</p>
Participants	<p>Number randomised: 501 children were "examined at baseline", 29 schools were randomised, number of children per group NR</p> <p>207 children analysed at 3 years (present at final examination, for which readable x-rays were available)</p> <p>Average age at start: 8 years</p> <p>Surfaces affected at start: 2.7 DFS</p> <p>Exposure to other fluoride: yes (toothpaste, tablets)</p>

Ruiken 1987 (Continued)

	Year study began: 1981 Location: The Netherlands Setting of recruitment and treatment: elementary schools, The Hague	
Interventions	Comparison: FR vs NT FR group: 0.2% neutral NaF (900 ppm F) NT group: no intervention School use/supervised, weekly (30 rinses/y), 10 mL applied for 1 minute Before application: NR Postop instruction: NR	
Outcomes	3yNetDFS increment (mean converted from median) - (CA/NCA)d+(DR/ER)xr Reported at 3 years' follow-up	
Declaration of Interest	No information provided	
Funding	Supported by a grant from Het Praeventiefonds	
Notes	Clinical (V) caries assessment by 2 examiners; diagnostic threshold = CA/NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold = DR/ER; partial recording. Diagnostic errors NR	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A sample of 29 schools stratified according to SES and randomly assigned to two groups was selected" Comment: not enough information provided about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "One group of schools (14) performed rinsing and the other group (15) served as controls" Comment: Control group had no treatment. No placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The radiographs were interpreted by the same investigators without reference to the clinical examination data" Comment: Clinical and radiographic exams were done independently. Randomisation was by school. It was unclear whether examiners would have known

		which assignment/school the radiographs were from. Blinded outcome assessment indicated but no placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall drop-out for length of follow-up (reported for individuals within clusters only): 58.7% (207/501) in 3 years Drop-outs by group: not reported Main reasons for losses/attrition: “natural losses”, and results reported only for children with readable radiographs Comment: unclear whether recruitment of children was done before clusters (schools) had been randomised. Numbers lost unduly high for length of follow-up; differential losses between groups not assessable. Reason for missing outcome data unacceptable. Caries data used in analysis pertain to participants with readable radiographs present at final examination (and analysis done at individual level within clusters does not take clustering into account)
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - cl+xr, reported at 3 years Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DFS: 2.8 FR, 2.6 PL Age: 8 years (both groups combined) Erupted surfaces: 38.3 (both groups combined). Comment: initial caries appears balanced between groups (for individuals within clusters). Other characteristics (erupted surfaces, age) described as 'balanced'
Free of contamination/co-intervention?	Unclear risk	No information provided

Spets-Happonen 1991

Methods	Study design: 4-arm parallel-group RCT (only 2 relevant arms used), placebo-controlled Study duration: 3 years	
Participants	Participants randomised: numbers NR 95 children analysed at 3 years (available at final examination) Average age at start: 11 years Surfaces affected at start: 5.8 DMFS (from 1 year sample) Exposure to other fluoride: varnish once a year (toothpaste assumed) Year study began: 1985 Location: Finland Setting of recruitment and treatment: school and school/home	
Interventions	FR(Chlor)+ptc vs PL(Chlor)+ptc** FR group: 0.04% NaF (180 ppm F) PL group: non-F rinse School use/supervised, 5 days every 3 weeks (115 rinses/y), 5 mL applied for 1 minute. Same schedule recommended for evening rinse at home (but no instruction for use of toothpaste given) Before application: prior toothbrushing without toothpaste in both groups (done at school, recommended for home) Postop instruction: not to eat or drink after rinse **Chlorhexidine present in both fluoride and non-fluoride mouthrinse (thus, other outcomes, such as tooth staining, not relevant for the comparison of interest)	
Outcomes	3yDMFS increment - (CA)cl+(DR)xr Reported at 3 years' follow-up	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA (FOTI assessment - loss of translucency on transillumination - for approximal surfaces of anterior teeth); state of tooth eruption included NR. Radiographic assessment; diagnostic threshold = DR ; kappa 0.7 and 0.79 for interexaminer and intraexaminer reliability	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were randomly divided into 4 groups" Comment: not enough information given
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "All rinsing solutions were used and other study procedures performed on

		<p>a double-blind basis...”</p> <p>“All rinsing solutions had same buffered pH”</p> <p>“Group CX rinsing with chlorhexidine solution...Group CXF with chlorhexidine-fluoride solution”</p> <p>“The examiners did not know which group the children belonged to”</p> <p>Comment: use of placebo described</p>
<p>Blinding of outcome assessment (detection bias)</p> <p>All outcomes</p>	<p>Low risk</p>	<p>Quotes: “All rinsing solutions were used and other study procedures performed on a double-blind basis...”</p> <p>“The examiners did not know which group the children belonged to”</p> <p>Comment: blinded outcome assessment and use of placebo described</p>
<p>Incomplete outcome data (attrition bias)</p> <p>All outcomes</p>	<p>High risk</p>	<p>Overall dropout for length of follow-up: 17.3% (42/243) in 3 years (all groups)</p> <p>Dropout by group: not assessable, but “greatest proportion of dropouts in the fluoride group”</p> <p>Reasons for losses: not reported</p> <p>Comment: numbers lost not unduly high for length of follow-up, but differential losses between groups not assessable. Reason for missing outcome data not reported. Caries data used in analysis pertain to participants available at final examination</p>
<p>Selective reporting (reporting bias)</p>	<p>Low risk</p>	<p>Outcomes reported</p> <p>DMFS increment - (CA) cl+(DR)xr, reported at 3 years’ follow-up</p> <p>Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way</p>
<p>Baseline characteristics balanced?</p>	<p>Low risk</p>	<p>Prognostic factors reported</p> <p>DMFS: 5.0(3.7) FR, 6.6(4.4) PL</p> <p>Gender (% Boys): 50 FR, 50 PL</p> <p>Comment: initial caries appears imbalanced, but “adjustment made no difference in the results”. Gender balanced</p>
<p>Free of contamination/co-intervention?</p>	<p>Unclear risk</p>	<p>No information provided</p>

Torell 1965

Methods	<p>Study design: 9-arm parallel-group RCT (only 3 relevant arms used), non-placebo-controlled</p> <p>Study duration: 2 school years</p>
Participants	<p>Participants randomised: N = 597</p> <p>494 children analysed at 2 years (available at final examination)</p> <p>Average age at start: 10 years</p> <p>Surfaces affected at start: 14.7 DMFS (from sample randomised)</p> <p>Exposure to other fluoride: none assumed</p> <p>Year study began: 1962</p> <p>Location: Sweden</p> <p>Setting of recruitment and treatment: school and home/school</p>
Interventions	<p>FR (2 groups) vs NT</p> <p>FR group 1: 0.05% NaF (230 ppm F), 10 mL applied daily (320 rinses/y), unsupervised at home (instructed to be done after toothbrushing every evening)</p> <p>FR group 2: 0.2% NaF (900 ppm F), 10 mL applied fortnightly (17 rinses/y), supervised at school</p> <p>NT group: no intervention</p> <p>Before application: NR</p> <p>Postop instruction: NR</p>
Outcomes	<p>2yDMFS increment - (CA)cl+(DR)xr</p> <p>Reported at 1 and 2 years' follow-up</p> <p>MD-DMFS</p> <p>FS</p> <p>Proportion of children with new carious lesions - (U)xr</p> <p>Dropout</p>
Declaration of Interest	No information provided
Funding	Financial support from the Swedish Medical Research Council, the City of Goteborg, the County of Stockholm and the National Board of Health, partial support (toothpastes in the trial) by Procter and Gamble Co
Notes	Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA; radiographic assessment (BW) by 2 examiners; diagnostic threshold = DR. State of tooth eruption included NR. Interexaminer and intraexaminer reproducibility checks done for clinical caries in 4% and 2% of sample, respectively; duplicate examination of x-ray records done, and any discrepancies discussed before final diagnosis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The groups were randomly constituted and randomly assigned to the test different test methods, according to a system worked out with the assistance of statisti-

Torell 1965 (Continued)

		cians...” Comment: It is likely a random method was used
Allocation concealment (selection bias)	Unclear risk	Method not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “The study was a blind test as the examination charts did not refer to the treatment or to the code number of the groups” Comment: no placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: “The study was a blind test as the examination charts did not refer to the treatment or to the code number of the groups” Comment: blinded outcome assessment but no placebo described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall dropout for length of follow-up: 17.25% in 2 years Dropout by group: 30/190 FR1, 39/211 FR2, 34/196 NT Reasons for losses: changing school, moving away, appearance of new caries, unpleasant taste and objectionable pigmentation (not reported by group) Comment: Numbers lost were not unduly high for the length of follow-up, with no differential losses. It is unclear whether reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported DMFS increment - (CA)cl+(DR)xr, reported at 1 and 2 years’ follow-up MD-DMFS FS Proportion of children with new carious lesions (U) xr Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DMFS: 14.4(7.30) FR1, 15.2(8.57) FR2, 14.5(7.42) NT

Torell 1965 (Continued)

		MD-DMFS: 3.54 FR1, 3.97 FR2, 3.59 NT Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

van Wyk 1986

Methods	Study design: 3-arm parallel-group RCT, placebo-controlled Study duration: 3 years	
Participants	Participants randomised: N = 925 569 children analysed at 3 years (available at final examination) Age range at start: 12 to 13 years Surfaces affected at start: 8.4 DFS Exposure to other fluoride: no Year study began: 1981 Location: South Africa Setting of recruitment and treatment: school	
Interventions	FR (2 groups) vs PL FR group 1: 0.2% neutral NaF solution (900 ppm F) FR group 2: 0.05% neutral NaF solution (230 ppm F) PL group: non-F rinse solution School use/supervised, weekly (30 rinses/y), 10 mL applied for 1 minute Before application: NR Postop instruction: children instructed not to eat or drink for at least 1/2 hour after rinsing	
Outcomes	3yNetDFS increment - (CA)cl Reported at 1, 2 and 3 years' follow-up Dropout	
Declaration of Interest	No information provided	
Funding	No information provided	
Notes	Clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA. State of tooth eruption included NR. Intraexaminer reproducibility checks for incremental caries data in 40% sample (ICC score 0.91)	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote: "...participants were randomly assigned to one of 3 rinsing groups" "Boys and girls were separately, randomly allocated to one of the three colours..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The trial was conducted on a double-blind basis. Boys and girls...were not informed of the meaning of the colour code. Nor was the examiner allowed to know to which colour code a subject belonged" "The solutions were indistinguishable in taste" Comment: use of placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: as above Comment: blinded outcome assessment and use of placebo described
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall dropout for length of follow-up: 38.49% in 3 years Dropout by group: 124/309 FR1, 114/306 FR2, 118/310 PL Reasons for losses: "main reasons were: scholastic failure and changing of schools" Comment: numbers lost unduly high for length of follow-up, with no differential losses between groups. Reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported DFS increment - (CA) CI reported at 1, 2 and 3 years' follow-up Comment: trial protocol not available. All prespecified outcomes (in Methods) were reported in the prespecified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported DFS: 8.7(6.6) FR1, 8.2(5.8) FR2, 8.4(6.5) PL Gender: 89 M, 96 F (FR1), 90 M, 102 F (FR2), 93M, 99 F (PL) Comment: initial caries appears balanced

		between groups. Gender also balanced
Free of contamination/co-intervention?	Low risk	Quote from correspondence: "We ensured that a child did not change the rinse during the study" Comment: overall prevention of contamination/co-intervention indicated

Dropout rate based only on groups relevant to the review, on relevant follow-ups, unless otherwise stated. Baseline caries experience averaged among relevant study arms, and based on the study sample analysed at the end of the study period (final sample), unless otherwise stated. Age range (average age when reported) at the time the study started based on all study participants (or on groups relevant to the review when data were available).

1stm = first permanent molar; AmF = amine fluoride; APF = acidulated phosphate fluoride; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor/walls) or showing frank cavitation; CAR = caries attack rate; CFS = caries-free surfaces; CFT = caries-free teeth; Chlor = chlorhexidine diguconate; CIR = caries incidence rate; cl = clinical examination; d(e)ft/s = decayed (extracted) and filled deciduous teeth or surface; dmft/s = decayed, missing (or extracted) and filled deciduous teeth or surface; D(M)FS/T = decayed (missing) and filled permanent surfaces or teeth; DR = radiolucency into dentin; E = teeth erupted at baseline; ER = any radiolucency in enamel/enamel-dentin junction; F = fluoride; FR = fluoride mouthrinse; ICC = intraclass correlation co-efficient (for interrater reliability); M = missing permanent teeth; MD = mesio and distal surfaces; N = numbers; Na = sodium; NaF = sodium fluoride; NCA = non-cavitated enamel lesions visible as white spots or discoloured fissures; NH4F = ammonium fluoride; NR = not reported; NS = not significant; NT = no treatment control; O = occlusal surfaces; PF = pit and fissure surfaces; PL = placebo mouthrinse; post BW = posterior bite-wing x-ray assessment; ppm F = parts per million of fluoride; ptc = prior tooth-cleaning performed with or without a non-fluoride paste; RCT = randomised controlled trial; SMFP = sodium monofluorophosphate; SnF2 = stannous fluoride; U = teeth unerupted at baseline; VT = visual-tactile assessment; xr = radiographic examination.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aasenden 1972	Fluoride solution swallowed after rinsing (even though no systemic effect should be anticipated for this age group)
Arcieri 1981	Random or quasi-random allocation not stated. Blind outcome assessment not stated
Axelsson 1976	Additional fluoride-based intervention associated with fluoride mouthrinse. Blind outcome assessment not stated
Badersten 1975	Additional non-fluoride-based intervention associated with fluoride mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated
Birkeland 1973	No relevant outcome reported. Blind outcome assessment not stated. Length of follow-up of less than 1 year/school year (6 months)

(Continued)

Bohannon 1985a	Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely
Boyd 1985	Additional fluoride-based intervention associated with fluoride mouthrinse. Clearly not randomised or quasi-randomised (systematic process of assignment). Length of follow-up of less than 1 year/school year
Bristow 1975	Additional interventions associated with fluoride mouthrinse. Not a randomised or quasi-randomised trial (only 2 clusters (schools) selected, each assigned to 1 of the 2 study groups)
Brodeur 1989	Open outcome assessment
Castellanos 1983	Open outcome assessment reported after contacting study author
Chen 2010	Open outcome assessment. Not a randomised or quasi-randomised trial (selection of 2 clusters only, each assigned to 1 of the 2 groups)
Chikte 1996	Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely
Cichocka 1981	No random or quasi-random allocation used (selected group comparisons). Blind outcome assessment not stated and unlikely
Clark 1985a	Clearly not randomised or quasi-randomised (concurrent control group taken from another study)
Corpus 1973	Clearly not randomised or quasi-randomised (systematic allocation according to participants' characteristics) . Blind outcome assessment not stated or indicated
De Canton 1983	Additional fluoride-based and non-fluoride-based interventions associated with fluoride mouthrinse. Random or quasi-random allocation not stated
DePaola 1967	Additional fluoride-based intervention associated with fluoride mouthrinse. Blind outcome assessment not stated
Disney 1989	Additional non-fluoride-based intervention associated with fluoride mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated
Esteva Canto 1991	Clearly not randomised or quasi-randomised (systematic group assignment). Blind outcome assessment not stated and unlikely
Fernandez 1979	Open outcome assessment. Random or quasi-random allocation not stated or indicated
Frankl 1972	Fluoride solution swallowed after rinsing (even though no systemic effect should be anticipated for this age group)
Gray 1980	Additional fluoride-based intervention associated with fluoride mouthrinse
Hall 1964	Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely

(Continued)

Heifetz 1979	Additional fluoride-based intervention associated with fluoride mouthrinse Note - inappropriate 'placebo' used
Irmisch 1974	Additional active agent associated with fluoride in mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely
Ivanova 1990	Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely
Kani 1973	Random or quasi-random allocation not stated. Blind outcome assessment not stated
Kasakura 1966	Random or quasi-random allocation not stated. Blind outcome assessment not stated and unlikely
Kitsugi 1978	Additional intervention associated with fluoride mouthrinse
Kunzel 1978	Not a randomised or quasi-randomised trial. Only 2 clusters (schools) selected, each assigned to 1 of the 2 study groups. Blind outcome assessment not stated and unlikely
Louw 1995	Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely
Luoma 1978	Additional fluoride-based intervention associated with fluoride mouthrinse
McCormick 1970	Random or quasi-random allocation not stated Note - only post-treatment effects reported
Mendonca 1995	Open outcome assessment reported after contacting study author
Morgan 1998	Additional non-fluoride-based intervention associated with fluoride mouthrinse. Blind outcome assessment not stated
Morozova 1983	Additional intervention associated with fluoride mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely
Moungtin 1975	Random or quasi-random allocation not stated or indicated. Outcome assessment not blind
Nenyeyi 1971	Random or quasi-random allocation not stated or indicated. Outcome assessment not blind
Ramos 1995	Open outcome assessment
Roberts 1948	Clearly not randomised or quasi-randomised (concurrent control group selected by matching procedure)
Rodriguez Miro 1983	Additional active agent associated with fluoride in mouthrinse. Not a randomised or quasi-randomised trial - only 3 clusters (school classes), each assigned to 1 of the 3 interventions compared
Shimada 1978	Not a randomised or quasi-randomised trial - only 3 clusters (schools), each assigned to 1 of the 3 study groups (method of assignment not stated). Outcome assessment not blinded

(Continued)

Suntsov 1991	Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely Note - only post-treatment effects reported
Swerdloff 1969	Length of follow-up of less than 1 year/school year
Torell 1969	Random or quasi-random allocation not stated or indicated Note - unclear study duration
Weisz 1960	Clearly not randomised or quasi-randomised (concurrent control group taken from a different population) . Open outcome assessment
Widenheim 1989	Clearly not randomised or quasi-randomised (concurrent control group taken from a different population) . Open outcome assessment
Wilson 1978	Random or quasi-random allocation not stated Note - abstract only; full text not obtainable; insufficient information available to include in review
Wycoff 1991	Clearly not randomised or quasi-randomised (systematic assignment of a few clusters to interventions). Blind outcome assessment not stated and unlikely Note - abstract only, full text not available/obtainable
Zickert 1982	Additional fluoride-based intervention associated with fluoride mouthrinse

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kawall 1981

Methods	
Participants	
Interventions	
Outcomes	
Notes	Additional information for this study report still missing

DATA AND ANALYSES

Comparison 1. Fluoride mouthrinse versus placebo or no treatment

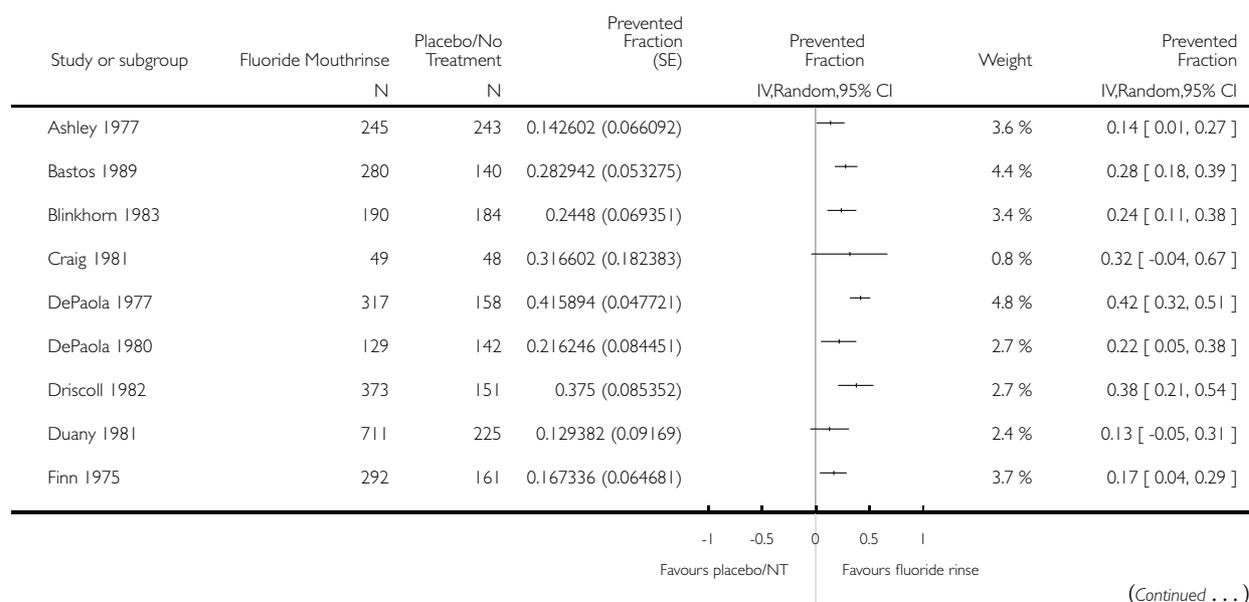
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 D(M)FS increment (PF) - nearest to 3 years (35 trials)	35	15305	Prevented Fraction (Random, 95% CI)	0.27 [0.23, 0.30]
2 D(M)FT increment (PF) - nearest to 3 years (13 trials)	13	5105	Prevented Fraction (Random, 95% CI)	0.23 [0.18, 0.29]
3 Developing 1 or more new caries (3 trials)	3	1805	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.46, 1.29]
4 Lack of acceptability of treatment as measured by leaving study early (4 trials)	4	1700	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.62, 2.83]

Analysis 1.1. Comparison 1 Fluoride mouthrinse versus placebo or no treatment, Outcome 1 D(M)FS increment (PF) - nearest to 3 years (35 trials).

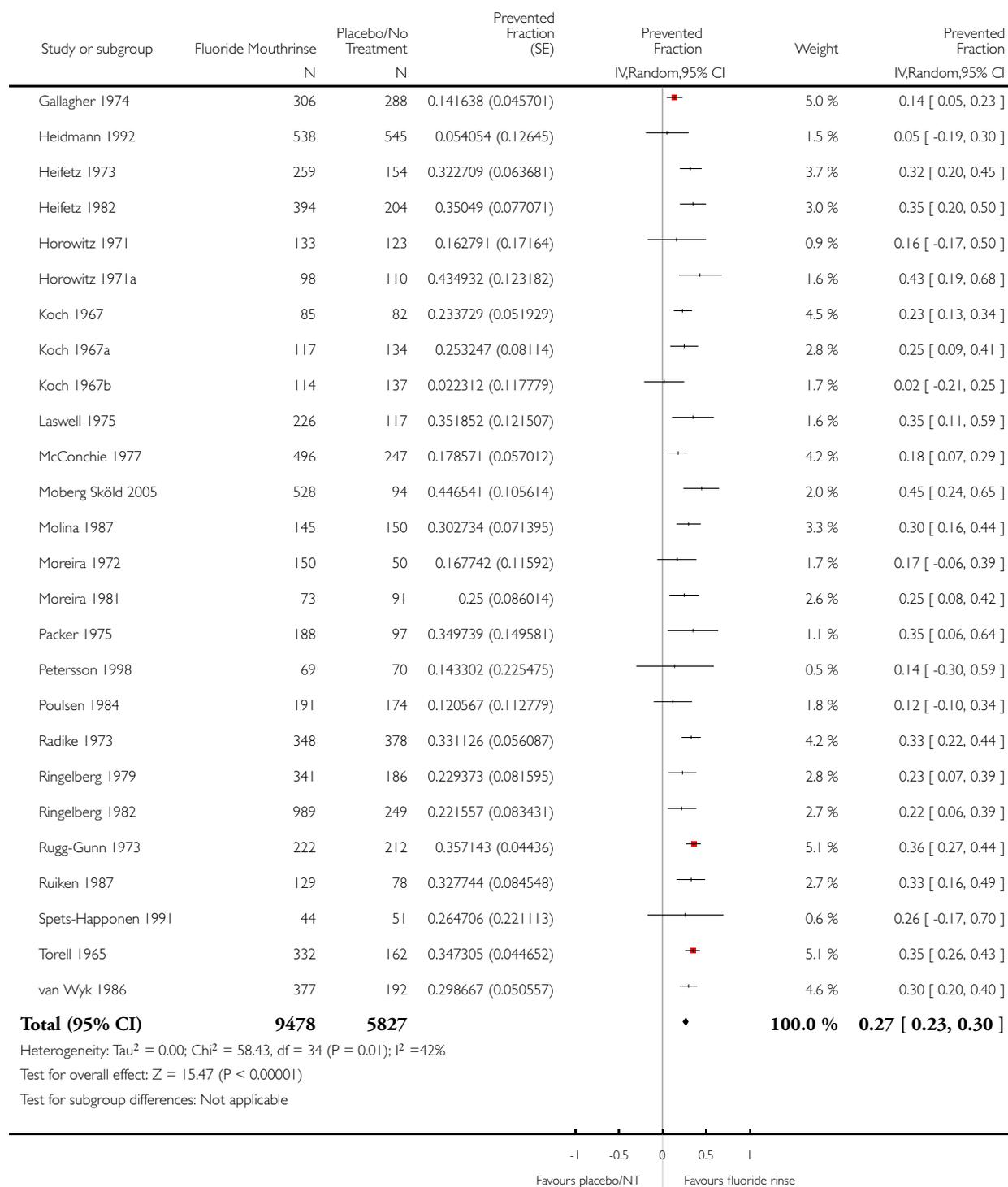
Review: Fluoride mouthrinses for preventing dental caries in children and adolescents

Comparison: 1 Fluoride mouthrinse versus placebo or no treatment

Outcome: 1 D(M)FS increment (PF) - nearest to 3 years (35 trials)



(... Continued)

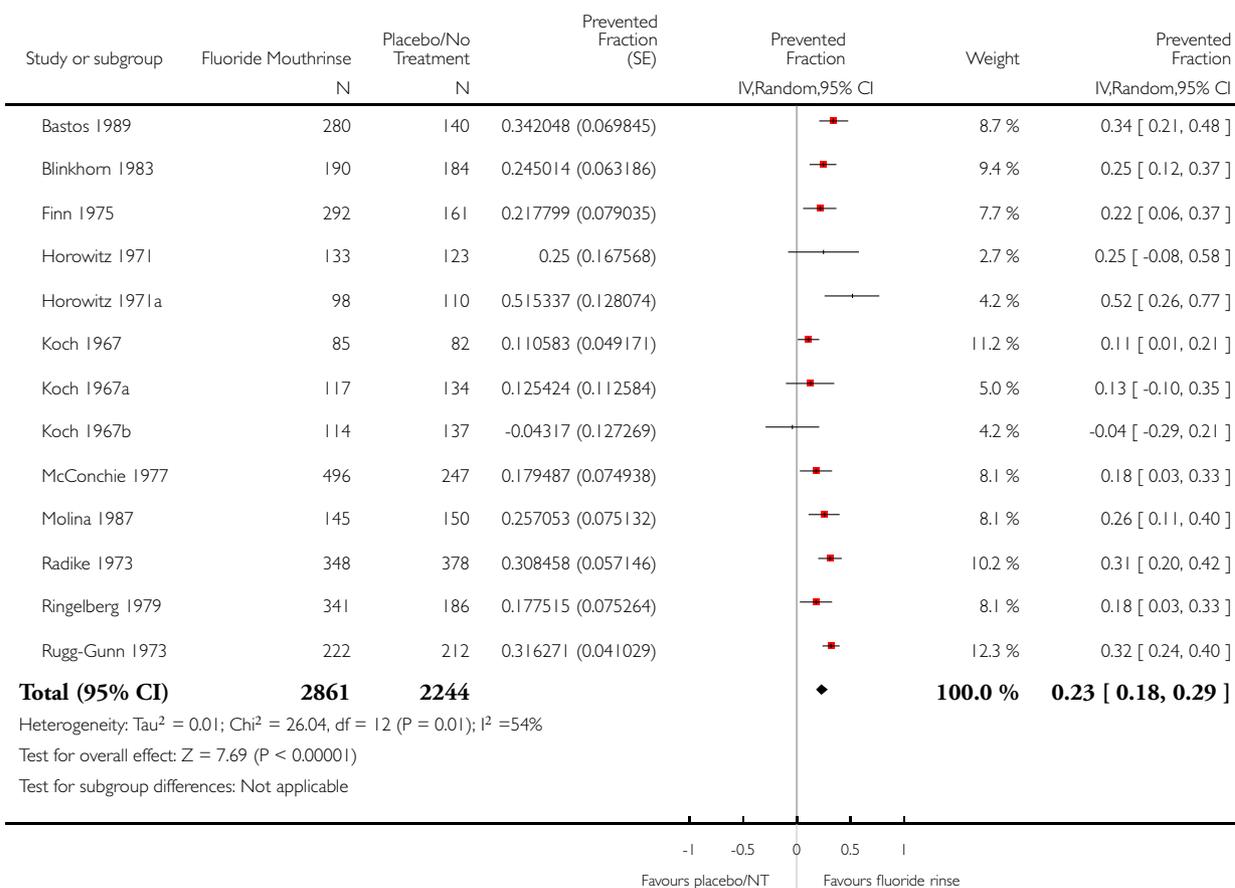


Analysis 1.2. Comparison 1 Fluoride mouthrinse versus placebo or no treatment, Outcome 2 D(M)FT increment (PF) - nearest to 3 years (13 trials).

Review: Fluoride mouthrinses for preventing dental caries in children and adolescents

Comparison: 1 Fluoride mouthrinse versus placebo or no treatment

Outcome: 2 D(M)FT increment (PF) - nearest to 3 years (13 trials)

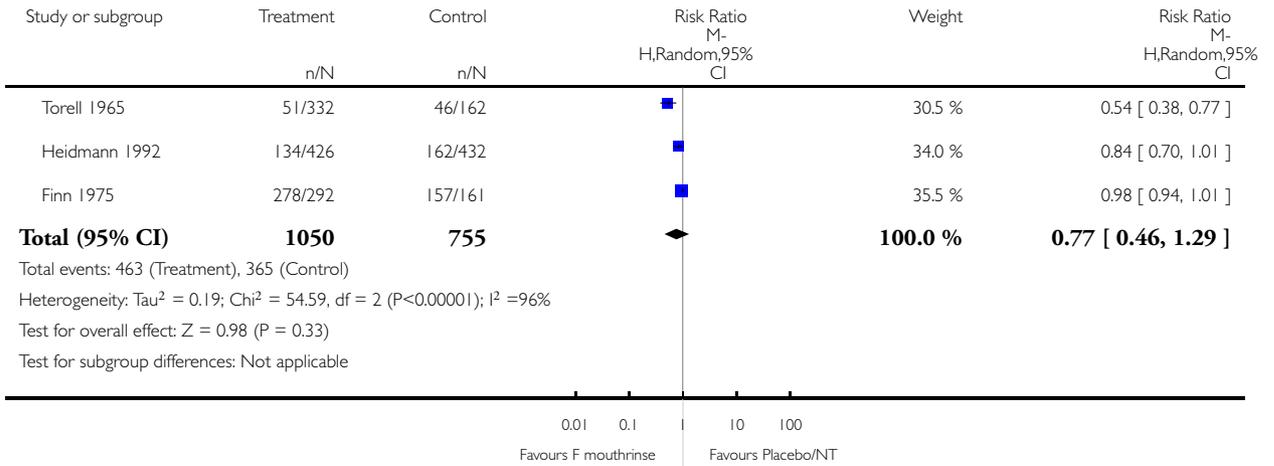


Analysis 1.3. Comparison 1 Fluoride mouthrinse versus placebo or no treatment, Outcome 3 Developing 1 or more new caries (3 trials).

Review: Fluoride mouthrinses for preventing dental caries in children and adolescents

Comparison: 1 Fluoride mouthrinse versus placebo or no treatment

Outcome: 3 Developing 1 or more new caries (3 trials)

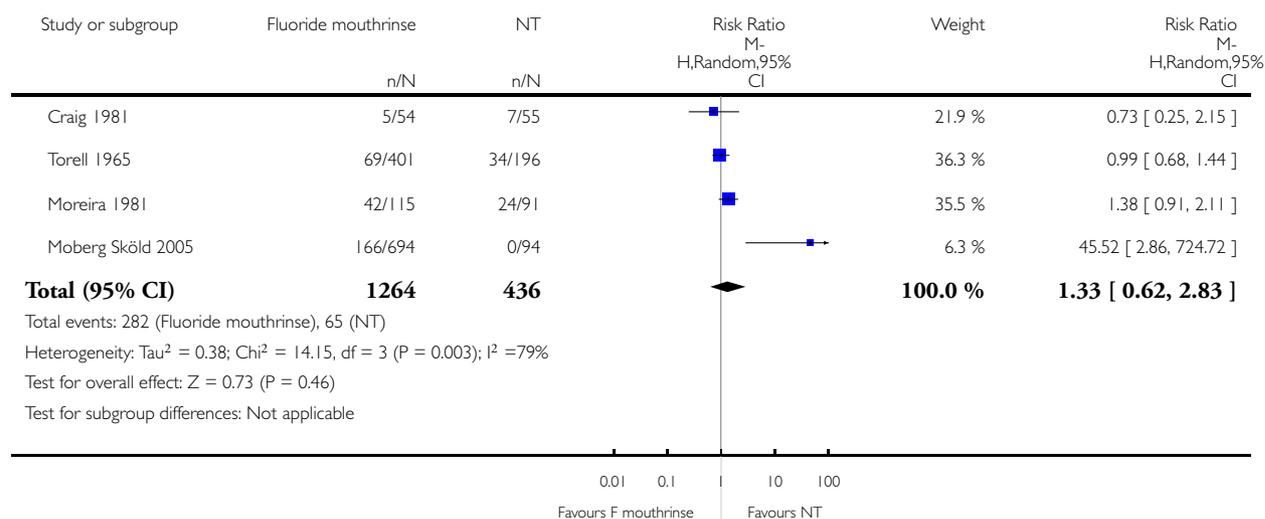


Analysis 1.4. Comparison 1 Fluoride mouthrinse versus placebo or no treatment, Outcome 4 Lack of acceptability of treatment as measured by leaving study early (4 trials).

Review: Fluoride mouthrinses for preventing dental caries in children and adolescents

Comparison: 1 Fluoride mouthrinse versus placebo or no treatment

Outcome: 4 Lack of acceptability of treatment as measured by leaving study early (4 trials)



ADDITIONAL TABLES

Table 1. Meta-analyses of prevented fractions: D(M)FS and D(M)FT

Analysis	Number of studies	RE PF estimate	95% CI	Meta-analysis P value	Heterogeneity test
D(M)FS - all studies	35	27%	23% to 30%	P value < 0.0001	Chi ² = 58.43 (34 df); P value = 0.006; I ² = 42%
D(M)FT - all studies	13	23%	18% to 29%	P value < 0.0001	Chi ² = 26.04 (12 df); P value = 0.011; I ² = 54%

D(M)FS = decayed (missing) and filled permanent surfaces

D(M)FT = decayed (missing) and filled permanent teeth

Table 2. Random-effects metaregression analyses of prevented fractions: D(M)FS

Characteristic	Number of studies	Slope estimate	95% CI	Slope interpretation	P value
Mean baseline caries	34	0.2%	(-0.8% to 1.3%)	Increase in PF per unit increase in mean baseline caries	0.7
Fluoridated water area	33	6.6%	(-4.8% to 17.9%)	Higher PF in presence of water fluoridation	0.3
Fluoride dentifrice use	33	4.8%	(-3.2% to 12%)	Higher PF in presence of fluoride dentifrice use	0.2
Background fluorides	33	5.8%	(-1.5% to 13.1%)	Higher PF in presence of background fluoride	0.12
Rinsing frequency	34	0.4%	(-4.3% to 5.0%)	Increase in PF per 100 extra applications/y	0.9
Fluoride concentration in solution	35	1.1%	(-3.9% to 6.0%)	Increase in PF per 1000 ppm F	0.7
Intensity (frequency times concentration)	33 (excludes De-Paola 1977)	8.3%	(-14% to 31%)	Increase in PF equivalent to doubling from 100 to 200 applications and increasing by 1000 ppm F	0.5
Control group	35	8.2%	(-2.0% to 18.4%)	Higher PF for no treatment compared with placebo	0.11
Dropout	32	0.4%	(-2.1% to 2.9%)	Increase in PF per 10 dropouts	0.7
Length of follow-up	35	1.1%	(-6.2% to 8.5%)	Increase in PF per extra year of follow-up	0.8

D(M)FS = decayed (missing) and filled permanent surfaces

PF = prevented fraction

ppm F = parts per million of fluoride

y = year

APPENDICES

Appendix 1. Cochrane Oral Health's Trials Register search strategy

- 1 (carie* or carious or DMF):ti,ab
- 2 ((dental or tooth or teeth or enamel or dentin*) and (decay* or cavit* or deminerali* or reminerali* or "white spot*")):ti,ab
- 3 #1 or #2
- 4 (fluorid* or fluor or "PPM F" or PPMF or APF or NAF or "Sodium F" or "Amine F" or SNF2 or "Stannous F" or "phosphat* F" or "acidulat* F" or "phosphat* fluor*" or fluorphosphat* or "amin* fluor*" or "sodium fluor*" or "stannous fluor*" or SMFP or MFP or monofluor*):ti,ab
- 5 (mouthwash* or mouthrins* or "mouth wash*" or "mouth rins*"):ti,ab
- 6 ((FluoriGard or Duraphat or Endekay or Act or Swirl or "Wisdom step by step" or Dentimint or AloeDent or Listerine) and (rins* or wash*)):ti,ab.
- 7 (oral next (rins* or wash*)):ti,ab
- 8 #5 or #6 or #7
- 9 (#3 and #4 and #8) AND (INREGISTER)

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

- #1 [mh "Tooth demineralization"]
- #2 (carie* or carious or DMF)
- #3 ((dental or tooth or teeth or enamel or dentin*) and (decay* or cavit* or deminerali* or reminerali* or "white spot*"))
- #4 {or #1-#3}
- #5 [mh Fluorides]
- #6 (fluorid* or fluor or "PPM F" or PPMF or APF or NAF or "Sodium F" or "Amine F" or SNF2 or "Stannous F" or "phosphat* F" or "acidulat* F" or "phosphat* fluor*" or fluorphosphat* or "amin* fluor*" or "sodium fluor*" or "stannous fluor*" or SMFP or MFP or monofluor*)
- #7 #5 or #6
- #8 [mh Mouthwashes]
- #9 (mouthwash* or mouthrins* or "mouth wash*" or "mouth rins*")
- #10 ((FluoriGard or Duraphat or Endekay or Act or Swirl or "Wisdom step by step" or Dentimint or AloeDent or Listerine) and (rins* or wash*))
- #11 (oral next (rins* or wash*))

Appendix 3. MEDLINE Ovid search strategy

1. exp Tooth demineralization/
2. (carie\$ or carious or DMF).ti,ab.
3. ((dental or tooth or teeth or enamel or dentin\$) and (decay\$ or cavit\$ or deminerali\$ or reminerali\$ or "white spot\$")):ti,ab.
4. or/1-3
5. exp Fluorides/
6. (fluorid\$ or fluor or "PPM F" or PPMF or APF or NAF or "Sodium F" or "Amine F" or SNF2 or "Stannous F" or "phosphat\$ F" or "acidulat\$ F" or "phosphat\$ fluor\$" or fluorphosphat\$ or "amin\$ fluor\$" or "sodium fluor\$" or "stannous fluor\$" or SMFP or MFP or monofluor\$).ti,ab.
7. 5 or 6
8. Mouthwashes/
9. (mouthwash\$ or mouthrins\$ or "mouth wash\$" or "mouth rins\$").ti,ab.
10. ((FluoriGard or Duraphat or Endekay or Act or Swirl or "Wisdom step by step" or Dentimint or AloeDent or Listerine) and (rins\$ or wash\$)).ti,ab.
11. (oral adj (rins\$ or wash\$)).ti,ab.
12. or/8-11
13. 4 and 7 and 12

The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [updated March 2011] ([Higgins 2011](#)).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid search strategy

1. Dental caries/
2. (carie\$ or carious or DMF).ti,ab.
3. ((dental or tooth or teeth or enamel or dentin\$) and (decay\$ or cavit\$ or deminerali\$ or reminerali\$ or "white spot\$")).ti,ab.
4. or/1-3
5. exp Fluoride/
6. (fluorid\$ or fluor or "PPM F" or PPMF or APF or NAF or "Sodium F" or "Amine F" or SNF2 or "Stannous F" or "phosphat\$ F" or "acidulat\$ F" or "phosphat\$ fluor\$" or fluorphosphat\$ or "amin\$ fluor\$" or "sodium fluor\$" or "stannous fluor\$" or SMFP or MFP or monofluor\$).ti,ab.
7. 5 or 6
8. Mouthwash/
9. (mouthwash\$ or mouthrins\$ or "mouth wash\$" or "mouth rins\$").ti,ab.
10. ((FluoriGard or Duraphat or Endekay or Act or Swirl or "Wisdom step by step" or Dentimint or AloeDent or Listerine) and (rins\$ or wash\$)).ti,ab.
11. (oral adj (rins\$ or wash\$)).ti,ab.
12. or/8-11
13. 4 and 7 and 12

The above subject search was linked to Cochrane Oral Health's filter for identifying RCTs in Embase Ovid:

1. random\$.ti,ab.
2. factorial\$.ti,ab.
3. (crossover\$ or cross over\$ or cross-over\$).ti,ab.
4. placebo\$.ti,ab.
5. (doubl\$ adj blind\$).ti,ab.
6. (singl\$ adj blind\$).ti,ab.
7. assign\$.ti,ab.
8. allocat\$.ti,ab.
9. volunteer\$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 NOT 15

Appendix 5. CINAHL EBSCO search strategy

S12 S3 and S6 and S11

S11 S7 or S8 or S9 or S10

S10 (oral n1 (rins\$ or wash\$))

S9 ((FluoriGard or Duraphat or Endekay or Act or Swirl or “Wisdom step by step” or Dentimint or AloeDent or Listerine) and (rins\$ or wash\$))

S8 (mouthwash* or mouthrins* or “mouth wash*” or “mouth rins”*)

S7 (MH “Mouthwashes+”)

S6 S4 or S5

S5 (fluoride* or fluor or “PPM F” or PPMF or APF or NAF or “Sodium F” or “Amine F” or SNF2 or “Stannous F” or “phosphat* F” or “acidulat* F” or “acidulat* fluor*” or “phosphat* fluor*” or fluorphosphat* or “amin* fluor*” or “sodium* fluor*” or “stannous* fluor*” or SMFP or MFP or monofluor*)

S4 (MH “Fluorides+”)

S3 S1 or S2

S2 (carie* or caries or carious or DMF* or cavit* or deminerali* or reminerali* or “white spot”*)

S1 (MH “Tooth demineralization+”)

Appendix 6. LILACS BIREME and BBO BIREME search strategy

(Mh Fluorides or fluoride\$ or fluoruro\$ or fluoreto\$) [Words] and (Mh Dental caries or carie\$ or carious) [Words] and (Mh Mouthwashes or mouthwash\$ or mouthrins\$ or “mouth wash\$” or “mouth rins\$” or “antisépticos bucal\$” or “antissépticos bucais”)

Appendix 7. Proquest Dissertations and Theses search strategy

all(fluoride) AND all(mouthwash* or mouthrins*) AND all(carries or carious or decay)

Appendix 8. Web of Science Conference Proceedings search strategy

#4 #1 and #2 and #3

#3 TS=(fluoride* or “PPM F” or “PPMF” or “APF” or “NAF” or “sodium F” or “amine F” or “SNF2” or “stannous F” or acidulat* or “phosphat* fluorid*” or “fluorophosphat* sodium fluorid*” or “amine* fluorid*” or “stannous* fluorid*” or SMFP or “MFP” or monofluor*)

#2 TS=(mouthwash* or mouthrins*)

#1 TS=(deminerali* or caries or carious or DMF* or fissure* or decay* or cavit* or “white spot”*)

Appendix 9. US National Institutes of Health Trials Register (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform search strategy

fluoride mouthrinse

fluoride mouthwash

WHAT'S NEW

Date	Event	Description
24 November 2016	Amended	Correcting typographical error in 'Author conclusions' (reduction in D(M)FS pooled PF with fluoride mouthrinse is 27% not 26%)

HISTORY

Date	Event	Description
10 May 2016	New citation required but conclusions have not changed	One new study included. Substantial update with some new methods but conclusions unchanged
22 April 2016	New search has been performed	Updated search. One new included study. Risk of bias assessment carried out for all included studies. Quality of the evidence assessed using GRADE. 'Summary of findings' table added
27 August 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

For the 2016 update, all members of the new review team decided on the updated methods to be used for this review. Valeria Marinho (VM) and Lee Yee Chong (LYC) undertook study selection, data extraction, 'Risk of bias' assessments and analyses. Tanya Walsh (TW) and Helen Worthington (HW) provided advice when consulted throughout the update and undertook some of the extra analyses. VM and LYC prepared the full review, and all review authors were active in its revision and approval.

For the original review, all four review authors contributed to the development of the protocol. VM wrote the protocol, conducted searches, selected studies and extracted data. Julian Higgins duplicated study selection and data extraction in a sample of studies, and Stuart Logan and Aubrey Sheiham were consulted when necessary. VM entered and analysed the data in consultation with Julian Higgins. VM prepared the full review, and all review authors were active in its revision and approval.

DECLARATIONS OF INTEREST

Valeria CC Marinho: none known. Valeria Marinho is an editor with Cochrane Oral Health.

Helen Worthington: none known. Helen Worthington is a Co-ordinating editor with Cochrane Oral Health.

Tanya Walsh: none known. Tanya Walsh is an editor with Cochrane Oral Health.

Lee Yee Chong: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2016 update, we further defined outcomes for clarity. We also trimmed the list of outcomes to those more relevant to patients. Information on use of healthcare service resources (such as visits to dental care units, length of dental treatment time) was not available from the studies and will no longer be collected. These data have limited applicability across settings.

Other changes implemented in this update are the addition of a full 'Risk of bias' assessment and the development of a 'Summary of findings' table for the primary outcomes in the review.

Finally, we made changes to the measures of effect used for the meta-analysis of some secondary outcomes, as well as changes to some of the investigations of heterogeneity performed through metaregression and subgroup analyses and to investigations of sensitivity analyses, including changes to the way a few co-variables were analysed in each. We have reported these changes and the rationale for them in relevant sections of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Dental Caries [*prevention & control]; Dentition, Permanent; Fluorides [*administration & dosage]; Mouthwashes [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Humans