Fluoride toothpastes of different concentrations for preventing dental caries

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Fluoride toothpastes of different concentrations for preventing dental caries

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Authors

Tanya Walsh[1], Helen V Worthington[2], Anne-Marie Glenny[1], Valeria CC Marinho[3], Ana Jeroncic[4]

[1]Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
[2]Cochrane Oral Health, Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
[3]Clinical and Diagnostic Oral Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[4]Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia

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Contact person

Tanya Walsh

Professor of Healthcare Evaluation
Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health
The University of Manchester
Coupland Building 3
Oxford Road
Manchester
M13 9PL
UK

E-mail: tanya.walsh@manchester.ac.uk

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What's new

Date	Event	Description
21 February 2019	New citation: conclusions changed	New co-author; broadened scope of review to include adults; review update including 13 new studies bringing the total to 96 included studies; methods updated; and 'Summary of findings' tables included
15 August 2018	Updated	Searches updated to 15 August 2018

History

Date	Event	Description
20 January 2010	Amended	Minor edits (contact details and acknowledgements)

Abstract

Background

Caries (dental decay) is a disease of the hard tissues of the teeth caused by an imbalance, over time, in the interactions between cariogenic bacteria in dental plaque and fermentable carbohydrates (mainly sugars). Regular toothbrushing with

fluoride toothpaste is the principal non-professional intervention to prevent caries, but the caries-preventive effect varies according to different concentrations of fluoride in toothpaste, with higher concentrations associated with increased caries control. Toothpastes with higher fluoride concentration increases the risk of fluorosis (enamel defects) in developing teeth. This is an update of the Cochrane Review first published in 2010.

Objectives

To determine and compare the effects of toothpastes of different fluoride concentrations (parts per million (ppm)) in preventing dental caries in children, adolescents, and adults.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 15 August 2018); the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7) in the Cochrane Library (searched 15 August 2018); MEDLINE Ovid (1946 to 15 August 2018); and Embase Ovid (1980 to 15 August 2018). The US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials (15 August 2018). No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria

Randomised controlled trials that compared toothbrushing with fluoride toothpaste with toothbrushing with a non-fluoride toothpaste or toothpaste of a different fluoride concentration, with a follow-up period of at least 1 year. The primary outcome was caries increment measured by the change from baseline in the decayed, (missing), and filled surfaces or teeth index in all permanent or primary teeth (D(M)FS/T or d(m)fs/t).

Data collection and analysis

Two members of the review team, independently and in duplicate, undertook the selection of studies, data extraction, and risk of bias assessment. We graded the certainty of the evidence through discussion and consensus. The primary effect measure was the mean difference (MD) or standardised mean difference (SMD) caries increment. Where it was appropriate to pool data, we used random-effects pairwise or network meta-analysis.

Main results

We included 96 studies published between 1955 and 2014 in this updated review. Seven studies with 11,356 randomised participants (7047 evaluated) reported the effects of fluoride toothpaste up to 1500 ppm on the primary dentition; one study with 2500 randomised participants (2008 evaluated) reported the effects of 1450 ppm fluoride toothpaste on the primary and permanent dentition; 85 studies with 48,804 randomised participants (40,066 evaluated) reported the effects of toothpaste up to 2400 ppm on the immature permanent dentition; and three studies with 2675 randomised participants (2162 evaluated) reported the effects of up to 1100 ppm fluoride toothpaste on the mature permanent dentition. Follow-up in most studies was 36 months.

In the primary dentition of young children, 1500 ppm fluoride toothpaste reduces caries increment when compared with non-fluoride toothpaste (MD -1.86 dfs, 95% confidence interval (CI) -2.51 to -1.21; 998 participants, one study, moderate-certainty evidence); the caries-preventive effects for the head-to-head comparison of 1055 ppm versus 550 ppm fluoride toothpaste are similar (MD -0.05, dmfs, 95% CI -0.38 to 0.28; 1958 participants, two studies, moderate-certainty evidence), but toothbrushing with 1450 ppm fluoride toothpaste slightly reduces decayed, missing, filled teeth (dmft) increment when compared with 440 ppm fluoride toothpaste (MD -0.34, dmft, 95%CI -0.59 to -0.09; 2362 participants, one study, moderate-certainty evidence). The certainty of the remaining evidence for this comparison was judged to be low.

We included 81 studies in the network meta-analysis of D(M)FS increment in the permanent dentition of children and adolescents. The network included 21 different comparisons of seven fluoride concentrations. The certainty of the evidence was judged to be low with the following exceptions: there was high- and moderate-certainty evidence that 1000 to 1250 ppm or 1450 to 1500 ppm fluoride toothpaste reduces caries increments when compared with non-fluoride toothpaste (SMD -0.28, 95% CI -0.32 to -0.25, 55 studies; and SMD -0.36, 95% CI -0.43 to -0.29, four studies); there was moderate-certainty evidence that 1450 to 1500 ppm fluoride toothpaste slightly reduces caries increments when compared to 1000 to 1250 ppm (SMD -0.08, 95% CI -0.14 to -0.01, 10 studies); and moderate-certainty evidence that the caries increments are similar for 1700 to 2200 ppm and 2400 to 2800 ppm fluoride toothpaste when compared to 1450 to 1500 ppm (SMD 0.04, 95% CI -0.07 to 0.15, indirect evidence only; SMD -0.05, 95% CI -0.14 to 0.05, two studies).

In the adult permanent dentition, 1000 or 1100 ppm fluoride toothpaste reduces DMFS increment when compared with non-fluoride toothpaste in adults of all ages (MD -0.53, 95% CI -1.02 to -0.04; 2162 participants, three studies, moderate-certainty evidence). The evidence for DMFT was low certainty.

Only a minority of studies assessed adverse effects of toothpaste. When reported, effects such as soft tissue damage and tooth staining were minimal.

Authors' conclusions

This Cochrane Review supports the benefits of using fluoride toothpaste in preventing caries when compared to non-fluoride toothpaste. Evidence for the effects of different fluoride concentrations is more limited, but a dose-response effect was observed for D(M)FS in children and adolescents. For many comparisons of different concentrations the caries-preventive effects and our confidence in these effect estimates are uncertain and could be challenged by further research. The choice of fluoride toothpaste concentration for young children should be balanced against the risk of fluorosis.

Plain language summary

Fluoride toothpastes of different strengths for preventing tooth decay

Review question

This review has been produced to assess the effects of toothpastes of different fluoride strengths on preventing tooth decay in children, adolescents and adults.

Background

Tooth decay (caries) is a widespread disease, affecting billions of people worldwide. Fluoride has long been used to prevent decay, through a variety of different methods including toothpaste, water, milk, mouthrinses, tooth gels and varnish. Regular toothbrushing is recommended to prevent decay and other oral diseases, and toothbrushing for 2 minutes twice daily with a fluoride toothpaste is generally recommended. The typical strength of regular or family toothpaste is around 1000 to 1500 parts per million (ppm) fluoride, but many other strengths are available worldwide. There is no minimum fluoride concentration, but the maximum permissible fluoride concentration for a toothpaste varies according to age and country. Higher concentrations are rarely available over the counter, and are classed as a prescription-only medicine. Stronger fluoride toothpaste may offer greater protection against decay but also increases the risk of fluorosis (enamel defects) in developing teeth. This is an update of the Cochrane Review first published in 2010.

Study characteristics

Authors from Cochrane Oral Health carried out this review and the evidence is current up to 15 August 2018. It includes 96 studies published between 1955 and 2014: seven studies with 11,356 randomised participants reported the effects of fluoride toothpaste up to 1500 ppm on the primary teeth; one study with 2500 randomised participants reported the effects of 1450 ppm toothpaste on the primary and permanent dentition; 85 studies with 48,804 randomised participants reported the effects of toothpaste up to 2400 ppm on the permanent teeth of children up to 18 years of age; and three studies with 2675 randomised participants reported the effects of up to 1100 ppm toothpaste on the permanent teeth of adults. Most studies assessed decay after participants had been using the toothpastes for 36 months.

Main results

We present below findings for which there is moderate- or high-certainty evidence.

In primary teeth of young children, brushing teeth with a toothpaste containing 1500 ppm fluoride reduced the amount of new decay when compared with non-fluoride toothpaste; the amount of new decay was similar with 1055 ppm compared with 550 ppm fluoride toothpaste; and there was a slight reduction in the amount of new decay with 1450 ppm toothpaste compared with 440 ppm fluoride toothpaste.

Eighty-one studies assessed the effects of different strengths of fluoride toothpaste compared against each other (seven different strengths in 21 combinations) in permanent teeth of children and adolescents. We found that there was less new decay when toothbrushing with toothpaste containing 1000 to 1250 ppm or 1450 to 1500 ppm fluoride compared with non-fluoride toothpaste, and that toothbrushing with 1450 to 1500 ppm fluoride toothpaste reduced the amount of new decay more than 1000 to 1250 ppm toothpaste. We found that there was a similar amount of new decay when children and adolescents used a toothpaste of 1700 to 2200 ppm or 2400 to 2800 ppm fluoride compared to 1450 to 1500 ppm toothpaste. The evidence for the effects of other strengths of toothpaste was less certain.

In permanent teeth of adults of all ages, 1000 or 1100 ppm toothpaste reduced decay compared with non-fluoride toothpaste.

Most studies did not measure harmful effects of toothpaste use, but when reported, effects such as soft tissue damage and tooth staining were minimal.

Certainty of the evidence

There is high-certainty evidence that toothpaste containing 1000 to 1250 ppm fluoride is more effective than non-fluoride toothpaste. There is moderate-certainty evidence for the other findings reported in 'Main results' above. For other toothpaste strengths compared against each other or against non-fluoride toothpaste, there are too few studies with too few participants to have any clarity about the effects.

Authors conclusions

There are benefits of using fluoride toothpaste at certain strengths to prevent tooth decay when compared with non-fluoride toothpaste. The stronger the fluoride concentration, the more decay is prevented. For many of the comparisons of different strengths of toothpaste, the findings are uncertain and could be challenged by further research. The choice of fluoride toothpaste for young children should be balanced against the risk of fluorosis.

Background

Description of the condition

Tooth mineral is lost and gained in a continuous process of de- and re-mineralisation. Caries (dental decay) is a disease of the hard tissues of the teeth caused by an imbalance in this process over time, where there is demineralisation of tooth structure by organic acids formed from the interactions between cariogenic bacteria in dental plaque and fermentable carbohydrates (mainly sugars). The dental caries process is influenced by the susceptibility of the tooth surface, the bacterial profile, the quantity and certainty of saliva and the presence of fluoride, which promotes remineralisation and inhibits demineralisation of the tooth structure. Aside from the pain arising from the dental carious lesions themselves, there is also the emotional distress of the disease and the potential consequences of medical intervention. Affected teeth cannot always be saved and may have to be

extracted. This has particular consequences for young children, for whom general anaesthesia may be required. There is an associated social impact of this disease in terms of absence from school for the children and absence from work for their carers. There are also important financial implications for this disease with a substantial proportion of healthcare budgets being spent every year on treating caries. On a population basis, traditional treatment of oral disease (dental caries and periodontal diseases) is the fourth most expensive chronic disease to treat according to the World Health Organization (WHO) (Petersen 2009). Further, in low-income countries, if treatment were available, the costs of treating dental caries in children alone would exceed the total healthcare budget for children (WHO 2019).

Caries in permanent teeth was the most prevalent condition among all those evaluated in the Global Burden of Disease 2016 study, affecting 2.4 billion people; the estimated prevalence of caries in deciduous teeth was 486 million children worldwide (GBD 2016). Whilst in some areas of middle-income and high-income countries, there has been evidence of a reduction in the prevalence and severity of dental caries in recent decades, social inequalities in dental health exist, with many individuals and communities having a clinically significant burden of preventable dental disease. Levels of dental decay vary considerably between and within countries, but children in lower socio-economic status (SES) groups have higher caries levels than those in upper SES groups, and in high-income countries, the association between socio-economic position and caries might be stronger (Chen 1995; Reisine 2001; Schwendicke 2015).

Description of the intervention

The link between fluoride and oral health dates back to the 1930s, and today fluoride remains one of dentistry's key strategies to prevent dental caries. There are many methods of fluoride delivery e.g. toothpaste, fluoridated water, milk, mouthrinses, gels, varnish, etc. Evidence regarding the effectiveness of topical fluoride interventions has been synthesized in a series of Cochrane Reviews (Marinho 2003; Marinho 2004; Marinho 2013; Marinho 2015; Marinho 2016; Marinho a 2004; Marinho b 2003).

Toothbrushing is the process used to mechanically remove and control the dental biofilm to help prevent caries and oral diseases. Recommendations on toothbrushing and the use of fluoride toothpaste including choice of concentration, the frequency of toothbrushing and amount of toothpaste to be, can vary. Toothbrushing is usually carried out using a manual or powered toothbrush and a fluoride toothpaste, for 2 minutes twice daily. Toothbrushing with fluoride toothpaste is by far the most common form of caries control, and fluoride toothpaste use is commonly linked to the decline in caries prevalence in many countries. There is an argument that the effects of fluoride toothpaste are underestimated in 'short-term' clinical trials of 2 to 3 years duration. It is reasonable to assume that a greater cumulative effect is conferred over time as fluoride toothpastes are used throughout life. In addition, some argue that the use of fluoride toothpaste in areas with community water fluoridation offers more protection than either alone. However, concern has been expressed that dental fluorosis, enamel defects caused by young children chronically ingesting excessive amounts of fluoride during the period of tooth formation (up to the age of 6 years), is increasing in both fluoridated and non-fluoridated communities, and the early use of fluoride toothpaste by young children may be an important risk factor (Ellwood 1995; Horowitz 1992; Stookey 1994).

In higher-income countries since the 1980s, nearly all commercially available toothpaste formulations contain fluoride. The formulation and fluoride concentration of toothpaste is diverse, with a variety of fluoride compounds used singly and in combination including sodium fluoride, sodium monofluorophosphate, amine fluoride and stannous fluoride, and, according to each manufacturer's specifications, these must be compatible with other basic ingredients, especially abrasive systems (which account for almost half of the entire toothpaste formulation). Fluoride toothpaste must be differentiated from fluoride prophylactic pastes, since their fluoride concentrations, methods and frequencies of application differ, as well as amounts of abrasives in their formulation (abrasives account for almost the entire content of a prophylactic paste). In addition, although some kinds of toothpastes are available in the translucent form of a gel, they differ from fluoride gels, which have higher fluoride levels, no abrasives and are applied much less frequently, usually by a professional. The usual concentration of fluoride in toothpaste ranges from 1000 to 1500 parts per million (ppm); toothpaste with higher and lower than conventional fluoride levels are available in many countries. There is no restriction on the minimum fluoride concentration, but the maximum permissible fluoride concentration for a toothpaste varies according to location and age. Higher concentrations are rarely available over the counter, classed as a prescription-only medicine. In the UK, 2800 ppm sodium fluoride toothpaste can be prescribed to high caries-risk patients aged 10 years and over, those with caries present, orthodontic appliances, or who have a highly cariogenic diet or medication; 5000 ppm toothpaste can be prescribed to high caries-risk patients aged 16 years and over, with present or potential for root caries, dry mouth, orthodontic appliances, overdentures, or those with highly cariogenic diet or medication (Public Health England 2017).

Toothpaste containing higher concentrations of fluoride may confer greater protection against caries but increase the risk of fluorosis (enamel defects caused by chronic ingestion of excessive amounts of fluoride during the period of tooth formation). Chronic ingestion of fluoride from toothpaste in young children is common (Bentley 1999; Rojas-Sanchez 1999) and despite the large variation in the amount swallowed, the younger children are, the more likely they are to swallow larger amounts, which often represent a substantial part of the total daily fluoride intake and can be enough to cause fluorosis (Levy 1994; Lewis 1996). Although the precise amount of fluoride (F) ingested beyond which fluorosis may occur is not known, a threshold of 0.05 mg F/kg to 0.07 mg F/kg body weight has been suggested (Burt 1992). A child-sized toothbrush covered with a full strip of toothpaste holds approximately 0.75 g to 1.0 g of toothpaste, and each gram of fluoride toothpaste, contains approximately 1.0 mg of fluoride; children aged less than 6 years may swallow an estimated 0.3 g of toothpaste per brushing (0.3 mg of fluoride) and can inadvertently swallow as much as 0.8 g (Levy 1994). As a result, it is generally recommended that children of 6 years of age and under should be supervised when

brushing their teeth with fluoride toothpaste and only a 'pea-sized' amount of toothpaste, is used. The frequency of toothpaste use along with the method of rinsing after toothbrushing are other factors influencing the effectiveness and safety of fluoride toothpaste. Brushing twice a day or more, or rinsing less thoroughly or not rinsing at all would confer greater caries reductions than brushing once a day or less, or rinsing with larger volumes of water after toothbrushing (Ashley 1999; Chesters 1992; Chestnutt 1998; O'Mullane 1997). Although acute toxicity is rare, young children are particularly at risk of ingesting toxic doses of fluoride from a standard toothpaste tube of 125 g, containing 1100 ppm F (1.1 mg F/g paste). As the probable toxic dose is around 5 mg F/kg body weight (Whitford 1992), the accidental swallowing of one- or two-thirds (45 g to 90 g) of a toothpaste tube is potentially life-threatening for a 1-year-old (10 kg) or for a 5 to 6-year-old (20 kg) respectively (Ellwood 1998). For this reason, it is recommended that a fluoride toothpaste should be kept out of the reach of young children.

How the intervention might work

The most important anti-caries effect of fluoride results from its local action on the tooth/plaque interface, through the promotion of remineralisation of early caries lesions and reduction in tooth enamel solubility (Featherstone 1988). The presence of fluoride at the time of the acid attack markedly reduces enamel demineralisation (mineral loss), and fluoride enhances mineral gain and provides a more resistant enamel structure (Ten Cate 1999). This occurs with all forms and concentrations of 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. The amount of fluoride deposited in the subsurface lesion is greater after topical application with high-concentration fluoride vehicles (Horowitz 1996; Ogaard 1994; Ogaard 2001). Regular use of fluoride toothpaste or mouthrinse (topical fluoride vehicles of relatively low concentration) 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

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles that were the most clinically important ones to maintain on the Cochrane Library (Worthington 2015). Initially published in 2010 (Walsh 2010), the paediatric dentistry expert panel identified this Cochrane Review as a priority title (Cochrane Oral Health priority review portfolio). For this update, the scope of the review has been broadened to include adults.

WHO state that poor oral hygiene and inadequate exposure to fluoride have negative effects on oral health (WHO 2018). Effective use of fluoride toothpaste in children and adolescents is a long-held recommended strategy to prevent caries (Lancet 2009), with WHO guidance that twice-daily toothbrushing with fluoride-containing toothpaste (1000 to 1500 ppm) should be encouraged (O'Mullane 2016). Despite these recommendations, cost may prohibit the widespread use of toothbrushing with fluoride toothpaste in many low- and middle-income countries.

Many systematic reviews have evaluated head-to-head (direct) comparisons of different fluoride. This Cochrane Review is the first to systematically evaluate a dose-response effect through an assessment of the overall body of evidence, including both direct and indirect evidence (evidence drawn from trials comparing each of the interventions with a common comparator) from randomised controlled trials (RCTs). In addition, the certainty of this evidence is rated for the first time using the standard GRADE approach (GRADE 2004). A companion Cochrane Review has evaluated the effects of topical fluoride, including toothpaste of different concentrations, on dental fluorosis (Wong 2010). These Cochrane Reviews should be considered together to be fully informed of the potential caries-preventive benefits of fluoride toothpastes of different concentrations and the potential risks of fluorosis.

The primary aim of this review update, therefore, is to provide a clear and robust summary of the current research evidence on the effects of toothpaste with higher fluoride concentrations, compared to lower or no concentration of fluoride to prevent dental caries in children, adolescents and adults.

Objectives

To determine and compare the effects of toothpastes of different fluoride concentrations (parts per million (ppm)) in preventing dental caries in children, adolescents, and adults.

Methods

Criteria for considering studies for this review

Types of studies

Parallel-group randomised controlled trials (RCTs) (individually or cluster-randomised), which compared toothbrushing with fluoride toothpaste with toothbrushing with a non-fluoride toothpaste or toothpaste of a different fluoride concentration, with a follow-up period of at least 1 year.

We excluded studies where random allocation was not used or indicated. Due to the high possibility of contamination of one part of the mouth from another, it would not be appropriate to use a split-mouth design to evaluate the effects of this intervention, and so we excluded any studies with this design.

Types of participants

Children, adolescents or adults, irrespective of the initial level of dental caries, background exposure to fluoride, receipt of dental treatment, nationality, setting where the intervention was received or age at recruitment to the trial.

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

Types of interventions

We included studies comparing toothbrushing with a fluoride toothpaste with toothbrushing with another fluoride toothpaste of a different concentration or with a non-fluoride toothpaste or no toothpaste. On the basis of fluoride concentrations of toothpastes in regular use, we proposed the following categories:

1. 0 (parts per million (ppm)) fluoride (F) (non-fluoride or placebo toothpaste)
2. 250 ppm F
3. 440 to 550 ppm F
4. 1000 to 1250 ppm F
5. 1450 to 1500 ppm F
6. 1700 to 2200 ppm F
7. 2400 to 2800 ppm F.

There were no restrictions placed on the fluoride agents which could be used singly or in combination:

- sodium fluoride (NaF)
- sodium monofluorophosphate (SMFP)
- stannous fluoride (SnF_2)
- acidulated phosphate fluoride (APF)
- amine fluoride (AmF).

Toothpastes could be formulated with any compatible abrasive system. These included dicalcium phosphate, sodium metaphosphate, calcium carbonate, silica, zirconium silicate, or calcium pyrophosphate.

There was no restriction on fluoride concentration (ppm), amount or duration of application, frequency of use, toothbrushing technique (including supervised toothbrushing), or post-toothbrushing procedure.

We excluded studies where the intervention group or both the intervention and control groups received any additional active agent or caries preventive measure (e.g. chlorhexidine agent, fluoride varnish application, fluoride mouthrinse) as part of the study in addition to the fluoride or placebo toothpaste.

Studies where the intervention group alone received any additional potentially active agent in the toothpaste such as xylitol, triclosan, N-lauroyl sarcosinate, and casein phosphopeptide-amorphous calcium phosphate (CPP–ACP) were excluded; studies where both the intervention group and comparator group received any additional potentially active agent in the toothpaste were included. This protocol change was instigated to reflect the change in toothpaste formulation since the initial review. Many types of toothpaste now combine the caries preventive benefit of fluoride with other therapeutic agents to control plaque (antibacterial agents), tartar, and gum disease.

Studies where both the intervention and control groups included participants receiving additional measures as part of their routine oral care such as supervised brushing, fissure sealants, were included, as were studies that were undertaken in areas with fluoridation of the community water supply.

Types of outcome measures

Primary outcomes

Caries increment as measured by:

- change from baseline in the decayed, (missing), and filled surface or teeth index (D(M)FS/T), in all permanent teeth erupted at the start and erupting over the course of the study (dental caries is defined here as being clinically and radiologically recorded at the dentine level of diagnosis);
- change from baseline in the decayed, (missing/extraction indicated), and filled surface or teeth index (d(e/m)fs/t) in all primary teeth;
- change in the proportion of participants developing new caries.

Where possible we extracted data on D(M)FS/T, d(e/m)fs/t, and the proportion of participants developing new caries.
We acknowledged that the primary outcome of caries could be measured and reported in a number of different ways.
To account for this, the choice of outcome followed an adapted version of the hierarchy presented in the earlier review (Walsh 2010):

- DFS/T data would be chosen over DMFS/T data, and these would be chosen over DS/T or FS/T
  - data for 'all surface types combined' would be chosen over data for 'specific types' only
  - data for 'all erupted and erupting teeth combined' (E + U) would be chosen over data for 'erupted' (E) only, and these over data for 'erupting' (U) only
- data for dentinal/cavitated caries lesions (D_3 level) would be chosen over data for enamel/non-cavitated lesions (D_1 level)
- net caries increment data would be chosen over crude (observed) increment data
- data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' (cl) only, and these over 'radiological' (xr) only. We defined clinical examinations as an examination using visual or tactile methods or both (VT) using a conventional lighting source. We excluded studies reporting caries using a non-clinical examination alone (e.g. electronic caries monitor, quantitative light-induced fluorescence)
- follow-up nearest to 3 years (often the one at the end of the study period) would be chosen over all follow-up.

Clinical and radiographic examinations provided the definition of different stages or grades of caries lesions. These have been grouped into two basic grades for each method of examination.

Clinical:

- non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures (NCA);
- lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor, walls) or showing frank cavitation (CA).

Radiographic:

- any radiolucency in enamel/enamel-dentine junction (ER);
- radiolucency into dentine (DR).

Secondary outcomes

Adverse effects such as irritation, dental staining/discolouration, etc.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials without language or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 15 August 2018) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7) in the Cochrane Library (searched 15 August 2018) (Appendix 2);
- MEDLINE Ovid (1946 to 15 August 2018) (Appendix 3);
- Embase Ovid (1980 to 15 August 2018) (Appendix 4).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid.

Searching other resources

The following trial registries were searched for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 15 August 2018) (Appendix 5);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 15 August 2018) (Appendix 6).

Previously published systematic reviews of fluoride toothpastes were also screened to identify any reports that met the inclusion criteria (Ammari 2003; Bartizek 2001; Clarkson 1993; Steiner 2004; Twetman 2003).

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

Data collection and analysis

Selection of studies

The downloaded set of records from each database were imported into the bibliographic software package EndNote. Duplicate records were identified and removed. Two review authors independently scanned all records for relevance on the basis of title and abstract (where available). We discarded irrelevant records and obtained the full text of the remaining records for further evaluation. Relevancy was assessed according to the characteristics of the participants, nature of the intervention, and comparison.

Following the initial screening, for studies appearing to meet the inclusion criteria, or for which there was insufficient information in the title and abstract to make a clear decision, we obtained the full report. Two review authors assessed these reports independently and in duplicate to establish whether the studies met the inclusion criteria. Disagreements were resolved by discussion. Studies written in a language not known by the review team were translated by members of Cochrane Oral Health and included or excluded as appropriate. Those studies awaiting translation are presented in the Studies awaiting classification section of the review.

We recorded studies rejected at this or subsequent stages in the Characteristics of excluded studies section with the reason for exclusion. Studies could be excluded for more than one reason.

Data extraction and management

All review authors undertook data extraction independently and in duplicate for all studies meeting the inclusion criteria using a piloted data extraction form. We recorded the following data for each included study in the Characteristics of included studies tables.

- Study information: location, duration of data collection (follow-up months), date of baseline collection[a], number of centres, other sources of fluoride exposure[b], duration of intervention, individual or cluster-randomisation.
- Participant information: age at baseline, number randomised, baseline caries[c], mean decayed missing and filled surfaces/teeth (standard deviation (SD)/standard error (SE)) for primary or permanent dentition or both (dmfs/t, DMFS/T).
- Intervention: concentration and formulation of fluoride, abrasive system, frequency of brushing, supervised brushing, duration of intervention.

- Assessment: teeth included, criteria for clinical diagnosis, calculation of change/increment, diagnostic threshold, net or crude caries increment.
- Outcome information: final caries and number evaluated, proportion of children developing new caries, mean DMFS/dmfs (SD/SE) increment, mean DMFT/dmft (SD/SE) increment, level of compliance.
- Reliability of primary outcome measurement: number of examiners and calibration details, method of clinical assessment.
- Adverse effects: e.g. soft tissue damage, dental stain, irritation.

[a]When data on the study start were not provided, we calculated a 'probable date' by subtracting the duration of the study (in years) plus 1 extra year, from the publication date of the study.
[b]Background exposure to other fluoride sources encompassed data on the use (outside the trial) of topical fluorides/fluoride rinses or even fluoride toothpastes (in studies where the intervention was tested under supervision at school and no supply of any toothpaste had been provided for home use), and the consumption of fluoridated water/salt/tablets. Background use of other fluorides (rinses, gels, tablets, etc.) should be clearly reported as used by the majority in a study to be considered as such.
[c]From the study sample analysed (final sample) and in connection with the caries increment index chosen.

Assessment of risk of bias in included studies

We assessed all studies included in the review for risk of bias independently and in duplicate as part of the data extraction process, with reference to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed included studies on the following:

- sequence generation (selection bias): high, low, unclear;
- allocation concealment (selection bias): high, low, unclear;
- blinding of participants and personnel (performance bias) and outcome assessment (detection bias): high, low, unclear;
- incomplete outcome data (attrition bias): high, low, unclear;
- selective reporting (reporting bias): high, low, unclear;
- other bias (baseline imbalance, contamination or co-intervention): high, low, unclear.

A judgement of 'high' indicated a high risk of bias, 'low' indicated low risk of bias, and 'unclear' indicated either a lack of information or uncertainty over the potential for bias.

We categorised the overall risk of bias of each study (Risk of bias in included studies). Studies were categorised as being at low, high, or unclear risk of bias according to the following criteria:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias;
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias; or
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were at unclear risk of bias.

A risk of bias table was completed for each included study (Characteristics of included studies). Results are also presented graphically by study (Figure 2) and by domain over all studies (Figure 3).

Measures of treatment effect

For continuous outcomes, we pooled data with the mean difference (MD), or standardised mean difference (SMD) if different measures were used to assess the same outcome. In the absence of an agreed consensus of minimally important clinical effect for caries increment, we chose an SMD value of 0.30 to indicate clinical importance, representing a small to moderate effect size. In terms of interpretation, mean caries increments are closely related to their standard deviations (approximately equal), and meta-analyses using SMDs will yield materially similar results to those using prevented fractions (Salanti 2009).

For dichotomous outcomes, we pooled data with the risk ratios (RR).

Unit of analysis issues

Studies with multiple treatment arms

In studies with more than one relevant intervention group and a common comparator group, such as those comparing fluoride NaF and SMFP toothpastes of the same concentration against a different fluoride concentration, we combined summary statistics (the number of participants analysed, number of participants developing caries, mean caries increments, and standard deviations) from all relevant intervention groups (and from any relevant comparator groups, if this was the case) to obtain a measure of treatment effect.

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 an intra-class correlation coefficient (ICC) value of 0.05 (a value commonly used in caries prevention trials) to reduce the numbers in intervention and control groups to their 'effective sample size.'

Dealing with missing data

For the main outcome data, missing standard deviations for caries increments not revealed through contact with the original researchers were imputed through linear regression of log (standard deviations) on log (mean caries) increments as per

Walsh 2010. This is a suitable approach for caries prevention trials as caries increments are closely related (similar) to their standard deviations, following approximately a Poisson distribution (van Rijkom 1998).

Assessment of heterogeneity

Clinical and methodological heterogeneity within treatment comparisons

We assessed the presence of clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants (e.g. age, community water fluoridation), and the interventions (e.g. additional potential active agents added to the toothpastes, supervised toothbrushing). Meta-analysis was restricted to studies of similar comparisons that reported the same outcomes.

Transitivity across treatment comparisons

Where possible, we planned to undertake a network meta-analysis (NMA) to compare the caries increments of the different fluoride concentrations.

We assessed the assumption of transitivity by comparing the distribution of the potential effect modifiers, community water fluoridation and supervised brushing, across the different elements of the network.

If the assumption of transitivity could be considered to be violated, for example, in terms of substantially imbalanced distributions of effect modifiers, then we would not conduct an overall network meta-analysis. Instead, we planned to revert to performing a series of independent meta-analyses if we observed heterogeneity across treatment comparisons.

Assessment of reporting biases

If at least 10 studies were included in a meta-analysis, we planned to assess publication bias according to the recommendations on testing for funnel plot asymmetry, as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If asymmetry was identified, we would examine possible causes. We were not able to assess publication bias in this way because, although we had a sufficient number of studies in our meta-analyses for the main comparisons, they were analysed as pairwise comparisons of fluoride concentrations that each contained fewer than 10 studies.

Data synthesis

Traditional approaches to meta-analysis have focused on direct (head-to-head) pairwise comparisons within studies. However, when many different interventions exist the number of possible pairwise comparisons can be large, making data analysis and interpretation difficult. In this review, we proposed seven different categories of fluoride concentration, ranging from non-fluoride toothpaste (0 ppm F) through to 2800 ppm F, and resulting in 21 possible comparisons of fluoride concentration. Reducing the number of categories would limit the number of comparisons, but could potentially obscure any subtle concentration-related differences in effect. Where sufficient data were available, where possible, we planned to undertake an NMA to compare the caries increments of the different fluoride concentrations. This method combines direct evidence from the head-to-head studies with indirect evidence from the included studies (Higgins 2011).

Methods for direct treatment comparisons

Where the number of available studies for each comparison was sparse, or where there was a disconnected network of comparisons, we planned to conduct standard pairwise meta-analyses using random-effects models using Review Manager (RevMan) software (Review Manager 2014).

Methods for indirect and mixed comparisons

We planned to conduct an NMA using a multivariate approach in Stata (Stata 2017), where included studies formed a connected network. A graphical representation of the different fluoride concentration interventions was undertaken to illustrate the nature of the network. Estimates of treatment effects (MD or SMD as appropriate) and random-effects NMA were undertaken using the 'Network' module in the Stata software package (White 2017) and self-programmed Stata routines available from www.mtm.uoi.gr.

We analysed studies evaluating the caries preventive effects on the primary and permanent dentition separately throughout, due to differences in their anatomical and subsequent disease sequelae manifestations.

Subgroup analysis and investigation of heterogeneity

Assumptions when estimating heterogeneity

In standard meta-analyses we estimated different heterogeneity variances for each pairwise comparison. In NMA we assumed a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

We assessed statistically the presence of heterogeneity within each comparison using a Chi^2 test, where a P value < 0.1 was taken to indicate statistically significant heterogeneity. We quantified heterogeneity using the I^2 statistic that measures the percentage of variability that cannot be attributed to random error. An I^2 statistic of:

- 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% considerable heterogeneity.

This is according to Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We assessed statistical heterogeneity in the entire network based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the NMA models. We intended to use the I^2 measure for NMA (i^2 option in mvmeta).

Assessment of statistical inconsistency

We evaluated the statistical agreement between the various sources of evidence in each network of interventions (consistency). Since different approaches may lead to different conclusions about the magnitude of inconsistency, we used both local and global approaches.

We used the loop-specific method to examine the presence of inconsistency locally (Bucher 1997; Veroniki 2013). This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). We assessed whether the inconsistency factor was incompatible with a zero null value using a 95% confidence interval (CI) and a loop specific z-test.

To assess statistical inconsistency in the entire network we used the 'design-by-treatment' interaction model (Higgins 2012). The presence of inconsistency from any source in the entire network will be inferred from a Chi^2 test. The network command was used in Stata for the design-by-treatment model (White 2017).

Investigation of heterogeneity and inconsistency

If we had observed important heterogeneity or inconsistency, or both, we planned to explore possible sources through subgroup analysis or meta-regression if sufficient data were available. Two potential sources of heterogeneity were specified a priori: supervised toothbrushing and community water fluoridation.

Sensitivity analysis

We proposed two forms of sensitivity analysis: removing studies where both the intervention group and comparator group received any additional potentially active agent(s) in the toothpaste; and removing studies with the shortest observed follow-up period (12 months).

Presentation of main results

Direct comparisons

We produced a 'Summary of findings' table for each comparison using GRADE methods (GRADE 2004) and GRADEpro GDT software (GRADEpro GDT 2015) for the outcomes caries increment (d(m)fs/t, D(M)FS/T), proportion of participants developing new caries, and adverse effects of toothpaste. We produced a separate table for each main comparison (young children (primary dentition), children and adolescents (immature permanent dentition), and adults (permanent dentition)). We assessed the certainty of the body of evidence for each direct comparison and outcome by considering the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates. We did not downgrade for reasons of reporting bias as too few studies contributed to the majority of the treatment estimates to draw meaningful conclusions. We categorised the certainty of each body of evidence as high, moderate, low, or very low.

NMA comparisons from the connected network

We used the Confidence in Network Meta-Analysis tool (CINeMA) (CINeMA 2017) to evaluate and present our confidence in the findings from the NMA . The tool uses a methodological framework which considers six domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity, and incoherence (Salanti 2014). The amount of information contributed by each study to the results of the NMA, as indicated by the contribution matrix, informs the confidence in the findings assessment.

Results

Description of studies

Results of the search

After applying the Cochrane randomised controlled trial (RCT) filter and removing duplicates, the search of electronic databases retrieved 3623 records.

The search for ongoing trials yielded no additional reports, as did the search of non-electronic resources.

Following screening, we considered 250 records to be potentially eligible, and obtained them for further detailed assessment. This resulted in 96 included studies (168 records), 61 excluded studies (81 records), no ongoing studies and one study awaiting classification (the study has been completed but not yet written-up). See Figure 1.

Included studies

See Characteristics of included studies table for details of included studies.

This version of the review includes 96 studies published between 1955 and 2014, of which 13 were new in this update: three studies published since the initial review (Cardoso 2014; Rao 2009; Vilhena 2010), five studies where additional information was obtained confirming eligibility (Biesbrock 2003a; Biesbrock 2003b; CL-213 1983; CL-216 1982; CL-220 1986), one study previously awaiting classification (Takeuchi 1968), and four studies as a result of

broadening the scope of the review (Jensen 1988; Lu 1980; Muhler 1957; Petersson 1991). The review includes placebo-controlled trials and trials comparing one active intervention to at least one other active intervention, in the form of two-, three-, four- and five-arm trials. One trial was cluster-randomised (Sønju Clasen 1995) though reported as an individually-randomised trial. The shortest follow-up period was 12 months, the longest reported was 7 years. Multiple studies were conducted in the USA (37 studies), UK (22 studies), Sweden (six studies), Switzerland (six studies), Brazil (three studies), France (five studies), Canada (two studies), Germany (two studies), Italy (two studies), Australia (two studies), Guatemala (two studies). Single studies were conducted in Iceland, Denmark, China, Puerto Rico, India, Japan, and Lithuania.

Some publications have reported on multiple trials within the same publication due to studies conducted and reported separately: for different age groups (Marthaler 1965; Marthaler 1965a; Marthaler 1970; Marthaler 1970a; Zacherl 1970; Zacherl 1970a); from different locations (Forsman 1974; Forsman 1974a; Held 1968; Held 1968a; Held 1968b); or for different age groups in different locations (Torell 1965; Torell 1965a; Torell 1965b).

Three placebo-controlled studies including 2675 randomised participants (2162 evaluated) assessed the effects of fluoride toothpaste on the mature permanent dentition in adults, whose age ranged from 18 to 93 years at the start of the studies. Reported mean decayed, missing, and filled permanent surfaces (DMFS) at baseline ranged from 27.3 to 53.35 carious surfaces (D_3 level (dentinal/cavitated)).

Eight studies including 13,856 randomised participants (9055 evaluated) assessed the effects of fluoride toothpaste on the primary dentition, with participants ranging from 1 to 4 years of age at the start of the studies. Reported mean decayed, missing, and filled primary surfaces (dmfs) at baseline ranged from 2.2 to 5.0 carious surfaces (three studies reporting baseline d_3 level), or from 0.95 to 1.85 non-cavitated caries lesions (two studies reporting at white spot lesion level).

Two studies used a zero fluoride concentration toothpaste as the comparator (placebo-controlled) (Cahen 1982; Fan 2008). Supervised toothbrushing was used in four studies (Cardoso 2014; Lima 2008; Sønju Clasen 1995; Winter 1989).

Eighty-six studies including 51,304 randomised participants (42,074 evaluated) assessed the effects of fluoride toothpaste on the immature permanent dentition in children and adolescents whose age ranged from 5 to 18 years of age at the start of the studies (one study also reported on the effects on the primary dentition). Reported mean DMFS at baseline ranged from 0.97 to 23.53 carious surfaces (D_3 level). 66 studies used a zero fluoride concentration toothpaste as the comparator (placebo-controlled). Supervised toothbrushing was used in 24 studies (Ashley 1977; Biesbrock 2003a; Biesbrock 2003b; Blinkhorn 1983; Chesters 2002; Conti 1988; Di Maggio 1980; Fogels 1988; Glass 1978; Glass 1983; Held 1968; Held 1968a; Held 1968b; Hodge 1980; Howat 1978; Marks 1994; Mitropolous 1984; Peterson 1979; Rao 2009; Rule 1984; Segal 1967; Stookey 2004; Takeuchi 1968; Thomas 1966).

The most commonly reported primary outcome measure was caries increment at the tooth surface level, which was reported in all studies. Caries increment at the tooth level was reported in 60 studies (three studies in the primary dentition, 56 in the immature permanent dentition and one in the mature permanent dentition); the proportion of participants developing new caries was reported in 13 studies (three studies in the primary dentition, and 10 studies in the immature permanent dentition).

Adverse effects of the intervention were unreported in the majority of studies, but when reported included oral (soft tissue) damage and tooth staining. No trials reported on fluorosis.

Excluded studies

Reasons for exclusion of a trial from the review are given in the Characteristics of excluded studies table. The 61 studies were excluded for the following reasons: non-random or systematic allocation; randomisation not stated or indicated; inappropriate randomisation (randomising two clusters, one to each of the groups compared); other fluoride-based interventions in addition to fluoride toothpaste; or participants were institutionalised children or adolescents with specific health problems. A study could be excluded for more than one reason.

Risk of bias in included studies

Allocation (selection bias)

Method of randomisation

We assessed 33 (34%) studies at low risk of bias for this domain, where a clear statement of the randomisation method was reported. The remaining 63 studies did not report sufficient information to enable us to make a judgement and we assessed them as at unclear risk of bias. Statements such as 'were randomised' or 'were stratified' appeared most commonly.

Allocation concealment

We assessed eight (8%) studies as at low risk of bias for this domain, where a clear statement of the methods of concealing the allocation method was reported. The remaining 88 studies reported insufficient information on how the randomisation sequence was concealed from individuals involved in the enrolment and assignment of participants to enable us to make a judgement and we assessed them as at unclear risk of bias.

The overall risk of selection bias (randomisation and allocation concealment) was low in eight studies and unclear in 88 studies.

Blinding (performance bias and detection bias)

Eighty-six studies (90%) reported that they had made sufficient efforts to ensure that the fluoridated toothpastes were

indistinguishable from each other and from the non-fluoride toothpastes, and either clearly reported that the outcome assessor(s) was not aware of the participants' assignment or reported the trial as being 'double-blind.' We assessed those studies as at low risk of bias for this domain.

For one study (Held 1968b) blinding of participants was not undertaken (placebo and fluoride toothpastes were packaged differently) and participants would have been aware of their assignment, thus introducing the potential for performance bias. We assessed this study as at high risk of bias. There was insufficient information from the remaining nine studies to form a judgement.

Incomplete outcome data (attrition bias)

We applied an arbitrary threshold for a judgement of attrition given each study's length of follow-up e.g. over 50% in 3 years, over 40% in 2 years, over 30% in 1 year resulting in a judgement of high risk of bias. We assessed 17 studies (18%) as at low risk of bias for this domain, with acceptable levels of attrition according to length of follow-up and where the distribution was fairly evenly distributed across groups. 71 studies (74%) did not report the number or reasons for losses or exclusions by group or both and were judged to be at unclear risk of bias. High levels of attrition were reported in eight studies (8%), where overall attrition for length of follow-up was not calculable as numbers randomised or evaluated or both were not provided for all groups (Beiswanger 1989; CL-213 1983; Takeuchi 1968); attrition was unduly high for length of follow-up, with or without differential losses between groups (Held 1968b; Lu 1987; Marthaler 1965a; Muhler 1957; Sønju Clasen 1995).

Selective reporting (reporting bias)

We assessed 83 studies (86%) as at low risk of bias for this domain, as they reported all pre-specified caries outcomes in full, according to the different units measured, methods of examination, diagnostic thresholds for caries, and approaches for reversals as stated in the methods section of each study report. Insufficient information was provided in 11 studies (11%) to form a judgement and we assessed those studies as at unclear risk of reporting bias.

We assessed the remaining two studies (2%) as at high risk of reporting bias due to no (Takeuchi 1968) or incomplete (Petersson 1991) reporting of the main outcome as stated in the methods section.

Other potential sources of bias

Other potential sources of bias considered included baseline imbalance for important factors such as caries and age, and contamination or co-intervention principally from additional sources of fluoride.

Baseline characteristics

Baseline characteristics were reported and comparable between groups in 81 studies (84%). Baseline similarity was achieved most often through stratification by important prognostic variables. Five studies (5%) were assessed at high risk of bias where baseline imbalance in caries levels was reported in the different fluoride groups (Held 1968; Held 1968a; Held 1968b; Lima 2008; Petersson 1991). An unclear judgment was given for 10 (10%) studies when baseline characteristics were not reported or were not differentially reported.

Free of contamination or co-intervention

One study (Biesbrock 2001) was judged to be at high risk of bias from contamination when a concurrent fluoride rinse programme was introduced to study participants. 67 trials (70%) were judged free from the possibility of any inadvertent application of the intervention being evaluated to people in the control group (contamination) or any additional treatment being given to one of the groups differentially (co-intervention) or both, and hence were judged to be at low risk of bias. In 28 trials (29%) there was insufficient information to enable a judgement to be made.

Overall risk of bias

We assessed only one study (Mitropolous 1984) at low risk of bias for all domains, and therefore at low risk of bias overall.

We assessed 14 studies (Beiswanger 1989; Biesbrock 2001; CL-213 1983; Held 1968; Held 1968a; Held 1968b; Lima 2008; Lu 1987; Marthaler 1965a; Muhler 1957; Muhler 1962; Petersson 1991; Sønju Clasen 1995; Takeuchi 1968) at high risk of bias for at least one domain, and therefore at high risk of bias overall. The most frequent high risk of bias judgements were in the incomplete outcome data domain (Beiswanger 1989; CL-213 1983; Held 1968b; Lu 1987; Marthaler 1965a; Muhler 1957; Sønju Clasen 1995; Takeuchi 1968), followed by other potential sources of bias from baseline imbalance (Held 1968; Held 1968a; Held 1968b; Lima 2008; Petersson 1991), selective reporting (Petersson 1991; Takeuchi 1968), and potential contamination or co-intervention (Biesbrock 2001).

We assessed 81 studies as being at unclear overall risk of bias. These studies had at least one domain judged to be at unclear risk of bias, but no domains judged to be at high risk of bias.

The results of the risk of bias assessments are presented graphically for each included study in Figure 2 and as percentages across all included studies in Figure 3.

Effects of interventions

Five studies did not report sufficient information necessary for inclusion in a meta-analysis. In one placebo-controlled study the fluoride concentration was not stated or indicated (Kinkel 1972), and in four placebo-controlled studies the caries increment data were not reported or obtainable (Piccione 1979; Powell 1981; Slack 1964; Takeuchi 1968). These studies are retained in the review for completeness and results reported narratively.

Standard deviations (SDs) were unreported in 10 studies (Abrams 1980; Fogels 1979; Forsman 1974; Forsman 1974a; Held 1968; Held 1968a; Held 1968b; James 1977; Muhler 1955; Petersson 1991). Due to the length of time since publication, we chose to impute the missing SDs rather than writing to authors to request this information. Based on the available data from studies reporting SDs of the caries increments, a regression equation to estimate the missing SDs was derived for the caries increment D(M)FS and D(M)FT (decayed, missing, filled surfaces/teeth) indices:

D(M)FS log(SD caries increment) = 0.7574 + 0.491 *log(mean caries increment)

D(M)FT log(SD caries increment) = 0.5264 + 0.3811 *log(mean caries increment).

We intended to assess the impact of the addition of potentially active agents and studies with a 12-month follow-up period through a sensitivity analysis, but there were insufficient studies to evaluate with confidence any differences arising from these factors.

The analyses are conducted and reported separately for the effects on the primary dentition of young children, the immature permanent dentition of children and adolescents, and the mature permanent dentition of adults.

Effects of fluoride toothpaste on dental caries in young children (primary dentition)

Eight studies, recruiting children between 1 and 6 years of age, evaluated the caries-preventive effect of different fluoride concentrations. One study (Cahen 1982) provided caries increment data expressed as df-rate, and so it could not be included in a meta-analysis. Due to the limited number of studies per comparison, we used pairwise random-effects meta-analyses, rather than network meta-analyses (NMA), to synthesise this evidence.

Four comparisons were evaluated: two studies (Cahen 1982; Fan 2008), at unclear risk of bias, compared the effects of unsupervised toothbrushing with a non-fluoride toothpaste (0 parts per million (ppm) fluoride (F)) with a toothpaste containing 1500 ppm F at 24 or 36 months; one study (Sønju Clasen 1995) at high risk of attrition bias, compared the effects of supervised toothbrushing with toothpaste containing fluoride concentrations of 250 or 1450 ppm F at 22 months; four studies, at unclear (Cardoso 2014; Vilhena 2010; Winter 1989) or high risk of bias from baseline imbalance (Lima 2008), compared the effects of toothbrushing with toothpaste containing fluoride concentrations of 500 to 550 with 1055 to 1100 ppm F, with follow-up periods ranging from 12 to 36 months; and one study (Davies 2002), at unclear risk of bias, compared the effects of toothbrushing with toothpaste containing fluoride concentrations of 440 ppm with 1450 ppm at 60 months.

Caries increment (surface index d(m)fs)

1500 ppm F compared with 0 ppm F

One study (Fan 2008), at unclear risk of bias, compared unsupervised toothbrushing with toothpaste containing 1500 ppm F with toothbrushing with a non-fluoride toothpaste (0 ppm F). The mean dfs increment (adjusted for baseline dfs) at 24 months was found to be lower in the 1500 ppm group (mean difference (MD) -1.86, 95% confidence interval (CI) -2.51 to -1.21; participants = 998, moderate-certainty evidence) in favour of fluoride toothpaste (Analysis 2.1).

1450 ppm F compared with 250 ppm F

One study (Sønju Clasen 1995) at high risk of attrition bias, compared the caries-preventive effects of supervised toothbrushing with toothpaste containing fluoride concentrations of 1450 ppm with 250 ppm. The study was cluster-randomised but analysed and reported as an individually-randomised trial. Using an intra-cluster coefficient (ICC) of 0.05 with the average cluster size of 17.20, a design effect of 1.81 was calculated (Higgins 2008) and the sample size (172 analysed) was adjusted accordingly. The mean dmfs increment was lower in the higher fluoride toothpaste (MD -1.20, 95% CI -2.92 to 0.52; effective sample size = 96, low-certainty evidence) in favour of the 1450 ppm fluoride toothpaste (Analysis 3.1).

1055 to 1100 ppm F compared with 500 to 550 ppm F

Four studies, at unclear (Cardoso 2014; Vilhena 2010; Winter 1989) or high risk of bias from baseline imbalance (Lima 2008), compared the effects of brushing with toothpaste containing fluoride concentrations of 500 to 550 ppm with 1055 to 1100 ppm. Two studies (Cardoso 2014; Lima 2008) evaluated the effects of supervised toothbrushing on caries progression and arrest at the white spot lesion level, and so for this comparison we presented the results separately for caries increment measured at the different levels of disease severity (non-cavitated incipient enamel lesions d_1 level and dentinal/cavitated caries lesions d_3 level).

The mean dmfs increment (d_3 level) favoured the 1055 to 1100 ppm group (MD -0.05, 95% CI -0.38 to 0.28; participants = 1958; studies = 2; I^2 = 0%; moderate-certainty evidence), as did the results for the active non-cavitated caries lesions (ANC, d_1 level) (MD -0.31, 95% CI -0.93 to 0.32; participants = 285; studies = 2; I^2 = 79%; low-certainty evidence) (Analysis 4.1). The high I^2 value indicated substantial heterogeneity, which could be attributed to the qualitative differences in results according to initial caries status.

Caries increment (tooth index d(m)ft)

1500 ppm F compared with 0 ppm F

No studies reported d(m)ft increment, although one study (Cahen 1982) at unclear risk of bias calculated the 'df-rate', denoted as the number of decayed or filled teeth per 100 observed primary teeth over the 12-month period of study. The df-rate in the placebo group was 18.25% (n = 708), with lower rates of 13.64% (n = 632) and 9.37% (n = 668) in the 1500 ppm

sodium monofluorophosphate (SMFP) and amine fluoride groups.

1450 ppm F compared with 250 ppm F

One study (Sønju Clasen 1995) at high risk of attrition bias, compared the caries-preventive effects of supervised toothbrushing with toothpaste containing fluoride concentrations of 250 ppm or 1450 ppm. The mean dmft increment was lower in the higher fluoride toothpaste (MD -0.40, 95% CI -1.14 to 0.34; effective sample size = 96; low-certainty evidence) (Analysis 3.2).

1055 to 1100 ppm F compared with 500 to 550 ppm F

One study (Winter 1989) at unclear risk of bias measured the effects of supervised brushing on mean dmft increment, with results favouring the higher fluoride concentration (MD -0.27, 95% CI -0.60 to 0.06; participants = 905; low-certainty evidence) (Analysis 4.2).

1450 ppm F compared with 440 ppm F

One study (Davies 2002) at unclear risk of bias compared the effects of brushing with toothpaste containing fluoride concentrations of 440 ppm F with 1450ppm F. The mean dmft increment was lower in the higher fluoride group (MD -0.34, 95% CI -0.59 to -0.09; participants = 2362; moderate-certainty evidence) (Analysis 5.1).

Proportion of children developing new caries

1450 ppm F compared with 250 ppm F

One study (Sønju Clasen 1995) at high risk of attrition bias, compared the caries-preventive effects of supervised toothbrushing with toothpaste containing fluoride concentrations of 250 ppm or 1450 ppm. The proportion of children developing new caries was lower in the higher fluoride group (risk ratio (RR) 0.92, 95% CI 0.54 to 1.57; effective sample size = 69, low-certainty evidence) (Analysis 3.3).

1055 to 1100 ppm F compared with 500 to 550 ppm F

One study (Winter 1989) at unclear risk of bias, measured the effects of supervised brushing on the proportion of young children developing new caries. The proportion of children developing new caries was lower in the higher fluoride group (RR 0.86, 95% CI 0.74 to 0.99; participants = 905; low-certainty evidence) (Analysis 4.3).

1450 ppm F compared with 440 ppm F

One study (Davies 2002) at unclear risk of bias compared the effects of brushing with toothpaste containing fluoride concentrations of 440 ppm F with 1450ppm F. The proportion of children developing new caries was lower in the higher fluoride group (RR 0.87, 95% CI 0.81 to 0.94; participants = 2362; moderate-certainty evidence) (Analysis 5.2).

Adverse effects of toothpaste

1500 ppm F compared with 0 ppm F

One study (Fan 2008) at unclear risk of bias, measured adverse effect of toothpaste, but none were reported.

1450 ppm F compared with 250 ppm F

No studies reported this outcome.

1055 to 1100 ppm F compared with 500 to 550 ppm F

Adverse effects were reported in only one study (Cardoso 2014) which stated that "There were no reports on adverse effects, but some children complained about the taste of the dentifrice."

1450 ppm F compared with 440 ppm F

No studies reported this outcome.

Main results are presented in Summary of findings table 1.

Effects of fluoride toothpaste on dental caries in the permanent dentition of older children and adolescents (immature permanent dentition)

Eighty-six studies evaluated the effects of toothbrushing with fluoride toothpastes of different concentrations in this population. Supervised toothbrushing was reported in 24 (27%) studies; 56 studies reported whether the study was undertaken in an area with community water fluoridation, of which nine (16%) reported community water fluoridation of 0.50 ppm or more. Four four-arm studies included additional agents in two of the arms: xylitol (Petersson 1991), trimetaphosphate (O'Mullane 1997; Stephen 1994), and zinc citrate (Stephen 1988), which were treated as distinct two-arm studies for the purpose of analysis.

Due to the large number of studies network meta-analyses (NMA) were undertaken for the effects on caries increment at the surface and tooth level.

As the studies used different measures (e.g. DS, DFS, DMFS) to assess the same caries increment outcome, standardised mean difference (SMD) was chosen as the measure of treatment effect, with a value of 0.30 as the threshold of clinical importance. Four studies (Biesbrock 2003a; Biesbrock 2003b; Marks 1994; Stookey 2004) reported summary data as adjusted means and standard deviations from an analysis of covariance (ANCOVA) and so were not included in meta-analyses. These results are presented qualitatively.

We were unable to include an additional five studies with a 0 ppm F comparator (placebo-controlled studies) in the

meta-analyses as: the fluoride concentration was not stated or indicated (Kinkel 1972), and the caries increment data were not reported or obtainable (Piccione 1979; Powell 1981; Slack 1964; Takeuchi 1968).

Caries increment (surface index D(M)FS)

NMA

The pooled analysis comprised 81 studies with available D(M)FS data, of which one study was judged at low risk of bias overall, 69 at unclear risk of bias, and 11 at high risk of bias. Interventions are displayed as a network meta-analysis diagram in Figure 4, where the different interventions are represented as nodes in the network and the links (edges) between them represent the treatment comparisons. The size of each node corresponds to the number of studies evaluated in each intervention; the thickness of the edges is proportional to the precision (inverse variance). The studies formed a connected network. There were 61 studies with 0 ppm F as the comparator group (placebo-controlled), four studies with 250 ppm F and 16 studies with 1000 to 1250 ppm F as the comparator group (lower fluoride concentration).

The distribution of studies with supervised toothbrushing and community water fluoridation > 0.50 ppm F are presented in Additional Table 1.

The 'loop-specific' approach was used to evaluate inconsistency separately in every closed loop of the network of interventions. None of the loops presented statistically significant inconsistency as the lower confidence limit of each loop reached zero. We also used random-effects design-by-treatment interaction model to globally test all the inconsistency parameters, and have confirmed coherence of the model (global Wald test of inconsistency, Chi^2 = 13.35, degrees of freedom (df) = 13, P = 0.421). Inconsistency was finally explored by side-splitting, the results again supporting consistency.

A consistency model was therefore used to generate effect estimates for the 21 possible pairwise concentration comparisons. The Tau^2 value from the consistency model was 0.0094. The NMA estimates and corresponding 95% confidence and predictive intervals are presented in Additional Table 2, and depicted graphically in Figure 5. There is evidence of a dose-response effect in the estimates, with the magnitude of the effect estimate increasing as the distance between the lower and higher fluoride concentration increases. Using a value for SMD of 0.30 as indicating clinical importance (SMD small to moderate effect size), the observed magnitude of effect is not always clinically important particularly when the difference in concentration between the higher (intervention) and lower (comparator) concentrations are small.

Main results of the NMA are presented in Summary of findings table 2.

Investigation of a dose-response relationship

A formal investigation of a possible dose-response relationship was carried out using a meta-regression approach on the NMA estimates. Following estimation of the SMD effect sizes for comparisons of different fluoride concentrations, potential heterogeneity of these estimates was further investigated with meta-regression analysis. (Full details of the analysis can be found in Appendix 7.) A meta-regression model was built on three different data sets: i) including effects of all comparisons, ii) without the effect of 250 ppm versus 0 ppm comparison, and iii) without the effects of 250 and 440 ppm versus 0 ppm comparisons, since the effects assigned to these low fluoride concentrations might belong to a non-linear section of an assumed, standard sigmoid dose-response curve. In all three models fluoride concentration was a strong effect modifier, as it explained most of the SMD heterogeneity in caries prevention (both adjusted R^2 = 100%, and residual T^2 = 0 with P values for goodness of fit of > = 0.999 observed in all models). The meta-regression coefficient assigned to fluoride concentration was significant and ranged from -0.29 (95% CI -0.38 to -0.19) to -0.33 (95% CI -0.47 to -0.20) (P < 0.001 for all data sets), indicating that a 10-fold increase in fluoride concentration further reduces SMD between 0.29 and 0.33. This means that, according to the meta-regression model of data set iii, after the SMDs are translated to number needed to treat (NNT) (Furukawa 2011; Kraemer 2006), NNTs assigned to common concentrations of fluoride are: 10.40 for 440 ppm, 6.30 for 1000 ppm, 5.40 for 1450 ppm and 5.10 for 1700 ppm.

Data not included in the NMA

Additional Table 3 reports the summary statistics and SMDs of the studies that were not suitable for inclusion in the NMA (studies that reported adjusted means and standard deviations from an analysis of covariance).

We were unable to include an additional five studies with a 0 ppm F comparator (placebo-controlled studies) in the meta-analysis as: the fluoride concentration was not stated or indicated (Kinkel 1972), and the caries D(M)FS increment data were not reported or obtainable (Piccione 1979; Powell 1981; Slack 1964; Takeuchi 1968).

One additional trial (Takeuchi 1968) reported on caries increment but reported on a surface level rather than an individual level. The trial reported that of 3445 caries-free surfaces that were brushed with fluoridated toothpaste (concentration not stated) 147 surfaces developed caries; for the placebo group of 3512 caries-free surfaces, 198 surfaces developed caries.

Caries increment (tooth index D(M)FT)

The pooled analysis comprised 53 studies with available D(M)FT data, of which one study was judged at low risk of bias overall, 45 at unclear risk of bias and seven at high risk of bias. Interventions are displayed as a network meta-analysis diagram in Figure 6. The size of each node corresponds to the number of studies evaluated in each intervention; the thickness of the edges is proportional to the precision (inverse variance). The studies formed a connected network. There were 46 studies with 0 ppm F as the comparator group (placebo-controlled), two studies with 250 ppm F, and five studies with 1000 to 1250 ppm F as the comparator group (lower fluoride concentration).

The distribution of studies with supervised toothbrushing and community water fluoridation > 0.50 ppm F are presented in Additional Table 1.

NMA

The 'loop-specific' approach was used to evaluate inconsistency separately in every closed loop of the network. None of the loops presented statistically significant inconsistency as the lower confidence limit of each loop reached zero. We also used random-effects design-by-treatment interaction model to globally test all the inconsistency parameters, and have confirmed consistency of the model (global Wald test of inconsistency, Chi^2 = 6.21, df = 8, P = 0.6236). Inconsistency was finally explored by side-splitting, the results again supporting consistency.

A consistency model was therefore used to generate effect estimates for the 21 possible pairwise concentration comparisons. The Tau^2 value from the consistency model was 0.01471. The NMA estimates and corresponding 95% confidence and predictive intervals are presented in Additional Table 4 and depicted graphically in Figure 7. There is evidence of a dose-response effect in the estimates, with the magnitude of the effect estimate increasing as the distance between the lower and higher fluoride concentration increases. Using a value of 0.30 as indicating clinical importance (SMD small to moderate effect size), the magnitude is not always clinically important particularly when the difference in concentration between the higher (intervention) and lower (comparator) concentrations are small.

Main results of the NMA are presented in Summary of findings table 2.

Data not included in the NMA

Additional Table 5 reports the summary statistics and SMDs of the studies that were not suitable for inclusion in the NMA (studies that reported adjusted means and standard deviations from an analysis of covariance).

We were unable to include an additional two studies with a 0 ppm F comparator (placebo-controlled studies) in the meta-analysis as the D(M)FT caries increment data were not reported or obtainable (Piccione 1979; Slack 1964).

Proportion of children and adolescents developing new caries

Eight placebo-controlled studies (Forsman 1974; Forsman 1974a; Hanachowicz 1984; Kleber 1996; Marthaler 1974; Muhler 1962; Rao 2009; Torell 1965), and two head-to-head studies (Conti 1988; Fogels 1988) contributed data for the analysis of the proportion of children and adolescents developing new caries in the immature permanent dentition. Due to the small number of studies for this outcome, pairwise random-effects meta-analyses, rather than NMA, were used to synthesise this evidence.

250 ppm F compared with 0 ppm F

Two placebo-controlled studies (Forsman 1974; Forsman 1974a) at unclear risk of bias evaluated the effects of 250 ppm toothpaste. The proportion of children developing new caries was similar in the lower and higher fluoride concentration groups (RR 1.07, 95% CI 0.91 to 1.27; participants = 684; studies = 2; I^2 = 0%; low-certainty evidence) (Analysis 6.3).

1000 to 1250 ppm F compared with 0 ppm F

Seven placebo-controlled studies at unclear (Forsman 1974; Forsman 1974a; Kleber 1996; Marthaler 1974; Rao 2009; Torell 1965) or high (Muhler 1962) risk of bias evaluated the effects 1000 to 1250 ppm. Overall, the risk of developing caries was lower in the higher fluoride group (RR 0.90, 95% CI 0.77 to 1.06; participants = 1898; studies = 7; I^2 = 80%; low-certainty evidence) (Analysis 8.3).

1450 to 1500 ppm F compared with 0 ppm F

One placebo-controlled study (Hanachowicz 1984) at unclear risk of bias evaluated the effects of 1500 ppm F, finding in favour of higher fluoride toothpaste (RR 0.95, 95% CI 0.91 to 0.98; participants = 945; low-certainty evidence) (Analysis 9.3).

1450 to 1500 ppm F compared to 1000 to 1250 ppm F

Two studies (Conti 1988; Fogels 1988) at unclear risk of bias evaluated the effects of 1000 to 1250 ppm and 1450 to 1500 ppm toothpaste, the results of the individual studies were equivocal, the pooled estimate favouring lower fluoride overall (RR 1.02, 95% CI 0.93 to 1.11; participants = 4328; I^2 = 82%; low-certainty evidence) (Analysis 14.3).

Main results are presented in Summary of findings table 3.

Adverse effects of toothpaste

Sixteen studies assessed possible side effects arising from toothpaste use, principally in terms of oral (soft tissue) pathologies and tooth staining. For the soft tissue findings, six studies reported either no untoward events or no untoward events which could be attributed to the use of the toothpaste (Conti 1988; Fogels 1979; Fogels 1988; Koch 1990; Rule 1984; Stephen 1994). For staining, six studies reported a greater incidence of staining in the stannous fluoride group (Fanning 1968; James 1967; Naylor 1967; Slack 1964; Slack 1967; Slack 1967a). One study (Jackson 1967) reported no differential in staining between the groups (2.5% fluoride group versus 1% placebo group) and no staining was found in another (Fogels 1979). No side effects of toothpaste were observed or reported in four trials (Fan 2008; Glass 1983; Kleber 1996; Rao 2009) (Summary of findings table 3).

Effects of fluoride toothpaste on dental caries in adults (mature permanent dentition)

Due to the limited number of studies per comparison, pairwise random-effects meta-analyses, rather than NMAs, were used to synthesise this evidence.

Caries increment (surface index DMFS)

1000 to 1100 ppm F compared with 0 ppm F

Three studies recruiting adults from 18 to 93 years, at unclear risk of bias (Jensen 1988; Lu 1980) or high risk of attrition bias (Muhler 1957), compared the effectiveness of 1000 or 1100 ppm F toothpaste to 0 ppm F toothpaste at 12 or 24 months. The mean DMFS increment was lower in the 1000 and 1100 ppm F groups than the 0 ppm F group (MD -0.53, 95% CI -1.02 to -0.04; participants = 2162; studies = 3; I^2 = 68%; moderate-certainty evidence) (Analysis 1.1). Heterogeneity was high, and could possibly be related to the higher caries increment DMFS in one study (Muhler 1957) than in the other two studies. Despite this, we did not downgrade for inconsistency as all studies showed a beneficial effect of the higher fluoride concentration, but the magnitude of that effect varied across studies.

Caries increment (tooth index DMFT)

1000 to 1100 ppm F compared with 0 ppm F

One study (Muhler 1957) at high risk of attrition bias additionally reported the caries-preventive effects on DMFT at 24 months. The mean DMFT increment at 12 months was lower in the 1000 ppm F group than the placebo group (MD -0.46, 95% CI -0.93 to 0.01; participants = 247; studies = 1; I^2 = 0%; low-certainty evidence) (Analysis 1.2).

Proportion of adults developing new caries

No studies reported on the proportion of adults developing new caries.

Adverse effects of toothpaste

No studies reported on the adverse effects of toothpaste.

Main results are presented in Summary of findings table 4.

Discussion

Summary of main results

We included 96 randomised controlled trials published between 1955 and 2014 in this review, of which 13 were new in this update. We assessed the body of evidence for each comparison and outcome using GRADE methodology (GRADE 2004). Over half of the included studies evaluated the effects of toothbrushing with a fluoride (F) toothpaste compared to a non-fluoride 0 parts per million (ppm) concentration (placebo) toothpaste.

Our main findings are as follows.

For the primary dentition of young children.

- Toothbrushing with 1500 ppm F toothpaste reduces decayed, filled surfaces (dfs) increment when compared with placebo toothpaste (moderate-certainty evidence). No other fluoride concentrations were compared with 0 ppm F toothpaste in this population.
- The caries-preventive effects (decayed, missing, filled surfaces (dmfs)) for the head-to-head comparison of 550 ppm with 1055 ppm F toothpaste are similar (moderate-certainty evidence), but toothbrushing with 1450 ppm F toothpaste slightly reduces decayed, missing, filled teeth (dmft) increment when compared with 440 ppm F toothpaste (moderate-certainty evidence).

For the immature permanent dentition of children and adolescents.

- The network meta-analysis of caries increment (D(M)FS/T) in the immature permanent dentition included 21 different comparisons of seven fluoride concentrations.
- Due to the small number of available studies and limitations in their design and conduct, there remains considerable uncertainty regarding the caries-preventive effects of many of the fluoride concentrations that were compared. The certainty of the evidence was judged to be low for all comparisons with the following exceptions:
  - 1000 to 1250 ppm or 1450 to 1500 ppm fluoride toothpaste confers a clinically meaningful caries-preventive benefit (D(M)FS/T) when compared with non-fluoride toothpaste (high- and moderate-certainty evidence);
  - 1450 to 1500 ppm slightly reduces caries increments (D(M)FS) when compared to 1000 to 1250 ppm (moderate-certainty evidence);
  - caries increments (D(M)FS) are similar for 1700 to 2200 ppm and 2400 to 2800 ppm toothpaste when compared to 1450 to 1500 ppm (moderate-certainty evidence).
- Notwithstanding the low certainty of the evidence base, a dose-response effect can clearly be seen from the NMA estimates, with the magnitude of the caries-preventive effect estimate increasing as the distance between the lower and higher fluoride concentration increases. This observation was confirmed though a formal dose-response analysis of the NMA caries increments (D(M)FS) estimates.
- Adverse effects of toothpaste was assessed in only a minority of studies. When reported, effects such as soft tissue damage and tooth staining were minimal.

For the mature permanent dentition of adults.

- Toothbrushing with 1000 or 1100 ppm fluoride toothpaste reduces DMFS when compared with non-fluoride toothpaste in adults of all ages (moderate-certainty evidence). We are uncertain as to the magnitude of this benefit, as there was considerable variability of effect across studies.

Overall completeness and applicability of evidence

The review identified a large volume of evidence from studies which have evaluated the use of fluoride toothpastes for the prevention of caries, and explicitly evaluated the preventive dose-response effect of fluoride at different concentrations. Over half of the included studies compared the effects of toothpastes with fluoride concentrations of 1000 to 1250 ppm to non-fluoride toothpastes, and were undertaken at a time when the caries-preventive effects of fluoride were much less certain. More recent 'head-to-head' studies have evaluated the caries-preventive effects of different fluoride concentrations. The use of an NMA within this review has provided a robust framework to simultaneously evaluate the effects of many different concentrations, and provided treatment estimates for comparisons that may or may not have been explicitly evaluated in primary studies. To establish the estimates of effect of fluoride concentrations from 250 ppm through to 2800 ppm and combine them with an assessment of certainty is a strength of the review, and is key to informing current clinical practice and policy. Further, articulating the dose-response effects of the range of concentrations can inform future product development.

The volume of evidence differs substantially according to the effects on the primary, immature permanent and permanent dentition. Most recent studies have evaluated the effects of lower fluoride concentrations on the primary dentition of young children, but only for a very limited number of fluoride concentration comparisons. The volume of evidence is far greatest for studies evaluating the effects of different fluoride concentrations on the permanent dentition of children and adolescents. Despite the large number of studies however, the dominance of studies for comparisons of fluoride toothpastes of concentrations from 1000 ppm to 1500 ppm with non-fluoride toothpaste means that there remains considerable uncertainty regarding the effects of other fluoride concentrations. The review included only three studies recruiting adults, all evaluating the effects of 1000 ppm or 1100 ppm F toothpaste compared with non-fluoride toothpaste. Due to the lack of published studies, the effects of different concentrations in adults compared to placebo or to other concentrations are unknown. It could be argued that extrapolating results from studies of the permanent dentition in children and adolescents to adults is acceptable and could eliminate the need for any further trials in adults.

Adverse effects of toothpaste use were measured in a minority of studies. Where reported, adverse effects included oral (soft tissue) damage and staining. An important consideration when advocating the use of topical fluoride in children and adolescents in different treatment modalities such as toothpastes, gels, varnishes, etc. and at different concentrations is the potential for fluorosis for developing permanent teeth arising from fluoride application in younger children. A published Cochrane Review (Wong 2010) concluded that there was no significant association between frequency of toothbrushing and amount of toothpaste used (imperfect proxies for the amounts of fluoride ingested) and fluorosis. To be fully informed of the potential caries-preventive benefits of fluoride toothpastes of different concentrations and the potential risks of fluorosis arising from fluoride use, both reviews should be read.

The review does not address cost effectiveness in terms of the potential reduction in financial cost associated with caries diagnosis prevention and treatment. However, it should be noted that given a constant level of disease across different populations the burden of disease (mean number of carious lesions) 'saved' by a higher level of fluoride toothpaste will increase as the underlying amount of disease in the population increases.

There were 10 studies where the higher or lower fluoride concentration toothpaste alone included non-fluoride agents with potential anti-caries benefit and these groups were excluded from the analysis. Agents identified in studies in this review included secondary calcium pyrophosphate (one study), heat-treated calcium orthophosphate (one study), sodium N-lauroyl sarcosinate (five studies), calcium phosphate/glycerophosphate (two studies), additional anti-calculus agents (one study). These groups were excluded from any analysis as the anti-caries effects had yet to be established, and it is plausible that their addition to toothpaste could exert an additional preventive benefit when compared to formulations which did not receive such additional benefits. However, studies where such agents were components of the toothpaste in all study arms were included (O'Mullane 1997; Petersson 1991; Stephen 1988; Stephen 1994). We intended to assess the impact of the addition of these potentially active agents through a sensitivity analysis, but there were insufficient studies to evaluate with confidence any differences arising from the use of these additional agents.

Information on background exposure to fluoride was absent from many studies, and poorly reported for others. Such a potential effect modifier could have been included as a covariate in a meta-regression analysis but due to insufficient information in many of the study reports this was not undertaken. Potential misclassification, especially due to the incomplete reporting of data for exposure to fluorides would call for a cautious interpretation of the results of any meta-regression. Information on whether toothbrushing was supervised was more comprehensively reported.

Quality of the evidence

The included studies range in publication date from 1955 to 2014. The conduct and reporting of trials has improved greatly during that time, and that is reflected in the studies included in the review. Many earlier studies lacked information on the methods of randomisation and the process of treatment allocation, hence the large number of studies classified as 'unclear' for these domains. Many studies used stratified randomisation to ensure as far as possible comparable baseline values in terms of unknown and known prognostic indicators, though failing to state the explicit method of randomisation. In terms of allocation concealment, participants were allocated different toothpastes without the involvement of the assessors, with a minimal risk of bias occurring. Blinding of participants to the allocated toothpaste was done in all but one study, by ensuring that the products were similarly packaged with taste and appearance, and assessment was carried out by examiners blinded to treatment allocation. Aside from a possible objection to taste, or tooth staining as a result of toothpaste use, lack of blinding would have been of minimal consequence to compliance or outcome assessment. All studies reported caries increment at a surface level as the outcome measure, the primary outcome measure traditionally reported in toothpaste trials, with the majority of studies additionally reporting on caries increment at the tooth level. Risk of bias arising from imbalance of baseline caries levels across groups was low. Stratification according to at least initial caries level was

employed and reported in most trials.

The minimum length of follow-up was stipulated as 12 months. A preferred follow-up period is closer to 36 months, and the caries increment reported closest to this time was chosen as the outcome measure for this review. With such a long follow-up some degree of attrition is to be expected, and largely unrelated to the allocated toothpaste. Reasons reported for attrition were principally due to participants moving schools, or absent from school on the day of the examination. Where participants were reported to be explicitly excluded from participation this was noted, but reflected only a very small proportion of the participants studied. The risk of bias of this domain was unclear for the majority of studies as reasons for dropout and differential losses were not reported.

A potential source of bias in the review is contamination from other sources of fluoride (toothpaste or otherwise) or co-intervention. If the intervention took place within a school setting contamination is ordinarily unlikely to have occurred, and extremely unlikely to have occurred if the toothbrushing session was carefully supervised or the toothpaste carried the child's name on tube. A possible source of contamination was the use of family toothpaste but this was reduced in studies where sufficient toothpaste was provided for the entire family's use. The risk of bias in this domain was low.

In general the studies can be considered to be largely free from bias in terms of the key domains identified, with the exception of randomisation, allocation concealment, and incomplete outcome data as discussed above, where the majority of studies received a judgement of 'unclear.'

For the comparisons evaluating effects on the adult dentition and the primary dentition the evidence for the caries increment outcome was downgraded for study limitations (as indicated above) and for imprecision, with either a negligible benefit from the higher fluoride concentration or a null effect. For the NMA effect estimates, downgrading (some concerns) was due to within-study bias, imprecision (95% confidence interval extends into clinically important effects), heterogeneity (prediction interval extends into clinically important or unimportant effects), and incoherence.

Potential biases in the review process

We attempted to minimise bias in the review process wherever possible. Our search strategy was inclusive and no restrictions were placed on the language or date of publication when searching databases. We had non-English language studies translated. One study, which has been completed but not published, is awaiting classification and we have contacted the authors for information. This study evaluated the effects of 1500 ppm fluoride toothpaste compared to 1000 ppm toothpaste in adolescents aged between 12 and 15 years of age at recruitment, with the primary outcome being D(M)FT. These concentrations have been directly evaluated by four of our included studies and the certainty of the evidence is currently judged to be low.

Due to the small number of studies comparing different fluoride concentrations, we were unable to formally assess reporting bias. Despite our exhaustive search strategy, the possible presence of reporting bias could not be totally excluded.

The external validity of the review is good, in that the baseline level of caries in the included studies was wide ranging, as was the age of participants at commencement of the studies, and baseline caries and sex was often used as a stratifying factor in the randomisation of the primary studies. The review includes studies with supervised and non-supervised toothbrushing at home and in school settings, and in areas with and without community water fluoridation schemes.

Agreements and disagreements with other studies or reviews

For completeness, comparisons with published reviews will be made but it should be borne in mind that differences in the review process are likely to impact on the results. In particular, this Cochrane Review explicitly evaluated fluoride concentrations rather than categorising above or below a certain threshold for concentration, or carrying out informal subgroup analyses according to age group.

In a review comparing the effects of fluoridated toothpaste compared to placebo and toothpaste of different concentrations, a certainty assessment was undertaken and the results were reported narratively (Twetman 2003). An overall effect of fluoride toothpaste when compared to placebo (simple average) was reported in the review comprising 26 trials (Twetman 2003). In the comparison of toothpastes with a fluoride concentration of less than 1000 ppm F relative to 1000 to 1100 ppm, results of four trials were presented narratively indicating either a benefit or no effect of higher fluoride levels. The caries-preventive effect of fluoride toothpaste containing 1500 ppm F relative to 1000 to 1100 ppm F was also reported (simple average, n = 9 trials) in favour of higher fluoride concentrations. Finally, a meta-analysis of standard and experimental toothpastes at fluoride concentrations ranging from 1700 ppm, 2200 ppm and 2800 ppm F relative to 1000 ppm F reported a caries preventive effect of higher fluoride concentration, though this was only statistically significant at the 2800 ppm F level (Bartizek 2001). The most recent systematic review published in this area looked specifically at the efficacy and safety of fluoride toothpaste in children younger than 6 years (Wright 2014). The scope of the review was broad, and included observational and experimental studies where toothpastes of different concentrations were evaluated singly or in combination with other caries-preventive measures (e.g. as part of a caries-preventive programme).

Authors' conclusions

Implications for practice

Overall, there does appear to be some evidence of a dose-response relationship in the caries-preventive effects of fluoride in toothpastes, with the magnitude of the caries-preventive effect estimate increasing as the distance between the lower and higher fluoride concentration increases. A formal analysis of the network meta-analysis (NMA) caries increment (D(M)FS) estimates confirmed the existence of a strong dose-response relationship.

The choice of fluoride toothpaste concentration should also be informed by concurrent fluoride use whether from self-care measures (e.g. fluoride mouthrinse, community water fluoridation) or professionally applied sources (e.g. fluoride varnish), and consideration of the risk of fluorosis in the developing dentition of younger children.

Implications for research

Further research that directly compares the effects of fluoride toothpastes at lower fluoride concentrations with higher concentrations would greatly enhance the current evidence base, adding data and securing more precise estimates of effect. The evidence for the caries-preventive effects of different fluoride toothpaste concentrations on the primary dentition of young children is particularly scarce. The potential caries-preventive benefit from higher fluoride concentrations needs to be balanced against potential harms of fluorosis, and future research should explore the minimally effective fluoride concentration, balancing these benefits and harms. A consensus on the magnitude of a clinically important effect in this area would be useful not only for interpreting the evidence synthesis, but could be used to guide the design of future primary research.

It is reasonable to assume that differential treatment effects could be observed according to initial caries levels and uptake of additional sources of fluoride, through individualised oral care or community/school programmes. Adverse effects should be measured and reported, including long-term assessment of fluorosis wherever possible. Taking these factors into account in the design and conduct of future research could provide a more realistic and meaningful estimate of the caries-preventive effects of different fluoride toothpaste concentrations to inform consumers.

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Contributions of authors

Draft the protocol	Anne-Marie Glenny (AMG), Tanya Walsh (TW), Helen Worthington (HW), Valeria Marinho (VM)
Develop a search strategy	AMG, VM
Search for trials	AMG, TW
Obtain copies of trials	TW
Select which trials to include	TW, HW, VM
Extract data from trials	TW, HW, VM
Enter data into Review Manager	TW
Carry out the analysis	TW, HW, Ana Jeroncic (AJ)
Interpret the analysis	AMG, TW, HW, VM, AJ
Draft the final review	AMG, TW, HW, VM, AJ
Update the review	AMG, TW, HW, VM, AJ

Declarations of interest

Tanya Walsh: none known. Professor Walsh is a Cochrane Oral Health Editor.
Helen V Worthington: none known. Professor Worthington was involved in the design and analysis of three included trials, but she did not undertake the risk of bias assessment or the data extraction for these trials. Professor Worthington is one of the Co-ordinating Editors of Cochrane Oral Health.
Anne-Marie Glenny: none known. Professor Glenny is Deputy Co-ordinating Editor of Cochrane Oral Health.
Valeria CC Marinho: none known. Dr Marinho is Cochrane Oral Health Editor.
Ana Jeroncic: none known. Professor Jeroncic is Cochrane Oral Health Editor.

Differences between protocol and review

- Changes to 'Title': broadened scope to include adults and removed 'children and adolescents from the title.'
- Change to 'Objectives' section: as consistency was indicated, the effects of supervised brushing and baseline caries were not formally explored in this update.
- Change to 'Types of interventions' section: studies where the intervention group alone received any additional potentially active agent(s) in the toothpaste such as xylitol, triclosan or casein phosphopeptide-amorphous calcium phosphate (CPP–ACP) were excluded; studies where both the intervention group and comparator group received any additional potentially active agent(s) in the toothpaste were included. This protocol change was instigated to reflect the change in

toothpaste composition over time.

- Change to 'Measures of treatment effect' section: the primary estimate of effect was the mean difference (MD) or standardised mean difference (SMD) using Cohen's d as appropriate. This was a protocol change from the initial review which used the prevented fraction (PF), the caries increment in the treatment group expressed as a percentage of the increment in the control group, as the primary outcome measure. We have been advised by members of Cochrane Methods Group that the use of PF with a network meta-analysis (NMA) is not appropriate. This should not affect the interpretation as mean caries increments are closely related to their standard deviations (approximately equal), and that meta-analyses using SMDs will yield materially similar results to those using prevented fractions (Salanti 2009).
- Formal analysis of a dose-response effect: we performed ancillary analyses to formally explore the possibility of a dose-response relationship of the network estimates. Details of the methods can be found in Appendix 7.

Published notes

Characteristics of studies

Characteristics of included studies

Abrams 1980

Methods	Trial design: 3-armed, double-blind, placebo-controlled and stratified RCT Location: USA Number of centres: 14 schools in San Francisco Bay area Recruitment period: study commenced in/before 1976
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 3.2 DFS (Gp A: 3.34 DFS; Gp B: 3.06 DFS; Gp C: 3.13 DFS; "balanced") Age at baseline (years): range 5 to 12 years. Mean not reported Sex: not reported Any other details of important prognostic factors: background exposure to fluoride not reported. Natural fluoride level of community water supply ranged from 0.015 to 0.093 ppm F Number randomised: 2210 (Gp A: 740; Gp B: 721; Gp C: 749) Number evaluated: 1141 at 3 years (present at final assessment: Gp A: 383; Gp B: 378; Gp C: 380) Attrition: 48% dropout after 3 years. Reasons for high dropout described: change of residence, absenteeism, non-adherence to study protocol; no differential group losses
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = 740): SnF_2 1000 ppm F; silica gel abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 721): SnF_2 1000 ppm F; Ca pyrophosphate abrasive system; home use/unsupervised, daily frequency assumed Gp C (n = 749): placebo; silica gel abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - (E + U) (CA) cl + (ER) xr; MD-DFS; DFS rate; DFT; DFT rate; DMFS; DMFT (at 1, 2 and 3 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: "grant from the Lever Brothers Company", Lever manufacture Aim (Gps A, and C - without fluoride) Declarations/conflicts of interest: not reported Data handling by review authors: combined 2 SnF_2 1000 groups with different abrasive systems Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (postBW) by 2 examiners, diagnostic threshold = ER. State of tooth eruption included = E/U. Intra- and inter-examiner reproducibility of clinical caries diagnosis (DFS) assessed annually by duplicate examination of 10% random sample (percentage of times diagnosis replicated in all 3 examinations ranged 42% to 97% and 77% to 92% for both examiners and for each respectively)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Children were randomly assigned to one of 3 treatment groups. A stratified sequential sampling technique was used within each school to balance the sample size with respect to sex and grade level for each dentifrice" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "A 3 year double-blind study of a dentifrice containing 0.4% stannous fluoride and a placebo..." "The examiners at all times were unaware of the children's dentifrice assignment" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 48% in 3 years. Dropout by group: 357/740 FT1, 343/721 FT2, 369/749 PL. Reasons for losses: change of residence, absenteeism, exclusion due to non-adherence to study requirements Comment: numbers lost were high for the length of follow-up. No differential loss between groups. It is unclear if 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: DFS increment - (E + U) (CA) cl + (ER) xr, reported at 1, 2 and 3 years follow-ups DMFT DMFS DFT MD-DFS DFT rate DFS rate Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 2.90 FT1, 3.28 FT2, 2.94 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quotes: "Provisions were made ensuring the randomization process to assure that only one dentifrice code would be available in each household.... A letter to parents was attached, giving brushing instructions and urging use of only the assigned dentifrice" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Andlaw 1975

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: UK Number of centres: 3 comprehensive schools (Henbury, Brislington, Withywood) in Bristol, UK Recruitment period: study commenced in 1970
Participants	Inclusion criteria: first-year intakes at each school Exclusion criteria: not reported Baseline caries: 6.9 DFS (Gp A: 6.85 DFS (SD 4.38); Gp B: 6.97 DFS (SD 4.72)). Baseline characteristics (TAR, DFS, DMFS, DFT, DMFT, ECSI) "balanced" Age at baseline (years): 11 to 12 years (Gp A: 11.72 (SD 0.35); Gp B: 11.70 (SD 0.34)). Baseline characteristic (age) "balanced" Sex: overall: 343 F:397 M (Gp A: 171 F:193 M; Gp B: 172 F:204 M). Evaluated participants reported only Any other details of important prognostic factors: no background exposure to fluoride reported; natural fluoride level of community water supply ranged from 0.07 to 0.14 ppm F Number randomised: 846 (Gp A: 418; Gp B: 428) Number evaluated: 740 at 3 years (present at final assessment. Gp A: 364; Gp B: 376) Attrition: 13% dropout after 3 years. Main reasons for attrition described: moved away, absent at final examination; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 418): SMFP 1000 ppm F; Al oxide trihydrate abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 428): placebo; Al oxide trihydrate abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - (E + U) (CA) cl + (ER) xr; DMFS; DFT; DMFT; PF-DMFS; MD-BL-DMFS; MD-DMFS; O-DMFS; ECSI (at 3 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: oral debris index; gingival index Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: "supported by Gibbs Dental Research" Declarations/conflicts of interest: not reported Data handling by review authors: none Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (2 postBW) by 2 examiners, diagnostic threshold = ER. State of tooth eruption included = E/U. Reproducibility ratio was less than 0.22 for intra-examiner reproducibility of clinical and radiographic caries diagnosis; "significant differences between examiners could not have affected caries increment figures since each examined same children annually"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Following baseline examinations, the children were grouped on the basis of age, sex, previous caries experience and the number of erupted second permanent molars; they were then randomly assigned to either the test or control group" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias)	Low risk	Quotes: "Radiographs were examined ..... without reference to the clinical examination data..." "The test dentifrice contained MFP.... The toothpastes were packed in similar but distinguishable tubes. The investigators did not know which of the tubes contained the test paste nor which of the pastes any child was using" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 13% in 3 years. Dropout by group: 54/418 FT, 52/428 PL. Reasons for losses: did not like taste of paste (1 from control group), changed school or moved away (63), exclusion due to absence at last examination Comment: numbers lost were not unduly high for the length of follow-up, with no differential loss between groups. It is unclear if 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: DFS increment - (E + U) (CA) cl + (ER) xr, reported at 3 years follow-up DMFS DFT DMFT PF-DMFS MD-BL-DMFS MD-DMFS O-DMFS ECSI Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 6.30 (4.04) FT, 6.43 (4.31) PL age (years): 11.73 (0.33) FT, 11.69 (0.32) PL TAR: 17.25 (4.35) FT, 17.35 (4.40) PL dental age: 21.75 (4.51) FT, 21.77 (4.47) PL DFT: 4.52 (2.56) FT, 4.42 (2.66) PL DMFT: 5.04 (2.68) FT, 4.96 (2.99) PL DMFS: 8.80 (6.55) FT, 9.10 (7.25) PL ECSI: 12.03 (8.34) FT, 12.41 (8.66) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The distribution of toothpastes and toothbrushes was the responsibility of two ladies called 'home visitors', whose duties were to visit each home every 5 weeks to supply enough of the appropriate toothpaste for the needs of the whole family.... and maintaining the interest and co-operation of participants throughout the trial" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Ashley 1977

Methods	Trial design: 4-armed, double-blind, placebo-controlled and stratified RCT Location: UK Number of centres: 9 comprehensive high schools in London, UK Recruitment period: study commenced 1973
Participants	Inclusion criteria: first-year high school students attending 1 of 9 selected schools Exclusion criteria: not reported Baseline caries: 9.1 DFS (Gp A: 8.44 DFS (SD 5.58); Gp B: 9.79 DFS (SD 7.28)). Baseline characteristics (DFS, DMFS, DMFT) "balanced" Age at baseline (years): mean 12 years (Gp A: 12.33; Gp B: 12.28). Baseline characteristic (age) "balanced" Sex: overall 279 F:210 M (Gp A: 138 F:108 M; Gp B: 141 F:102 M) Any other details of important prognostic factors: no background exposure to fluoride. Water supply fluoridated to 0.3 ppm F Number randomised: 1135 (numbers for relevant groups not reported) Number evaluated: overall: 1002 at 2 years; relevant groups to this review: 489 at 2 years (present at final assessment. Gp A: 246; Gp B: 243) Attrition: 12% dropout (for all study groups combined) after 2 years. Natural losses; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = not reported): SMFP 1000 ppm F; IMP (main abrasive) abrasive system; school use/supervised, daily, 1 g applied for 1 min, post-brushing water rinse done (non-fluoride toothpaste provided to all for home use) Gp B (n = not reported): placebo; IMP (main abrasive) abrasive system; school use/supervised, daily, 1 g applied for 1 min, post-brushing water rinse done (non-fluoride toothpaste provided to all for home use)
Outcomes	Primary: 2-year net DFS increment - (E + U) (NCA) cl + (ER) xr; DFS (U); PF-DFS; MD-BL-DFS; MD-DFS Secondary: none assessed Assessments irrelevant to this review's scope: compliance; inflamed gingival units/person; calculus sites/person Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: "support of the Warner-Lambert Research Institute" (manufacturers of Listerine mouthwash and Dentyne chewing gum) Declarations/conflicts of interest: not reported Data handling by review authors: Gps C and D (fluoride mouthrinse and fluoride mouthrinse + fluoride toothpaste) irrelevant to this review Other information of note: clinical (V) caries assessment by 1 examiner (FOTI used), diagnostic threshold = NCA. Radiographic assessment (postBW) by 1 examiner, diagnostic threshold = ER. State of tooth eruption included = E/U. Intra-examiner 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 table

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"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The control dentifrice was identical, except that it did not contain sodium MFP..." "The study was organised on a double-blind basis..." "Records of earlier examinations were not available at the subsequent examination sessions" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 12% in 2 years (133/1135, all 4 groups combined). Dropout by group: not reported. Reasons for losses: mainly due to moving from the area Comment: numbers lost were not unduly high given length of follow-up; it is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at baseline and 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 pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 8.44 (5.58) FT, 9.79 (7.28) PL DMFT: 5.35 (3.03) FT, 6.06 (3.66) PL DMFS: 9.89 (6.94) FT, 11.05 (7.98) PL age: 12.33 FT, 12.28 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "...all subjects received ample supplies of the non-fluoride control toothpaste and toothbrushes. This ensured that the exposure of the subjects to fluoride dentifrice or rinse was restricted to the experimental regime" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Beiswanger 1989

Methods	Trial design: 4-armed, triple-blind, active-controlled and stratified RCT Location: USA Number of centres: not reported Recruitment period: study commenced 1983
Participants	Inclusion criteria: not reported Exclusion criteria: orthodontic appliances; unsuitable medical history Baseline caries: not reported for all groups (Gp A: mean 1.93 DMFS (SEM 0.075); Gp B: not reported; Gp C: mean 1.87 DMFS (SEM 0.072); Gp D: not reported). Baseline characteristics similar according to DMFS (reported for SMFP 1100 ppm F group and NAF 1100 ppm F group) Age at baseline (years): 6 to 16 years (Gp A: mean 9.07 years; Gp B: not reported; Gp C: 9.02 years; Gp D: not reported). Baseline characteristics similar according to age (reported for SMFP 1100 ppm F group and NAF 1100 ppm F group) Sex: Gp A: 841 F:803 M; Gp B: not reported; Gp C: 831 F:815 M; Gp D: not reported Any other details of important prognostic factors: background exposure to fluoride in drinking water, containing approximately 0.5 ppm F from natural sources Number randomised: 3290 (1100 ppm Gps only. Not reported for 1700 ppm Gps). Gp A: 1644; Gp B: not reported; Gp C: 1646; Gp D: not reported Number evaluated: 4458 at 3 years (present at final assessment. Gp A: 1122; Gp B: 1109; Gp C: 1151; Gp D: 1076) Attrition: overall percentage dropout after 3 years not calculable as numbers randomised at baseline not presented for 1700 ppm groups. Percentage dropout for 1100 ppm F groups 1017/3290 = 31%
Interventions	**Comparison: FT versus FT** Gp A (n = 1644): SMFP 1100 ppm F; hydrated silica abrasive system; home use (unsupervised) and school use (not clear whether supervised brushing), at least once a day Gp B (n = not reported): SMFP 1700 ppm F; hydrated silica abrasive system; home use (unsupervised) and school use (not clear whether supervised brushing), at least once a day Gp C (n = 1646): NaF 1100 ppm F; hydrated silica abrasive system; home use (unsupervised) and school use (not clear whether supervised brushing), at least once a day Gp D (n = not reported): NaF 1700 ppm F; hydrated silica abrasive system; home use (unsupervised) and school use (not clear whether supervised brushing), at least once a day
Outcomes	Primary: 3-year net DMFS increment - (CA) cl + DR; DMFS (at 2 and 3 years follow-ups) Secondary: none assessed Assessments irrelevant to this review's scope: mean number of sealed occlusal surfaces after 3 years Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported, however intervention (Gp C: Crest toothpaste) is manufactured by Procter & Gamble, therefore probable trial was funded by the manufacturer as a co-author is also employed by them Declarations/conflicts of interest: not reported Data handling by review authors: Gps A + C, and Gps B + D combined in analyses Other information of note: additional information provided in Bartizek 2001. Caries assessment determined by visual-tactile examinations according to Radike criteria by single examiner and supplemented with radiographs. Diagnostic threshold not stated, CA assumed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Within each stratum, the subjects were randomly assigned to one of the two dentifrice groups" Comment: random sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Both dentifrices were formulated using the same …. And were essentially identical with regard to common excipients" and "At no time during the course of the study did the subjects or the examiner know to which dentifrice group any subject was assigned" Comment: investigators and participants blinded
Incomplete outcome data (attrition bias)	High risk	Comment: overall dropout for length of follow-up: not calculable as numbers randomised not provided for all groups. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (CA) cl (DR) xr, reported at 24 and 36 month follow-up mean number of reversals after 3 years mean number of sealed occlusal surfaces after 3 years Comment: trial protocol not available. Fluoride concentration for 1 group not reported so unable to include in meta-analysis
Baseline characteristics balanced?	Unclear risk	Prognostic factors reported: age, caries Comment: all appear balanced but only reported for 2 of the 4 FT groups
Free of contamination/co-intervention?	Low risk	Quote: "Care was exercised to ensure that siblings were assigned to the same treatment group to avoid having different dentifrices in the same household" Comment: contamination not observed

Biesbrock 2001

Methods	Trial design: 4-armed, double-blind, active-controlled and stratified RCT Location: USA Number of centres: not reported. Sample comprised of elementary schoolchildren resident in urban central Ohio Recruitment period: study commenced in/before 2001
Participants	Inclusion criteria: not reported Exclusion criteria: conditions preventing thorough oral examination (e.g. orthodontic or extensive prosthetic appliances) Baseline caries: 5.3 DMFS (Gp A: 5.29 DMFS (SEM 0.184); Gp B: 5.49 DMFS (SEM 0.181); Gp C: 5.19 DMFS (SEM 0.178); Gp D: 5.39 DMFS (SEM 0.180)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 6 to 15 years; mean 9.5 years (Gp A: 9.47; Gp B: 9.47; Gp C: 9.47; Gp D: 9.50). Baseline characteristics (age) "balanced" Sex: overall: 2777 F:2662 M (Gp A: 702 F:659 M; Gp B: 685 F:675 M; Gp C: 702 F:657 M; Gp D: 688 F:671 M) Any other details of important prognostic factors: background exposure to fluoride: community water supply < 0.3 ppm F Number randomised: 5439 (Gp A: 1361; Gp B: 1360; Gp C: 1359; Gp D: 1359) Number evaluated: 4431 at 1 year (present at 1 year assessment. Gp A: 1127; Gp B: 1129; Gp C: 1082; Gp D: 1093) Attrition: 18.5% dropout (for all groups combined) after 1 year. Reasons for attrition not reported
Interventions	**Comparison: FT versus FT (4 groups)** Gp A (n = 1361): NaF 1100 ppm F; silica abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 1360): NaF 1700 ppm F; silica abrasive system; home use/unsupervised, daily frequency assumed Gp C (n = 1359): NaF 2200 ppm F; silica abrasive system; home use/unsupervised, daily frequency assumed Gp D (n = 1359): NaF 2800 ppm F; silica abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 1-year net DMFS increment cl + xr, reported at 1 year follow-up; DMFS increment by surface (at 1, 2, and 3 years follow-ups); DMFT increment (at 1 year follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: "supported by the Procter & Gamble Company" Declarations/conflicts of interest: first author is employed by Procter & Gamble Data handling by review authors: only results for 1 year follow-up analysed in review. Results at years 2 and 3 confounded by a concurrent fluoride rinse programme, which involved half of the study population. Gps A versus B + C versus D in analysis Other information of note: clinical (VT) caries assessment and radiographic assessment carried out by a single examiner established as "repeatably sensitive" based on prior trial experience. Additional information published in Bartizek 2001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned to one of the four dentifrice groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "...double-blind study..." "They [dentifrices] were supplied in plain white 2.7 oz tubes" and "Subject and examiner blindness to treatment were maintained throughout the study"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: 38% dropout at 3 years. No reasons are given for those not examined but similar attrition rate in each of the 4 groups. Not stated but assumed that ITT analysis carried out for those present at exam. No imputation carried out
Selective reporting (reporting bias)	Unclear risk	Comment: unclear but DMFS data not presented by surface for years 2 and 3, unlike year 1
Baseline characteristics balanced?	Low risk	Quote: "..well balanced with respect to ....mean caries experience as measured by DMFS and DMFT at baseline"
Free of contamination/co-intervention?	High risk	Quote: "Results at years 2 and 3 confounded by a concurrent fluoride rinse programme" Comment: after 1 year schools participated to varying degrees in a fluoride rinse programme. Only results for 1 year follow-up analysed in review

Biesbrock 2003a

Methods	Trial design: 2/3-armed, placebo/active-controlled and stratified RCT (placebo-controlled until 9 months when placebo participants re-allocated to active groups) Location: Guatemala Number of centres: not reported. Sample comprised of elementary schoolchildren resident in an urban area of Guatemala Recruitment period: not reported
Participants	Inclusion criteria: not reported Exclusion criteria: conditions preventing thorough oral examination (e.g. orthodontic or extensive prosthetic appliances) Baseline caries: 7.71 DMFS (Gp A: 8.02 (SD 5.61); Gp B: 9.14 (SD 6.30); Gp C: 7.95 (SD 6.10); Gp D: 7.47 (SD5.67)). Evaluated participants at 21 months reported. Baseline DMFS appears balanced Age at baseline (years): range 9 to 12 years; mean 10.4 years (Gp A: 10.4 (SEM 0.07); Gp B: 10.4 (0.07); Gp C:10.4 (SEM 0.08)) Sex: 214 F:430 M (Gp A: 72 F:144 M; Gp B: 70 F:142 M; Gp C: 72 F:144 M) Any other details of important prognostic factors: background exposure to fluoride in community water < 0.3 ppm F Number randomised: 644 (Gp A: 216; Gp B: 212; Gp C: 216) Number evaluated: 494 at 21 months (Gp A: 83; Gp B: 90; Gp C: 168; Gp D: 153) Attrition: 23.3% dropout after 21 months, reasons for dropout reported. Highest dropout observed in highest fluoride concentration group
Interventions	**Comparison: FT versus FT** Gp A (n = not reported): placebo - NaF 1100 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily Gp B (n = not reported): placebo - NaF 2800 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily Gp C (n = 216): NaF 1100 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily Gp D (n = 212): NaF 2800 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily
Outcomes	Primary: 21-month net DMFS increment - (CA) cl + (DR) xr; DMFS-O; DMFS-BL; DMFS-MD (at 9 and 21 months follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 21 months
Notes	Adverse effects: not reported Funding source: "Support for this study was provided by the Procter & Gamble Company" Declarations/conflicts of interest: 4 of 5 authors (AR Biesbrock, RW Gerlach, SA Jacobs, and RD Bartizek) are employed by Procter & Gamble. L Archila is an academic at University of Texas Health Science Center Dental School, Texas, USA Data handling by review authors: after 9 months the participants in the placebo group were randomised to the fluoride groups. The data used for analysis are for the 2 active intervention groups receiving the same fluoride concentration for the duration of the study (Gps C and D). Results reported for 3 examiners. Integrated results (VT + radiograph) reported for Examiner A used for analysis Other information of note: clinical (VT) and radiographic (DR) caries assessment by 3 trained and calibrated examiners according to a modification of the Radike criteria, diagnostic threshold = CA. Weighted Kappa scores of 0.77, 0.94, 0.96 for VT on 50 children

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "and randomly assigned…" Comment: random sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Subject and examiner blindness to treatment were maintained throughout the study" and "Dentifrice products were labeled with the subject's name and a unique identification number" Comment: participants and examiners blinded
Incomplete outcome data (attrition bias)	Low risk	Comment: overall dropout rate of 23.3% with slight difference in rate (20% for initial placebo group and 23% and 29% for fluoride groups). Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (CA) cl + (DR) xr, reported at 9 and 21 months follow-ups Comment: trial protocol not available. All outcomes listed in Methods section were reported (DMFS)
Baseline characteristics balanced?	Low risk	Prognostic factors reported: age, sex, caries Comment: baseline DMFS appears balanced
Free of contamination/co-intervention?	Unclear risk	Quote: "Siblings residing in the same household were automatically assigned to minimise risk from cross-usage of assigned dentifrice" Comment: contamination not observed

Biesbrock 2003b

Methods	Trial design: initially 3-armed, placebo/active-controlled and stratified RCT (placebo-controlled until 9 months when placebo participants re-allocated to active intervention groups) Location: Guatemala Number of centres: 2 elementary schools, in urban Guatemala Recruitment period: not reported
Participants	Inclusion criteria: not reported Exclusion criteria: conditions preventing thorough oral examination (e.g. orthodontic or extensive prosthetic appliances) Baseline caries: 9.8 DMFS (Gp A: 9.64 (SD 6.73); Gp B: 10.27 DMFS (SD 6.39); Gp C: 9.56 DMFS (SD 6.56); Gp D: 9.96 (SD 5.30)). Evaluated participants at 21 months reported. Baseline DMFS appears balanced Age at baseline (years): 9 to 12 years; mean 10.3 years (Gp A: 10.3; Gp B: 10.2; Gp C: 10.3; Gp D 10.3) Sex: 289 F:245 M (Gp A: 51 F:46 M; Gp B: 51 F:37 M; Gp C: 89 F:80 M; Gp D: 98 F:82 M) Any other details of important prognostic factors: background exposure to fluoride in community water < 0.3 ppm F Number randomised: 657 (Gp A: 219; Gp B: 218; Gp C: 220) Number evaluated: 534 at 21 months (present at final assessment. Gp A: 266 (original allocation: 169; Gp C re-allocation: 97); Gp B: 268 (original allocation: 180; Gp C re-allocation: 88); Gp C: participants re-randomised after 9 months and allocated between Gps A and B) Attrition: 19.8% dropout after 21 months, reasons for dropout not reported. No differential dropout
Interventions	**Comparison: FT versus FT** Gp A (n = not reported): placebo - NaF 500 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily Gp B (n = not reported): placebo - NaF 1450 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily Gp C (n = 219): NaF 500 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily Gp D (n = 218): placebo - NaF 1450 ppm F; hydrated silica abrasive system; home use (unsupervised) with supervised brushing at school twice daily
Outcomes	Primary: 21-month net DMFS increment - (CA) cl + DR (xr); DMFS-O; DMFS-BL; DMFS-MD (at 9 and 21 months follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 21 months
Notes	Adverse effects: not reported Funding source: "Support for this study was provided by the Procter & Gamble Company" Declarations/conflicts of interest: 4 authors are employed by Procter & Gamble Data handling by review authors: after 9 months the participants in the placebo group were randomised to the fluoride groups. The data used for analysis are for the 2 active intervention groups receiving the same fluoride concentration for the duration of the study. Results reported for 3 examiners. Integrated results (VT + radiograph) reported for Examiner A used for analysis Other information of note: clinical (VT) and radiographic (DR) caries assessment by a trained and calibrated examiner according to a modification of the Radike criteria, diagnostic threshold = CA. Weighted Kappa scores of 0.77, VT on 20 children. Sensitivity of 98%, specificity of 91% relative to expert consensus panel for radiographic interpretation

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ".. and randomly assigned…" Comment: random sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Subject and examiner blindness to treatment were maintained throughout the study" and "Each tube was labeled with the subject's name and a unique identification number" Comment: participants and examiners blinded
Incomplete outcome data (attrition bias)	Low risk	Comment: overall dropout rate of 18.8% with slight difference in rate (15.9% for initial placebo group and 22.8% and 17.4% for fluoride groups. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (CA) cl + (DR) xr, reported at 9 and 21 months follow-up Comment: trial protocol not available. All outcomes listed in Methods section were reported (DMFS)
Baseline characteristics balanced?	Low risk	Prognostic factors reported: age, sex, caries Comment: baseline DMFS appears balanced
Free of contamination/co-intervention?	Unclear risk	Quote: "Siblings residing in the same household were assigned to the same treatment group to eliminate the potential for cross-usage of test dentifrices" Comment: contamination not observed

Blinkhorn 1983

Methods	Trial design: 4-armed, double-blind, placebo-controlled and stratified RCT Location: UK Number of centres: 7 secondary schools, Greater Manchester, UK Recruitment period: study commenced in 1972
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 8.2 DMFS (Gp A: 7.83 DMFS (SD 5.17); Gp B: 8.48 DMFS (6.29)). Baseline characteristics (DMFS, DMFT, SAR) "balanced" (DFS baseline data not reported) Age at baseline (years): 11 to 12 years (not reported by group) Sex: 225 F:143 M (groups relevant to review: Gp A: 115 F:69 M; Gp B: 110 F:74 M) (evaluated participants only) Any other details of important prognostic factors: no background exposure to fluoride was reported. Fluoride content of the water supplies was less than 0.10 mg/L Number randomised: 826 (groups relevant to review: 410: Gp A: 205; Gp B: 205) Number evaluated: 751 at 3 years (present at final assessment. Groups relevant to review: 368: Gp A: 184; Gp B: 184) Attrition: 10% dropout after 3 years. Reasons for attrition described with respective total numbers for all 4 arms: 57 left school, 12 withdrawn by parents, 6 absent at final examination; no differential group losses: Gp A: 21/ 205; Gp B: 21/205
Interventions	**Comparison: FT versus PL** Gp A (n = 205): SMFP 1000 ppm F; IMP (main abrasive) abrasive system; school use/supervised, daily, for 1 min, post-brushing water rinse done. FT provided to all groups for use at home Gp B (n = 205): placebo; IMP (main abrasive) abrasive system; school use/supervised, daily, for 1 min, post-brushing water rinse done. FT provided to all groups for use at home
Outcomes	Primary: 3-year net DFS increment - (E+U) (CA) cl + (DR) xr; PF-DFS; MD-BL-DFS; MD-DFS; posterior MD-DFS; DMFT; DMFT (U); anterior DMFT; posterior DMFT; DFS (U) (at 3 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: SAR Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: "supported from a grant from the Colgate-Palmolive Company" Declarations/conflicts of interest: none reported Data handling by review authors: study contained 4 arms. Gp 1: fluoride paste + fluoride rinse; Gp 2: placebo paste + placebo rinse; Gp 3: fluoride paste + placebo rinse; Gp 4: placebo paste + fluoride rinse. Only Gps 2 (Gp B) and 3 (Gp A) are used in this review Other information of note: 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. Intra-examiner reproducibility checks for incremental clinical and radiographic caries data in 10% sample (ICC score 0.9)

Risk of bias table

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" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The trial was organized on a double-blind basis, neither the children nor the examiner being aware of who was receiving test or control products" and "...another group used the fluoride dentifrice..... and a fourth group....a placebo dentifrice" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 10% in 3 years. Dropout by group: 21/ 205 FT, 21/205 PL. Reasons for losses: left school (57), withdrawn by parents (12), absent at final examination (6) (not reported by group) Comment: numbers lost were not unduly high for the length of follow-up with no differential loss between groups. It is unclear if 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: DFS increment (E+U) (CA) cl + (DR) xr, reported at 3 years follow-up PF-DFS MD-BL-DFS MD-DFS posterior MD-DFS DFS (U) DMFT anterior DMFT posterior DMFT DMFT (U) Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFT: 4.94 (2.86) FT, 5.26 (3.47) PL DMFS: 7.83 (5.17) FT, 8.48 (6.29) PL SAR: 93.41 (21.30) FT, 93.61 (20.43) PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "..both dentifrice tubes and rinse bottles were colour coded so that the children received the correct products. Independent laboratory checks of the dispensed rinse and dentifrice were made at regular intervals to assess the reliabilty of the supervisors who dispensed agents. The coded dentifrice and rinse was dispensed in the school..." Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Brudevold 1966

Methods	Trial design: 5-armed, double-blind, placebo/active-controlled and stratified RCT Location: USA Number of centres: not reported, only that the sample derived from a "large school population" Recruitment period: study commenced 1961
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 15.4 DFS (Gp A: 16.88 DFS (SD 12.81); Gp B: 14.03 DFS (SD 10.16); Gp C: 14.89 DFS (SD 10.19); Gp D: 15.70 DFS (SD 10.96)). Baseline characteristics (DFS, DFT, DMFS, DMFT) "balanced" Age at baseline (years): range 7 to 16 years. Baseline characteristic (dental age) "balanced" Sex: 650 F:628 M (Gp A: 168 F:167 M; Gp B: 164 F:177 M; Gp C: 150 F:129 M; Gp D: 168 F:155 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 2156 (numbers for relevant groups not reported) Number evaluated: 1278 at 2 years (present at all assessments. relevant groups to this review: Gp A: 335; Gp B: 341; Gp C: 279; Gp D: 323) Attrition: 25% dropout after 2 years. Reasons for attrition not reported; any differential group losses not assessable
Interventions	**Comparison: FT (3 groups)[a] versus PL** Gp A (n = evaluated 335): SnF_2 1000 ppm F; Ca pyrophosphate abrasive system; home use/unsupervised, daily frequency assumed (GP 1) Gp B (n = evaluated 341): SnF_2 1000 ppm F; IMP abrasive system; home use/unsupervised, daily frequency assumed (GP 4) Gp C (n = evaluated 279): APF 1000 ppm F; IMP abrasive system; home use/unsupervised, daily frequency assumed (GP 3) Gp D (n = evaluated 323): placebo; abrasive system not reported; home use/unsupervised, daily frequency assumed (GP 2)
Outcomes	Primary: 2-year DFS increment - cl + xr; DFT; DMFS; DMFT (at 2 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: "supported in part by the Bristol-Myers company, New York" manufacturers of toothpastes used by Gps B (experimental formula, Bristol-Myers) and C (Ipana Durenamel, Bristol-Myers) Declarations/conflicts of interest: not reported Data handling by review authors: [a]NaF-secondary Ca pyrophosphate toothpaste Gp E not considered (abrasive system known to be incompatible with NaF). Adjusted mean values and SEMs used in analysis. Gps A, B and C combined versus Gp D Other information of note: clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA. Radiographic assessment (10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the initial exam, the record cards of these youngest, or master, siblings were stratified (ordered) simultaneously according to 12 characteristics....The ordered cards of the 'master' siblings were then divided into 5 dentifrice groups by superimposing the numbers 1 through 5 in random sequence. The same dentifrice was assigned automatically to the other, or "trailing", siblings in his household" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Each (of 2) examiner assessed about half of the subjects in each group, and each subject had the same dentist-examiner throughout the study. Separate records were used for each examination, and previous records were never available to the examiner. All observations were recorded in code for subsequent transfer to machine data processing. The radiographs were read and recorded independently by a third dentist. At no time was it possible for the examiners to identify a subject with a dentifrice group" and "An independent laboratory was assigned the responsibility of coding, packaging, and shipping all dentifrices in this study... NaF dentifrice was compared to.....and a fluoride free dentifrice" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 24.7% in 2 years (534/2156, all 5 groups combined). Dropout by group: not reported. Reasons for losses: not reported Comment: numbers lost were not unduly high given length of follow-up; It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants examined after 2 years
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - cl + xr, reported at 2 years follow-up DMFS DMFT DFT Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 16.88 (12.81) FT 1; 14.03 (10.16) FT 2; 14.89 (10.19) FT 3; 15.70 (10.96) PL DFT: 8.53 (5.49) FT 1; 7.61 (4.80) FT 2; 6.04 PL; 7.59 (5.01) FT 3; 8.07 (5.02) PL DMFT: 8.84 (5.86) FT 1; 7.87 (4.80) FT 2; 2.94 PL; 7.91 (5.34) FT 3; 8.35 (5.21) PL DMFS: 18.43 (13.91) FT 1; 15.33 (11.08) FT 2; 16.48 (12.86) FT 3; 17.09 (11.68) PL dental age: 21.12 (6.59) FT 1; 22.28 (6.47) FT 2; 20.49 (6.51) FT 3; 21.70 (6.29) PL Comment: initial caries appears balanced although adjustment for baseline imbalance was made in the analysis

Bias	Authors' judgement	Support for judgement
Free of contamination/co-intervention?	Low risk	Quotes: "As the study group was assembled, all siblings were noted to permit limitiation of one dentifrice code to a family" and "New shipments supplied every 8 to 10 weeks, and new toothbrushes supplied every 6 months" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Buhe 1984

Methods	Trial design: 3-armed, double-blind, placebo/active-controlled and stratified RCT Location: West Germany (Federal Republic of Germany) Number of centres: not reported Recruitment period: study commenced 1976
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 17.4 DMFS (Gp A: 17.1; Gp B: 17.4; Gp C: 17.8 DMFS). Baseline characteristic (DMFS) "balanced" (DFS baseline data not reported) Age at baseline (years): range 11 to 13 years, mean 12.3 years (for all groups). Baseline characteristic (age) "balanced" Sex: not reported Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 1562 (Gp A: 520; Gp B: 520; Gp C: 522) Number evaluated: 1286 at 3 years (present at final assessment) (Gp A: 421; Gp B: 438; Gp C: 427) Attrition: 18% dropout after 3 years. No differential group losses
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = 520): SMFP 1500 ppm F; IMP abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 520): SMFP 1000 ppm F; IMP abrasive system; home use/unsupervised, daily frequency assumed Gp C (n = 522): placebo; IMP abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - cl + xr; DMFS; DMFS (U); DMFT (at 3 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: supported by The Borrow Foundation Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment, diagnostic threshold not reported; state of tooth eruption included = E/U; radiographic caries assessment, diagnostic threshold not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...stratified randomisation..." Comment: translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Translation of report not detailed enough to make a categorical decision regarding allocation concealment
Blinding (performance bias and detection bias)	Low risk	Quotes: "Double blind study" and "...as compared to the placebo group.." Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 17.7% in 3 years. Dropout by group: FT 1: 99/520, FT 2: 82/520, PL: 95/522. Reasons for losses not reported Comment: numbers lost were not unduly high given length of follow-up and showed no differential loss between groups. It is unclear if reasons for the 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: DFS increment - cl + xr, reported at 3 years follow-up DMFS DMFS (U) DMFT Comment: trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	Low risk	Prognostic factors reported: mean age 12.3 years (for all groups) DMFS: 17.1 FT 1; 17.4 FT 2; 17.8 PL TAR: 15.4 FT 1; 15.5 FT 2; 15.3 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	Translation of report not detailed enough to make a categorical decision regarding any contamination/co-intervention

Cahen 1982

Methods	Trial design: 3-armed, double-blind, placebo/active-controlled and stratified RCT Location: France Number of centres: not reported. Sample derived from schools in Strasbourg, France Recruitment period: study commenced 1977
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: Gp C: 1.4 DMFS (Gps A and B not reported) Age at baseline (years): range 6 to 8 years. Baseline characteristic (age) "balanced" Sex: 980 F:1028 M (Gp A: 300 F:332 M; Gp B: 296 F:372 M; Gp C: 384 F:324 M) (evaluated participants only). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 2500 (numbers per group not reported) Number evaluated: 2008 at 3 years (present at all assessments) (Gp A: 632; Gp B: 668; Gp C: 708) Attrition: 20% dropout after 3 years. Natural losses and exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = assessed 632): SMFP 1500 ppm F; IMP abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = assessed 668): AmF 1500 ppm F; Ca carbonate/Na and Al silicates abrasive system; home use/unsupervised, daily frequency assumed Gp C (n = assessed 708): placebo; IMP abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - cl + xr; DMFT; df-rate (at 3 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: Gps A + B combined (both 1500 ppm concentration) versus Gp C in analyses. SD of means imputed from SEM and combined using methods specified in Cochrane Handbook. Other information of note: clinical (V) caries assessment by 6 examiners, diagnostic threshold not reported; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold not reported; partial recording. Inter- and intra-examiner reproducibility of clinical and radiographic caries diagnosis assessed in 10% sample ("good reproducibility, no significant difference between or within examiners")

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...children were stratified by age, sex... were then randomly distributed into 3 groups. Additional modifications were made by placing brothers and sisters in the same groups in order to ensure that only one type of dentifrice entered the household during the trial period" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The dentifrices were packed in neutral white tubes with no other inscription than 'Pate Dentifrice'...allocation code was known only by the manufacturer until the final results were obtained" and "The whole study was conducted double-blind. The yellow toothpaste was not fluoridated and ..." Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 19.7% in 3 years (492/2500). Dropout by group: not reported. Reasons for losses: sickness, change of address, exclusion based on presence at all examinations (not reported by group). Quote: "The balance between boys and girls, and between age groups was preserved in each treatment group...allowing unbiased comparisons" Comment: overall dropout not unduly high for length of follow-up; it is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced, and how balance between groups was maintained. Caries data used in the analysis pertain to participants present at all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 3 years follow-up DMFT df rate Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Unclear risk	Prognostic factors reported: age and sex reported as balanced Comment: initial caries derived for the control group only
Free of contamination/co-intervention?	Low risk	Quote: "...by placing brothers and sisters in the same groups in order to ensure that only one type of dentifrice entered the household during the trial period" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Cardoso 2014

Methods	Trial design: 3-armed, active-controlled and stratified RCT Location: Brazil Number of centres: 5 public primary schools in Bauru (each in a different geographical region of the city), Brazil Recruitment period: study commenced in 2010
Participants	Inclusion criteria: (from NCT01049503) ≥ 2 and ≤4 years old; absence of very large carious lesions/dentine sensitivity during the study Exclusion criteria: participation in other trials in prior 3 months; orthodontic appliance use Baseline caries: 0.947 ANC; (Gp A: 1.14; Gp B 0.84) Age at baseline (years): range 2 to 4 years; mean 3.4 (SD 0.6) (distribution of mean age between groups not reported) Sex: 167 F:148 M (distribution of sex between groups not reported) Any other details of important prognostic factors: background exposure to fluoride in community water supply (0.6 to 0.8 ppm F) Number randomised: 315 (Gp A: 104; Gp B: 211) Number evaluated: 195 at 1 year (present at final assessment. Gp A: 71; Gp B: 124) Attrition: 38% dropout after 1 year, reasons for dropout reported. No differential dropout
Interventions	**Comparison: FT versus FT** Gp A (n = 104): NaF 1100 ppm F (pH 7.0); abrasive system not reported; home use (unsupervised) with supervised brushing at school at least twice daily Gp B (n = 211): NaF 550 ppm F (pH 4.5 (n = 104) and 7.0 (n = 107)); abrasive system not reported; home use (unsupervised) with supervised brushing at school at least twice daily
Outcomes	Primary: 12-month net white spot lesion increment - (ANC) cl (at 1 year) Secondary: adverse effects Assessments irrelevant to this review's scope: compliance; change in fluorescence; lesion area (mm) Follow-up duration: 1 year
Notes	Adverse effects: "There were no reports on adverse effects, but some children complained about the taste of the dentifrice" Funding source: "This study was funded by FAPESP (2008/58402-9, 2010/11916-8, and 2010/01944-4)." FAPESP is São Paulo's state-funded research foundation. "...experimental formulations, manufactured by Dental Prev Ind. Com. Ltda (Lorena, Brazil)" Declarations/conflicts of interest: "University of São Paulo has a patent request in Brazil (INPI) for 'Low-fluoride acidic liquid dentifrice and its use'" Data handling by review authors: data entered separately for caries-active and caries-inactive at baseline. Both 550 ppm F arms combined in this review under Gp B Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = NCA. Kappa scores of 0.88 and 0.78 for intra-rater reliability and 0.78 for inter-rater reliability at baseline on 20 children and at 0.84 and 0.75 at the end of the study 0.75 inter-rater reliability

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "was randomly reassigned into three subgroups…" and "The software Excel generated random numbers ranging from 0 to 0.99" Comment: random sequence generation stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "All formulations were NaF-based and identical, except for the dentifrices' color. The colors' code was kept by one person not involved in the examination of the children" Comment: probably done. Participants and examiners blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "38% loss, mainly due to the fact that parents changed their children's school" Comment: overall dropout rate of 38.1% with no differential dropout. Reasons for dropout reported. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: progression of caries in caries inactive group (lesions/child) net increment for children in caries active group - (NCA)cl, reported at 12-month follow-up Comment: all outcomes listed in Methods section were reported
Baseline characteristics balanced?	Unclear risk	Baseline caries unbalanced in the caries active group mean 1.55 active white spot lesions in the 550 ppm group and mean 2.61 in the 1100 ppm group Comment: some imbalance in caries in the active caries group. No other prognostic factors reported
Free of contamination/co-intervention?	Low risk	Quotes: "Kits containing dentifrices and toothbrushes were supplied for the whole family every 3 months to guarantee the use of experimental LD by the children, facilitating compliance with study protocol" and ".. and were also asked not to use other oral hygiene products" Comment: contamination not observed

Chesters 2002

Methods	Trial design: 2-armed, double-blind, active-controlled and stratified RCT Location: Lithuania Number of centres: 28 secondary schools in Vilnius, Lithuania Recruitment period: study commenced in 1999
Participants	Inclusion criteria: ≥ 1 erupted second permanent molar; CVA D_3MFS score of 2 to 24 Exclusion criteria: low-caries subjects; parent/guardian unwilling to disclose medical/dental history; intra-oral x-ray for caries diagnosis in prior 6 months; > 2 occlusal surfaces in second permanent molars restored/clinically cavitated/sealed; conduct of oral examination liable to cause unacceptable stress to participant; medical/dental conditions with potential to affect caries development (including antibiotic therapy); heart condition; cancer treatment receipt; fixed orthodontic appliances present at baseline prohibiting assessment of all erupted teeth Baseline caries: baseline characteristic (baseline caries) "well balanced." Baseline values D_3MF not reported but "not statistically different". Baseline D_1MFS for assessed participants at 24 months: 32.48 D_1MFS (Gp A: mean 32.95 (SEM 0.40); Gp B: mean 32.01 (SEM 0.37)) Age at baseline (years): range 11 to 14 years, mean 13 years (Gp A: 13.0; Gp B: 13.1) Sex: 1330 F:1057 M (Gp A: 665 F:528 M; Gp B: 665 F:529 M). Baseline characteristic (sex) "well balanced" Any other details of important prognostic factors: background exposure to fluoride not reported Number randomised: 2387 (Gp A: 1193; Gp B: 1194) Number evaluated: 2011 at 2 years (present for final assessment. Gp A: 994; Gp B: 1017) Attrition: 15.8% dropout (for all study groups combined) after 2 years. Gp A: 16.7%; Gp B: 14.8%. Reasons for attrition absent from assessment (Gp A: 24, Gp B: 17); withdrawn (Gp A: 175, Gp B: 160)
Interventions	**Comparison: FT versus FT** Gp A (n = 1193): SMFP 1000 ppm F; silica abrasive system; home use twice daily/unsupervised; daily brushing at school Gp B (n = 1194): SMFP 2500 ppm F; silica abrasive system; home use twice daily/unsupervised; daily brushing at school
Outcomes	Primary: 2-year net DMFS increment cl(DSTM) FOTI at D_3 all radiographic lesions; D_1MFS increment (DSTM only); D_3MFS increment (DSTM only); D_1MFS events (DSTM); D_3MFS events (DSTM). Reported at 1 and 2 year follow-ups Secondary: none assessed Assessments irrelevant to this review's scope: none Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: "funded by Unilever Dental Research" Declarations/conflicts of interest: 5 (including lead author) of 14 authors employed by Unilever: RK Chesters, E Huntington, JR Matheson; JA Nicholson, D Savage Data handling by review authors: n/a Other information of note: examinations carried out by a single examiner. Intra-examiner reliability: repeat DSTM and FOTI examinations held throughout the baseline, 12 and 24 month examinations on 5% to 10% of subjects. For radiography, baseline and 12 and 24 month radiographs re-assessed for 5% to 10% of subjects. Reproducibility "excellent", Kappa values > 0.8

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: " . .randomized to one of two silica-based dentifrices" and "...stratified into 12 strata ...allocated to a product group according to a pre-prepared list of randomized blocks?"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "... double-blind study" and "Neither the subjects, clinical examiners, nor those distributing the test products were aware of the product identities at any time during the trial. The investigators were supplied with sealed code-break envelopes that could be opened in an emergency. This was not required and the integrity of the product code was confirmed with regular GPC monitoring and independent audit" and "The products were identical except for the fluoride level and different coloured packaging for each product code?"
Incomplete outcome data (attrition bias)	Low risk	2387 randomised (994/1193 included in final main analysis in low fluoride group; 1017/1194 in high fluoride group) Comment: not unreasonable dropout rate; similar in both groups. Reasons unlikely to be due to intervention. Numbers absent and withdrawn are given for each group. Well balanced between groups. No further information about dropouts given
Selective reporting (reporting bias)	Unclear risk	Comment: results reported traditional increment and DSTM increment at different levels of diagnosis. DMFT and proportion developing new caries missing. DSTM, FOTI and radiographic assessments
Baseline characteristics balanced?	Low risk	Comment: balance of sex and baseline DMFS
Free of contamination/co-intervention?	Unclear risk	Comment: unlikely as used different colours for toothpaste tubes/cartons, but possibility of contamination during school brushing sessions

CL-213 1983

Methods	Trial design: 2-armed, double-blind, active-controlled and stratified RCT Location: Pennsylvania, USA Number of centres: not stated Recruitment period: study commenced in 1979
Participants	Inclusion criteria: male and female schoolchildren in Grades 1 to 6 Exclusion criteria: schoolchildren with a condition which prohibited a thorough oral examination, including orthodontic therapy and extensive prosthetic appliances Baseline caries: not reported Age at baseline (years): range 6 to 11 years Sex: not reported Any other details of important prognostic factors: background exposure to fluoride not reported. Community water supply fluoride < 0.3 ppm Number randomised: not reported Number evaluated: 1197 at 3 years (present for final assessment. Gp A: 582; Gp B: 615) Attrition: unable to calculate due to missing information from number randomised
Interventions	**Comparison: FT versus FT** Gp A (n = 582 evaluated): NaF 1100 ppm F; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed) Gp B (n = 615 evaluated): NaF 1700 ppm F; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed)
Outcomes	Primary: 3-year DMFS increment - cl + xr Secondary: none reported Assessments irrelevant to this review's scope: none Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: The Procter & Gamble Company Declarations/conflicts of interest: none reported. Procter & Gamble data Data handling by review authors: n/a Other information of note: all clinical (Radike criteria) and radiographic examinations were carried out by a single examiner. "The sponsor decided to begin another study immediately upon completion of the Year 3 examinations. For logistical reasons, it was decided to only perform Year 3 examinations on those subjects who agreed to participate in Study E (approximately 40% to 45% of the subjects who completed Year 2)." Unpublished data on file from The Procter & Gamble Company, published in Bartizek 2001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...subjects were stratified based on gender, age and baseline DMFS scores derived from the visual-tactile examination, and randomly assigned to one of the treatment groups in the study"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "... double-blind study" "Subject and examiner blindness to treatment were maintained throughout the study" and "Dentifrices were supplied in plain white tubes"
Incomplete outcome data (attrition bias)	High risk	Quotes: "The studies each enrolled approximately 1200 to 2000 male and female schoolchildren per treatment group" and "The sponsor decided to begin another study immediately upon completion of the Year 3 examinations. For logistical reasons, it was decided to only perform Year 3 examinations on those subjects who agreed to participate in Study E (approximately 40% to 45% of the subjects who completed Year 2)" Comment: actual number randomised not reported, so unable to calculate attrition. Selective examination at Year 3
Selective reporting (reporting bias)	Low risk	Comment: results reported traditional increment using clinical and radiographic assessments
Baseline characteristics balanced?	Low risk	Comment: not explicitly stated, but stratified randomisation according to gender, age and baseline DMFS scores with large sample size so probably balanced
Free of contamination/co-intervention?	Low risk	Quote: "...siblings, all were automatically assigned to the same treatment group as the first sibling to minimise the risk from cross-usage of assigned dentifrice"

CL-216 1982

Methods	Trial design: 2-armed, double-blind, active-controlled and stratified RCT Location: Oregon, USA Number of centres: not stated Recruitment period: study commenced in 1980
Participants	Inclusion criteria: male and female schoolchildren in Grades 1 to 5 Exclusion criteria: schoolchildren with a condition which prohibited a thorough oral examination, including orthodontic therapy and extensive prosthetic appliances Baseline caries: not reported Age at baseline (years): range 6 to 10 years Sex: not reported Any other details of important prognostic factors: background exposure to fluoride not reported. Community water supply fluoride < 0.3 ppm Number randomised: not reported Number evaluated: 2758 at 2 years (present for final assessment. Gp A: 1371; Gp B: 1387) Attrition: unable to calculate due to missing information from number randomised
Interventions	**Comparison: FT versus FT** Gp A (n = 1371 evaluated): NaF 1100 ppm F; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed) Gp B (n = 1387 evaluated): NaF 1700 ppm F; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed)
Outcomes	Primary: 2-year DMFS increment - cl + xr Secondary: none reported Assessments irrelevant to this review's scope: none Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: The Procter & Gamble Company Declarations/conflicts of interest: none reported. Procter & Gamble data Data handling by review authors: n/a Other information of note: all clinical (Radike criteria) and radiographic examinations were carried out by a single examiner. Study "...was terminated following the Year 2 examinations." "Per the study protocols, Studies A and B were each designed to cover a period of two to three years, so collecting Year 3 data for a subset of subjects or omitting the Year 3 examinations were actions within the scope of the protocols." Unpublished data on file from The Procter & Gamble Company, published in Bartizek 2001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...subjects were stratified based on gender, age and baseline DMFS scores derived from the visual-tactile examination, and randomly assigned to one of the treatment groups in the study"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "... double-blind study" "Subject and examiner blindness to treatment were maintained throughout the study" and "Dentifrices were supplied in plain white tubes"
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "The studies each enrolled approximately 1200 to 2000 male and female schoolchildren per treatment group" Comment: actual number randomised not reported, so unable to calculate attrition
Selective reporting (reporting bias)	Low risk	Comment: results reported traditional increment using clinical and radiographic assessments
Baseline characteristics balanced?	Low risk	Comment: not explicitly stated, but stratified randomisation according to gender, age and baseline DMFS scores with large sample size so probably balanced
Free of contamination/co-intervention?	Low risk	Quote: "...siblings, all were automatically assigned to the same treatment group as the first sibling to minimise the risk from cross-usage of assigned dentifrice"

CL-220 1986

Methods	Trial design: 4-armed, double-blind, active-controlled and stratified RCT Location: Pennsylvania, USA Number of centres: not stated Recruitment period: study commenced in 1983
Participants	Inclusion criteria: male and female schoolchildren in Grades 1 to 8 Exclusion criteria: schoolchildren with a condition which prohibited a thorough oral examination, including orthodontic therapy and extensive prosthetic appliances Baseline caries: not reported Age at baseline (years): range 6 to 14 years Sex: not reported Any other details of important prognostic factors: background exposure to fluoride not reported. Community water supply fluoride < 0.3 ppm Number randomised: not reported Number evaluated: 3265 at 3 years (present for final assessment. Gp A: 840; Gp B: 757; Gp C: 848; Gp D: 820) Attrition: unable to calculate due to missing information from number randomised
Interventions	**Comparison: FT versus FT** Gp A (n = 840 evaluated): NaF 1100 ppm F; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed) Gp B (n = 757 evaluated): NaF 1700 ppm F; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed) Gp C (n = 848 evaluated): NaF 2200 ppm F; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed) Gp D (n = 820 evaluated): "Experimental" SMFP ppm F concentration not reported; abrasive system not reported; home use *ad libitum* (twice daily, unsupervised assumed)
Outcomes	Primary: 3-year DMFS increment - cl + xr Secondary: none reported Assessments irrelevant to this review's scope: none Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: The Procter & Gamble Company Declarations/conflicts of interest: none reported. Procter & Gamble data Data handling by review authors: Gp D excluded from analysis, concentration not reported Other information of note: all clinical (Radike criteria) and radiographic examinations were carried out by a single examiner. Unpublished data on file from The Procter & Gamble Company, published in Bartizek 2001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...subjects were stratified based on gender, age and baseline DMFS scores derived from the visual-tactile examination, and randomly assigned to one of the treatment groups in the study"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "... double-blind study" "Subject and examiner blindness to treatment were maintained throughout the study" and "Dentifrices were supplied in plain white tubes"
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "The studies each enrolled approximately 1200 to 2000 male and female schoolchildren per treatment group" Comment: actual number randomised not reported, so unable to calculate attrition
Selective reporting (reporting bias)	Low risk	Comment: results reported traditional increment using clinical and radiographic assessments
Baseline characteristics balanced?	Low risk	Comment: not explicitly stated, but stratified randomisation according to gender, age and baseline DMFS scores with large sample size so probably balanced
Free of contamination/co-intervention?	Low risk	Quote: "...siblings, all were automatically assigned to the same treatment group as the first sibling to minimise the risk from cross-usage of assigned dentifrice"

Conti 1988

Methods	Trial design: 2-armed, double-blind, active-controlled and stratified RCT Location: USA Number of centres: 11 elementary schools, Polk County, Florida, USA Recruitment period: study commenced in/before 1984
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 2.8 DMFS (Gp A: 2.85 (SD 3.71); Gp B: 2.82 (SD 3.25); 1.9 DMFT (Gp A: 1.89 (SD 2.11); Gp B: 1.90 (SD 1.89)) (evaluated participants reported only). Baseline characteristics (sound surfaces, DMFT, DMFS) "balanced" Age at baseline (years): range 7 to 14 years, mean 10 years (Gp A: 10.06 years (no SD); Gp B: 10.06 years (no SD)) (evaluated participants only; baseline distribution of age for all randomised unreported). Baseline characteristic (age) "balanced" Sex: 1213 F:1202 M (Gp A: 628 F:600 M; Gp B: 585 F:602 M) (Evaluated participants reported only). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: community water supply < 0.3ppm F Number randomised: 3957 (Gp A: 1979; Gp B: 1978) Number evaluated: 2415 at 3 years (present at final assessment. Gp A: 1228; Gp B: 1187) Attrition: 39% dropout (for all study groups combined: Gp A: 751 (38%); Gp B: 791 (40%)) after 3 years. Reasons for high attrition described: moved, withdrew, absent or not available for examination; no differential group losses
Interventions	**Comparison: FT versus FT** Gp A (n = 1979): SMFP 1000 ppm; silica abrasive system; home use/supervised brushing at school, daily frequency assumed Gp B (n = 1978): SMFP 1500 ppm; silica abrasive system; home use/supervised brushing at school, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - cl + xr; DFS proximal; DFT; DMFS; DMFT (at 3 years follow-up) Secondary: adverse effects (oral (soft tissue) findings) Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: "low incidence of soft tissue aberrations in this population. Increasing gingival inflammation was the only area where [Gp B] had a higher prevalence at 3 years, 3.37% [n = 40] to 2.69% [n = 33]" Funding source: "supported by a grant from the Lever Brothers Company (#123404006)" Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical examinations carried out by 1 primary examiner and 2 back-up examiners. 10% of children randomly selected each year to be re-examined

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " . .stratified according to age and sex and then randomly assigned to one of two treatment groups by a computer program"
Allocation concealment (selection bias)	Low risk	Quote: "assigned by computer program designed for this purpose"
Blinding (performance bias and detection bias)	Low risk	Quote: "The study was double blind, multiple codes were used for each product, the dentrifices used were identical in appearance and flavour and the packaging were similar for both products"
Incomplete outcome data (attrition bias)	Unclear risk	2415/3957 children received clinical and radiographic assessment (39% attrition rate; similar across both groups) Quote: "Moved, withdrew, absent or not available" Comment: attrition rate was high after 3 years, 38% and 40% in the groups. Although reasons for dropouts unlikely to be due to intervention, high rates could influence results
Selective reporting (reporting bias)	Low risk	Comment: results reported DMFT, DMFS, per cent caries free at 3 years. Clinical and radiography assessments
Baseline characteristics balanced?	Low risk	Comment: comparable age, sex, baseline DMFT DMFS
Free of contamination/co-intervention?	Low risk	Comment: school co-ordinators hired and trained to supervise daily toothbrushing. Contamination possible in school brushing sessions but unlikely under supervision

Davies 2002

Methods	Trial design: 3-armed, single-blind, active-controlled RCT Location: UK Number of centres: "examinations in 808 schools, in nine districts, throughout the North West of England." Districts include: Blackburn; Bolton; Burnley; Oldham; Salford; Skelmersdale; South Sefton; Tameside; Wigan Recruitment period: study commenced in 1993 (5 health districts), and 1994 (4 health districts)
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 0 dmfs. Baseline characteristics not quantitatively reported Age at baseline (years): 1 year. Baseline characteristics not reported Sex: baseline characteristics not reported Any other details of important prognostic factors: background exposure to fluoride not reported. Community water supply < 0.1 ppm F Number randomised: 7422 (Gp A: 2488; Gp B: 2472; Gp C: 2462) Number evaluated: 3467 (Gp A: 1186; Gp B: 1176; Gp C: 1369) Attrition: 32% dropout after 5 years. Reasons for attrition: refused to participate (9%), change of residence (19%); product related and dental recommended withdrawals in high fluoride group only (0.07%)
Interventions	**Comparison: FT versus FT[a]** Gp A (n = 2488): NaF 1450 ppm; abrasive system not reported; home use/unsupervised, daily frequency assumed Gp B (n = 2472): NaF 440 ppm; abrasive system not reported; home use/unsupervised, daily frequency assumed Gp C (n = 1369): no intervention control
Outcomes	Primary: 5-year dmft increment - cl; prevalence of caries experience (dmft > 0). Reported at 5 years follow-up Secondary: none assessed Assessments irrelevant to this review's scope: cost per tooth saved; cost per child saved from caries experience/extraction experience Follow-up duration: 5 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: [a]Comparator group (n = 2462) receiving no intervention also reported but not considered in this review Other information of note: clinical (VT) caries assessments by trained, standardised, calibrated examiners. Clinical data only. Reliability values not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "..randomised controlled parallel group clinical trial" and "..centrally allocated to either one of the two test groups or a control group using random number tables"
Allocation concealment (selection bias)	Low risk	Quote: "..centrally allocated to either one of the two test groups or a control group" Comment: centralised allocation
Blinding (performance bias and detection bias)	Unclear risk	Quote: "Dental examinations were conducted under blind conditions but as "off the shelf" toothpaste was delivered to the participants, subjects and their families were aware of which toothpaste they were using" Comment: clinical assessors blinded, but participants and their families were not. Participants very young children so knowledge of intervention unlikely to influence outcome
Incomplete outcome data (attrition bias)	Low risk	1677/2472 available for examination in low fluoride group; 1696/2488 available in the high fluoride group. Total dropout rate of 32% Comment: dropout rate mainly due to refusal to participate, change of residence; product related and dental recommended withdrawals in high fluoride group only but this number is very small. Reasons for dropouts primarily unlikely to be due to intervention
Selective reporting (reporting bias)	Low risk	Comment: routine caries diagnosis. No radiographs taken; clinical examination only. Caries indices reported: mt, dmft, caries free
Baseline characteristics balanced?	Unclear risk	Comment: no baseline data presented. Study undertaken in deprived areas of North West of England with comparable caries prevalence in 5 year olds
Free of contamination/co-intervention?	Unclear risk	Comment: contamination possible. Toothpaste supplied for use by children participating in the trial only and not to other family members

Di Maggio 1980

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: Italy Number of centres: not reported Recruitment period: study commenced in/before 1977
Participants	Inclusion criteria: age between 11 and 12 years and resident at the orphanage Exclusion criteria: not reported Baseline caries: 11.7 DMFS (Gp A: 11.50 DMFS/5.68 DMFT; Gp B: 11.85 DMFS/5.90 DMFT) (evaluated participants at 2 years reported only). Baseline characteristics (DMFS, DMFT) '"balanced" Age at baseline (years): range 11 to 12 years (mean, or by group not reported) Sex: not reported Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 50 (group distribution unreported) Number evaluated: 42 (present at final assessment. Gp A: 22; Gp B: 20) Attrition: 16% dropout (for both study groups combined) after 2 years. Main reason for attrition described: left institution; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 22): SMFP-NaF 2500 ppm F; abrasive system not clearly specified; linstitution use/supervised, 3 times a day Gp B (n = evaluated 20): placebo; abrasive system not clearly specified; institution use/supervised, 3 times a day
Outcomes	Primary: 2-year DMFS increment - cl; DMFT (at 1 and 2 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical caries assessment by 2 examiners; diagnostic threshold not reported; state of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... following a randomisation list the children were allocated to 2 groups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "...to 2 treatment groups that differed only by the presence or absence of fluoride. ...the dentifrices were indistinguishable by colour or flavour" and "...using the most strict double-blind condition" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 16% (8/50) in 2 years. Dropout by group: not reported. Reasons for losses: essentially due to leaving the orphanage Comment: numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if 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 - cl, reported at 1 and 2 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFT: 5.68 FT, 5.90 PL DMFS: 11.50 FT, 11.85 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The institute personnel actively collaborated in controlling the regular dentifrice use, as prescribed" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Fan 2008

Methods	Trial design: 3-armed, double-blind, active/placebo-controlled and stratified RCT Location: China Number of centres: not reported. Chengdu area, China Recruitment period: study commenced in/before 2005
Participants	Inclusion criteria: not reported Exclusion criteria: children with orthodontic appliances, participating in any other clinical study during the 3 months prior to baseline examination, or a condition impeding participation at baseline were excluded Baseline caries: 3.6 dfs (Gp A: 3.54 (SD 5.34); Gp B: 3.53 (SD 5.62); Gp C: 3.60 (SD 6.07)). Baseline characteristic (dfs) "well balanced" (evaluated participants at 2 years reported only) Age at baseline (years): range 4.0 to 4.5 years; mean 4 years (Gp A: 4.23 years (SD 0.134); Gp B: 4.28 years (SD 0.141); Gp C: 4.19 years (SD 0.129)). Baseline characteristic (age) "well balanced" (evaluated participants at 2 years reported only) Sex: 431 F:567 M (Gp A: 136 F:193 M; Gp B: 141 F:200 M; Gp C: 154 F:174 M). Baseline characteristic (sex) "well balanced" (evaluated participants at 2 years reported only) Any other details of important prognostic factors: background exposure to fluoride: community water supply fluoridated 0.3 ppm F Number randomised: 1200 (group distribution not reported) Number evaluated: 998 at 2 years (present for all assessments) (Gp A: 329; Gp B: 341; Gp C:328) Attrition: dropouts not obtainable. Reasons for attrition not fully reported: "Subjects who did not complete the study dropped out for reasons unrelated to the use of the treatments." Differential losses not assessable
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = assessed 329): SMFP 1500 ppm F; abrasive system Ca-carbonate; home use/unsupervised, twice daily frequency assumed Gp B (n = assessed 341): SMFP 1500 ppm F; abrasive system not reported silica; home use/unsupervised, twice daily frequency assumed Gp C (n = assessed 328): placebo; abrasive system not reported Ca-carbonate; home use/unsupervised, twice daily frequency assumed
Outcomes	Primary: 2-year dfs increment - cl (at 2 years) Secondary: adverse effects Assessments irrelevant to this review's scope: compliance Follow-up duration: 2 years
Notes	Adverse effects: "Throughout the study, there were no adverse effects on the oral hard or soft tissues, which were observed by the dental examiner, or reported by the subjects when questioned in this regard" Funding source: "This clinical study was funded by the Colgate-Palmolive Company" Declarations/conflicts of interest: half of the authors were employed by the product manufacturer (3 of 6 authors work at Colgate-Palmolive Technology Center, New Jersey, USA: Yun Po Zhang; Anthony R Volpe; William DeVizio) Data handling by review authors: Gp A + B versus C for analysis. Combined 2 SMFP 1500 groups with different abrasive systems Other information of note: analysis of covariance adjusted for baseline dfs. Clinical (VT) assessment by 1 examiner. A subsample of 40 children were re-assessed Kappa > 0.9

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned..."
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "...employed a double-blind..." and "Dentifrices were packaged in white tubes or overwrapped with white tape so as to mask their identity"
Incomplete outcome data (attrition bias)	Unclear risk	Quotes: "A total of 1200 qualifying children...entered the study" and "Subjects who did not complete the study dropped out for reasons unrelated to the use of the treatments" Comment: number randomised/excluded/withdrawn not reported
Selective reporting (reporting bias)	Low risk	Mean dfs increment. Clinical (VT) assessment only
Baseline characteristics balanced?	Unclear risk	Comment: analysis adjusted for baseline dfs. Baseline data reported for participants completing the trial only. However, groups analysed are similar with respect to sex and mean dfs score at baseline
Free of contamination/co-intervention?	Unclear risk	Comment: insufficient information. Possibility of contamination during brushing sessions

Fanning 1968

Methods	Trial design: 3-armed, double-blind, active/placebo-controlled and stratified RCT Location: Australia Number of centres: 10 secondary schools, across Adelaide metropolitan area Recruitment period: study commenced 1964
Participants	Inclusion criteria: children with completed adolescent dentitions Exclusion criteria: fixed orthodontic appliance use; prior fluoride exposure by tablet-form or topically Baseline caries: 19.8 DMFS (from sample randomised) (Gp A: 19.84 DMFS/10.39 DMFT; Gp B: 19.89 DMFS/10.39 DMFT). Baseline characteristics (DMFS, DMFT, SAR) "balanced" Age at baseline (years): range 12 to 14 years, mean 13 years (age distribution by group unreported) Sex: distribution of sex by group, or overall unreported Any other details of important prognostic factors: no background exposure to fluoride reported Number randomised: 2364 (1576 for Gps A and B - Gp A: 788; Gp B: 788). Note: Gp C (excluded[**]): 788 Number evaluated: 1266 at 2 yrs (844 for Gps A&B - Gp A: 422; Gp B: 422). Note: Gp C (excluded[**]): 422 Attrition: 22% natural dropout after 2 years; no differential group losses (46% dropout based on analysis performed for randomised block design); Gp A: 139/788; Gp B: 163/788
Interventions	**Comparison: FT[a] versus PL** Gp A (n = 788): SnF_2 1000 ppm F; IMP abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 788): placebo; IMP abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - (CA) cl + (ER) xr Secondary: stain score Assessments irrelevant to this review's scope: calculus; periodontal indices Follow-up duration: 2 years
Notes	Adverse effects: stain score: "the increment for stain in group A, stannous fluoride, was significantly larger (P < 0.001) than for the other two groups" Funding source: "the research project was supported through a grant from Colgate-Palmolive Pty, Ltd. Toothbrushes were supplied by Johnson and Johnson Pty, Ltd" Declarations/conflicts of interest: not reported Data handling by review authors: [a]Na N-lauroyl sarcosinate/SMFP 1000 ppm F toothpaste group not considered (additional non-F active agent used in this group only) Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (5 BW) by 2 examiners, diagnostic threshold = ER. State of tooth eruption included = E/U. Intra- and inter-examiner reproducibility of clinical caries diagnosis (DFS) assessed annually by duplicate examination of 10% random sample ("error relatively small, NS difference between or within examiners")

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Within each school students were separated into groups according to sex and examiner; within each group they were listed in order of increasing DMFS, and then allotted at random to the treatments by the method of taking successive groups of three subjects from the ordered lists... in a randomised block design"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "At no time was it possible for the examiners or recorders to identify a subject with a dentifrice group.... subjects did not know what dentifrice they were using" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 46.4% in 2 years. Dropout by group: 139/788 FT, 163/788 PL. Reasons for losses: children leaving school Comment: numbers lost were unduly high for the length of follow-up. No differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants in complete randomised blocks at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (CA) cl + (ER) xr, reported at 2 years follow-up stain score Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 19.84 FT, 19.89 PL SAR: 112.42 FT, 112.58 PL DMFT: 10.39 FT, 10.39 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quotes: "At the beginning of each month, enough dentifrice was sent for the entire family" and "All siblings were placed in the same treatment group to ensure that only one dentifrice formula was sent to a home" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Fogels 1979

Methods	Trial design: 3-armed, double-blind, placebo/active-controlled RCT Location: USA Number of centres: 9 parochial elementary schools, location in USA not reported Recruitment period: study commenced in 1972
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 4.9 DFS (Gp A: 4.50 DFS; Gp B: 5.08 DFS; Gp C: 5.05 DFS). Baseline characteristics (DFS) "balanced" Age at baseline (years): range 5 to 13 years Sex: not reported, either overall or by group Any other details of important prognostic factors: background exposure to fluoride not reported Number randomised: 2218 (Gp A: 731; Gp B: 735; Gp C: 752) Number evaluated: 1339 at 3 years (present at final assessment. Gp A: 451; Gp B: 439; Gp C: 449) Attrition: 40% dropout after 3 years. Reasons for attrition described: graduations, change of residence/school, parental requests, and orthodontic treatment; no differential group losses
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = 731): SnF_2 1000 ppm F; silica gel abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 735): SnF_2 1000 ppm F; Ca pyrophosphate abrasive system; home use/unsupervised, daily frequency assumed Gp C (n = 752): placebo; silica gel abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - (CA) cl + (ER) xr; DFS (U); MD-DFS; DMFT (at 3 years) Secondary: adverse effects (proportion of children with tooth staining; oral soft tissue lesions) Assessments irrelevant to this review's scope: none Follow-up duration: 3 years
Notes	Adverse effects: "During the three years if the study, no problems with soft tissues were observed that could be attributed to participation in the study, and there was no staining of teeth" Funding source: "this investigation was supported by the Personal Products Division of the Lever Brothers Co., Edgewater, NJ" Declarations/conflicts of interest: not reported Data handling by review authors: combined 2 SnF_2 1000 groups with different abrasive systems Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (postBW) by 2 examiners, diagnostic threshold = ER. State of tooth eruption included = E/U. Results shown for each examiner and for the pooled data from both (F-ratios less than unit for examiner by treatment interactions); combined results considered

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Children were stratified according to age and sex, and randomly assigned one of the 3 dentifrices" Comment: insufficient information
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Throughout the duration of the study, the double-blind design was maintained; neither the examiners nor the hygienists had access to the identity of the dentifrice codes or to the findings of the previous examination" and "Parents were informed that the dentifrices would be assigned randomly and that their children had 1:3 chance to be assigned a non-fluoride dentifrice" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 40% in 3 years. Dropout by group: 280/731 FT 1, 296/735 FT 2, 303/752 PL Reasons for losses: graduations, change of residence/school, parental requests, and orthodontic treatment Comment: numbers lost are not unduly high for length of follow-up, with no differential loss between groups. It is unclear if reasons for the missing data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (CA) cl + (ER) xr, reported at 3 years follow-up MD-DFS DFS (U) DMFT oral soft tissues lesions (data not reported) proportion of children with tooth staining (data not reported) Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 5.69 FT 1, 6.04 FT 2, 6.04 PL FS: 2.69 FT 1, 2.30 FT 2, 2.94 PL age (months): 114.0 FT 1, 114.6 FT 2, 115.0 PL dental age: 14.93 FT 1, 15.23 FT 2, 15.09 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quotes: "To avoid assigning two different dentifrices to children in the same household, only one child per family, usually the oldest child, was used in the randomisation" "No evidence of switching dentifrices among children was found" and "Care was taken to ensure each child got the correct product" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Fogels 1988

Methods	Trial design: 2-armed, double-blind, active-controlled and stratified RCT Location: USA Number of centres: 23 parochial schools in greater Boston area, Massachusetts Recruitment period: study commenced 1981
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 3.7 DMFS (Gp A: 3.85 (SD 3.92); Gp B: 3.55 (SD 3.74)); 2.3 DMFT (Gp A: 2.36 (SD 2.06); Gp B: 2.23 (SD 2.03)). Baseline characteristics (DMFS, DMFT, sound surfaces) "balanced" (from 3 year follow-up attendees) Age at baseline (years): range 6 to 11 years, mean 9 years (Gp A: 9.36 years (SD 1.05); Gp B: 9.40 years (SD 1.09)). Baseline characteristic (age) "balanced" (from 3 year follow-up attendees) Sex: 1041 F:872 M (Gp A: 502 F:448 M; Gp B: 539 F:424 M). Baseline characteristic (sex) "balanced" (from 3 year follow-up attendees) Any other details of important prognostic factors: background exposure to fluoride in community water supply 1.0 ppm F Number randomised: 2411 (Gp A: 1200; Gp B: 1211) Number evaluated: 1913 at 3 years (present at final assessment. Gp A: 950; Gp B: 963) Attrition: 20.7% dropout (for all study groups combined) after 3 years. Reasons for attrition: withdrawal from the study or absent from final examination; no differential group losses
Interventions	**Comparison: FT versus FT** Gp A (n = 1200): SMFP 1000 ppm F; silica abrasive system; home use/supervised brushing at school, daily frequency assumed Gp B (n = 1211): SMFP 1500 ppm F; silica abrasive system; home use/supervised brushing at school, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment cl + xr; DMFT increment; proportion developing caries (at 3 years) Secondary: adverse effects Assessments irrelevant to this review's scope: none Follow-up duration: 3 years
Notes	Adverse effects: "no adverse experiences related to the dentifrices were observed throughout the course of this trial" Funding source: not reported Declarations/conflicts of interest: 2 of 5 authors employed by the product manufacturer (Lever Brothers Co, Edgewater, NJ, USA: Robert Miragliuolo and Lewis P Cancro) Data handling by review authors: n/a Other information of note: 18.8% of children had orthodontic treatment, with banded teeth excluded from the analysis and 8.4% were given sealants. 1 trained and calibrated examiner used. 10% of children randomly re-examined to assess consistency of scoring: decayed surfaces 84.7% to 88.9% consistent, filled surfaces 95.1% to 98.8% consistent

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... subjects were stratified according to age and sex and were randomly assigned to one of two fluoride dentifrices"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quote: "...double-blind study"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: attrition rate was moderate after 3 years, 21% and 21% in 1000, 1500 groups Quote: "The dropouts either withdrew from the study during the course of the trial or were absent at the third year clinical or radiographic examination" Comment: not given for each group separately
Selective reporting (reporting bias)	Low risk	Comment: results reported DMFT, DMFS, per cent caries free at 3 years
Baseline characteristics balanced?	Low risk	Comment: balance of sex, age and caries disease at baseline comparable
Free of contamination/co-intervention?	Unclear risk	Comment: possible in school brushing sessions A proportion of the subjects were fitted with sealants during the course of the study and this proportion was higher (9.6% as opposed to 7.2%) in the higher fluoride group which showed a lower caries increment

Forsman 1974

Methods	Trial design: 4-arm, double-blind, active/placebo-controlled RCT Location: Sweden Number of centres: not reported. Schools in Växjö, Sweden Recruitment period: study commenced in/before 1970
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 5.02 DMFS (Gp A: 4.53; Gp B: 4.87; Gp C: 5.57; Gp D: 5.16 DMFS). Baseline characteristic (DMFS) "balanced" Age at baseline (years): range 10 to 11 years (not reported by group) Sex: 255 F:304 M (Gp A: 64 F:73 M; Gp B: 63 F:77 M; Gp C: 62 F:75 M; Gp D: 66 F:79 M) Any other details of important prognostic factors: background weekly supervised exposure to fluoride mouthrinse (NaF 1000 ppm), continued fortnightly throughout study. Community water supply naturally fluoridated (< 0.2 ppm F) Number randomised: 681 (group numbers not reported) Number evaluated: 559 at 2 years (present at final assessment. Gp A: 137; Gp B: 140; Gp C: 137; Gp D: 145) Attrition: 18% dropout after 2 years. Reasons for attrition described with respective total numbers: change of residence/school, orthodontic treatment, did not wish to continue; no differential group losses reported (but not assessable)
Interventions	**Comparison: FT (3 groups) versus PL** Gp A (n = 137 evaluated): NaF 250 ppm; silicon dioxide abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 140 evaluated): SMFP 250 ppm; silicon dioxide system; home use/unsupervised, daily frequency assumed Gp C (n = 137 evaluated): SMFP 1000 ppm ; silicon dioxide system; home use/unsupervised, daily frequency assumed Gp D (n = 145 evaluated): placebo; silicon dioxide system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - (NCA) cl; (BLMD-DFS) cl; (MD-DFS) xr; proportion of children with new smooth surface caries (at 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 2 years
Notes	Adverse effects: "In Växjö, where type K was used, some pupils complained after a short time that they had stains on their teeth" Complainants examined, and blue-green colouring agent mostly removed. Authors report participants (and parents) understanding and cooperative throughout study irrespective of issue Funding source: materials provided by the manufacturer, Barnängen Company, Stockholm. Financial support provided by Barnängen Company, Stockholm and the Swedish patent revenue research fund (Patentmedelsfonden för odontologisk profylaxforskning) Declarations/conflicts of interest: not reported Data handling by review authors: Gps A + B (250 ppm F NaF and SMFP) combined for meta-analysis. Same trial report as Forsman 1974a, intervention differed solely according to abrasive system Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = NCA. Radiographic assessment (postBW) by 1 examiner, diagnostic threshold = ER. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "From lists for girls resp. boys in all classes each fourth child on the Vaxjo lists and each third child on the Ljungby lists was randomly selected for the respective groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The toothpaste was delivered in tubes with the word 'Toothpaste' printed in different colours. During the period of investigation, only the manufacturer knew the code" and "...study was designed as a double-blind experiment" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 17.9% (122/681) in 2 years. Dropout by group: not reported. Reasons for losses: orthodontic treatment (6), moved away (39), did not wish to continue (77) (not reported by group) Comment: numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants continuing the study up to year 2 (children completing tests)
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (NCA) cl, reported at 2 years follow-up (BLMD-DFS) cl (MD-DFS) xr proportion of children with new smooth surface caries Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 5.57 FT 1, 4.87 FT 2, 4.53 FT 3, 5.16 PL dental age: 18.89 FT 1, 19.08 FT 2, 18.66 FT 3, 19.03 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The dentifrice was distributed every second month in amounts calculated to meet the needs of the whole family, to ensure as far as possible that the participants did not have access to other toothpastes" Comment: no reported indication of contamination/co-intervention

Forsman 1974a

Methods	Trial design: 3-armed, double-blind, active/placebo-controlled RCT Location: Sweden Number of centres: not reported. Schools in Ljungby, Sweden Recruitment period: study commenced in/before 1970
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 12.90 DMFS (DMFS Gp A: 12.90; Gp B: 13.08; Gp C: 12.74). Baseline characteristic (DMFS) "balanced" Age at baseline (years): range 10 to 12 years (not reported by group) Sex: 184 F:210 M (Gp A: 59 F:71 M; Gp B: 66 F:66 M; Gp C: 59 F:73 M) Any other details of important prognostic factors: background weekly supervised exposure to fluoride mouthrinse (NaF 1000 ppm), continued fortnightly throughout study. Community water supply naturally fluoridated (< 0.2ppm F) Number randomised: 469 (group numbers not reported) Number evaluated: 394 at 2 years (present at final assessment. Gp A: 130; Gp B: 132; Gp C: 132) Attrition: 16% dropout after 2 years. Reasons for attrition described with respective total numbers: change of residence/school, orthodontic treatment, did not wish to continue; no differential group losses reported (but not assessable)
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = 130 evaluated): SMFP 250 ppm F; calcium carbonate abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 132 evaluated): SMFP 1000 ppm F; calcium carbonate abrasive system; home use/unsupervised, daily frequency assumed Gp C (n = 132 evaluated): placebo; calcium carbonate abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - (NCA) cl; (BLMD-DFS) cl; (MD-DFS) xr; proportion of children with new smooth surface caries (at 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: materials provided by the manufacturer, Barnängen Company, Stockholm. Financial support provided by Barnängen Company, Stockholm and the Swedish patent revenue research fund (Patentmedelsfonden för odontologisk profylaxforskning) Declarations/conflicts of interest: not reported Data handling by review authors: same trial report as Forsman 1974, intervention differed solely according to abrasive system Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = NCA. Radiographic assessment (postBW) by 1 examiner, diagnostic threshold = ER. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "From lists for girls resp. boys in all classes each fourth child on the Vaxjo lists and each third child on the Ljungby lists was randomly selected for the respective groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The toothpaste was delivered in tubes with the word 'Toothpaste' printed in different colours. During the period of investigation, only the manufacturer knew the code" and "... study was designed as a double-blind experiment" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 16% (75/469) in 2 years. Dropout by group: not reported. Reasons for losses: orthodontic treatment (27), moved away (22), did not wish to continue (26, not reported by group) Comment: numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants continuing the study up to year 2 (children completing tests)
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (NCA) cl, reported at 2 years follow-up (BLMD-DFS) cl (MD-DFS) xr proportion of children with new smooth surface caries Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 13.08 FT 1, 12.90 FT 2, 12.74 PL dental age: 20.72 FT 1, 21.21 FT 2, 21.24 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The dentifrice was distributed every second month in amounts calculated to meet the needs of the whole family, to ensure as far as possible that the participants did not have access to other toothpastes" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Gish 1966

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: USA Number of centres: Frankfort, Indiana, USA Recruitment period: study commenced in/before 1963
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 3.9 DMFS (Gp A: 3.99; Gp B: 3.99). Baseline characteristic (DMFS) "balanced" Age at baseline (years): range 6 to 14 years, mean 9.1 years (Gp A: 9.20; Gp B: 9.05). Baseline characteristic (age) "balanced" Sex: not reported Any other details of important prognostic factors: background exposure to fluoride in community water supply (0.9 ppm F) Number randomised: 500 (group numbers not reported) Number evaluated: 328 at 3 years (present at final assessment. Gp A: 165; Gp B: 163) Attrition: 34% dropout after 3 years (study duration = 5 years). Reasons for attrition not reported; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = 165 evaluated): SnF_2 1000 ppm F; Ca pyrophosphate abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 163 evaluated): placebo; Ca pyrophosphate abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - cl + xr; DMFT (at 1, 2, 3, 4 and 5 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 5 years
Notes	Adverse effects: not reported Funding source: Procter & Gamble, Cincinnati, USA Declarations/conflicts of interest: affiliations do not indicate immediate conflict of interests exist Data handling by review authors: examiners 1 and 2's reported assessments were pooled Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold not reported. Radiographic assessment (5 to 7 BW), diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were stratified by past caries experience and dental age, and then assigned at random to test or control groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The dentifrices were packed in plain, white, coded tubes. The code was not known by either the subjects or the examiners" and "...those in group 2 received an identical dentifrice minus the stannous fluoride" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 34, 4% (172/500) in 3 years. Dropout by group: not reported. Reasons for losses: not reported Comment: numbers lost were not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data pertain to participants present at final examinations (completing the relevant follow-up exam)
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 1, 2, 3, 4 and 5 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFMS: 3.73 FT, 4.17 PL age: 9.27 FT, 9.25 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "All of the children and their families received as much dentifrice as they wished, and no instructions were given to either group as to oral hygiene or frequency of use of either product" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Glass 1978

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: USA Number of centres: not reported. Schools in Eastern Massachusetts, USA Recruitment period: study commenced in/before 1974
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 4.1 DFS (Gp A: 3.87 DFS (SD 4.22)/2.32 DFT (SD 2.14); Gp B: 4.38 DFS (SD4.36)/2.73 DFT (SD 2.45)). Baseline characteristics (DFS, DFT) "balanced" Age at baseline (years): range 6 to 11 years, mean 9 years (Gp A: mean 108.80 months (SD 17.21); Gp B: mean 110.16 months (SD 18.29)). Baseline characteristic (age) "balanced" Sex: not reported Any other details of important prognostic factors: no background exposure to fluoride reported; community water supply naturally fluoridated < 0.1 ppm F Number randomised: 533 (group numbers not reported) Number evaluated: 346 at 3 years (present for all assessments. Gp A: 178; Gp B: 168) Attrition: 35% dropout after 3 years. Natural losses, increased during 3rd year because an entire grade graduated; exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = 178 evaluated): SMFP 1000 ppm F; Ca carbonate abrasive system; school use/supervised, 1 g applied daily (appropriate toothpastes and toothbrushes also provided for home use) Gp B (n = 168 evaluated): placebo; Ca carbonate abrasive system; school use/supervised, 1 g applied daily (appropriate toothpastes and toothbrushes also provided for home use)
Outcomes	Primary: 3-year net DFS increment - (CA) cl + (ER) xr; MD-DFS; O-BL-DFS; DFT; CIR; O-BL-CIR; MD-CIR (at 1, 2 and 3 years follow-up) Secondary: none assessed Assessments irrelevant to this review's scope: none assessed Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: Beecham Products, Inc Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment (FOTI used) by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Reversals were small in both groups (about 6% of DFS increments) and equally common (NS different)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The initial total of 533 subjects, stratified according to age and sex, were assigned at random to one of 2 groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "One group brushed with dentifrice containing MFP, the other with the same dentifrice without MFP" and "At no time during the clinical examinations or during the interpretation of the radiographs was the identity of the experimental and control group codes known to the examiner or his recorder" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 35% (187/533) in 3 years. Dropout by group: not reported. Reasons for losses: left school, exclusion based on presence at all examinations Comment: numbers lost were not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data pertain to participants present at all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (CA) cl + (ER) xr, reported at 1, 2 and 3 years follow-ups MD-DFS O-BL-DFS DFT CIR O-BL-CIR MD-CIR Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 3.87 (4.22) FT, 4.38 (4.36) PL age (months): 108.80 (17.21) FT, 110.16 (18.29) PL DFT: 2.32 (2.14) FT, 2.73 (2.45) PL SAR: 63.90 (27.63) FT, 61.63 (24.93) PL TAR: 11.30 (5.10) FT, 10.38 (4.48) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Subjects living at the same street address were assigned to the same group to avoid the presence of two dentifrices in the same household" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Glass 1983

Methods	Trial design: 3-armed, double-blind, active/placebo-controlled and stratified RCT Location: USA Number of centres: not reported Recruitment period: study commenced in 1976
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 2.1 DFS (Gp A: 2.20 DFS (SD 2.91)/1.59 DFT (SD 1.74); Gp B: 2.04 DFS (SD 2.63)/1.51 DFT (SD 1.61); Gp C: 2.09 DFS (SD 2.53)/1.61 DFT (SD 1.69)). Baseline characteristics "balanced" (for DFT/DFS) Age at baseline (years): range 7 to 11 years, mean 9 years (Gp A: 8.80 (SD 1.49); Gp B: 8.65 (SD 1.41); Gp C: 8.89 (SD 1.46)) Sex: not reported Any other details of important prognostic factors: background exposure to fluoride in naturally fluoridated community water supply (1 ppm F) Number randomised: 1017 (group numbers not reported) Number evaluated: 853 at 2.5 years (present at final assessment. Gp A: 269; Gp B: 298; Gp C: 286) Attrition: 16% dropout after 2.5 years. Natural losses; no losses due to any adverse effects; any differential group losses not assessable
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = 269 evaluated): SMFP 1000 ppm F; IMP (main abrasive) abrasive system; school use/supervised, daily (appropriate toothpastes and toothbrushes also provided for home use) Gp B (n = 269 evaluated): SMFP 1000 ppm F; Ca carbonate abrasive system; school use/supervised, daily (appropriate toothpastes and toothbrushes also provided for home use) Gp C (n = 286 evaluated): placebo; IMP (main abrasive) abrasive system; school use/supervised, daily (appropriate toothpastes and toothbrushes also provided for home use)
Outcomes	Primary: 2.5-year net DFS increment - (CA) cl + (ER) xr; DFT; CIR (at 2.5 years) Secondary: adverse effects (at 2.5 years) Assessments irrelevant to this review's scope: none assessed Follow-up duration: 2.5 years (30 months)
Notes	Adverse effects: "No side-effects were observed or reported" Funding source: partially funded by Beecham Products, Inc. Remainder of funding's source unreported Declarations/conflicts of interest: not explicitly reported, although indicated that the lead (RL Glass) author's workplace was given a grant by the product manufacturer which partially funded the study Data handling by review authors: Gps A and B (1000 ppm) combined. Of the study's 2 examiners' results, Examiner A's was used in this review's analyses: "Examiner A consistently showed higher mean values for all measures of incremental caries. However, the direction of the differences was the same for both examiners" Other information of note: clinical (VT) caries assessment by 2 examiners (independently), diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 2 examiners (independently), diagnostic threshold = ER. Results of 1 examiner chosen (findings consistent throughout)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "....within strata, subjects were assigned group codes using computer generated random permutations of the digits 1, 2 and 3"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "One group of children brushed with a control dentifrice (no NaMFP), the other groups brushed with one of the dentifrices containing NaMFP" and "The study was conducted in a double-blind basis until the results had been analysed" Comment: use of placebo described, but blind outcome assessment not described but probably done since earlier report from same author clearly describe blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 16% (164/1017) in 2.5 years. Dropout by group: not reported. Reasons for losses: change of residence or school (no losses due to any adverse effect) Comment: numbers lost were not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced between groups. Caries data pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (CA) cl + (ER) xr, reported at 2.5 years follow-up DFT CIR Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 2.20 (2.91) FT 1, 2.04 (2.63) FT 2, 2.09 (2.53) PL TAR: 11.40 (4.82) FT 1, 11.11 (4.14) FT 2, 12.20 (5.11) PL SAR: 62.65 (25.54) FT 1, 60.98 (22.27) FT 2, 66.73 (26.63) PL age: 8.80 (1.49) FT 1, 8.65 (1.41) FT 2, 8.89 (1.46) PL DFT: 1.59 (1.74) FT 1, 1.51 (1.61) FT 2, 1.61 (1.69) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Sufficient dentifrice was provided for home use by the entire family in order to minimize the chance of use of other than the dentifrice provided" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Hanachowicz 1984

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: France Number of centres: 42 schools (33 primary, 7 secondary, 2 independent) across 9 suburbs in the Villefranche/Saone Lyon area, France Recruitment period: study commenced in 1979
Participants	Inclusion criteria: not reported Exclusion criteria: surfaces covered by orthodontic bands Baseline caries: 5.39 DMFS (Gp A: 5.36; Gp B: 5.43). Baseline characteristic (DMFS) "balanced" Age at baseline (years): range 10 to 12 years Sex: not reported Any other details of important prognostic factors: no background exposure to fluoride reported. Median natural fluoride level of community water supply 0.8 ppm F (range 0.07 to 0.28 ppm F) Number randomised: 1318 (Gp A: 659; Gp B: 659) Number evaluated: 945 at 3 years (present and cooperative at final assessment. Gp A: 473; Gp B: 472) Attrition: 28% dropout after 3 years. Natural losses and exclusions based on compliance (analysis based on 945 co-operative children from 1061 who completed a final examination); no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 659): SMFP 1500 ppm F; Al oxide trihydrate abrasive system; home use/unsupervised, daily frequency assumed Gp B (n = 659): placebo; Al oxide trihydrate abrasive system; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DMFS increment - (E) (CA) cl + xr; DMFS (U); O-DMFS; MD-DMFS; BL-DMFS; premolar DMFS; DMFT; premolar DMFT; proportion of children with new caries (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: indicated for dropouts only and distribution between groups not reported: unacceptable taste n = 5; unacceptable abrasivity n = 1 Funding source: provided by toothpaste manufacturer, Elida Gibbs Declarations/conflicts of interest: not reported, although singular author employed by French Union for Oral Health Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA; radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included = E/U. Consistency of clinical and x-ray diagnosis assessed by duplicate examinations of 6% sample (inter-examiner reproducibility ratios 0.24 for clinical and 0.13 for x-ray; intra-examiner reproducibility 0.27 for clinical and 0.14 for x-ray)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After baseline examination, the children were stratified with regard to their examiner, caries experience..... Each child was then randomly allocated to the test or toothpaste group. In order that only one type of toothpaste was used in each household an exception was made where two children from one household were participating ... it was arranged for them to have the same toothpaste" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Neither the subjects nor the examiners knew who was receiving the test or the control toothpaste" and "The control toothpaste was without sodium monofluorophosphate" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 19.5% in 3 years. Dropout by group: 186/659 FT, 185/659 PL. Reasons for losses: family moved away (116), lack of co-operation (42) (by not brushing at least 5 times a week), refusal from final examination (30), refused consent for examination (21), moved to boarding school (18), discontinued (11), family difficulties (6), unacceptable taste of toothpaste (equally divided between groups (5)), illness (2), lost to follow-up (2), unacceptable abrasivity of toothpaste (not reported by group (1)) Comment: numbers lost were not unduly high for length of follow-up, and showed no differential loss between groups. It is unclear if reasons for missing data are acceptable and balanced between groups. Caries data pertain to participants present and co-operative at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (E) (CA) cl + xr, reported at 3 years follow-up DMFT DMFS (U) O-DMFS MD-DMFS BL-DMFS premolar DMFT premolar DMFS proportion of children with new caries Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 5.36 FT, 5.43 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quotes: "In order that only one type of toothpaste was used in household, an exception was made where two children from one household were participating in the trial... it was arranged for them to have the same toothpaste" and "The distribution of the toothpastes was the responsibility of three ladies...Their duty was to visit each home every 5 weeks to supply the whole family with sufficient amounts of toothpaste. This was considered important to prevent the use of other commercial toothpastes" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Held 1968

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: France Number of centres: 1, Les Vaux Recruitment period: study commenced in 1962
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 14.3 DMFS (Gp A: 16.9 DMFS/7.9 DMFT; Gp B: 11.7 DMFS/5.7 DMFT). Baseline characteristics (DMFS, DMFT) not balanced Age at baseline (years): range 15 to 16 years Sex: all male Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 178 (Gp A: 86; Gp B: 92) Number evaluated: 63 at 3 years (present at final assessment. Gp A: 32; Gp B: 31) Attrition: 65% dropout after 3 years (study duration = 3 years). Reasons for high dropout due to age range at which many leave the institutions; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 86): NaF-SnF_2 1000 ppm F; abrasive system: not clearly specified (silica used); institution use/supervised, twice a day Gp B (n = 92): placebo; abrasive system: not clearly specified (silica used); institution use/supervised, twice a day
Outcomes	Primary: 3-year DMFS increment - (E) cl; DMFT (at 3 years); annual CAR Secondary: none reported Assessments irrelevant to this review's scope: none Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported; state of tooth eruption included = E. Intra-examiner reproducibility checks done

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...distributed at random to 2 groups" Comment: translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "Double blind study" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Low risk	Overall dropout for length of follow-up: 64.6% in 3 years. Dropout by group: 54/86 FT, 61/92 PL. Reason for losses: participants leaving school (due to age range at which many leave the institutions) Comment: numbers lost are unduly high for length of follow-up. Although no differential losses between groups are apparent and the only reason given for the missing data is acceptable and balanced between groups, this balance may have occurred by chance, because sample size is too small. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Unclear risk	Outcomes reported: DMFS increment - (E) cl, reported at 3 years follow-up DMFT annual CAR Comment: trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	High risk	Prognostic factors reported: DMFS: 16.9 FT, 11.7 PL DMFT: 7.9 FT, 5.7 PL Comment: initial caries (DMFS) appears imbalanced
Free of contamination/co-intervention?	Unclear risk	Translation of report not detailed enough to make a categorical decision regarding any contamination/co-intervention

Held 1968a

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: France Number of centres: 1, Thiais Recruitment period: study commenced in 1961
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 9.6 DMFS (Gp A: 11.0 DMFS/5.6 DMFT; Gp B: 8.0 DMFS/4.6 DMFT). Baseline characteristics (DMFS, DMFT) not balanced Age at baseline (years): range 15 to 16 years Sex: all males Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 101 (Gp A: 52; Gp B: 49) Number evaluated: 36 at 3 years (present at final assessment. Gp A: 19; Gp B: 17) Attrition: 64% dropout after 3 years (study duration = 3 years). Reasons for high dropout due to age range at which many leave the institutions; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 52): NaF-SnF_2 1000 ppm F; abrasive system: not clearly specified (silica used); institution use/supervised, twice a day Gp B (n = 49): placebo; abrasive system: not clearly specified (silica used); institution use/supervised, twice a day
Outcomes	Primary: 3-year DMFS increment - (E) cl; DMFT (at 3 years); annual CAR Secondary: none reported Assessments irrelevant to this review's scope: none Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner; diagnostic threshold not reported; state of tooth eruption included = E. Intra-examiner reproducibility checks done

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...distributed at random to 2 groups" Comment: translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "Double blind study" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Low risk	Overall dropout for length of follow-up: 64.4% in 3 years. Dropout by group: 33/52 FT, 32/49 PL. Reasons for losses: participants leaving school (due to age range at which many leave the institutions) Comment: numbers lost are unduly high for length of follow-up. Although no differential losses between groups are apparent and the only reason given for the missing data is acceptable and balanced between groups, this balance may have occurred by chance, because sample size is too small. Caries data used in analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Unclear risk	Outcomes reported: DMFS increment - (E) cl, reported at 3 years follow-up DMFT annual CAR Comment: trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	High risk	Prognostic factors reported: DMFS: 11.0 FT, 8.0 PL DMFT: 5.6 FT, 4.6 PL Comment: initial caries (DMFS) appears imbalanced
Free of contamination/co-intervention?	Unclear risk	Translation of report not detailed enough to make a categorical decision regarding any contamination/co-intervention

Held 1968b

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: France Number of centres: 1 Recruitment period: study commenced in 1961
Participants	Inclusion criteria: males born in 1944, 1945 and 1946 and residing in French institution (Meudon) Exclusion criteria: not reported Baseline caries: 10.2 DMFS (Gp A: 13.7 DMFS/7.1 DMFT; Gp B: 7.0 DMFS/4.3 DMFT). Baseline characteristics (DMFS, DMFT) not balanced Age at baseline (years): mean 15 years Sex: all male Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 85 (Gp A: 44; Gp B: 41) Number evaluated: 32 at 2 years[a] (present at interim 2-year assessment. Gp A: 14; Gp B: 18) Attrition: 62% dropout after 2 years (study duration = 3 years). Reasons for high dropout due to age range at which many leave the institutions; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 44): NaF 500 ppm F; abrasive system: not clearly specified (silica used); institution use/supervised, twice a day Gp B (n = 41): placebo; abrasive system: not clearly specified (silica used); institution use/supervised, twice a day
Outcomes	Primary: 2-year[a] DMFS increment - (E) cl; DMFT (reported at 2 and 3 years follow-up) Secondary: none reported Assessments irrelevant to this review's scope: annual CAR Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: [a]results for 3 years follow-up not considered due to very high dropout rate Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported; state of tooth eruption included = E. Intra-examiner reproducibility checks done

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...distributed at random to 2 groups" Comment: translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "double blind study" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	High risk	Overall dropout for length of follow-up: 62.4% in 2 years. Dropout by group: 30/44 FT, 23/41 PL. Reasons for losses: participants leaving school Comment: numbers lost are unduly high for length of follow-up, with differential losses between groups (68%, 56%). Reasons for the missing data are not balanced between groups. Caries data used in analysis pertain to participants present at each examination
Selective reporting (reporting bias)	Unclear risk	Outcomes reported: DMFS increment - (E) cl, reported at 2 years follow-up DMFT annual CAR Comment: trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	High risk	Prognostic factors reported: DMFS: 13.7 FT, 7.0 PL DMFT: 7.1 FT, 4.3 PL Comment: initial caries (DMFS) appears imbalanced
Free of contamination/co-intervention?	Unclear risk	Translation of report not detailed enough to make a categorical decision regarding any contamination and/or co-intervention

Hodge 1980

Methods	Trial design: 4-armed, double-blind, placebo/active-controlled and stratified RCT Location: UK Number of centres: 6 schools in North-West England, UK Recruitment period: study commenced in/before 1976
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 7.3 DMFS (Gp A: DMFS 6.97 (SD 4.91)/DMFT 4.40 (SD 2.84); Gp B: DMFS 7.81 (SD 5.76)/DMFT 4.82 (SD 3.02); Gp C: DMFS 7.63 (SD 6.23)/DMFT 4.62 (SD 3.12); Gp D: DMFS 6.93 (SD 4.59)/DMFT 4.37 (SD 2.62)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 11 to 12 years Sex: 391 F:408 M (Gp A: 94 F:100 M; Gp B: 100 F:100 M; Gp C: 96 F:107 M; Gp D: 101 F:101 M) Any other details of important prognostic factors: no background exposure to fluoride reported. Natural fluoride level of community water supply 0.8 ppm F Number randomised: 979 (group numbers not reported) Number evaluated: 799 at 3 years (present at final assessment. Gp A: 194; Gp B: 200; Gp C: 203; Gp D: 202) Attrition: 18% dropout after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers: 158 left school, 14 withdrawn by own choice, 8 lack of co-operation; any differential group losses not assessable
Interventions	**Comparison: FT (3 groups) versus PL** Gp A (n = 194 evaluated): SMFP 1000 ppm F; alumina abrasive system; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use) Gp B (n = 200 evaluated): SMFP-NaF 1450 ppm F; alumina abrasive system; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use) Gp C (n = 203 evaluated): SMFP-NaF 1450 ppm F; dicalcium phosphate abrasive system; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use) Gp D (n = 202 evaluated): placebo; abrasive system: alumina abrasive system; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use)
Outcomes	Primary: 3-year net DFS increment - (E) (CA) cl + (DR) xr; DMFT (at 3 years) Secondary: not assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: supported by grant from manufacturer, Colgate Palmolive Ltd Declarations/conflicts of interest: not reported Data handling by review authors: Gps B and C (1450 ppm F groups) pooled in analyses Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U; radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = DR. Reproducibility checks done in 10% sample clinically and radiographically (ICC of incremental data between 0.92 and 0.97)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Following the initial baseline examination, subjects were stratified according to school and sex, and randomly assigned to 1 of 4 groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "The trial was double-blind, neither the subjects nor the examiner knew who was receiving test or control products. The test and control dentifrices were indistinguishable in taste and appearance" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 18.4% (180/979) in 3 years. Dropout by group: not reported. Reasons for losses: changing school (184), moving away, withdrawal from study (14), exclusion due to lack of co-operation (7) Comment: numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if 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: DFS increment - (E) (CA) cl + (DR) xr, reported at 3 years follow-up DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFT: 4.82 (3.02) FT 1, 4.62 (3.12) FT 2, 4.40 (2.84) FT 3, 4.37 (2.62) PL DMFS: 7.81 (5.76) FT 1, 7.63 (6.23) FT 2, 6.97 (4.91) FT 3, 6.93 (4.59) PL SAR: 90.61 (20.13) FT 1, 88.05 (22.00) FT 2, 90.00 (22.95) FT 3, 87.09 (22.36) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Dentifrices were used daily in school, either immediately following morning or afternoon registration, the children being under the care of brushing supervisors" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Howat 1978

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: UK Number of centres: single mobile dental unit visiting 2 secondary comprehensive schools in North-West England, UK Recruitment period: study commenced in/before 1974
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 7.4 DMFS (Gp A: 7.42 DMFS (SD 5.92)/4.63 DMFT (SD 3.32); Gp B: 7.37 DMFS (SD 5.59)/4.65 DMFT (SD 3.17)) (evaluated participants only). Baseline characteristics (DMFS, DMFT, SAR) "balanced" Age at baseline (years): range 11 to 12 years (group distribution not reported) Sex: distribution not reported Any other details of important prognostic factors: no background exposure to fluoride reported (community water supply suboptimally fluoridated (0.15 ppm F)) Number randomised: 560 (Gp A: 279; Gp B: 281) Number evaluated: 495 at 3 years (present at final assessment. Gp A: 253; Gp B: 242) Attrition: 12% dropout after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers (56 left school, 7 withdrawn by own choice, 2 lack of co-operation); no differential dropout - 65 failed to complete the trial, 39 in placebo group and 26 in fluoride group
Interventions	**Comparison: FT versus PL** Gp A (n = 279): SMFP 1000 ppm F; abrasive system: silica zerogel; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use) Gp B (n = 281): placebo; abrasive system: silica zerogel; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use)
Outcomes	Primary: 3-year net DMFS increment - (E) (CA) cl + (DR) xr; anterior DMFS; posterior DMFS; PF-DMFS; MD-DMFS; MD-BL-DMFS; DMFT (at 8 months, 2 years, 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: Colgate-Palmolive Ltd Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U; radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = DR. Reproducibility checks done in 10% sample clinically and radiographically (ICC of incremental data between 0.96 and 0.99)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were randomly allocated to test and control groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "The trial was double-blind with neither the subjects nor the examiner being aware who was receiving test or control products..... dentifrices were indistinguishable in taste and appearance and their composition varied only in their fluoride content" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 11.6% (in 3 years). Dropout by group: 26/279 FT, 39/281 PL. Reasons for losses: changing school (56), withdrawal from study by choice (7), exclusion due to lack of co-operation (2) Comment: numbers lost were not unduly high for the length of follow-up, with no differential losses between groups. It is unclear if 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: DMFS increment - (E) (CA) cl + (DR) xr, reported at 3 years follow-up anterior DMFS posterior DMFS PF-DMFS MD-DMFS MD-BL-DMFS DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 7.42 (5.92) FT, 7.37 (5.59) PL DMFT: 4.63 (3.32) FT, 4.65 (3.17) PL SAR: 93.48 (19.74) FT, 92.81 (21.52) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Active and control dentifrices were used daily at school ... under the care of brushing supervisors... subjects were also given liberal supplies of the same dentifrice for home use.... and independent checks of the dispensed dentifrices were carried out at regular intervals to assess the accuracy of the trial supervisors" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Jackson 1967

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: UK Number of centres: 8 grammar schools in West Riding of Yorkshire, Leeds Recruitment period: study commenced 1962
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 8.7 DMFS (Gp A: 8.42 DMFS/5.39 DMFT; Gp B: 8.93 DMFS/5.71 DMFT). Baseline characteristics (DMFS, DMFT, TAR) "balanced" Age at baseline (years): range 11 to 12 years (Gp A: 11.7 years; Gp B: 11.7 years). Baseline characteristic (age) "balanced" Sex: 466 F:520 M (Gp A: 235 F:259 M; Gp B: 231 F:261 M) Any other details of important prognostic factors: no background exposure to fluoride reported Number randomised: 986 (Gp A: 494; Gp B:492) Number evaluated: 871 at 3 years (present at final assessment. Gp A: 438; Gp B: 433) Attrition: 12% dropout rate after 3 years (study duration = 3 years). Natural losses; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 494): SnF_2 1000 ppm F; abrasive system: dicalcium pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 492): placebo; abrasive system: dicalcium pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - (E + U) (CA) cl; DMFT; proportion of caries-free teeth/surfaces (by tooth type/ surface type) which developed caries (at 3 years) Secondary: adverse effects (proportion of children who complained of tooth staining) (at 3 years) Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: Gp A: mouth prevalence of staining: 234% increase in girls, 152% increase in boys; tooth prevalence of staining: 140% increase in girls, 78.4% increase in boys. Not reported for Gp B. Complaints due to stain: Gp A: n = 11; Gp B: n = 4. "Of those complaining of stain, only 9 withdrew from the trial for this reason." Distribution of dropouts not reported Funding source: Procter & Gamble grant to University of Leeds Declarations/conflicts of interest: not specifically reported; however, both authors employed by Procter & Gamble's grant recipient, University of Leeds Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Consistency of clinical diagnosis maintained by re-examination of 10% sample and calibration checks made against reserve examiner

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Method used was stratification according to sex, age and school..... Age was calculated to a standard date... boys were paired according to age so that 2 groups were obtained in which mean age and distribution of age was as identical as possible. A coin toss determined whether the group should be nominated O and N"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "The two groups were called O and N respectively. Whereas it was not known at the time which group was the control and which was the experimental group, it is now known that group O was that which received the stannous fluoride dentifrice" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 12% in 3 years. Dropout by group: 56/494 FT, 59/492 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if the reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (E + U) (CA) cl, reported at 3 years follow-up DMFT proportion of caries-free teeth/surfaces (by tooth type/surface type) which developed caries proportion of children who complained of tooth staining Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 8.42 (5.36) FT, 8.93 (5.87) PL DMFT: 5.43 FT, 5.14 PL age: 11.7 FT, 11.7 PL treatment index: 65 % FT, 64% PL TAR: 17.74 FT, 17.46 PL staining: 19.9 FD, 18.7 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The duties of the home visitors were to provide a continuous supply of toothpaste to each home for each member of the family... to encourage co-operation..." Comment: there is sufficient indication overall of prevention of contamination/co-intervention

James 1967

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: UK Number of centres: 11 schools (5 grammar/high schools; 6 county secondary schools), Buckinghamshire Recruitment period: study commenced in 1962
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 11 DFS (Gp A: 10.73 DFS and DMFS; Gp B: 11.32 DFS and DMFS). Baseline characteristics (DFS, DFT, DMFS, DMFT) "balanced" Age at baseline (years): range 11 to 12 years (Gp A: 11.35 years; Gp B: 11.35 years). Baseline characteristic (age) "balanced" Sex: 518 F:525 M (Gp A: 268 F:262 M; Gp B: 250 F:263 M) Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 1043 (Gp A: 530; Gp B: 513) Number evaluated: 803 at 3 years (present at final assessment. Gp A: 406; Gp B: 397) Attrition: 23% dropout rate after 3 years (study duration = 3 years). Reasons for dropout described with respective total numbers: moved away, unco-operative, not present on examination day, disliked toothpaste, staining of teeth, others; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 530): SnF_2 1000 ppm F; abrasive system: dicalcium pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 513): placebo; abrasive system: dicalcium pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DFS increment - (E) (CA) cl + (ER) xr; DFT; DMFS; DMFT; posterior MD-DFS (at 3 years) Secondary: adverse effects (proportion of children who complained of tooth staining) (at 3 years) Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: "Proportions of children with dark stain increased in all groups and the increase was significantly larger in test group children" Funding source: study funded by Procter & Gamble and "financial contribution from the Royal Dental Hospital Endowments Fund for the purchase of a counter-sorter" Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "These children were divided, by sex and by school, into 2 groups, using a random number technique for designation into groups. Each school therefore contained approximately equal numbers of test and control children, with similar representation of boys and girls"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Children in the test group were supplied with stannous fluoride... dentifrice, while the control dentifrice was identical in colour, texture and flavour" and "Nobody involved in the study, except the manufacturers, knew the identity of the test dentifrice, and the double-blind technique was maintained throughout the investigation" and "All radiographs were read by one of us at the end of the study without knowledge of group allocation" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 23% in 3 years. Dropout by group: 124/530 FT, 116/513 PL. Reasons for losses: moved away (59 FT, 59 PL), unco-operative (31 FT, 24 PL), not present on examination day (27 both groups), disliked toothpaste (3 FT, 2 PL), staining of teeth (2 FT, 2 PL), others (18 FT, 13 PL) Comment: numbers lost were not unduly high given the length of follow-up with no differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced between groups. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (E) (CA) cl + (ER) xr, reported at 3 years follow-up DMFS DFT DMFT posterior MD-DFS proportion of children with tooth staining Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 10.73 FT, 11.32 PL age: 11.35 FT, 11.35 PL DFS: 10.73 FT, 11.32 PL DFT: 6.12 FT, 6.48 PL DMFT: 6.12 FT, 6.48 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "It was decided to supply the whole of the subject's family with the appropriate dentifrice to reduce the risk of other brands being used during the test period" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

James 1977

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: UK Number of centres: 12 schools in Shropshire Recruitment period: study commenced in 1970
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 11.2 DMFS (Gp A: 11.0 DMFS; Gp B: 11.4 DMFS). Baseline characteristic (DMFS) "balanced" Age at baseline (years): range 11 to 12 years (Gp A: mean 11.9 years; Gp B: mean 12.0 years). Baseline characteristic (age) "balanced" Sex: randomised 490 F:474 M; evaluated 397 F:385 M (Gp A: 204 F:199 M; Gp B: 193 F:186 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: data unavailable for site fluoridation status Number randomised: 964 (group distribution not reported) Number evaluated: 782 at 3 years (present at all assessments. Gp A: 403; Gp B: 379) Attrition: 19% dropout after 3 years (study duration = 3 years). Reasons for attrition not reported; exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 403): SMFP 2400 ppm F; abrasive system: Al oxide trihydrate; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 379): placebo; abrasive system: Al oxide trihydrate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - (CA) cl + (ER) xr; posterior MD-DMFS; O-DMFS; BL-DMFS; O-BL-MD-DMFS; anterior DMFS (at 3 years) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: "supported by a grant from the Unilever Research Laboratories" Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA; radiographic assessment (2 postBW); state of tooth eruption included not reported. Inter- and intra-examiner reliability for clinical and radiographic diagnosis revealed by re-examination of 10% sample

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After baseline examination, they were stratified by sex, school and level of caries experience and randomly allocated to one or other of two groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "... one of the groups was supplied with the dentifrice containing fluoride, while the other received the paste without it. The two dentifrices were identical in taste, appearance and texture, and the trial was conducted on a double-blind basis" and "After the analysis the code was broken...." Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 18.9% (182/964) in 3 years. Dropout by group: not reported. Reasons for losses: exclusion due to absence from any examination Comment: numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants who took part in all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (E + U) (CA) cl, reported at 3 years follow-up posterior MD-DMFS O-DMFS BL-DMFS O-BL-MD-DMFS anterior DMFS proportion of caries-free teeth/surfaces (by tooth type/ surface type) which developed caries proportion of children who complained of tooth staining Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 11.0 FT, 11.4 PL mean age: 11.9 FT, 12.0 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Unclear risk	Quote: "The appropriate pastes were distributed by home visitors to the children's homes... they were not instructed to supervise or monitor the usage of the paste" Comment: not enough information provided

Jensen 1988

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: USA Number of centres: not reported Recruitment period: study commenced in 1986
Participants	Inclusion criteria: ≥ 54 years old; ≥ 10 natural teeth; residing in non-fluoridated community Exclusion criteria: current fluoride treatment receipt; current antibiotic use; severe periodontal disease Baseline caries: 53.35 DMFS (Gp A: 53.1 DMFS (SD 19.84); Gp B: 53.6 DMFS (SD 19.40). Baseline characteristic (DMFS) "balanced" Age at baseline (years): 54 to 93 years (Gp A: mean 68.63; Gp B: mean 68.50). Baseline characteristic (age) "balanced" Sex: 510 F:300 M (Gp A: 254 F:150 M; Gp B: 256 F:150 M) (evaluated participants only). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: conducted in a non-fluoridated area (exclusion criteria: water fluoride content in home > 0.3 ppm F) Number randomised: 913 (group distribution not reported) Number evaluated: 810 at 1 year (present at final assessment. Gp A: 404; Gp B: 406) Attrition: 11% dropout after 1 year (study duration = 1 year). Reasons for dropout given. Dropouts not reported by group so unable to state whether differential dropout occurred
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 404): SnF 1100 ppm F; abrasive system: not reported; home use (unsupervised) twice daily Gp B (n = evaluated 406): placebo; abrasive system: not reported; home use (unsupervised) twice daily
Outcomes	Primary: 1-year DMFS increment - cl + xr; DMFS coronal; DFS root (at 1 year) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1 year
Notes	Adverse effects: not reported Funding source: Procter & Gamble Company and Center for Clinical Studies, College of Dentistry, University of Iowa, USA Declarations/conflicts of interest: institutional affiliations reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment according to Radike criteria, number of examiners not reported, diagnostic threshold not reported. Radiographic caries assessment (BW) on posterior interproximal surfaces. No data reported on number of examiners or intra/ inter-examiner agreement

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Within strata, subjects were assigned to treatment groups by random permutations of 2" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	Quote: "The groups were assigned at the examination site, using a programmed portable computer…" Comment: not enough information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "Neither the subjects nor the research staff members were aware of the group to which any subject had been assigned. Test and control dentifrices were identical except for the fluoride content" Comment: blinded
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "This attrition was essentially random" Comment: overall dropout for length of follow-up: 11% in 1 year. Dropout by group not stated. Reasons for losses not explicitly reported. Cannot establish whether differential loss between groups as number randomised at baseline not reported. It is unclear if reasons for missing outcome data are acceptable and balanced
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 1 year follow-up DMFS coronal DFS root Comment: trial protocol not available. All expected outcomes were reported and were reported in the usual way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: age, sex, baseline coronal DMFS and root DFS Comment: prognostic factors appear balanced
Free of contamination/co-intervention?	Low risk	Quotes: "Cohabitants were assigned by the computer to the same group to eliminate the chance of their accidentally using the wrong dentifrice" and "Subjects were instructed to… desist from use of their regular dentifrice during the study period" Comment: contamination and co-intervention reduced

Kinkel 1972

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: Switzerland Number of centres: 37 elementary school classes from the Basel-Landschaft canton Recruitment period: study commenced in/before 1969
Participants	Inclusion criteria: children 10 years of age Exclusion criteria: not reported Baseline caries: 2.2 DMFS (Gp A: 2.21 DMFS; Gp B: 2.29 DMFS). Baseline characteristic (DMFS) "balanced" Age at baseline (years): mean 10 years (age by group not reported) Sex: not reported (age by group not reported) Any other details of important prognostic factors: background exposure to fluoride not reported Number randomised: 927 (group numbers not reported) Number evaluated: 699 at 3 years (Gp A: 354; Gp B: 345) Attrition: 25% dropout rate after 3 years (study duration = 7 years). Reasons for dropout not described; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 354): SMFP F concentration not reported; abrasive system: not reported; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 345): placebo; abrasive system: not reported; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - (CA) cl + (DR) xr (at 1, 2, 3, 4, 5 and 7 years) Secondary: none assessed Assessments irrelevant to this review's scope: none Follow-up duration: 7 years
Notes	Adverse effects: incidence of metabolic disorders measured. No events reported Funding source: toothpaste was provided by Mibelle AG, Kasmetik und Seifenfabrik der Migros Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (V) caries assessment, diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW), diagnostic threshold = DR and ER

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... randomly allocated" Comment: translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "double blind study" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 24.6% (228/927) in 3 years. Dropout by group: not reported. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if 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)	Unclear risk	Outcomes reported: DMFS increment - (CA) cl + (DR) xr, reported at 1, 2, 3, 4, 5 and 7 years follow-ups Comment: trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 2.21 FT, 2.29 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Unclear risk	Translation of report not detailed enough to make a categorical decision regarding any contamination/co-intervention

Kleber 1996

Methods	Trial design: [a]3-armed, double-blind, placebo-controlled and stratified RCT Location: USA Number of centres: 3 rural elementary schools in North-Central Indiana Recruitment period: study commenced in/before 1994
Participants	Inclusion criteria: children lacking dental care and caries-susceptible; good general health; no serious medical condition/transmissible diseases Exclusion criteria: absence of dmfs/t/DMFS/T; undergoing orthodontic treatment Baseline caries: 4.2 DMFS (Gp A: 4.38 DMFS (SD 5.35)/2.81 DMFT (SD 2.81); Gp B: 3.95 DMFS (SD 4.53)/2.73 DMFT (SD 2.58)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 10 to 11 years, mean 10.7 years (Gp A: 10.7 years; Gp B: 10.6 years). Baseline characteristic (age) "balanced" Sex: Gp A: 42 M:45 F; Gp B: 42 M:45 F. Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: no background exposure to fluoride reported. Community water supplies < 0.4 ppm F; request to dentists in area not to apply topical fluoride to study population children Number randomised: 174 (Gp A: 87; Gp B: 87) Number evaluated: 156 at 1 year (present at final assessment. Gp A: 77; Gp B: 79) Attrition: 10% dropout after 1 year (study duration = 1 year). Main reasons for attrition: changes in residence, few exclusions for initiation of orthodontic treatment; no differential group losses
Interventions	**Comparison: FT (+ Al rinse) versus PL (+ Al rinse)[b]** Gp A (n = 87): NaF 1100 ppm F; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp B (n = 87): placebo; abrasive system: silica; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 1-year DMFS increment - (CA) cl + (ER) xr; DMFT; proportion of children with new DMFS; proportion of children remaining caries free (at 6 months, 1 year) Secondary: adverse effects (oral soft tissues lesions) (at 6 months, 1 year) Assessments irrelevant to this review's scope: compliance Follow-up duration: 1 year
Notes	Adverse effects: "No adverse oral effects attributable to any treatment regimens were observed during the study. Due to the low incidence of soft tissue aberrations in this population, the soft tissue findings are not presented" Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: results of 1 examiner chosen (findings consistent throughout). [a]Third trial arm (fluoride toothpaste and no mouthrinse) excluded from this review due to no eligible comparator arm. [b]Rinsing with 500 ppm Al solutions performed daily at school in both relevant groups compared. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (postBW) by 2 examiners (independently), diagnostic threshold = ER. Reversals were small in both groups and equally common

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects with evidence of caries activity were stratified according to age, sex... then randomly assigned to one of the balanced groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "A double blind comparison of three parallel groups of children... who used a test or placebo dentifrice for a twelve month period" and "Radiographs were scored independently by each examiner at a later date.." Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Low risk	Overall dropout for length of follow-up: 10% in 1 year. Dropout by group: 10/87 FT, 8/87 PL. Reasons for losses: changes in residence, exclusion based on orthodontic treatment Comment: numbers lost were not unduly high given the length of follow-up with no differential losses between groups. Reasons for the missing outcome data are acceptable. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (CA) cl + (ER) xr, reported at 6 months and 1 year follow-ups DMFT proportion of children remaining caries free proportion of children with new DMFS oral soft tissues lesions Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 5.06 (0.58) FT, 4.78 (0.50) PL DMFT: 3.31 (0.32) FT, 3.32 (0.27) PL Age: 10.7 FT, 10.6 PL Sex: 42 M, 45 F (FT); 42 M, 45 F (PL). Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "Sufficient quantities of the respective products were provided for the participants and their families to use throughout the study. Participants with the same telephone number or address were assigned to the same group to avoid confusion with different test products in the same household" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Koch 1990

Methods	Trial design: 5-armed, double-blind, active-controlled and stratified RCT Location: Iceland Number of centres: 7 elementary schools, Reykjavik Recruitment period: study commenced in 1983
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 9.9 DFS (Gp A: 9.9 DMFS (SD 7.0); Gp B: 10.6 DMFS (SD 7.2); Gp C: 9.7 DMFS (SD 6.5); Gp D: 9.3 DMFS (SD 6.4); Gp E: 10.2 DMFS (SD 7.4). Baseline characteristic (DFS) "balanced" Age at baseline (years): range 11 to 12 years (group distribution reported by year of birth 1971/2). Baseline characteristic (age) "balanced" Sex: 587 F:559 M (Gp A: 113 F:116 M; Gp B: 114 F:115 M; Gp C: 113 F:116 M; Gp D: 133 F:101 M; Gp E: 114 F:111 M). Baseline characteristics (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride in community water supply < 0.1 ppm F Number randomised: 1161 (Gp A: 231; Gp B: 232; Gp C: 231; Gp D: 237; Gp E: 230) Number evaluated: 1035 at 3 years (present at final assessment. Gp A: 203; Gp B: 209; Gp C: 209; Gp D: 211; Gp E: 203) Attrition: 10.9% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: relocation, compliance, others; no differential group losses
Interventions	**Comparison: FT versus FT (5 groups)[a]** Gp A (n = 231): 250 ppm NaF (no anti-calculus agent); abrasive system: silica; home use/unsupervised, daily frequency assumed Gp B (n = 232): 940 ppm F SMFP (no anti-calculus agent); abrasive system: $CaHPO_4 2H_2O$; home use/unsupervised, daily frequency assumed Gp C (n = 231): 970 ppm F NaF (no anti-calculus agent); abrasive system: silica; home use/unsupervised, daily frequency assumed Gp D (n = 237): 980 ppm F NaF (anti-calculus agent AHBP); abrasive system: silica; home use/unsupervised, daily frequency assumed Gp E (n = 230): 940 ppm F NaF (anti-calculus agent AHBP); abrasive system: silica; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment cl + xr; DFS increment by surface; DFT increment; new lesions only and restorations (at 3 years) Secondary: adverse effects Assessments irrelevant to this review's scope: gingival health (gingival bleeding index); compliance Follow-up duration: 3 years
Notes	Adverse effects: "Adverse experiences were only noted [sic] one occasion when a child, belonging to [Gp D], claimed an allergic reaction to the dentifrice and was withdrawn from the study" Funding source: Henkel KGaA, manufacturer of experimental toothpaste Declarations/conflicts of interest: manufacturer engaged in funding the study, administration support of study: "The authors gratefully acknowledge... the financial, administrative and scientific support of Henkel KGaA, Düsseldorf, FRG" Data handling by review authors: [a]1000 ppm F groups combined for analysis Gps B + C versus Gp A. Groups with anti-calculus agents excluded from analysis (Gps D and E) Other information of note: clinical examinations performed by 2 examiners. Prior to each exam, both dentists examined 20 of their assigned children at random who were re-examined at least 1 day later to gauge consistency. ICC of at least 0.75 for acceptable reliability but exact values not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " ...randomly assigned to one of five treatment groups"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "...unsupervised double-blind study" and "...dentifrices were purchased and refilled in laminated tubes to ensure dentifrices were identical"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: reasons for attrition stated. Attrition rate was low after 3 years, 11% overall and similar in all toothpaste groups. Query compliance as reason for withdrawal and this negates ITT analysis, although only 23/1146 (2%) withdrew or were withdrawn for this reason
Selective reporting (reporting bias)	Low risk	Comment: results reported DFT, DFS, on different surface types
Baseline characteristics balanced?	Low risk	Comment: balance of age, sex, DFS
Free of contamination/co-intervention?	Unclear risk	Comment: insufficient information

Lima 2008

Methods	Trial design: 2-armed, single-blind, active-controlled RCT Location: Brazil Number of centres: single public day nursery, São Luis Recruitment period: study commenced in/before 2006
Participants	Inclusion criteria: low-income public nursery attendees Exclusion criteria: not reported Baseline caries: 5.1 "cavities" (Gps A + B caries inactive; Gp C: 2.5 ANC (SD 1.5); Gp D: 5.3 ANC (SD 6.5)). Baseline characteristic (caries status) "balanced" (evaluated participants only) Age at baseline (years): range 2 to 4 years, mean 3.3 years (Gp A: 3.3 years; Gp B 3.2 years; Gp C: 3.4 years; Gp D: 3.2 years). Baseline characteristic (age) "balanced" (evaluated participants only) Sex: Gp A: 13 F:11 M; Gp B: 10 F:13 M; Gp C: 10 F:12 M; Gp D: 8 F:13 M). Baseline characteristic (sex) "balanced" (evaluated participants only) Any other details of important prognostic factors: background exposure to fluoride in community water supply < 0.3 ppm F Number randomised: 120 (Gp A: 30; Gp B: 30; Gp C: 30; Gp D: 30) Number evaluated: 90 at 1 year (present at final assessment. Gp A: 24; Gp B: 23; Gp C: 22; Gp D: 21) Attrition: 25% dropout rate after 1 year (study duration = 1 year). Reasons for attrition: moved away from study area, children leaving nursery setting; no differential group losses
Interventions	**Comparison: FT versus FT** Gp A (n = 30): 500 ppm NaF; caries-inactive participants; abrasive system: none reported; school use/supervised daily frequency; home use/unsupervised, daily frequency assumed Gp B (n = 30): 1100 ppm NaF; caries-inactive participants; abrasive system: none reported; school use/supervised daily frequency; home use/unsupervised, daily frequency assumed Gp C (n = 30): 500 ppm NaF; caries-active participants; abrasive system: none reported; school use/supervised daily frequency; home use/unsupervised, daily frequency assumed Gp D (n = 30): 1100 ppm NaF; caries-active participants; abrasive system: none reported; school use/supervised daily frequency; home use/unsupervised, daily frequency assumed
Outcomes	Primary: number of lesions becoming active/cavities or inactive by initial caries status (at 1 year) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1 year
Notes	Adverse effects: not reported Funding source: materials provided by manufacturer (Colgate-Palmolive) and funding obtained from CNPq (Brazilian National Council for Scientific and Technological Development) Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: caries-inactive and caries-active groups analysed separately Other information of note: clinical caries assessment by single examiner; intra-examiner agreement assessed by second clinical exam in 10% of the sample after 15 days (Kappa 0.95)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ".. randomised single-blind clinical trial"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: ".. randomised single-blind clinical trial" and "The study was blinded only for the examiner..." Comment: examiner was blinded to the treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Comment: reasons for attrition stated. Attrition rate was moderate after 1 year, 25% overall and similar in both toothpaste groups and unlikely to be related to intervention
Selective reporting (reporting bias)	Low risk	Comment: all pre-specified outcomes reported (progression and arresting of lesions by toothpaste group and inital caries status)
Baseline characteristics balanced?	High risk	Comment: more males in 1100 ppm F group than females (26:18 versus 23:23), lower mean activated non-cavitated caries lesions in 500 ppm F group (2.5 (1.5 SD) versus 5.3 (6.5 SD))
Free of contamination/co-intervention?	Unclear risk	Comment: possible contamination in school brushing sessions but unlikely under supervision. Possible contamination at home brushing

Lind 1974

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: Denmark Number of centres: not reported. Vordingborg School Dental Health District, South Zealand Recruitment period: study commenced in 1970
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 5.1 DMFS (Gp A: 5.06 DMFS/3.60 DMFT; Gp B: 5.08 DMFS/3.57 DMFT). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 7 to 12 years, mean 10 years (Gp A: 9.95 years; Gp B: 9.93 years). Baseline characteristic (age) "balanced" Sex: 583 F:584 M (Gp A: 302 F:290 M; Gp B: 281 F:294 M) (evaluated subjects only) Any other details of important prognostic factors: background exposure to fluoride in community water supply (naturally fluoridated: 1.2 to 1.4 ppm F) Number randomised: 1407 (Gp A: 719; Gp B: 688) Number evaluated: 1167 at 3 years (present at intermediate and final assessments. Gp A: 592; Gp B: 575) Attrition: 17% dropout rate after 3 years (study duration = 3 years). Main reasons for dropout: moved away, sickness; exclusions based on presence in 1 interim examination; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 719): SMFP 2400 ppm F; abrasive system: Al oxide trihydrate; home use/unsupervised, daily frequency assumed Gp B (n = 688): placebo; abrasive system: Al oxide trihydrate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DMFS increment - (E + U) (CA) cl + (DR) xr; DMFT; ECSI (at 1, 2 and 3 years) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: Unilever Research Laboratories, England Declarations/conflicts of interest: acknowledgements indicate Unilever staff provided "assistance" throughout the study in addition to financial support, although it is not stated how they were involved Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA/NCA; radiographic assessment (2 postBW) by 2 examiners, diagnostic threshold = ER/DR; state of tooth eruption included = E/U. Inter-examiner diagnostic error reported to have no effect on results; reversal rates small and similar in both groups

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... children were stratified according to age, sex... The experimental and control groups were formed using random assignment. Children from the same household were allocated to the same treatment group to ensure that only one type of dentifrice entered the household during the trial period" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "The trial was in... a double-blind design... The only persons who, of necessity, knew the allocation code of the dentifrices were the factory personnel who manufactured the dentifrices. The packages containing the dentifrices differed only in the color of the neutral text" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 17% in 3 years. Dropout by group: 127/719 FT, 113/688 PL. Reasons for losses: sickness, change of address and exclusions from analysis due to presence at the 1st, 4th and at least 1 other intermediate examination (not reported by group) Comment: numbers lost were not unduly high given the length of follow-up, and show no differential loss between groups. Reasons for missing data are acceptable, but it is unclear if they are balanced. Caries data used in the analysis pertain to participants present for the first, last and at least 1 other follow-up exam
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (E + U) (CA) cl + (DR) xr, reported at 1, 2, and 3 years follow-ups DMFT ECSI Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 9.32 FT, 9.24 PL Mean age: 10.04 FT, 9.99 PL DMFT: 5.51 FT, 5.44 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "Children from the same household however, were allocated to the same treatment group to ensure that only one type of dentifrice entered the household during the trial period" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Lu 1980

Methods	Trial design: 2-armed, double-blind, placebo-controlled and stratified RCT Location: USA Number of centres: not reported, University of Oregon Health Sciences Center Recruitment period: study commenced in/before 1978
Participants	Inclusion criteria: good health, in possession of at least 16 natural teeth excluding 3rd molars Exclusion criteria: gross dental neglect, ill-fitting prosthetic appliances or extensive full coverage restorations of their teeth Baseline caries: 38.6 DMFS (Gp A: mean 38.23 (SE 0.931); Gp B: mean 38.96 (SE 0.885)). Baseline characteristic (DMFS) balanced Age at baseline (years): range 18 to 78 years (Gp A: 33.4 years; Gp B: mean 33.7 years). Baseline characteristic (age) balanced Sex: 704 F:401 M (Gp A: 355 F:203 M; Gp B: 349 F:198 M). Baseline characteristic (sex) balanced Any other details of important prognostic factors: background exposure to fluoride: none. Community water supply < 0.05 ppm F Number randomised: 1337 (Gp A: 669; Gp B: 668) Number evaluated: 1105 at 1 year (present at final assessment. Gp A: 558; Gp B: 547) Attrition: 17% dropout (for all study groups combined) after 1 year (study duration = 2 year). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 669): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised: daily frequency assumed Gp B (n = 668): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised: daily frequency assumed
Outcomes	Primary: 1-year DMFS increment - cl + xr; DMFS increment (at 1 year) Secondary: none Assessments irrelevant to this review's scope: none Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: Procter & Gamble Declarations/conflicts of interest: none reported Data handling by review authors: n/a Other information of note: analysis of covariance undertaken. Clinical examination by 1 examiner. Clinical (VT) caries assessment by single examiner according to Radike criteria and FOTI, diagnostic threshold not reported; radiographic (7 BW) caries assessment by single examiner, diagnostic threshold not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: stratified allocation undertaken by trial statistician. Industry sponsored and other trials randomised. Probably done
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "The dentifrices were identical except for the absence of the active ingredient...." and "double blind"
Incomplete outcome data (attrition bias)	Low risk	Comment: no reasons for attrition reported but low attrition rate 18% overall. No differential group losses
Selective reporting (reporting bias)	Unclear risk	Comment: DMFS increments over 1 year, of stated 2-year trial. Unable to identify 2-year report
Baseline characteristics balanced?	Low risk	Comment: balance of age, sex, DMFS at baseline. Adjusted analysis (analysis of covariance)
Free of contamination/co-intervention?	Low risk	Quote: "Cohabiting adults were assigned to the same treatment group in order to avoid the presence of two different dentifrices in the same household" Comment: contamination unlikely

Lu 1987

Methods	Trial design: 3-armed, double-blind, active-controlled and stratified RCT Location: USA Number of centres: not reported. Area surrounding Portland, Oregon Recruitment period: study commenced in/before 1983
Participants	Inclusion criteria: not reported Exclusion criteria: orthodontic appliances; unsuitable medical history (examiner-determined) Baseline caries: 4.01 DMFS (Gp A: 3.89 DMFS (SE 0.160); Gp B: 4.08 DMFS (SE 0.184); Gp C: 4.07 DMFS (SE 0.186). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 7 to 15 years, mean 10.48 years (Gp A: 10.22; Gp B: 10.18; Gp C: 10.50). Baseline characteristic (age) "balanced" Sex: 2273 F:2221 M (Gp A: 339 F:364 M; Gp B: 334 F:339 M; Gp C: 345 F:334 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: community water supply < 0.3 ppm F Number randomised: 4494 (Gp A: 1491; Gp B: 1503; Gp C: 1500) Number evaluated: 2055 at 3 years (present at final assessment. Gp A: 703; Gp B: 673; Gp C: 679) Attrition: 55% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition not reported; any differential group losses not assessable
Interventions	**Comparison: FT versus FT (3 groups)[a]** Gp A (n = 1491): NaF 1100 ppm F; abrasive system: silica; home use/unsupervised: daily frequency assumed Gp B (n = 1503): SMFP 2800 ppm F; abrasive system: silica; home use/unsupervised: daily frequency assumed Gp C (n = 1500): NaF 2800 ppm F; abrasive system: silica; home use/unsupervised: daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - cl + xr; DMFT increment (at 1, 2 and 3 years) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: grant from Procter & Gamble Declarations/conflicts of interest: 2 (OP Sturzenberger, RW Lehnhoff) of 5 authors employed by the manufacturer, Procter & Gamble. Remaining authors employed by Oregon Health Sciences University. 2 additional Procter & Gamble employees (BW Bollmer, WE Cooley - neither are authors) undertook the study's statistical analyses and data presentation Data handling by review authors: [a]Gps B + C versus Gp A combined in analysis Other information of note: analysis of covariance undertaken. Clinical examination by 1 examiner

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " ... assigned at random.."
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: " double-blind clinical study" and "Toothbrushes and assigned dentifrices labelled with the subjects name and unique identification number were supplied by the study's sponsor in plain white 2,7 oz tubes every 6 months"
Incomplete outcome data (attrition bias)	High risk	Comment: no reasons for attrition reported and 3-year withdrawals are high 53%, 55%, 55% in the 1100, 2800 SMFP, 2800 NaF groups
Selective reporting (reporting bias)	Low risk	Comment: DMFT, DMFS increments over 3 years
Baseline characteristics balanced?	Low risk	Comment: balance of age, sex, DMFS, DMFT at baseline. Adjusted analysis (analysis of covariance)
Free of contamination/co-intervention?	Unclear risk	Comment: toothpaste given at school in named tube for home use for all the family. Contamination unlikely

Mainwaring 1978

Methods	Trial design: [a]5-armed, double-blind, placebo-controlled and stratified RCT Location: UK Number of centres: not reported, although multicentre: conducted in 2 areas: Isle of Wight and South East London Recruitment period: study began in/before 1974
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 7.9 DFS (Gp A: 7.99 DFS (SD 6.08); Gp B: 8.00 DFS (SD 5.97); Gp C: 7.59 DFS (SD 5.56)). Baseline characteristics (SAR, DFS) "balanced" Age at baseline (years): range 11 to 12 years (Gp A: 11.9 years; Gp B: 11.9 years; Gp C: 11.9 years) (relevant groups evaluated). Baseline characteristics (age) "balanced" Sex: 691 F:416 M (Gp A: 205 F:106 M; Gp B: 288 F:192 M; Gp C: 198 F:118 M) (relevant groups evaluated). Sex imbalance between groups Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supplies < 0.3 ppm F Number randomised: 2104 (group distribution not reported) Number evaluated: 1718 at 3 years (1107 for groups included in review: Gp A: 311; Gp B: 480; Gp C: 316) Attrition: 18% dropout (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = evaluated 311): SMFP 1000 ppm F + placebo gel; abrasive system: Ca carbonate in all toothpastes; home use/unsupervised, for 1 min, daily frequency assumed Gp B (n = evaluated 480): SMFP 1000 ppm F + placebo gel; abrasive system: Ca carbonate in all toothpastes; home use/unsupervised, for 1 min, daily frequency assumed Gp C (n = evaluated 316): placebo; abrasive system: Ca carbonate in all toothpastes; home use/unsupervised, for 1 min, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - (E) (CA) cl + (ER) xr; PF-DFS; posterior MD-DFS; CIR (at 3 years) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: grant provided by Beecham Group Ltd, manufacturer of test pastes Declarations/conflicts of interest: not reported Data handling by review authors: [a]4th (placebo toothpaste + fluoride gel) and 5th trial arms (SMFP 1000 ppm F toothpaste + fluoride gel) excluded from this review due to ineligibility of additional caries preventive measures. Gps A + B differ only in flavouring. Gps A + B versus Gp C in analysis Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Intra-examiner reproducibility checks for DFS in 10% sample (ICC for VT/xr over 0.95); error variance less than 5% of total variance; reversal rate less than 5% of observed DFS increment in all groups

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were stratified according to age, sex and then randomly assigned to one of the treatment groups; children from the same family were assigned to the same group" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The study was of double-blind design, neither examiner nor participants knowing the identity of the treatment group to which the subjects had been allocated" and "... control group were provided with non-fluoride toothpaste" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 18.4% 386/2104 in 3 years (for all 5 groups). Dropout by group: not reported. Reasons for losses: not reported Comment: numbers lost were not unduly high given length of follow-up. It is unclear if there were any differential losses, and if 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: DFS increment - (E) (CA) cl + (ER) xr, reported at 3 years follow-up PF-DFS posterior MD-DFS caries incidence rate Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: mean age: 142.2 months (for each group) SAR: 87.73 (20.95) FT, 89.38 (20.94) PL DFS: 8.19 (6.01) FT, 7.59 (5.56) PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "Sufficient toothpaste was delivered by specifically appointed home visitors at monthly intervals to the subjects' homes for total family requirements" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Mainwaring 1983

Methods	Trial design: 4-armed, double-blind, placebo-controlled and stratified RCT Location: UK Number of centres: not reported. Isle of Wight Recruitment period: study began in/before 1978
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 6.9 DFS (Gp A: 7.38 DFS (SE 0.37); Gp B: 6.85 DFS (SE 0.35); Gp C: 6.30 DFS (SE 0.34)). Baseline characteristic (SAR, DFS, FS) "balanced" Age at baseline (years): range 11 to 12 years. Mean 11.6 years (Gp A: 11.61 years (SE 0.02); Gp B: 11.62 years (SE 0.02); Gp C: 11.62 years (SE 0.02)). Baseline characteristic (age) "balanced" (evaluated subjects only) Sex: 347 F:335 M (Gp A: 121 F:109 M; Gp B: 117 F:111 M; Gp C: 109 F:115 M) (evaluated subjects only) Any other details of important prognostic factors: background exposure to fluoride not reported. Community water supplies < 0.3 ppm F Number randomised: 1133 (group distribution not reported) Number evaluated: 923 at 4 years (relevant groups = 682: Gp A: 230; Gp B: 228; Gp C: 224) Attrition: 19% dropout (for all study groups combined) after 4 years (study duration = 4 years). Natural losses, no losses due to any adverse effects; any differential group losses not assessable
Interventions	**Comparison: FT (2 groups)[a] versus PL** Gp A (n = evaluated 230): SMFP 1000 ppm F; abrasive system: Ca carbonate in all toothpastes; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 228): SMFP-NaF 1000 ppm F; abrasive system: Ca carbonate in all toothpastes; home use/unsupervised, daily frequency assumed Gp C (n = evaluated 224): placebo; abrasive system: Ca carbonate in all toothpastes; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 4-year net DFS increment - (CA) cl + (ER) xr; O-DFS; MD-DFS; posterior MD-DFS; MD-BL-DFS (at 4 years) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 4 years
Notes	Adverse effects: "None withdrew on account of any local or systemic adverse effects" Funding source: partial funding by grant from Beecham Products Ltd, manufacturer of test pastes Declarations/conflicts of interest: not reported, author affiliations only Data handling by review authors: [a]Ca glycerophosphate/SMFP toothpaste group not considered (additional non-F active agent in this group only). Groups A + B versus C in analysis Other information of note: clinical (VT) caries assessment (FOTI used) by 1 examiner, diagnostic threshold = CA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Intra-examiner reproducibility checks for DFS in 10% sample (ICC for VT/xr over 0.95)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were stratified according to age and sex, and assigned by means of a table of random numbers to one of four dentifrice groups. Siblings were assigned to the same group"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "At no time during the study was the identity of these groups known to the examiner, the subjects or anyone directly associated with the study" and "Control group received dentifrice without fluoride" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 19% 210/1133 in 4 years (all 4 groups). Dropout by group: not reported. Reasons for losses: moving away from the area (and no losses due to any adverse effects) Comment: numbers lost were not unduly high for the length of follow-up. Any differential losses between groups are not assessable. Reasons for missing outcome data are acceptable but it is unclear if they are balanced between groups. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (CA) cl + (ER) xr, reported at 4 years follow-up O-DFS MD-DFS posterior MD-DFS MD-BL-DFS Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 7.38 (0.37) FT 1, 6.85 (0.35) FT 2, 6.30 (0.34) PL FS: 4.87 (0.26) FT 1, 4.35 (0.26) FT 2, 4.12 (0.27) PL SAR: 91.60 (1.38) FT 1, 93.04 (1.39) FT 2, 90.49 (1.46) PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "The dentifrices were delivered to the subjects homes by home visitors calling at monthly intervals. At each visit, sufficient toothpaste was provided to satisfy the needs of the whole family" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Marks 1994

Methods	Trial design: 5-armed, double-blind, stratified RCT Location: USA Number of centres: 25 elementary schools at baseline, Polk County, Florida; 39 schools overall (allowing for subjects followed-up after moving to middle school) Recruitment period: study began 1983
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 2.5 DMFS (Gp A: 2.48 (SD 3.40); Gp B: 2.52 (SD 3.44); Gp C: 2.50 (SD 3.76); Gp D: 2.61 (SD 3.64); Gp E: 2.46 (SD 3.48)). Baseline characteristics (sound surfaces, DMFS, DMFT, DFS inter) "very well balanced" (evaluated subjects only) Age at baseline (years): range: 6 to 14 years; mean 9.6 years (Gp A: 9.6; Gp B: 9.6; Gp C: 9.6; Gp D: 9.7; Gp E: 9.7). Baseline characteristic (age) "very well balanced" (evaluated subjects only) Sex: 2717 F:2757 M (Gp A: 560 (50.0%) F:560 (50.0%) M; Gp B: 562 (50.4%) F:554 (49.6%) M; Gp C: 528 (49.1%) F:548 (50.9%) M; Gp D: 547 (49.2%) F:565 (50.8%) M; Gp E: 520 (49.5%) F:530 (50.5%) M). Baseline characteristic (sex) "very well balanced" (evaluated subjects only) Any other details of important prognostic factors: background exposure to fluoride in community water at baseline < 0.3 ppm F; new water fluoridation programs commenced during trial affecting 17 of 39 schools (44%), although levels not reported ("A separate analysis was done for the water-fluoride children, and the results between dose groups were no different in schools having new water fluoridation than in schools not implementing water fluoridation") Number randomised: 8027 (Gp A: 1597; Gp B: 1615; Gp C: 1609; Gp D: 1604; Gp E: 1602) Number evaluated: 5474 at 3 years (Gp A: 1120; Gp B: 1116; Gp C: 1076; Gp D: 1112; Gp E: 1050) Attrition: 31.8% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT versus FT (5 groups)** Gp A (n = 1597): SMFP 1000 ppm F; abrasive system: silica; home use/supervised toothbrushing at school, daily frequency Gp B (n = 1615): SMFP 1500 ppm F; abrasive system: silica; home use/supervised toothbrushing at school, daily frequency Gp C (n = 1609): SMFP 2000 ppm F; abrasive system: silica; home use/supervised toothbrushing at school, daily frequency Gp D (n = 1604): SMFP 2500 ppm F; abrasive system: silica; home use/supervised toothbrushing at school, daily frequency Gp E (n = 1602): NaF 2000 ppm F; abrasive system: silica; home use/supervised toothbrushing at school, daily frequency
Outcomes	Primary: 3-year DMFS increment - cl xr; DMFT increment; DFS interproximal increment (at 3 years) Secondary: not assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: grant from Chesebrough-Pond's Inc (toothpaste manufacturer of Mentadent) Declarations/conflicts of interest: not reported Data handling by review authors: Gp A versus B versus C + E versus D in analysis. Summary data obtained from 1994 paper Other information of note: clinical caries assessment by 1 examiner. Analysis of covariance adjusting for baseline age, sex and DMFS. This is a re-analysis of a previous study with inclusion of 2000 ppm NaF group

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... block randomisation scheme was used to balance study groups for age, sex and baseline experience.."
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "double-blind caries trial" and "All dentifrices were identical in appearance and flavour" Comment: although not stated examiners probably blinded to group
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "Attrition rates ranged from 29.9 per cent in 1000 ppm group to 34.5 in 2000 ppm NaF group and the overall attrition rate over all groups was 31.8 per cent" Comment: no reasons given for losses
Selective reporting (reporting bias)	Low risk	Comment: DMFT, DMFS, DFS on interproximal surfaces increments over 3 years reported
Baseline characteristics balanced?	Low risk	Comment: balance of age, sex, baseline caries. Analysis of covariance adjusting for baseline age, sex and DMFS
Free of contamination/co-intervention?	Unclear risk	Comment: daily supervised toothbrushing and normal home use so contamination unlikely. Insufficient information

Marthaler 1965

Methods	Trial design: 5-armed, double-blind, placebo-controlled RCT Location: Switzerland Number of centres: 3 school dental clinics servicing 4 city areas of Zürich (Hongg, Industriequartier, Seebach, Wipkingen) Recruitment period: study began 1958
Participants	Inclusion criteria: not reported Exclusion criteria: non-attenders of regular community school dental clinics (10% to 15% of sample population); severe hypoplasia; orthodontic appliance use Baseline caries: 3.3 DMFS (Gp A: 3.19; Gp B: 3.45). Baseline characteristics (DFS, DMFT) "balanced" (DFS baseline data not reported) Age at baseline (years): 6 to 10 years (mean 7.6 years) (Gp A: 7.6 years; Gp B: 7.6 years). Baseline characteristic (age) "balanced" Sex: 137 F:132 M (Gp A: 76 F:69 M; Gp B: 61 F:63 M) (evaluated subjects only) Any other details of important prognostic factors: background exposure to fluoride in salt (suboptimal) Number randomised: 589 (group distribution not reported) Number evaluated: 269 at 3 years (present for all assessments) (Gp A: 145; Gp B: 124) Attrition: 43% dropout (for all study groups combined) after 3 years (study duration = 7 years). Exclusions based on variation in toothpaste provision and presence in follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 145): AmF 1250 ppm F; abrasive system: IMP (Gp B in trial report)/barium sulphate (Gp D in trial report); home use/unsupervised, daily frequency assumed Gp B (n =evaluated 124): placebo; abrasive system: IMP (Gp A in trial report)/barium sulphate (Gp C in trial report); home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - (CA) cl + (DR) xr; posterior MD-DFS; anterior MD-DFS; BL-DFS; O-DFS; DMFT (at 1.5, 3, 5, 7 years) Secondary: none assessed Assessments irrelevant to this review's scope: FT; FS; MT; compliance Follow-up duration: 7 years
Notes	Adverse effects: not reported Funding source: GABA AG (Basel, Switzerland), manufacturer of Elmex intervention toothpaste Declarations/conflicts of interest: not reported Data handling by review authors: this study reported 2 age groups of children: 6 to 10 years (Marthaler 1965: 7 years duration)/11 to 14 years (Marthaler 1965a: 3 years duration); 5 arms distributed between 3 intervention groups (B, D, E in papers) and 2 placebo groups (A and C in papers); information for Gp E in trial report not available. Pooled groups in analyses Other information of note: clinical (V) caries assessment by 1 examiner, diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = DR and ER; partial recording. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was carried out with the aid of the alphabetical class lists. The dentifrices were assigned to the children listed in this way, in a fixed order according to the code numbers printed on the tubes. The numbers in turn had been randomly assigned to the dentifrices A, B, C, D, E. In this way a random assignment of the dentifrices throughout the school was obtained" Comment: not enough information provided
Allocation concealment (selection bias)	Low risk	Central allocation described
Blinding (performance bias and detection bias)	Low risk	Quotes: "... the examinations were carried out without knowledge of the dentifrice used by the children" and "Tubes and content were only distinguishable with the aid of a small mark printed on the neutral tube" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 43% 256/589 dropout (for all 5 groups) after 3 years. Dropout by group: not reported. Reasons for losses: exclusions based on variation in toothpaste provision and presence in follow-up examinations (not reported by group) Comment: numbers lost were high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (CA) cl + (DR) xr, reported at 3 years follow-up posterior MD-DFS anterior MD-DFS BL-DFS O-DFS DMFT FT FS MT Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: mean age: 7.6 FT, 7.6 PL DMFS: 3.45 FT, 3.19 PL DMFT: 2.39 FT, 2.27 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "In order to exclude exchange of tubes at the start of the study, two tubes of dentifrices... were sent to the parents. The parents were told that upon returning the empty tubes, their child could get new dentifrice at the local school dental clinic" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1965a

Methods	Trial design: 4-armed, double-blind, placebo-controlled RCT Location: Switzerland Number of centres: 3 school dental clinics servicing 4 city areas of Zürich (Hongg, Industriequartier, Seebach, Wipkingen) Recruitment period: study began 1958
Participants	Inclusion criteria: not reported Exclusion criteria: non-attenders of regular community school dental clinics (10% to 15% of sample population); severe hypoplasia; orthodontic appliance use Baseline caries: 18.9 DMFS (Gp A: 18.50; Gp B: 19.34). Baseline characteristics (DMFS, DMFT) "balanced" (DFS baseline data not reported) Age at baseline (years): range 11 to 14 years (mean 12.7) (Gp A: 12.8 years; Gp B: 12.5 years). Baseline characteristic (age) "balanced" Sex: 31 F:43 M (Gp A: 15 F:27 M; Gp B: 16 F:16 M) Any other details of important prognostic factors: background exposure to fluoride in salt (suboptimal) Number randomised: 381 (group distribution not reported) Number evaluated: 74 at 3 years (present at all assessments) (Gp A: 42; Gp B: 32) Attrition: 66% dropout (for all study groups combined) after 3 years (study duration = 3 years). Main reason for high dropout: children leaving public school on completion of last compulsory year; exclusions based on variation in toothpaste provision (51 children excluded from analysis due to non-compliance resulting in increased losses to 81%) and presence in all follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 42): AmF 1250 ppm F; abrasive system: IMP (Gp B in trial report)/barium sulphate (Gp D in trial report); home use/unsupervised, daily frequency assumed Gp B (n = evaluated 32): placebo; abrasive system: IMP (Gp A in trial report)/barium sulphate (Gp C in trial report); home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - (CA) cl + (DR) xr; posterior MD-DFS; anterior MD-DFS; BL-DFS; O-DFS; DMFT (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: FT; FS; MT; compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: GABA AG (Basel, Switzerland), manufacturer of Elmex intervention toothpaste Declarations/conflicts of interest: not reported Data handling by review authors: this study reported 2 age groups of children: 6 to 10 years (Marthaler 1965: 7 years duration)/11 to 14 years (Marthaler 1965a: 3 years duration). 4 arms distributed between 2 intervention groups (B and D in trial reports) and 2 placebo groups (A and C in trial reports). Pooled groups in analyses Other information of note: clinical (V) caries assessment by 1 examiner, diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = DR and ER; partial recording. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was carried out with the aid of the alphabetical class lists. The dentifrices were assigned to the children listed in this way, in a fixed order according to the code numbers printed on the tubes. The numbers in turn had been randomly assigned to the dentifrices A, B, C, D, E. In this way a random assignment of the dentifrices throughout the school was obtained" Comment: not enough information provided
Allocation concealment (selection bias)	Low risk	Central allocation described
Blinding (performance bias and detection bias)	Low risk	Quotes: "... the examinations were carried out without knowledge of the dentifrice used by the children" and "Tubes and content were only distinguishable with the aid of a small mark printed on the neutral tube" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	High risk	Overall dropout for length of follow-up: 66.2% 245/370 (for all 4 groups) in 3 years. Dropout by group: not reported. Reasons for losses: children completing school; exclusions based on variation in toothpaste provision (51 children attending final examination were excluded from analysis due to non-compliance) and presence in follow-up examinations, including those unsatisfactorily radiographed (not reported by group) Comment: numbers lost are unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (CA) cl + (DR) xr, reported at 1.5, 3, 5 and 7 years follow-ups posterior MD-DFS anterior MD-DFS BL-DFS O-DFS DMFT FT FS MT Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: mean age: 12.8 FT, 12.5 PL DMFS: 18.5 FT, 19.34 PL DMFT: 9.93 FT, 10.25 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "In order to exclude exchange of tubes at the start of the study, two tubes of dentifrices...were sent to the parents. The parents were told that upon returning the empty tubes, their child could get new dentifrice at the local school dental clinic" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1970

Methods	Trial design: 4-armed placebo-controlled RCT (1st phase) Location: Switzerland Number of centres: not reported. Zürich Recruitment period: study began 1966
Participants	Inclusion criteria: not reported Exclusion criteria: fixed orthodontic appliance use Baseline caries: mean 0.97 DMFS (Gp A: 1.14 DMFS ; Gp B: 0.84 DMFS). Baseline characteristics (DMFS, 1st molar DMFS) "balanced" (DFS baseline data not reported) Age at baseline (years): range 6 to 7 years; mean 7.14 years. Baseline characteristic (age) "balanced" Sex: not reported Any other details of important prognostic factors: background exposure to fluoride in community water supply < 0.2 ppm F; 0.3 mg daily dose of salt assumed from F domestic salt Number randomised: 246 (group distribution not reported) Number evaluated: 201 at 3 years (present for all assessments: Gp A: 43; Gp B: 57) Attrition: 18% dropout (for all study groups combined) after 3 years (study duration = 3 years). Exclusions based on use of orthodontic bands and presence in all follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 43): AmF 1250 ppm F; abrasive system: IMP; home use/unsupervised, twice/3 times a day/680 times a year estimated Gp B (n = evaluated 57): placebo; abrasive system: IMP; home use/unsupervised, twice/3 times a day/680 times a year estimated
Outcomes	Primary: 3-year net DFS increment - (CA) cl + (DR) xr; 1st molar PF-DFS; 1st molar MD-DFS (at 1 and 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: GABA AG (Basel, Switzerland), manufacturer of Elmex intervention toothpaste Declarations/conflicts of interest: not reported Data handling by review authors: 2 of 4 trial arms not included in the scope of this review (group 3 in trial report: F gel + placebo paste; group 4 in trial report: F gel + F paste) Other information of note: clinical (V) caries assessment by 2 examiners, diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 2 examiners, diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of the two examiners known from earlier work." "Of the first grade children from 1967, only one in three was assigned to the fluoride dentifrice group. Moreover these children were included in the mailing system not before 1968, so that they were without a "dentifrice treatment" during the first 15 months of the 36 month total observation period"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Children were paired according to their sequence in the class lists. The first and second child of each pair was allocated control and fluoride respectively when, in a table of random digits, an even digit was present. In the case of an odd random digit, the first child was allocated fluoride, and the second one control"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	Quotes: "... the first child was allocated fluoride, and the second one control" and "Control group received exactly the same dentifrice, just without fluoride" Comment: use of placebo described. No direct information on whether the examiners were blinded to treatment allocations, although it is probable that clinical and radiographic exams were done independently
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 18.3% 45/246 in 3 years (for all 4 groups). Dropout by group: not reported. Reasons for losses: exclusions based on use of orthodontic bands and presence in all follow-up examinations Comment: numbers lost not unduly high for length of follow-up; any differential losses between groups not assessable. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment (CA) cl + (DR) xr, reported at 1 and 3 years follow-ups 1st molar PF-DFS 1st molar MD-DFS Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 1.14 FT, 0.84 PL 1st molar DMFS: 0.07 FT, 0.04 PL Comment: initial caries appears (DMFS) balanced
Free of contamination/co-intervention?	Low risk	Quote: "... in this case however siblings were both randomly allocated to either the fluoride or control dentifrice group to prevent the exchange of different types of toothpaste within the families" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1970a

Methods	Trial design: 4-armed placebo-controlled RCT (2nd phase) Location: Switzerland Number of centres: not reported. Zürich Recruitment period: study began 1966
Participants	Inclusion criteria: not reported Exclusion criteria: fixed orthodontic appliance use Baseline caries: mean 2.35 DMFS (Gp A: 2.75 DMFS; Gp B: 2.00 DMFS). Baseline characteristics (DMFS, 1st molar DMFS) "balanced" (DFS baseline data not reported) Age at baseline (years): range: 7 to 9 years; mean 8.18. Baseline characteristic (age) "balanced" Sex: not reported Any other details of important prognostic factors: background exposure to fluoride in community water supply < 0.2 ppm F; 0.3 mg daily dose of salt assumed from F domestic salt Number randomised: 128 (group distribution not reported) Number evaluated: 90 at 4 years (present for all assessments. Gp A: 23; Gp B: 20) Attrition: 30% dropout (for all study groups combined) after 4 years (study duration = 4 years). Exclusions based on: use of orthodontic bands, and presence in all follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 23): AmF 1250 ppm F; abrasive system: IMP; home use/unsupervised, twice/3 times a day/800 times a year estimated Gp B (n = evaluated 20): placebo; abrasive system: IMP; home use/unsupervised, twice/3 times a day/800 times a year estimated
Outcomes	Primary: 2-year net DFS increment - (CA) cl + (DR) xr; 1st molar PF-DFS; 1st molar MD-DFS (at 2 and 4 years) Secondary: none assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 4 years
Notes	Adverse effects: not reported Funding source: GABA AG (Basel, Switzerland), manufacturer of Elmex intervention toothpaste Declarations/conflicts of interest: not reported Data handling by review authors: 2 of 4 trial arms not included in the scope of this review (Gp 3: F gel + placebo paste; Gp 4: F gel + F paste). Final 4-year results not considered due to concurrent active caries intervention delivery after 2 years (bimonthly (6 times per year) supervised brushing with 1.0% NaF solution) Other information of note: clinical (V) caries assessment by 2 examiners, diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 2 examiners, diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of examiners known from earlier work"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Children were paired according to their sequence in the class lists. The first and second child of each pair was allocated control and fluoride respectively when, in a table of random digits, an even digit was present. In the case of an odd random digit, the first child was allocated fluoride, and the second one control"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	Quotes: "..... the first child was allocated fluoride, and the second one control" and "Control group received exactly the same dentifrice, just without fluoride" Comment: use of placebo described. No direct information on whether the examiners were blinded to treatment allocations, although it is probable that clinical and radiographic exams were done independently
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 29.7% 38/128 in 3 years (for all 4 groups). Dropout by group: not reported. Reasons for losses: exclusions based on use of orthodontic bands and presence at all follow-up examinations Comment: numbers lost not unduly high for length of follow-up; any differential losses between groups not assessable. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment (CA) cl + (DR) xr, reported at 1 and 3 years follow-up 1st molar PF-DFS 1st molar MD-DFS Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 2.00 FT, 2.75 PL 1st molar DMFS: 0.0 FT, 0.1 PL Comment: initial caries appears (DMFS) balanced
Free of contamination/co-intervention?	Low risk	Quote: "... in this case however siblings were both randomly allocated to either the fluoride or control dentifrice group to prevent the exchange of different types of toothpaste within the families" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1974

Methods	Trial design: double-blind (assessor), placebo-controlled RCT Location: Switzerland Number of centres: not reported. Primary school authorities in Kilchberg, border of Zürich Recruitment period: study began 1966
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 2.6 DMFS (Gp A: 2.54 DMFS; Gp B: 2.59 DMFS) (evaluated participants only). Baseline characteristics (DMFS, DMFT, FS, FT, TAR) "balanced" (DFS baseline data not reported) Age at baseline (years): range 6 to 9 years; mean 7.5 years (Gp A: 7.48 years; Gp B: 7.52 years) (evaluated participants only) Sex: not reported Any other details of important prognostic factors: background exposure to fluoride community water supplies < 0.2 ppm F; 0.3 mg daily dose of salt assumed from F domestic salt, and 44 evaluated participants also received fluoride tablets at home (Gp A: 17; Gp B: 27). Fluoridation of community water supply not reported Number randomised: 161 (Gp A: 81; Gp B: 80) Number evaluated: 109 at 6 years (Gp A: 50; Gp B: 59) Attrition: 32% dropout after 6 years (study duration = 6 years). Exclusions based on presence in all follow-up examinations; differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 81): AmF 1250 ppm F; abrasive system: IMP; home use/unsupervised, daily frequency assumed Gp B (n = 80): placebo; abrasive system: IMP; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 6-year[a] net DFS increment - (E) (CA) cl + (DR) xr; PF-DFS; posterior MD-DFS; anterior MD-B-DFS; DFT; proportion of children with new DFS (at 2 and 6 years) Secondary: none assessed Assessments irrelevant to this review's scope: gingivitis; calculus Follow-up duration: 6 years
Notes	Adverse effects: not reported Funding source: "Gaba AG Basle [sic], for providing and mailing the dentifrices." Funding not specifically reported, although inferred by Elmex's manufacturer (Gaba AG, Basel, Switzerland) providing intervention and placebo materials for the study Declarations/conflicts of interest: not reported Data handling by review authors: [a]results at 6 years follow-up chosen (reported for all outcomes) Other information of note: clinical (V) caries assessment by 2 examiners, diagnostic threshold = CA and NCA; state of tooth eruption included = E. Radiographic assessment (2 postBW) by 2 examiners, diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of examiners known from earlier work"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were randomly assigned to either control or fluoride dentifrice. There were 9 pairs of siblings.... each pair received either the control or fluoride dentifrice to avoid the provision of one family with different types of dentifrices" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The tubes showed no indication whether they contained fluoride or not" and "The type of dentifrice to which the child was assigned remained unknown to the examiner during the whole course of the study" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 32.3% in 6 years. Dropout by groups: 29/81 FT, 21/80 PL. Reasons for losses: exclusions based on presence at all follow-up examinations Comment: numbers lost were not unduly high for the length of follow-up, with a differential loss between groups (35.8% FT, 26.3% PL). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at all examinations. Group losses unlikely to be related to intervention
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (E) (CA) cl + (DR) xr reported at 2 and 6 years follow-ups PF-DFS posterior MD-DFS anterior MD-B-DFS DFT proportion of children with new DFS Comment: trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 2.59 FT, 2.54 PL DMFT: 1.81 FT, 1.74 PL FS: 2.07 FT, 1.80 PL TAR: 10.47 FT, 10.88 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "Two dentifrice tubes were mailed once a month to the children via their parents" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Mergele 1968

Methods	Trial design: 4-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported. Public schools in North-East Houston, Texas, USA Recruitment period: study began in/before 1964
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 6.5 DMFS (Gp A: 6.42 DMFS (SD 6.30); Gp B: 6.52 DMFS (SD 6.25)) (evaluated participants only). Baseline characteristics (age, SAR, DMFS, DMFT) "balanced" Age at baseline (years): range 10 to 13 years, mean 11 years (Gp A: 10.88 years; Gp B: 11.04 years) (evaluated participants only) Sex: 365 F:357 M (groups relevant to this review: 192 F:195 M. Gp A: 97 F:100 M; Gp B: 95 F:95 M) (evaluated participants only) Any other details of important prognostic factors: background exposure to fluoride through community water supply (1.0 ppm F) Number randomised: 929 (group distribution not reported) Number evaluated: 722 (groups relevant to this review: 387 at 3 years (available at final examination) (Gp A: 197; Gp B: 190)) Attrition: 22% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: natural losses to follow up; any differential group losses not assessable
Interventions	**Comparison: FT[a] versus PL** Gp A (n = evaluated 197): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 190): placebo; abrasive system: IMP; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DMFS increment - cl; DMFT (at 3 years) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: [a]Na N-lauroyl sarcosinate/SMFP toothpaste groups not considered (additional non-F active agent used in this group only) Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... population was stratified according to examiner, sex, age, permanent teeth present, past caries experience, oral hygiene rating and prior fluoride history. This stratified population was divided by means of random numbers into 4 balanced groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "All 4 dentifrices were packed in plain white tubes.... the labelling was identical except for the name of the subject" "One group used a control toothpaste... did not contain active agent" and "All clinical exams performed without reference to previous records" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 22% 207/929 in 6 years (for all 4 groups). Dropout by groups: not reported. Reasons for losses: moved away Comment: numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are balanced, although the reasons are acceptable. Caries data used in the analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl, reported at 3 years follow-up DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 6.42 (6.30) FT, 6.52 (6.25) PL age: 10.88 FT, 11.04 PL DMFT: 3.95 (2.85) FT, 3.99 (3.02) PL SAR: 86.30 (29.17) FT, 87.17 (28.88) PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "Additional dentifrice was provided for the family of a subject as were brushes" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Mitropolous 1984

Methods	Trial design: 2-armed, double-blind, stratified RCT Location: UK Number of centres: 5 secondary schools in North-West England, UK Recruitment period: study began in/before 1982
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 7.7 DMFS (Gp A: 7.76 DMFS (SD 5.67); Gp B: 7.69 DMFS (SD 5.71)) (evaluated participants only). Baseline characteristics (baseline DMFS, baseline DMFT, surfaces at risk) "balanced" Age at baseline (years): range 12 to 13 years (mean/group distribution not reported) Sex: 379 F:346 M (Gp A: 198 F:167 M; Gp B: 181 F:179 M) (evaluated participants only) Any other details of important prognostic factors: background exposure to fluoride in community water supply < 0.1 ppm F Number randomised: 818 (group distribution not reported) Number evaluated: 725 (Gp A: 365; Gp B: 360) Attrition: 11% dropout. Reasons for attrition: lack of co-operation, own volition, left study schools, absent at time of final examination; no differential group losses
Interventions	**Comparison: FT versus FT** Gp A (n = evaluated 365): SMPF 250 ppm F; abrasive system: silica; home use/unsupervised but some children (n = 477, across both groups) also brushed at school under supervision Gp B (n = evaluated 360): SMPF 1000 ppm F; abrasive system: silica; home use/unsupervised but some children (n = 477, across both groups) also brushed at school under supervision
Outcomes	Primary: 32-month net DFS increment - cl + xr; DMFT increment; DFS increment teeth erupting during the study; DMFT increment teeth erupting during the study (at 32 months) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 32 months
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical caries assessment by 1 examiner

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... stratified .... before being randomly assigned to one of two study groups" Comment: as author and statistician on study (Helen Worthington) the children were randomised using random numbers from random number table
Allocation concealment (selection bias)	Low risk	Comment: not mentioned in trial report, but as author and statistician (Helen Worthington) this was done
Blinding (performance bias and detection bias)	Low risk	Quotes: "trial was double-blind neither the subjects not the examiner being aware who was receiving test or control products" and "Control and test dentifrices were indistinguishable in taste and appearance"
Incomplete outcome data (attrition bias)	Low risk	Quotes: ".. dropout rate of 11 per cent (32 months)" and "Of the 93 subjects who failed to complete the trial (51 in control and 42 in control), four were removed from the trial through lack of co-operation, three left trial of their own choice, 49 left the study schools and 37 were absent at the time of the examination" Comment: low dropout (10% test, 12% control), and balanced between the groups. Reasons not connected to toothpaste
Selective reporting (reporting bias)	Low risk	Comment: DMFT, DMFS clinical and combined with radiographs, erupting teeth
Baseline characteristics balanced?	Low risk	Comment: balance for baseline sex and caries comparable
Free of contamination/co-intervention?	Low risk	Comment: pupils received dentifrice for home use through post. 3 of 5 schools had daily brushing sessions. This was checked at regular intervals to assess accuracy of trial supervisors

Muhler 1955

Methods	Trial design: 3-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: 1 centre. Dental clinic at Indiana University, USA. Participants from Bloomington area of Indiana Recruitment period: study began in/before 1954
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 9.3 DMFS (evaluated participants only) (Gp A: 9.7 DMFS; Gp B: 10.0 DMFS). Baseline characteristics (DMFS) "balanced" Age at baseline (years): range 6 to 15 years (group means not reported) Sex: not reported Any other details of important prognostic factors: background exposure to fluoride: data not available for fluoridation status of site Number randomised: 852 (groups relevant to review: 568 (Gp A: 290; Gp B: 278)) Number evaluated: 656 at 1 year (available at final examination) (groups relevant to review: 444 (Gp A: 219; Gp B: 225)) Attrition: 23% dropout after 1 year (study duration = 1 year). Reasons for attrition not reported; differential group losses
Interventions	**Comparison: FT[a] versus PL** Gp A (n = 290): SnF_2 1000 ppm F; abrasive system: heat-treated Ca orthophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 278): placebo; abrasive system: heat-treated Ca orthophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 1-year DMFS increment - cl + xr; DMFT (at 6 months and 1 year) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1 year
Notes	Adverse effects: not reported Funding source: intervention manufacturer, Procter & Gamble Declarations/conflicts of interest: 2 of 4 authors (AW Radike, WH Nebergall) employed by the manufacturer. Remaining authors employed by Indiana University Data handling by review authors: [a]NaF-heat treated Ca orthophosphate toothpaste group not considered (abrasive system known to be incompatible with NaF) Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Criteria for caries diagnosis reported to have been carefully standardized, diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After the initial exam of a subject, his total previous caries experience in terms of DMFS... was corrected by a factor corresponding to his dental age. This factor is one of a series of ratios.... The corrected term was taken as an indication of caries expectancy and the subject assigned to one of nine classes on this basis. Within each class, he was assigned to one of the three treatment groups at random" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The examiner had no information about any child relative to group assignment, previous exam data, and so on" and "The control dentifrice had no fluoride content" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 22% in 1 year. Dropout by group: 71/290 FT, 53/278 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up, with differential losses between groups (24.5% FT, 19.1% PL). It is unclear if 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: DMFS increment - cl + xr, reported at 6 months and 1 year follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factor reported: DMFS: 9.5 FT, 9.1 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "The entire family of each child was supplied with the dentifrice assigned to the child. Although this increased the cost of the study considerably, it provided additional assurance that the child would use only the dentifrice assigned" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Muhler 1957

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: 1. 1953 freshman class at Indiana University Recruitment period: study began 1953
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: DMFS 27.3 for those completing at 12 months (24-month data not reported). (Gp A: 26.9 DMFS; Gp B: 27.7 DMFS) Age at baseline (years): range 17 to 36 years Sex: not reported Any other details of important prognostic factors: background exposure to fluoride not reported Number randomised: 425 (group distribution not reported) Number evaluated: 247 at 2 years (available at final examination) (Gp A: 131; Gp B: 116) Attrition: 42% dropout after 2 years (study duration = 2 years). Reasons for dropout not described: change of residence, absenteeism, non-adherence to study protocol; differential group losses unclear as number randomised to groups at baseline not stated
Interventions	**Comparison: FT versus PL** Gp A (n = evaluated 131): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 116): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - cl + xr; DMFS-P; DMFS-O; DMFS-BL; DMFT (at 6 months, 1 year and 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: partial funding from Procter & Gamble. Other source of funding not reported Declarations/conflicts of interest: 1 author (A Radike) employed by toothpaste manufacturer (Procter & Gamble). Remaining author reports institutional affiliation Data handling by review authors: standard deviations imputed from reported P value Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment by 1 examiner, diagnostic threshold not reported. Criteria for caries diagnosis reported to have been carefully standardized, diagnostic errors not reported. Study report states that methods used in this study were identical to those used in their previous study (Muhler 1955)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were then divided into two groups at random after stratification according to caries experience" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	Quote: ".... were provided with dentifrices the composition of which were identical except that one contained 4 mg of SnF_2" Comment: participants blinded. No information provided for blinding of outcome assessment
Incomplete outcome data (attrition bias)	High risk	Overall dropout for length of follow-up: 42% in 2 years. Dropout by group not stated. Reasons for losses not stated Comment: numbers lost were high for the length of follow-up. Cannot establish whether differential loss between groups as number randomised at baseline not reported. It is unclear if 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: DMFS increment - cl + xr, reported at 6-, 12- and 24-month follow-ups DMFT DMFS DMFS-P DMFS-O DMFS-BL Comment: trial protocol not available. All expected outcomes were reported. No standard deviations provided for caries increment outcomes so cannot be entered into meta-analysis
Baseline characteristics balanced?	Low risk	Prognostic factors reported: age, caries Comment: appears balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Muhler 1962

Methods	Trial design: 2-armed, placebo-controlled, stratified RCT Location: USA Number of centres: (Not specifically reported but indicated to be as in Muhler 1955.) 1 centre. Dental clinic at Indiana University, USA. Participants from Bloomington area of Indiana Recruitment period: study began in/before 1958
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 13 DMFS (Gp A: 13.08 DMFS; Gp B: 12.98 DMFS). Baseline characteristics (DMFS) comparable Age at baseline (years): range 6 to 18 years, mean 11 years (group mean age not reported) Sex: 178 F:149 M (Gp A: 93 F:72 M; Gp B: 85 F:77 M) (evaluated participants at all assessments only: n = 327) Any other details of important prognostic factors: background exposure to fluoride in community water 0.05 ppm F Number randomised: 492 (Gp A: 242; Gp B: 250) Number evaluated: 343 at 3 years (available at final examination) (Gp A: 174; Gp B: 169) Attrition: 30% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: not stated; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 242): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 250): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - cl; DMFS increment; DMFT increment; cumulative caries increment; DMFS increment (children present at every examination); DMFT increment (children present at every examination); proportion developing caries (at 3 years (6 months, 1 year, 18 months, 2 years, 3 years)) Secondary: not assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: grant from intervention (Crest) manufacturer, Procter & Gamble Declarations/conflicts of interest: sole author employed by Indiana University Data handling by review authors: n/a Other information of note: clinical caries assessment by 1 examiner. 3% aged 17-18 years at start of study (Gp A: n = 16; Gp B: n = 14)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... assigned at random to study groups after stratification"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	High risk	Quote: "Elements of blindness were compounded in that subjects from several different tests being conducted simultaneously appeared for examination in mixed order" Comment: dentifrices were different. Test was described as "standard factory product"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: moderate dropout (36 months 32% control 28% test), and balanced between the groups. No reasons for dropouts given
Selective reporting (reporting bias)	Low risk	DMFS and DMFT increments
Baseline characteristics balanced?	Low risk	Comment: stratified on dental age, past caries, age and sex. Balance for baseline sex, age and disease comparable
Free of contamination/co-intervention?	Unclear risk	Comment: unclear but as dentifrices were very different it is unlikely that errors occurred over their use

Muhler 1970

Methods	Trial design: 3-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported Recruitment period: study began in/before 1967
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 10.3 DMFS (Gp A: 10.71 DMFS (SE 0.746); Gp B: 9.72 DMFS (SE 0.585)). Baseline characteristic (DMFS) with some imbalance Age at baseline (years): range 5 to 17 years, mean 10 years (Gp A: 10.33 years; Gp B: 10.16 years). Baseline characteristic (age) with some imbalance Sex: 426 F:336 M (groups relevant to review: 284 F:226 M (Gp A: 140 F:106 M; Gp B: 144 F:120 M)). Baseline characteristic (sex) with some imbalance Any other details of important prognostic factors: background exposure to fluoride: data not available for fluoridation status of site Number randomised: 762 (groups relevant to review: n = 510 (Gp A: 246; Gp B: 264) Number evaluated: at 1 year (available at final examination) (groups relevant to review: n = 436 (Gp A: 201; Gp B: 235)) Attrition: 15% dropout after 1 year (study duration = 1 year). Reasons for attrition not reported; differential group losses
Interventions	**Comparison: FT[a] versus PL** Gp A (n = 246): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 264): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 1-year DMFS increment - cl + xr; DMFT (at 6 months and 1 year) Secondary: not assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1 year
Notes	Adverse effects: not reported Funding source: partially funded by Procter & Gamble. Other source of funds not reported Declarations/conflicts of interest: sole author employed by Indiana University Data handling by review authors: [a]Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only) Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5 to 7 BW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... children were divided into 3 groups by separation of age, sex and DMFS, followed by randomization with restrictions to balance by three's within each cell" Comment: block randomisation performed
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The first group of children received placebo dentifrice...." "All dentifrices were furnished in plain white tubes with appropriate codes to identify the products" and "At no time during the study did the examiner, the recorder or the clinical staff have any knowledge of the patient being examined or the product being used" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 15% in 1 year. Dropout by group: 45/246 FT, 29/264 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up, but there is differential loss between groups (18% FT, 11% PL). It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination. Group losses unlikely to be related to intervention
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 6 months and 1 year follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 10.71 FT, 9.72 PL age: 10.33 FT, 10.16 PL gender: 106 M, 140 F FT; 120 M, 144 F PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "All the children were given new toothbrushes and sufficient dentifrice for their personal use and for their entire family" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Naylor 1967

Methods	Trial design: 3-armed, double-blind, placebo-controlled, stratified RCT Location: UK Number of centres: single mobile dental unit attending 14 secondary schools in East and South-East London districts Recruitment period: study began 1961
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 9.5 DMFS (groups relevant to review: 9.5 DMFS (Gp A: 9.45 DMFS (SD 6.22); Gp B: 9.61 DMFS (SD 6.43)). Baseline characteristics (SAR, DMFS, DMFT, posterior MD-DFS) "balanced" Age at baseline (years): range 11 to 12 years (group means not reported). Baseline characteristic (age) "balanced" Sex: 813 F:676 M (groups relevant to review: 543 F:430 M (Gp A: 274 F:220 M; Gp B: 269 F:210 M)). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride in community water supply approximately 0.3 ppm F Number randomised: 1789 (groups relevant to review: not reported. Group distribution unknown) Number evaluated: 1489 at 3 years (available at final examination) (groups relevant to review: 973 (Gp A: 494; Gp B:479)) Attrition: 17% dropout (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable
Interventions	**Comparison: FT[a] versus PL** Gp A (n = 494 evaluated): SnF_2 1000 ppm F; abrasive system: IMP (main abrasive); home use/unsupervised, daily frequency assumed Gp B (n = 479 evaluated): placebo; abrasive system: dicalcium phosphate (dihydrate); home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year crude DFS increment - (E + U) (CA) cl + (ER) xr; posterior MD-DFS; 1st molar MD-DFS; DMFS; DMFT (at 3 years) Secondary: proportion of children with tooth staining (at 3 years) Assessments irrelevant to this review's scope: subjective oral hygiene rating assessment Follow-up duration: 3 years
Notes	Adverse effects: staining grades (subjective assessment. Scale 0 to 4, lower better): Gp A: Grade 0 n = 242 (49.0%); Grade 1 n = 124 (25.1%); Grade 2 n = 94 (19.0%); Grade 3 n = 32 (6.5%); Grade 4 n = 2 (0.4%) Gp B: Grade 0 n = 368 (76.8%); Grade 1 n = 70 (14.6%); Grade 2 n = 33 (6.9%); Grade 3 n = 7 (1.5%); Grade 4 n = 1 (0.2%) Funding source: Colgate-Palmolive provided toothpastes and funding Declarations/conflicts of interest: not reported, authors employed by Guy's Hospital, London Data handling by review authors: [a]Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only) Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Reversal rate less than 4% of observed DFS increment in all groups. High accuracy of diagnosis revealed by 10% sample checks (clinically and radiographically)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were stratified according to age, sex, race.... The stratified population was then divided into three groups A, B and C by means of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "A sealed envelope containing the allocation of the toothpastes to groups was placed in the safe of the Dean, Guy's Hospital Medical School before the trial began and not opened until analysis of third year results were complete"
Blinding (performance bias and detection bias)	Low risk	Quote: "Throughout the trial, each group received the corresponding toothpaste, the formular of which was unknown to both the examiner and the user.." Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 16.9% (300/1789) in 3 years (for all 3 groups). Dropout by group: not reported. Reasons for losses: "low dropout due to the fact that exams were completed before school leaving age" Comment: numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if 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)	Low risk	Outcomes reported: DFS increment - (E + U) (CA) cl + (ER) xr, reported at 3 years follow-up DMFT DMFS posterior MD-DFS 1st molar MD-DFS proportion of children with tooth staining Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 9.45 (6.22) FT, 9.61 (6.43) PL gender: (55.5% F) FT, (56.2% F) PL DMFT: 5.34 (2.84) FT, 5.51 (2.93) PL SAR: 107.69 (20.46) FT, 106.91 (20.93) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "In an attempt to ensure that the subjects did not use other pastes, enough was sent to provide for the needs of the whole family" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Naylor 1979

Methods	Trial design: 3-armed, double-blind, placebo-controlled, stratified RCT Location: UK Number of centres: not reported. Secondary schools in Winchester, Andover and Basingstoke across Hampshire Recruitment period: study began in 1973
Participants	Inclusion criteria: not reported Exclusion criteria: absence from school at baseline examination Baseline caries: 7.9 DFS (groups relevant to review: 7.9 DFS (Gp A: 8.00 DFS (SD 5.92); Gp B: 7.78 DFS (SD 5.36))). Baseline characteristics (SAR, TAR, DFS, DFT) "balanced" Age at baseline (years): range 11 to 12 years (groups relevant to review: Gp A: 11.94 years (SD 0.3); Gp B: 11.94 years (SD 0.3)). Baseline characteristic (age) "balanced" Sex: 465 F:479 M (groups relevant to review: 313 F:312 M (Gp A: 160 F:159 M; Gp B: 153 F:153 M)) (assessed participants only) Any other details of important prognostic factors: background exposure to fluoride in community water supply < 0.3 ppm F Number randomised: 1183 (groups distribution not reported) Number evaluated: 944 at 3 years (available at final examination) (groups relevant to review: 625 (Gp A: 319; Gp B: 306)) Attrition: 20% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition not reported; any differential group losses not assessable
Interventions	**Comparison: FT[a] versus PL** Gp A (n = 319 evaluated): SMFP 1000 ppm F; abrasive system: Ca carbonate; home use/unsupervised, daily frequency assumed Gp B (n = 306 evaluated): placebo; abrasive system: Ca carbonate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DFS increment - (E) (CA) cl + (ER) xr; O-BL-DFS; MD-DFS; DFT; DFT (U); CIR (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: subjective oral hygiene rating assessment Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: partial funding by Beecham Group Ltd. Other source of funds not reported Declarations/conflicts of interest: not reported, authors employed by Guy's Hospital, London and Forsyth Dental Center, Massachusetts Data handling by review authors: [a]Ca glycerophosphate/SMFP toothpaste group not considered (additional non-F active agent used in this group only) Other information of note: clinical (VT) caries assessment (FOTI used) by 2 examiners (independently), diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 2 examiners (independently), diagnostic threshold = ER. Results of 1 examiner chosen (findings consistent throughout)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were stratified according to age and sex and assigned by means of a table of random numbers to dentifrice groups"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "... at no time during the study was the identity of these groups known to the examiners or anyone directly associated with the study" and ".. control dentifrice same as for group 1 but without the fluoride" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 20.2% (239/1183) in 3 years (for all 3 groups). Dropout by group: not reported. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (E) (CA) cl + (ER) xr, reported at 3 years follow-up DFT DFT (U) O-BL-DFS MD-DFS CIR Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 7.36 FT, 7.62 PL mean age: 11.94 (0.30) FT, 11.94 (0.30) PL TAR: 17.6 FT, 17.66 PL DFT: 4.99 FT, 5.08 PL SAR: 95.84 FT, 96.21 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Sufficient supplies were also left for all other members of the family" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

O'Mullane 1997

Methods	Trial design: 4-armed, double-blind, stratified RCT Location: UK Number of centres: single, 2-surgery mobile dental unit, attending secondary schools in Clwyd and Gwynedd, North Wales, UK Recruitment period: study began 1989
Participants	Inclusion criteria: not reported Exclusion criteria: caries-free children, dentally immature children, or fitted with a fixed orthodontic appliance Baseline caries: 4.9 DMFS (Gp A: 5.11 DMFS (SD 4.15); Gp B: 4.69 DMFS (SD 3.78); Gp C: 5.10 (SD 4.15); Gp D: 4.74 (SD3.71)) (evaluated attendees only). Baseline characteristics (DMFS) "very good" Age at baseline (years): range 11 to 12 years, mean not reported (group distribution not reported) Sex: 1754 F:1713 M (Gp A: 854 F:867 M; Gp B: 900 F:846 M; Gp C: 874 F:856 M; Gp D: 800 F:857 M) (evaluated attendees only (clinical only)) Any other details of important prognostic factors: background exposure to fluoride: none reported, although Anglesey resident children were excluded as water supply was fluoridated Number randomised: 4196 (group distribution not reported) Number evaluated: 3467 at 3 years (available at final clinical examination; 1942 for clinical and radio examinations) (evaluated attendees only). (Groups relevant to review: Gp A: 491; Gp B: 474; Gp C: 477; Gp D: 500) Attrition: 17% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: only changing area of residence given; "this did not affect the balance between/among the toothpaste groups"
Interventions	**Comparison: FT (4 groups)[a]** Gp A (n = evaluated 491): 1000 ppm NaF; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 474): 1500 pppm NaF; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp C (n = evaluated 477): 1000 ppm NaF + 3% TMP; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp D (n = evaluated 500): 1500 pppm NaF + 3% TMP; abrasive system: silica; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment cl (VT, FOTI) + xr; DMFS increment cl (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: compliance; rinsing method Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: grant from Unilever Dental Research Declarations/conflicts of interest: none stated Data handling by review authors: [a]factorial design, SMFP and TMP Other information of note: 2 clinical examiners re-examined 5% of their allocated and 5% of children allocated to the other clinician. Intra- and inter-reliability > 0.93

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quotes: "... prospective participants allocated sequential identification numbers" and "... children randomly allocated to 1 of 4 toothpaste groups based on 4 stratifying factors"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "... double-blind" and "radiographs were read by clinical examiners without reference to the clinical findings"
Incomplete outcome data (attrition bias)	Low risk	3467/4196 children available for analysis. Attrition mainly due to moving away from area; did not alter balance between groups Comment: reasonable dropout rate for duration of study; unlikely to be due to intervention
Selective reporting (reporting bias)	Low risk	DMFS increment. Clinical and radiographic assessments
Baseline characteristics balanced?	Low risk	Comment: no statistically significant difference in DMFS score at baseline for NaF only paste (8% lower in 1500 ppm group for combined NaF/NaF + TMP groups)
Free of contamination/co-intervention?	Low risk	Comment: no apparent cause for concern regarding contamination. Sufficient toothpaste supplied for whole family so contamination unlikely

Peterson 1967

Methods	Trial design: 3-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported Recruitment period: study began in/before 1964
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 14.3 DMFS (Gp A: 13.65 DMFS; Gp B: 13.91 DMFS; Gp C: 15.20 DMFS) (evaluated participants only). Baseline characteristics (DMFS, DMFT, dental age) "balanced" Age at baseline (years): range 9 to 15 years, mean not reported (dental age (erupted permanent teeth): Gp A: 22.62; Gp B: 22.61; Gp C: 22.77) (evaluated participants only) Sex: not reported, although recorded as used to stratify participants Any other details of important prognostic factors: background exposure to fluoride: data not available for fluoridation status of site Number randomised: 1136 (group distribution not reported) Number evaluated: 954 at 2 years (available at this examination) (Gp A: 323; Gp B: 311; Gp C: 320) Attrition: 16% dropout after 2 years (study duration = 3 years). Reasons for attrition not described; any differential group losses not assessable
Interventions	**Comparison: FT (2 groups) versus 'PL'** Gp A (n = evaluated 323): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 311): APF 1000 ppm F; abrasive system: IMP; home use/unsupervised, daily frequency assumed Gp C (n = evaluated 320): placebo; abrasive system: not reported; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year[a] DMFS increment - cl + xr; O-DMFS; BL-DMFS; MD-DMFS; DMFT (at 1, 2, 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: partially funded by 1 of the intervention toothpaste's manufacturer, Bristol-Myers Company, New York. Other partial source of funding not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: groups A + B combined versus C in analysis. [a] Results for 3 years follow-up not considered (not fully reported) Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported; state of tooth eruption included not reported; radiographic assessment (3 BW) by 1 examiner, diagnostic threshold not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Age, sex and family records were supplied to a computing centre, where the subjects were grouped according to these factors and randomly assigned to three groups" Comment: most likely computer generated sequence used
Allocation concealment (selection bias)	Low risk	Sequence generated centrally
Blinding (performance bias and detection bias)	Low risk	Quotes: "The double blind procedure was used throughout the study" and "The dentifrice was supplied in white painted tubes and cartons with 1 of 3 code letters for each dentifrice group" ".. Group 3, a non-fluoride dentifrice.." and "Radiographs were developed and read later..." Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 16% (182/1136) in 2 years. Dropout by group: not reported. Reasons for missing data: not reported Comment: numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination (though it was a 2-year report)
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 1, 2 and 3 years follow-ups DMFT O-DMFS BL-DMFS MD-DMF Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 13.91 FT 1, 13.65 FT 2, 15.20 PL DMFT: 7.63 FT 1, 7.47 FT 2, 8.02 PL dental age: 22.61 FT 1, 22.62 FT 2, 22.77 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The participating children were periodically supplied with toothbrushes and a sufficient amount of dentifrice, the amount varying according to the size of the family" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Peterson 1979

Methods	Trial design: 3-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported. Parochial schools in Bismarck and Fargo, North Dakota Recruitment period: study began 1971
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 2.9 DFS (Gp A: 3.04 (SD 3.50); Gp B: 2.85 (SD 2.92); Gp C: 2.69 (SD 2.66)). Baseline characteristics (DFS, MD-DFS, DFT, SAR, TAR) "balanced" (evaluated participants only) Age at baseline (years): range 8 to 12 years, mean 10 years (Gp A: 123.88 months (SD 13.01); Gp B: 124.84 months (SD 11.94); Gp C: 124.64 months (SD 12.11)) (evaluated participants only) Sex: not reported Any other details of important prognostic factors: background exposure to fluoride: community water supply fluoridated 1.2 ppm F Number randomised: 950 (group distribution not reported) Number evaluated: 712 at 2.5 years (present for all examinations) (Gp A: 237; Gp B: 230; Gp C: 245) Attrition: 25% dropout after 2.5 years (study duration = 2.5 years). Natural losses; exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = evaluated 237): SMFP 1000 ppm F; abrasive system: Ca carbonate; school use/supervised, daily (appropriate toothpastes also provided for home use) Gp B (n = evaluated 230): SMFP 1000 ppm F; abrasive system: IMP; school use/supervised, daily (appropriate toothpastes also provided for home use) Gp C (n = evaluated 245): placebo; abrasive system: Ca carbonate; school use/supervised, daily (appropriate toothpastes also provided for home use)
Outcomes	Primary: 2.5-year DFS increment - cl + xr; DMFT; MD-DFS (at 2.5 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2.5 years
Notes	Adverse effects: not reported Funding source: grant from manufacturer, Beecham Inc Declarations/conflicts of interest: not reported Data handling by review authors: groups A + B combined versus C in analysis Other information of note: clinical (VT) caries assessment (FOTI used) by 1 examiner, diagnostic threshold = CA; state of tooth eruption included not reported; radiographic assessment (postBW) by 1 examiner, diagnostic threshold = ER. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were then stratified by age and sex and assigned at random to 1 of 3 dentifrice groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Except for the absence of NaMFP, this placebo formulation was identical to that of experimental dentifrice" and "The double blind technique was used, neither the examiner nor the subjects knowing to which dentifrice group they had been assigned" Comment: blinding outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 25.1% 238/950 in 2.5 years (all groups). Dropout by group: not reported. Reasons for losses: mainly due to moving from the area, and exclusion based on presence at all examinations Comment: numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - cl + xr, reported at 2.5 years follow-up DMFT MD-DFS Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 3.04 (3.50) FT 1; 2.85 (2.92) FT 2; 2.69 (2.66) PL age (months): 123.88 (13.01) FT 1; 124 (11.94) FT 2; 124.64 (12.11) PL TAR: 14.49 (5.10) FT 1; 15.16 (5.35) FT 2; 14.84 (5.24) PL DFT: 2.23 (2.16) FT 1; 2.06 (1.71) FT 2; 2.05 (1.70) PL SAR: 79.73 (26.22) FT 1; 83.78 (27.28) FT 2; 81.53 (26.37) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "All subjects periodically received toothbrushes and dentifrices individually labelled for school and home use" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Petersson 1991

Methods	Trial design: 4-armed, double-blind, head-to-head RCT Location: Sweden Number of centres: not reported. Halland, West coast of Sweden Recruitment period: study began 1982
Participants	Inclusion criteria: healthy schoolchildren Exclusion criteria: not reported Baseline caries: range 12.7 DFS to 15.9 DFS (group distributions not fully reported). Baseline characteristics differed according to DMS (reported for groups A and B) Age at baseline (years): range 12 to 13 years (group distribution not reported) Sex: not reported Any other details of important prognostic factors: background exposure to fluoride: community water supply approximately 0.1 ppm F Number randomised: 322 (Gp A: 78; Gp B: 83; Gp C: 78; Gp D: 83) Number evaluated: 284 at 3 years (available at final examination) (Gp A: 67; Gp B: 74; Gp C: 68; Gp D: 75) Attrition: overall 12% dropout after 3 years (study duration = 3 years). Reasons reported and no differential dropout
Interventions	**Comparison: FT versus FT** Gp A (n = 78): MFP (6% sorbitol 3% xylitol) 1100 ppm F; abrasive system: aluminium trihydrate; home use (unsupervised) twice daily Gp B (n = 83): NaF (6% sorbitol 3% xylitol) 135 ppm F; abrasive system: aluminium trihydrate; home use (unsupervised) twice daily Gp C (n = 78): MFP (9% sorbitol) 1100 ppm F; abrasive system: aluminium trihydrate; home use (unsupervised) twice daily Gp D (n = 83): NaF (9% sorbitol) 135 ppm F; abrasive system: aluminium trihydrate; home use (unsupervised) twice daily
Outcomes	Primary: 3-year net DFS - (CA) cl + DR (xr); DFS (at 1, 2, 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: number of *mutans Streptococci* and *Lactobacilli* in saliva Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: Kema Nobel Consumer Goods Division, Stockholm, Sweden Declarations/conflicts of interest: not reported Data handling by review authors: Gp A versus Gp B, and Gp C versus Gp D for purposes of analysis. SDs imputed Other information of note: clinical (VT) and radiographic (DR) caries assessment by single examiner according to Koch and Grondal criteria, diagnostic threshold = CA

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " All children taking part were randomly distributed into four experimental groups ...." Comment: random sequence generation not stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "The study was carried out double blind for subjects as well as for examiners, and the code was not broken until all data had been statistically evaluated" Comment: investigators and participants blinded
Incomplete outcome data (attrition bias)	Low risk	Overall dropout for length of follow-up: 12%. Reasons for dropout given as children moving from the area. No differential dropout. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	High risk	Outcomes reported: DFS final value - (CA) cl + (DR) xr, reported at 1, 2 and 3 years follow-ups. Numerical data not available for all groups, no standard deviations reported number of *mutans Streptococci* and *lactobacilli* in saliva Comment: trial protocol not available. All outcomes listed in Methods section were reported (DFS) but not numerically
Baseline characteristics balanced?	High risk	Prognostic factors reported: caries Comment: statistically significant imbalance reported in baseline DFS
Free of contamination/co-intervention?	Low risk	Quote: "Children were given toothpastes free of charge every 3 months throughout the study, in an amount sufficient to supply the whole household" Comment: contamination not observed

Piccione 1979

Methods	Trial design: 2-armed, unreported-blinding, placebo-controlled RCT Location: Italy Number of centres: 1; Leguano provincial hospital, Italy Recruitment period: study began in/before 1977
Participants	Inclusion criteria: residence within a 15 km radius of the hospital, and within an area served by the same aqueduct Exclusion criteria: requiring orthodontic treatment Baseline caries: 12.8 DMFS (Gp A: 13.0 DMFS; Gp B: 12.6 DMFS). Baseline characteristics (DMFS, DMFT) "homogeneous" Age at baseline (years): range 6 to 11 years (Gp A: mean 8.2 years; Gp B: mean 7.9 years) Sex: 22 F:28 M (Gp A: 12 F:13 M ; Gp B: 10 F:15 M) Any other details of important prognostic factors: background exposure to fluoride: none reported, although all participants received the same water supply Number randomised: 50 (Gp A: 25; Gp B: 25) Number evaluated: 35 (Gp A: 18; Gp B: 17) Attrition: dropout rate 30% after 12 months (study duration = 1 year). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT (1000 ppm SMFP + 1500 ppm NaF) versus PL** Gp A (n = 25): combination 2500 ppm F (SMFP 1000 ppm F + NaF 1500 ppm F); abrasive system: not reported; home use/unsupervised, daily frequency assumed Gp B (n = 25): placebo; abrasive system: not reported; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 1-year DMFS increment; DMFT (at 6 months, 1 year) Secondary: none assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 1 year
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: none

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... at random, subjects were assigned to one of two groups.."
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Unclear risk	Comment: insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	35/50 available for analysis. No reasons given; did not alter balance between groups. 30% dropout rate at 1 year
Selective reporting (reporting bias)	Unclear risk	Caries indices reported. Unclear whether clinical or radiographic data or both reported
Baseline characteristics balanced?	Unclear risk	Comment: baseline characteristics (DMFS, DMFT) "homogeneous"
Free of contamination/co-intervention?	Unclear risk	Comment: possible contamination. Sufficient toothpaste supplied for trial participant only

Powell 1981

Methods	Trial design: 4-armed, double-blind, placebo-controlled, stratified RCT Location: Australia Number of centres: not reported Recruitment period: study began 1963
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 21.4 DMFS (from sample developing caries) (Gp A: 21.5 DMFS (SE 1.12); Gp B: 21.2 DMFS (SE 0.90)). Baseline characteristic (DMFS) "balanced" Age at baseline (years): range 12 to 14 years (Gp A: 13.4 years (SE 0.04); Gp B: 13.4 years (SE 0.03)) (from sample developing caries). Baseline characteristic (age) "balanced" Sex: Gp A: 25 F (33%):51 M (67%); Gp B: 43 F (42%):59 M (58%)) (from sample developing caries). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride in community water supply fluoridated < 0.1 ppm F Number randomised: not reported, nor group distribution Number evaluated: not reported, nor group distribution Attrition: dropout rate not reported nor obtainable (study duration = 4 years). Reasons for attrition not reported; any differential group losses not assessable
Interventions	**Comparison: FT (pp/PIsol) versus PL (pp/PIsol)[a]** Gp A (n = not reported): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = not reported): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp C (n = not reported): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed; topical SnF_2 solution Gp D (n = not reported): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed; topical SnF_2 solution
Outcomes	Primary: progression rate of initial carious lesions in MD surfaces of permanent posterior teeth (caries increment data not reported nor obtainable) (at 1, 2, 3, and 4 years) Secondary: not reported Assessments irrelevant to this review's scope: none Follow-up duration: 4 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations only Data handling by review authors: [a]prior prophylaxis with lava pumice followed by professional application of placebo solution performed every 6 months for 2 years in both relevant groups compared. Not included in analyses. 2 other arms in trial ineligible for inclusion due to concurrent fluoride topical fluoride solution Other information of note: radiographic (postBW) enamel caries progression assessment by 1 examiner; state of tooth eruption included = E. High reproducibility of radiographic diagnosis (ICC = 0.91)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... subjects were assigned to four groups, using systematic random sampling by age, sex, class, and school" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	Quotes: "To determine the reproducibility of radiographic diagnoses, duplicate readings of radiographs taken at 48 month exam were made by the same examiner. To ensure that the examiner had no knowledge of the group, an independent observer randomly selected the subjects and nominated, at random, one or two lesions from each" and "Participants issued with either test or control dentifrice for the full 4 year period of the study" Comment: blinding of outcome assessor is mentioned but although it appears that only a small sample was assessed blindly for reproducibility
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: not reported. Dropout by group: not reported. Reasons for losses: not reported Comment: it is unclear if numbers lost were high for length of follow-up, if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants who had developed caries at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: caries increment (data not obtainable) progression rate of initial carious lesions in MD surfaces of permanent posterior teeth at annual intervals (for 4 years) Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 21.2 (0.90) FT, 21.5 (1.12) PL gender (M): 58 FT, 67 PL age: 13.4 (0.03) FT, 13.4 (0.04) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Rao 2009

Methods	Trial design: 3-armed, triple-blind, placebo-controlled, stratified RCT Location: India Number of centres: 2 schools, Bangalore, India Recruitment period: study began 2004
Participants	Inclusion criteria: healthy; high caries risk + previous caries experience (dmft/DMFT > 2) + deep pits/fissures; poor oral hygiene; low socio-economic status Exclusion criteria: illness; caries risk-antagonist medication use; severe malocclusion; current orthodontic treatment; dental hypoplasia presence; consent refusal Baseline caries: 2.42 DMFS (groups relevant to review: Gp A: 2.20 DMFS (SD 2.57); Gp B: 2.62 DMFS (SD 2.62)) (evaluated participants only). Baseline characteristics similar (DMFS, proportion caries free, oral hygiene) Age at baseline (years): range 12 to 15 years, mean 13.4 years (groups relevant to review: Gp A: mean 13.46 years (SD 0.89); Gp B: mean 13.48 years (SD 0.86)) (evaluated participants only). Baseline characteristic similar (age) Sex: 73 F:77 M (groups relevant to review: Gp A: 22 F:25 M; Gp B: 21 F:24 M) (evaluated participants only) Any other details of important prognostic factors: background exposure to fluoride: not reported Number randomised: 150 (groups relevant to review: Gp A: 50; Gp B: 50) Number evaluated: 139 at 2 years (available at final examination) (groups relevant to review: Gp A: 47; Gp B: 45) Attrition: 8% dropout after 2 years (study duration = 2 years). Reason for dropout given as change to school and thus no longer eligible. No differential group losses
Interventions	**Comparison: FT, CPP versus PL** Gp A (n = 50): SMFP 1000 ppm F; abrasive system: Ca carbonate; home use (unsupervised) and school use (supervised), twice daily Gp B (n = 50): placebo; abrasive system: Ca carbonate; home use (unsupervised) and school use (supervised), twice daily Gp C (n = 50): CPP; abrasive system: Ca carbonate; home use (unsupervised) and school use (supervised), twice daily
Outcomes	Primary: 2-year DS increment - (CA) cl; DMFS; DS; number of new lesions (at 1, 2 years) Secondary: adverse events Assessments irrelevant to this review's scope: OHI; compliance Follow-up duration: 2 years
Notes	Adverse effects: "There were no incidents of allergy or any adverse reactions" Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: Gp C (CPP) omitted from analysis Other information of note: participants at high caries risk with previous caries dmft/DMFT > 2, poor oral hygiene and low socio-economic status. Clinical (VT) caries assessment by 1 examiner according to WHO criteria, diagnostic threshold not stated, CA assumed. No radiographic assessment. Intra- examiner reproducibility of clinical caries diagnosis (DMFS) assessed in 20 children. Kappa 0.74 to 0.85

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 150 selected subjects were first stratified according to age. From each age group subjects were randomly allocated to three groups of 50 by shuffling and picking the chits containing the subjects' names" Comment: random sequence generation stated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	Quotes: "The toothpastes prepared as below were coded by coloring the toothpaste tubes red, green or black, to ensure blinding of the investigator, the subjects and the statistician" and "All three types of toothpaste were similar in consistency, color and flavor to avoid any bias" Comment: investigators and participants blinded
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "11 children dropped out since they changed to nonparticipating schools after 1 year and were not available for the 24-month follow-up" Comment: overall dropout for length of follow-up: 7% in 2 years. No differential dropout. Reasons for losses stated. Caries data used in analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Unclear risk	Outcomes reported: DS increment - (CA) cl, reported at 1 and 2 years follow-ups DS OHI compliance adverse events Comment: trial protocol not available. Not all outcomes listed in Methods section were reported (DMFS)
Baseline characteristics balanced?	Unclear risk	Prognostic factors reported: age, sex, caries, OHI Comment: all appear balanced
Free of contamination/co-intervention?	Unclear risk	Quote: "There were no cases of exchange of toothpaste tubes since the color of the toothpaste tube was cross- checked against the assigned color" Comment: contamination not observed

Reed 1973

Methods	Trial design: 4-arm, double-blind, placebo-controlled, RCT Location: USA Number of centres: not reported ("several elementary schools") Kansas City, Missouri, USA Recruitment period: study began in/before 1970
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 3.3 DMFS (Gp A: 3.36 DMFS (SE 0.158); Gp B: 3.39 DMFS (SE 0.172); Gp C: 3.47 DMFS (SE 0.163); Gp D: 3.46 DMFS (SE 0.165)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 6 to 14 years, mean 9 years (Gp A: 9.02 years; Gp B: 9.00 years; Gp C: 9.02 years; Gp D: 9.06 years). Baseline characteristic (age) "balanced" Sex: 1022 F:1082 M (Gp A: 252 F:279 M; Gp B: 264 F:273 M; Gp C: 251 F:262 M; Gp D: 255 F:268 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: Background exposure to fluoride: none reported. Community water supply not fluoridated. Number randomised: 2104 (Gp A: 531; Gp B: 537; Gp C: 513; Gp D: 523) Number evaluated: 1525 at 2 years (available at final examination) (Gp A: 379; Gp B: 387; Gp C: 362; Gp D: 397) Attrition: 28% dropout after 2 years (study duration = 2 years). Reasons for attrition not described; no differential group losses
Interventions	**Comparison: FT (3 groups) versus PL** Gp A (n = 531): NaF 250 ppm F; abrasive system: high beta-phase calcium pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 537): NaF 500 ppm F; abrasive system: high beta-phase calcium pyrophosphate; home use/unsupervised, daily frequency assumed Gp C (n = 513): NaF 1000 ppm F; abrasive system: high beta-phase calcium pyrophosphate; home use/unsupervised, daily frequency assumed Gp D (n = 523): placebo; abrasive system: high beta-phase calcium pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - cl + xr; DMFT (at 1, 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported, institutional affiliation only Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported; state of tooth eruption included not reported. Radiographic assessment (up to 7 BW) by 1 examiner, diagnostic threshold not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After initial clinical caries examination, children were placed in strata by age, sex and visual DMFS scores. Children within each strata were assigned by random permutation of four, to one of these dentifrices"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The dentifrices were similar in colour, flavour and other consumer properties and were supplied in coded tubes. Participants were not aware of the contents of the assigned dentifrice" and "The investigator was unaware of the dentifrice assignment for the participants during the examinations and radiographic interpretations" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 28% in 2 years. Dropout by group: 151/513 FT 1, 150/537 FT 2, 142/531 FT 3, 126/523 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high given length of follow-up with some differential losses between 2 groups (29.4% FT 1, 27.9% FT 2, 26.7% FT 3, 24.1% PL). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 1 and 2 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 3.36 (3.64) FT 1, 3.39 (3.99) FT 2, 3.47 (3.69) FT 3, 3.46 (3.77) PL DMFT: 2.32 (2.17) FT 1, 2.37 (2.41) FT 2, 2.45 (2.22) FT 3, 2.40 (2.26) PL gender: 279 M, 252 F FT 1; 273 M, 264 F FD2; 262 M, 251 F FT 3; 268 M, 255 F PL age: 9.02 FT 1, 9.00 FT 2, 9.02 FT 3, 9.06 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "A family supply of the appropriate toothpaste (in coded tubes) and toothbrushes were distributed every 2 months..." Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Reed 1975

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported ("several elementary schools") Kansas City, Missouri, USA Recruitment period: study began in/before 1968
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 5 DMFS (Gp A: 4.83 DMFS (SE 0.256); Gp B: 5.19 DMFS (SE 0.273)). Baseline characteristics (DMFS, DMFT) with some imbalance Age at baseline (years): range 8 to 13 years, mean 9.7 years (Gp A: 9.7 years; Gp B: 9.7 years). Baseline characteristic (age) with some imbalance Sex: 272 F:295 M (Gp A: 136 F:143 M; Gp B: 136 F:152 M). Baseline characteristic (sex) with some imbalance Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply not fluoridated Number randomised: 567 (Gp A: 279; Gp B: 288) Number evaluated: 344 at 2 years (available at final examination) (Gp A: 168; Gp B: 176) Attrition: 39% dropout after 2 years (study duration = 2 years). Reasons for high dropout not described; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 279): NaF 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 288): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - cl + xr; DMFT (at 1, 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported, institutional affiliation only Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported; state of tooth eruption included not reported. Radiographic assessment (up to 7 BW) by 1 examiner, diagnostic threshold not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Following the initial clinical caries examinations, the subjects were stratified by age, sex, visual DMFS and assigned at random to one of the following 2 dentifrices.." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "... to one of the following 2 dentifrices: control dentifrice.... or test dentifrice.... Both products were similar in colour, flavour, and other consumer properties" and "A double blind study...." Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 39% in 2 years. Dropout by group: 111/279 FT, 112/288 PL. Reasons for losses: not reported Comment: numbers lost were high given length of follow-up. No differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 1 and 2 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 4.83 FT, 5.19 PL DMFT: 3.00 FT, 3.24 PL age: 9.73 FT, 9.70 PL gender: 143 M, 136 F FT; 152 M, 136 F PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "A family supply of the appropriate toothpaste (in coded tubes) and toothbrushes were distributed every 2 months..." Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Ringelberg 1979

Methods	Trial design: 8-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: 9 middle schools, Pensacola, Florida, USA Recruitment period: study began 1973
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 4.2 DMFS (groups relevant to review: Gp A: 4.21 DMFS (SE 0.40); Gp B: 3.69 DMFS (SE 0.34); Gp C: 4.30 DMFS (SE 0.41); Gp D: 4.95 DMFS (SE 0.54)) (evaluated participants only). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): 10 to 11 years, mean 11 years (group distribution not reported) Sex: 292 F:264 M (groups relevant to review: Gp A: 97 F:87 M; Gp B: 98 F:88 M; Gp C: 44 F:50 M; Gp D: 53 F:39 M) (evaluated participants only) Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply fluoridated < 0.1 ppm F Number randomised: 2056 for all groups (group distribution not reported) Number evaluated: 1245 at 2.5 years (available at final examination) (groups relevant to review: 556 (Gp A: 184; Gp B: 186; Gp C: 94; Gp D: 92)) Attrition: 37% dropout after 2.5 years (study duration = 2.5 years). Reasons for attrition not described; no differential group losses
Interventions	**Comparison: FT (2 groups) versus PL (2 groups)** Gp A (n = evaluated 184): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = evaluated 186): AmF 1250 ppm F; abrasive system: not reported; home use/unsupervised, daily frequency assumed Gp C (n = evaluated 94): placebo; abrasive system: Ca pyrophosphate (SnF_2 's placebo); home use/unsupervised, daily frequency assumed Gp D (n = evaluated 92): placebo; abrasive system: not reported; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2.5-year net DMFS increment - (CA) cl + (DR) xr; DMFT (at 2.5 years) Secondary: stain score (at 2.5 years) Assessments irrelevant to this review's scope: n/a Follow-up duration: 2.5 years
Notes	Adverse effects: not reported Funding source: National Institute of Dental Research by National Caries Program grant (Contract no. N01-DE-32427) Declarations/conflicts of interest: SnF_2 toothpaste formulated by Menley and James Laboratories, Philadelphia; AmF toothpaste formulated by Procter & Gamble, Cincinatti. Institutional affiliations reported Data handling by review authors: Gps A + B versus C + D combined in analyses Other information of note: 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 not reported. Reversal rate between 4% and 9% of observed caries increment in the groups. 4 additional study arms irrelevant to scope of this review due to additional active caries agent use (fluoride mouthrinses)

Risk of bias table

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 (performance bias and detection bias)	Low risk	Quotes: "A double-blind design was used; neither examiner nor subjects were aware of the type of treatment received" and "The placebo preparations were all fully formulated like their active fluoride ingredient, but did not have the specific active fluoride ingredient" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 37% in 2.5 years. Dropout by group: 111/295 FT 1, 111/297 FT 2, 52/147 PL 1, 55/149 PL 2. Reasons for losses: not reported Comment: numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if reasons for the 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 - (CA) cl + (DR) xr, reported at 2.5 years follow-up DMFT stain score Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFT: 2.27 (0.17) FT 1, 2.49 (0.20) PL 1, 2.15 (0.18) FT 2, 2.72 (0.28) PL 2 DMFS: 4.21 (0.40) FT 1, 4.30 (0.41) PL 1, 3.69 (0.34) FT 2, 4.95 (0.54) PL 2 Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Family members were supplied with the same dentifrice to encourage the use of the test products only by the study participants during the trial. The dentifrice was mailed to their homes to minimize the possibility of the dentifrice being lost, discarded or exchanged" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Ripa 1988

Methods	Trial design: 3-armed, double-blind, head-to-head, stratified RCT Location: USA Number of centres: 2 school districts in 20 mile range (number of schools not reported), Long Island, New York, USA Recruitment period: study began 1982
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 3.8 DMFS (Gp A: 3.71 DMFS (SD 4.00); Gp B: 3.92 DMFS (SD 4.10); Gp C: 3.91 DMFS (SD 4.41)). Baseline characteristic (baseline DMFS) "comparable" Age at baseline (years): range 9 to 15 years, mean 11.7 (Gp A: 11.7 years; Gp B: 11.7 years; Gp C: 11.7 years). Baseline characteristic (age) "comparable" Sex: distribution not reported. Baseline characteristic (sex) reported to be "comparable" Any other details of important prognostic factors: background exposure to fluoride: community water supply < 0.1 ppm F Number randomised: 3785 (Gp A: 1242; Gp B: 1250; Gp C: 1293) Number evaluated: 2509 at 3 years (available at final examination) (Gp A: 827; Gp B: 824; Gp C: 858) Attrition: 34% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: change of residence (54%), withdrew (27.4%), orthodontically banded, absent at final examination; no differential group losses
Interventions	**Comparison: FT (3 groups)** Gp A (n = 1242): SMFP 1000 ppm F; abrasive system: IMP then dicalcium phosphate dihydrate; home use/unsupervised, daily frequency assumed Gp B (n = 1250): combination 1000 ppm F (SMFP 500 ppm F + NaF 500 ppm F); abrasive system: silica; home use/unsupervised, daily frequency assumed Gp C (n = 1293): combination 2500 ppm F (SMFP 1250 ppm F + NaF 1250 ppm F); abrasive system: silica; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - cl; DMFS increment by surface (at 3 years). DMFT results reported for 2-year follow-up only Secondary: none assessed Assessments irrelevant to this review's scope: compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: partial funding by National Institute of Dental Research, US Public Health Service, Contract no. NO1DE12431. Other partial source not reported Declarations/conflicts of interest: institutional affiliations reported Data handling by review authors: groups A + B versus C in analyses Other information of note: clinical caries assessment by 2 calibrated examiners, whose results were pooled and analysed together. No values for reliability

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quotes: ".... stratified according to age, sex, and initial caries score and were randomly assigned to one [of] three dentrifice groups" and "randomly assigned to one of three dentifrice groups"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "A double-blind protocol was used" and "... dentrifices were identically packaged in plain white tubes except for subject's name and code number on a plain label"
Incomplete outcome data (attrition bias)	Unclear risk	2509/3785 available at 3 years. Attrition mainly due to moving away from area; did not alter balance between groups. 34% dropout at 3 years; unlikely to be due to intervention Comment: some participants were withdrawn
Selective reporting (reporting bias)	Low risk	Clinical assessments only
Baseline characteristics balanced?	Low risk	Comment: comparable values for age, sex and DMFS at baseline
Free of contamination/co-intervention?	Low risk	Comment: no apparent cause for concern regarding contamination. Participant's siblings assigned same toothpaste. Toothpaste clearly labelled with participant's name. Compliance assessed by telephone

Rule 1984

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: 7 schools in 3 semi-rural North-Eastern Connecticut communities Recruitment period: study began 1977
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 8.6 DMFS (Gp A: 8.28 DMFS (SE 0.25); Gp B: 8.72 DMFS (SE 0.27)). Baseline characteristics (TAR, DMFS, DMFT, DS, DT) "balanced" (DFS baseline data not reported) Age at baseline (years): range 9 to 12 years, mean 11 (Gp A: 11.30 years (SE 0.05); Gp B: 11.24 years (SE 0.05)). Baseline characteristic (age) "balanced" Sex: 551 F:603 M (Gp A: 275 F:320 M; Gp B: 276 F:283 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: community, home, school water supplies < 0.3 ppm F except for 1 school at 1.4 ppm F Number randomised: 1154 (Gp A: 595; Gp B: 559) Number evaluated: 876 at 2 years (present for all examinations) (Gp A: 460; Gp B: 416) Attrition: 24% dropout after 2 years (study duration = 2 years). Reasons for attrition not described; exclusions based on presence in all follow-up examinations; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 595): SMFP 1000 ppm F; abrasive system: silica zerogel; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use) Gp B (n = 559): placebo; abrasive system: silica zerogel; school use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use)
Outcomes	Primary: 2-year DFS increment - (E + U) (CA) cl + (ER) xr; O-DFS; MD-DFS; DFT; DMFS; DMFT(at 1, 2 years) Secondary: oral soft tissue lesions (at 1, 2 years) Assessments irrelevant to this review's scope: not reported Follow-up duration: 2 years
Notes	Adverse effects: "No lesions attributable to product use were noted" Funding source: grant from Lever Brothers Company Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment (FOTI used) by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Reproducibility checks done in 10% sample clinically and radiographically

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were stratified according to school, grade and sex and randomly assigned to one of two groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "One group received the sodium monofluorophosphate dentifrice, and other group the placebo. The study was conducted under double-blind conditions" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 24% in 2 years. Dropout by group: 135/595 FT, 143/559 PL. Reasons for losses: exclusion based on presence at all examinations Comment: numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (E + U) (CA) cl + (ER) xr, reported at 1 and 2 years follow-ups DFT DMFS DMFT O-DFS MD-DFS oral soft tissue lesions Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: age: 11.30 FT, 11.24 PL TAR: 13.84 FT, 13.37 PL sex: 320 M, 275 F FT; 283 M, 276 F PL DMFS: 8.28 FT, 8.72 PL DMFT: 5.21 FT, 5.48 PL DS: 5.87 FT, 6.16 PL DT: 3.55 FT, 3.78 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Sufficient quantity were provided to ensure adequate supply for both students and families throughout the year, including summer vacation" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Segal 1967

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: single school district (number of schools not reported), in rural Western Pennsylvania Recruitment period: study began in/before 1964
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: not reported Baseline characteristics (SAR) "balanced" Age at baseline (years): range 7 to 12 years (group distribution not reported) Sex: not reported Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply which did not contain significant levels of the fluoride ion (F level not reported) Number randomised: 845 (Gp A: 425; Gp B: 420) Number evaluated: 648 at 2 years (available at final examination) (Gp A: 338; Gp B: 310) Attrition: 23% dropout after 2 years (study duration = 2 years). Reasons for attrition not reported; slight differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 425): SnF_2 1000 ppm F; abrasive system: IMP (mainly); school use/supervised, daily (appropriate toothpaste also provided for home use) Gp B (n = 420): placebo; abrasive system: IMP (mainly); school use/supervised, daily (appropriate toothpaste also provided for home use)
Outcomes	Primary: 2-year DFS increment - (CA) cl + xr; DFS (U) (at 1, 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: partially funded by Lever Brothers Company. Other partial source of funding not reported Declarations/conflicts of interest: 1 (A Picozzi) of 4 authors employed by Lever Brothers. Remaining authors declare institutional affiliations Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment as a supplementary aid, diagnostic threshold not reported. State of tooth eruption included E/U. Inter- and intra-examiner reproducibility checks done

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In order to achieve adequate balance between test and control groups in terms of previous caries experience, all the children were classified in blocks according to school, age, sex..... Within each block the subjects were assigned at random to one of four subgroups..." Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "... No reference to the findings of previous examinations was permitted at any time. The study was conducted as a double blind investigation. At the time of the initial exam, preassigned coded dentifrices were distributed to the children" and "Control dentifrice contained no stannous fluoride" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 23% in 2 years. Dropout by group: 87/425 FT, 110/420 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high given length of follow-up, but with some differential losses between groups (20% FT, 26% PL). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (CA) cl + xr, reported at 1 and 2 years follow-ups DFS (U) Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factor reported: SAR: 77.34 FT, 76.49 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "Sufficient dentifrice was distributed to the panelists for family use" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Slack 1964

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: UK Number of centres: 4 secondary schools, Kent, UK Recruitment period: study began 1962
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: not reported. Baseline characteristics "balanced" Age at baseline (years): range 11 to 13 years (group distribution not reported). Baseline characteristics "balanced" Sex: 459 F:600 M (Gp A: 231 F:303 M; Gp B: 228 F:297 M). Baseline characteristics "balanced" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supplies 0.07 ppm F Number randomised: 1059 (Gp A: 534; Gp B: 525) Number evaluated: 719 at 2 years (present for all examinations) (Gp A: 365; Gp B: 354) Attrition: 32% dropout rate after 2 years (study duration = 2 years). Reasons for attrition: natural losses and other reasons; exclusions based on presence in all follow-up examinations; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 534): SnF_2 1000 ppm F; abrasive system: IMP; home use/unsupervised, 3 times/day instructed but daily frequency assumed Gp B (n = 525): placebo; abrasive system: dicalcium phosphate (dihydrate); home use/unsupervised, 3 times/day instructed but daily frequency assumed
Outcomes	Primary: proportion of carious teeth/surfaces (by tooth type); proportion of caries-free teeth/surfaces (by tooth type) developing caries annually (at 1, 2 years) (caries increment data not reported nor obtainable) Secondary: proportion of children with tooth staining (at 1, 2 years) Assessments irrelevant to this review's scope: gum condition, dental cleanliness Follow-up duration: 2 years
Notes	Adverse effects: stains "In all, 178 black/brown [stains at 1 year examinations] were recorded and it was found subsequently that these fell into both the study and control groups. A similar result was obtained in the 1964 examinations [2 years]. On both occasions, however, there were significantly more black/brown stains in the study groups [Gp A]" Funding source: funded by Unilever Declarations/conflicts of interest: institutional affiliations only Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children, whose parents had accepted the invitation, were then allocated at random to the study and control groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The trial was conducted double-blind; the examiner, scribe and the subjects did not know who was receiving the stannous fluoride dentifrice. Furthermore, the identity of the test group was not disclosed until the analysis of the 2 year results had been completed" and "Control dentifrice issued to control group" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 32% in 2 years. Dropout by group: 169/534 FT, 171/525 PL. Reasons for losses: attrition: "three children (boys) who withdrew from the trial. In two cases no reason was given, but in the third case, it was stated that 'the toothpaste was staining the teeth'. This family was receiving the control paste", exclusions based on presence at all examinations Comment: numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced between groups. Caries data used in the analysis pertain to participants present for all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: caries increment (data not obtainable) proportion of carious teeth/surfaces (by tooth type) reported at 1 and 2 years follow-ups proportion of caries-free teeth/surfaces (by tooth type) which developed caries after each year proportion of children with tooth staining Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Unclear risk	Prognostic factors reported: percentage DMFT: incisors: 8.6 FT, 8.8 PL; canines: 0.8 FT, 0.7 PL; premolar: 16.2 FT, 17.8 PL percentage DMFS: incisors: 3.3 FT, 3.6 PL; canines: 0.2 FT, 0.2 PL; premolar: 4.8 FT, 4.7 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The aim was to maintain a constant and adequate supply of dentifrice and brushes for the whole family" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Slack 1967

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: UK Number of centres: 11 secondary technical/grammar schools across Kent, UK Recruitment period: study began 1963
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 8.9 DFS (Gp A: 8.72 DFS (SE 0.281); Gp B: 9.13 DFS (SE 0.317)). Baseline characteristics (DFS, DFT, DMFS, DMFT, TAR) "balanced" Age at baseline (years): mean 11 years 11 months (Gp A: 11 years 11.5 months; Gp B: 11 years 11.4 months). Baseline characteristics (age, dental age) "balanced" Sex: 886 F:0 M Any other details of important prognostic factors: background exposure to fluoride: none reported Number randomised: 886 (Gp A: 443; Gp B: 443) Number evaluated: 696 at 3 years, all female (present for all examinations) (Gp A: 356; Gp B: 340) Attrition: 21% dropout rate after 3 years (study duration = 3 years). Reasons for dropout described with numbers: left school, moved away, staining of teeth, on parents request; exclusions based on presence in all follow-up examinations; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 443): SnF_2 1000 ppm F; abrasive system: IMP; home use/unsupervised, daily frequency assumed Gp B (n = 443): placebo; abrasive system: dicalcium phosphate (dihydrate); home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DFS increment - (E) (CA) cl; posterior MD-DFS; DFT; DMFS; DMFT (at 1, 2, 3 years) Secondary: proportion of children with tooth staining (at 1, 2, 3 years) Assessments irrelevant to this review's scope: soft tissues; dental cleanliness Follow-up duration: 3 years
Notes	Adverse effects: stains (all stains at 3 years: percentage of each group. Gp A: 39.2%; Gp B: 12.7%). Reasons for losses: staining: Gp A n = 6; Gp B n = 1 Funding source: Unilever Ltd Declarations/conflicts of interest: institutional affiliations only Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Consistency of clinical diagnosis maintained by re-examination of 10% sample and calibration checks made against reserve examiner

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "As permission was received for participation, each child was randomly allocated within his own school, to the control and study groups" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "This 3 year clinical trial..... was conducted double-blind" and "The films from all 4 examinations were read at the end of the trial by one examiner, and charted seperate from the clinical examination data. The examiner did not know to which group the films belonged" and "The control dentrifice was essentially the insoluble metaphosphate silica paste as used for the study product" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Low risk	Overall dropout for length of follow-up: 21% in 3 years. Dropout by group: 87/443 FT, 103/443 PL. Reasons for losses: staining: 6 FT, 1 PL; moved away: 29 FT, 39 PL; changed school: 5 FT, 5 PL; parents' request: 5 FT, 6 PL; exclusion based on presence at all examinations: 42 FT, 52 PL Comment: numbers lost were not unduly high given length of follow-up with no differential losses between groups. Reasons for the missing outcome data are acceptable and balanced, except for staining, which although related to the intervention, would not affect outcome due to very small loss (causing no obvious imbalance). Caries data used in the analysis pertain to participants present at all examinations
Selective reporting (reporting bias)	Low risk	Outcomes repoted: DFS increment - (E) (CA) cl, reported at 1, 2 and 3 years follow-ups DFT DMFS DMFT posterior MD-DFS proportion of children with tooth staining Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 8.72 FT, 9.13 PL DFT: 6.21 FT, 6.06 PL DMFS: 12.36 FT, 12.25 PL DMFT: 6.82 FT, 6.86 PL age: 12 FT, 12 PL dental age: 24.80 FT, 24.33 PL TAR: 18.61 FT, 18.27 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The dentifrices were supplied by mail to the participants and their families.... One tube per person per month in each family was supplied..." Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Slack 1967a

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: UK Number of centres: 18 'educationally selective' secondary schools (assuming high socio-economic status?) across Essex, UK Recruitment period: study began 1962
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 7 DFS (Gp A: 7.18 DFS (SE 0.208); Gp B: 6.76 DFS (SE 0.190)). Baseline characteristics (DFS, DFT, DMFS, DMFT, TAR) "balanced" Age at baseline (years): range 11 to 12 years, mean 11.7 years (Gp A: 11 years 7.3 months (SE 0.152 months); Gp B: 11 years 8.2 months (SE 0.169 months)). Baseline characteristics (age, dental age) "balanced" Sex: 961 F:0 M Any other details of important prognostic factors: background exposure to fluoride: none reported Number randomised: 961 (Gp A: 479; Gp B: 482) Number evaluated: 757 at 3 years, all female (present for all examinations) (Gp A: 376; Gp B: 381) Attrition: 21% dropout rate after 3 years (study duration = 3 years). Reasons for dropout described with numbers: left school, moved away, staining of teeth, on parents request; exclusions based on presence in all follow-up examinations; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 376): SnF_2 1000 ppm F; abrasive system: dicalcium pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 381): placebo; abrasive system: dicalcium pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DFS increment - (E) (CA) cl; posterior MD-DFS; DFT; DMFS; DMFT (at 1, 2, 3 years) Secondary: proportion of children with tooth staining (at 1, 2, 3 years) Assessments irrelevant to this review's scope: soft tissues; dental cleanliness Follow-up duration: 3 years
Notes	Adverse effects: stains (all stains at 3 years: percentage of each group. Gp A: 42%; Gp B: 16%). Reasons for losses: staining: Gp A n = 2; Gp B n = 0 Funding source: Procter & Gamble Declarations/conflicts of interest: institutional affiliations only Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Consistency of clinical diagnosis maintained by re-examination of 10% sample and calibration checks made against reserve examiner

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "These girls were randomly allocated within the 18 schools to either the control or study group" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The films from all were read at the end of the trial by one examiner, and charted seperate from the clinical examination data. The examiner did not know to which group the films belonged" and "The dentifrices were wrapped in non-proprietary wrapping and package identified by the manufacturer's code" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Low risk	Overall dropout for length of follow-up: 21% in 3 years. Dropout by group: 103/479 FT, 101/482 PL. Reasons for losses: staining: 2 FT, 0 PL; moved away: 35 FT, 32 PL; changed school: 2 FT, 3 PL; parents' request: 7 FT, 3 PL; exclusion based on presence at all examinations: 57 FT, 63 PL Comment: numbers lost were not unduly high given length of follow-up with no differential losses between groups. Reasons for the missing outcome data are acceptable and balanced, except for staining, which although related to the intervention, did not affect outcome (very small loss causing no real imbalance). Caries data used in the analysis pertain to participants present at all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - (E) (CA) cl, reported at 1, 2 and 3 years follow-ups DFT DMFS DMFT posterior MD-DFS proportion of children with tooth staining Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 7.18 FT, 6.76 PL DFT: 4.90 FT, 4.75 PL DMFS: 9.23 FT, 9.23 PL DMFT: 5.31 FT, 5.24 PL age: 12 FT, 12 PL dental age: 23.98 FT, 23.62 PL TAR: 19.06 FT, 18.87 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "To aid co-operation and the opportunity for personal contact, two home visitors were appointed to deliver the products personally. The toothpastes were delivered to the homes of the subjects in quantities sufficient to provide a constant supply for all members of the household" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Slack 1971

Methods	Trial design: 5-armed, double-blind, placebo-controlled RCT Location: UK Number of centres: 21 secondary schools across Hounslow borough, London Recruitment period: study began 1965
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 11.6 DMFS (Gp A: 12.20 DMFS; Gp B: 10.87 DMFS; Gp C: 11.59 DMFS; Gp D: 11.81 DMFS) (evaluated participants only). Baseline characteristic (DMFS) "balanced" Age at baseline (years): range 11 to 12 years (Gp A: 12 years 1 month; Gp B: 12 years 1 month; Gp C: 12 years 1 month; Gp D: 12 years 0 month). Baseline characteristic (age) "balanced" Sex: not reported overall (Gp A: 47.1% F:52.9% M; Gp B: 47.0% F:53.0% M; Gp C: 47.4% F:52.6% M; Gp D: 47.4% F:52.6% M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: none reported. Baseline characteristic (previous F toothpaste use) "balanced" Number randomised: 2063 (groups relevant to review: 1665; Gp A: 423; Gp B: 412; Gp C: 422; Gp D: 408) Number evaluated: 1415 at 3 years (available at final examination) (groups relevant to review: 1110; Gp A: 260; Gp B: 282; Gp C: 279; Gp D: 289) Attrition: 33% dropout rate after 3 years (study duration = 3 years). Main reasons for dropout: moved away, left school, away on examination day, disliked toothpaste taste, brown staining of teeth; no differential group losses
Interventions	**Comparison: FT (3 groups) versus 'PL'** Gp A (n = 423): SnF_2 1000 ppm F; abrasive system: IMP; home use/unsupervised, daily frequency assumed Gp B (n = 412): SnF_2 1000 ppm F; abrasive system: dicalcium pyrophosphate; home use/unsupervised, daily frequency assumed Gp C (n = 422): APF 1000 ppm F; abrasive system: IMP; home use/unsupervised, daily frequency assumed Gp D (n = 408): placebo; abrasive system: not reported; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year crude DMFS increment - (CA) cl + (ER) xr (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: Dr W Elvers and Bristol-Myers Company, New York Declarations/conflicts of interest: institutional affiliations only Data handling by review authors: 5th study arm ineligible for inclusion in review due to no intervention ("unsupervised"). Gps A + B + C versus D in analyses Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner, diagnostic threshold = ER. Consistency of clinical diagnosis revealed by 10% sample checks at each examination

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were randomly allocated to groups, apart from brothers, sisters and others living in the same household who were allocated to the same group" Comment: not enough information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "Dentifrices were made up in large white tubes marked only with a double letter codes... 3 fluoride and 1 non-fluoride" and "At the time of examination, the examiner had no knowledge of the group to which any child belonged" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 33% in 3 years. Dropout by group: 163/423 FT 1, 153/422 FT 2, 130/412 FT 3, 119/408 PL. Reasons for losses: staining of teeth: 3 FT, 4 PL; unpleasant taste (mainly fluoride groups); moved away, changed school, away on examination day Comment: numbers lost were not unduly high given length of follow-up with differential losses between groups (FT 1 39%, FT 2 34%, FT 3 32%, PL 29%). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination. Group losses unlikely to be related to intervention
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (CA) cl + (ER) xr, reported at 3 years follow-up Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 12.20 FT 1, 11.59 FT 2, 10.87 FT 3, 11.81 PL mean age: 12 years (all groups) gender (M/F percentage): 52.9%/47.8% FT 1, 52.6%/47.4% FT 2, 53%/47% FT 3, 52.6%/47.4% PL F users (percentage): 10.4% FT 1, 11% FT 2, 10.8% FT 3, 10.1% PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "... children joining the trial were randomly allocated to 5 groups, apart from brothers, sisters and others living in the same household who were allocated to the same group" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Stephen 1988

Methods	Trial design: 6-armed, double-blind, head-to-head, stratified RCT Location: UK Number of centres: 12 secondary schools, Lanarkshire, Scotland, UK Recruitment period: study began 1983
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 10.2 DMFS (Gp A: 10.02 (SD 8.39); Gp B: 10.34 (SD 8.23); Gp C: 10.14 (SD 8.51)) and 10.2 DMFS zinc citrate trihydrate groups (Gp D: 10.10 (SD 7.89); Gp E: 10.01 (SD 8.29); Gp F: 10.42 (SD 8.53)). Baseline characteristics (baseline DMFS) "well balanced" Age at baseline (years): range 11 to 14 years, mean 12.55 years (group distribution not reported) Sex: 1199 F:1118 M (Gps A + D: 468 F:453 M; Gps B + E: 490 F:440 M; Gps C + F: 241 F:225 M) Any other details of important prognostic factors: background exposure to fluoride: not reported Number randomised: 3003 (Gp A: 599; Gp B: 600; Gp C: 299; Gp D: 596; Gp E: 603; Gp F: 306) Number evaluated: 2317 at 3 years (available at final examination) (Gp A: 469; Gp B: 464; Gp C: 239; Gp D: 452; Gp E: 466; Gp F: 227) Attrition: 23% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: excluded for non-compliance, withdrew, absent at final examination; no differential group losses
Interventions	**Comparison: FT (6 groups)[a]** Gp A (n = 599): SMFP 1000 ppm F; abrasive system: alumina trihydrate; home use/unsupervised, daily frequency assumed Gp B (n = 600): SMFP 1500 ppm F; abrasive system: alumina trihydrate; home use/unsupervised, daily frequency assumed Gp C (n = 299): SMFP 2500 ppm F; abrasive system: alumina trihydrate; home use/unsupervised, daily frequency assumed Gp D (n = 596): SMFP 1000 ppm F + 0.5% zinc citrate trihydrate; abrasive system: alumina trihydrate; home use/unsupervised, daily frequency assumed Gp E (n = 603): SMFP 1500 ppm F + 0.5% zinc citrate trihydrate; abrasive system: alumina trihydrate; home use/unsupervised, daily frequency assumed Gp F (n = 306): SMFP 2500 ppm F + 0.5% zinc citrate trihydrate; abrasive system: alumina trihydrate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DMFS increment - cl + xr; DMFS increment by sex, clinician, tooth type, surface type (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: none reported Data handling by review authors: [a]TMP groups entered separately in analysis Other information of note: clinical (VT) caries assessment undertaken by 2 calibrated examiners. 5% re-examined annually by allocated examiner and 5% by alternate examiner. Good intra- (0.92 to 0.99 clinical, 0.98 to 0.99 radiographic) and inter-examiner (0.92 to 0.97 clinical, 0.99 radiographic) reliability

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... prospective participants were allocated sequential numbers ... one clinician saw all odd-numbered .... the other all even-numbered ... [following baseline examination] children were allocated to one of six toothpaste groups by stratified randomisation ... using computer constructed random number tables"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "double blind" and "The dentrifices were supplied in colour coded tubes, the particular composition of the toothpastes being unknown to the clinicians, home visitors or subjects"
Incomplete outcome data (attrition bias)	Unclear risk	2317/3044 available for analysis. Due to leaving the trial, excluded for non-compliance, or absent at examination; did not alter balance between groups. 23% dropout rate at 3 years Comment: some participants were excluded for non-compliance
Selective reporting (reporting bias)	Low risk	DMFS increment. Clinical and radiographic assessments
Baseline characteristics balanced?	Low risk	Comment: baseline caries scores from combined clinical/radiographic data comparable
Free of contamination/co-intervention?	Low risk	Comment: no apparent cause for concern regarding contamination. Sufficient toothpaste supplied for whole family

Stephen 1994

Methods	Trial design: 6-armed, double-blind, head-to-head, stratified RCT Location: UK Number of centres: not reported. Secondary schools in Lanarkshire, Scotland, UK Recruitment period: study began 1988
Participants	Inclusion criteria: caries in permanent dentition; dental maturity (≥ 1 erupted second permanent molar) Exclusion criteria: fixed orthodontic appliances Baseline caries: 7.4 DMFS (Gp A: 7.47 (SD 5.94); Gp B: 7.23 (SD 5.65); Gp C: 7.46 (SD 5.89); Gp D: 7.33 (SD 5.77); Gp E: 7.34 (SD 5.51); Gp F: 7.48 (SD 5.96)). Baseline characteristics (DMFS) comparable Age at baseline (years): range 11 to 13 years, mean 12.6 years (group distribution not reported) Sex: not reported Any other details of important prognostic factors: background exposure to fluoride: not reported Number randomised: 4294 (Gp A: 858; Gp B: 860; Gp C: 859; Gp D: 856; Gp E: 429; Gp F: 432) Number evaluated: 3517 at 3 years (available at final examination) (Gp A: 721; Gp B: 698; Gp C: 698; Gp D: 703; Gp E: 344; Gp F: 353) Attrition: 18% dropout (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: change of residence/withdrew (8.4%), absent at final examination (8.6%), fixed orthodontic appliance (1%); no differential group losses
Interventions	**Comparison: FT (6 groups)[a]** Gp A (n = 858): SMFP 1000 ppm F; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp B (n = 860): SMFP 1500 ppm F; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp C (n = 859): NaF 1000 ppm F; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp D (n = 856): NaF 1500 ppm F; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp E (n = 429): NaF 1000 ppm F + 3% sodium TMP; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp F (n = 432): NaF 1500 ppm F + 3% sodium TMP; abrasive system: silica; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year net DMFS increment - cl (VT + FOTI); DMFS increment - xr (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: subgingival calculus; plaque; oral pathologies (assessed but not reported); oral hygiene habits (assessed, reported in Chestnutt 1998); compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: [a]Gps A + C versus B + D in analysis. TMP groups analysed separately (additional agent in these groups) Other information of note: selected for participation on grounds of caries in the permanent dentition and dental maturity. 42% of children were radiographed at baseline and 86% at final examination (36% at both); being restricted initially for ethical reasons. Clinical (VT and FOTI) caries assessment by 2 examiners. 5% of children re-examined at each annual examination. Intra- and inter-examiner reliabilities of 0.93 to 0.95 (reliability coefficient) and 0.91 to 0.97 by Kappa for DMFS. All radiographs read by 1 examiner. 5% of radiographs re-assessed for reproducibility. Kappa 0.87 DFS. Analysis adjusted for examiner, baseline caries, baseline calculus, active type and fluoride level, plus all 2-way interactions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... subjects allocated by a stratified randomisation process"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "... they [toothpastes] could not be differentiated by appearance, flavour, or other in-use characteristics. The dentifrices were supplied to participants in coded tubes, ensuring the double-blind nature of the study" and "double blind" "... carried out under strict observance of the double-blind principle" Comment: dentrifices could not be identified by appearance, flavour or any other characteristic
Incomplete outcome data (attrition bias)	Low risk	Low attrition rate, mainly due to moving away from area or absent from school on day of examination; did not alter balance between groups. 18% dropout rate at 3 years; unlikely to be due to intervention
Selective reporting (reporting bias)	Low risk	Clinical and radiographic assessments
Baseline characteristics balanced?	Low risk	Comment: baseline caries scores comparable
Free of contamination/co-intervention?	Low risk	Comment: no apparent cause for concern regarding contamination. Sufficient toothpaste supplied for whole family

Stookey 2004

Methods	Trial design: 4-armed, double-blind, head-to-head, stratified RCT Location: Puerto Rico Number of centres: not reported. Elementary schools, Puerto Rico Recruitment period: study began in/before 2001
Participants	Inclusion criteria: not reported Exclusion criteria: undergoing orthodontic therapy; extensive prosthetic appliance use Baseline caries: 8.0 DMFS (Examiner A) (Gp A: 6.84 DMFS (SD 6.33); Gp B: 8.01 DMFS (SD 7.46); Gp C: 7.26 DMFS (SD 6.79); Gp D: 7.68 DMFS (SD 6.33)). Baseline characteristic (baseline caries) "well balanced" Age at baseline (years): range 9 to 12 years, mean 10.6 years (Gp A: 10.6 years (SD 1.10); Gp B: 10.5 years (SD 1.12); Gp C: 10.6 years (SD 1.08); Gp D: 10.6 years (SD 1.14)). Baseline characteristic (age) "well balanced" Sex: Gp A: 50.8% F:49.2% M; Gp B: 51.7% F:48.3% M; Gp C: 51.9% F:48.1% M; Gp D: 48.3% F:51.7% M. Baseline characteristic (sex) '"well balanced" Any other details of important prognostic factors: background exposure to fluoride: community water supply fluoridated < 0.3 ppm F Number randomised: 955 (Gp A: 242; Gp B: 240; Gp C: 235; Gp D: 238) Number evaluated: 683 at 2 years (available at final examination) (Gp A: 168; Gp B: 174; Gp C: 180; Gp D: 160) Attrition: 29% dropout (for all study groups combined) after 2 years (study duration = 2 years). Reasons for attrition (84% of non-completers): change of residence, withdrew, absent at final examination, fixed orthodontic appliance; no differential group losses
Interventions	**Comparison: FT (4 groups)[a]** Gp A (n = 242): NaF 500 ppm F; abrasive system: silica; school use/supervised, twice daily Gp B (n = 240): NaF 1100 ppm F; abrasive system: silica; school use/supervised, twice daily Gp C (n = 235): NaF 2800 ppm F; abrasive system: silica; school use/supervised, twice daily Gp D (n = 238): SnF_2-HMP 1100 ppm F; abrasive system: silica; school use/supervised, twice daily
Outcomes	Primary: 2-year DMFS increment - cl (VT) + xr D_2 through D_4; subgroup analysis for children who attended at least 60% of supervised brushing sessions (at 1, 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: Procter & Gamble Company Declarations/conflicts of interest: 2 (RD Bartizek, AR Biesbrock) of 6 authors employed by Procter & Gamble. Remaining authors report institutional affiliations only Data handling by review authors: [a]SnF_2-HMP toothpaste group excluded from analysis (anti-calculus agent with possible caries inhibiting action) Other information of note: clinical (VT) and radiographic assessments undertaken by 2 calibrated examiners. 50 participants re-examined for clinical repeatability; bite-wing films for 20 participants re-examined for radiographic repeatability. Weighted Kappa for clinical assessment was 0.90 to 0.95; x-ray sensitivity 97.7% to 100% and x-ray specificity 92.6% to 95.8% Covariance analysis adjusted for age, baseline DMFS, baseline dental age, baseline surfaces at risk, dental age

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... randomised double-blind study"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "... randomised double-blind study" and "Subject and examiner blindness to treatment were maintained throughout the study"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: 28.5% attrition in year 2, reasons not stated
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Quote: ".. baseline caries level ... similar amongst the four treatment groups" Comment: balance for baseline sex and caries comparable
Free of contamination/co-intervention?	Low risk	Comment: siblings assigned the same toothpaste to reduce contamination but possible with home brushing

Sønju Clasen 1995

Methods	Trial design: 2-armed, single-blind (assessors), head-to-head, cluster-randomised (participant-analysed) RCT Location: Germany Number of centres: 10 kindergartens (5 in each cluster), Salzgitter, Germany Recruitment period: study began August 1991
Participants	Inclusion criteria: not reported Exclusion criteria: fluoride supplement (fluoride tablet) consumption Baseline caries: 2.2 dmfs (Gp A: 2.0 dmfs (SD 5.5); Gp B: 2.4 dmfs (SD 6.6)) (evaluated participants only). Baseline characteristics (proportion caries free, dmft) comparable Age at baseline (years): range 2 to 5 years, mean 4 years (Gp A: median 4.1 years; Gp B: median 4.2 years) (evaluated participants only). Baseline characteristic (age) comparable Sex: 77 F:95 M (Gp A: 39 F:44 M; Gp B: 38 F:51 M) (evaluated participants only). Baseline characteristic (sex) comparable Any other details of important prognostic factors: background exposure to fluoride: none reported Number randomised: 319 participants in 10 clusters (Gp A: 164; Gp B: 155) Number evaluated: 172 at 22 months (available at final examination) (Gp A: 89; Gp B: 83) Attrition: 46% dropout after 22 months (study duration 22 months). Reasons for attrition: change in residence or moving to new kindergarten in the area; no differential group losses
Interventions	**Comparison: FT versus FT** Gp A (n = 164): NaF 1450 ppm F; abrasive system: silica; school use/supervised daily brushing Gp B (n = 155): NaF 250 ppm F; abrasive system: silica; school use/supervised daily brushing
Outcomes	Primary: 2-year dmfs increment - cl; dmft increment; ds; dt; fs; ft; proportion remaining caries free (at 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 22 months
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: sample size adjusted by design effect (ICC 0.05) to account for cluster randomisation Other information of note: cluster-randomised trial reported as individual randomised. Clinical (VT) caries assessments by 1 examiner. Clinical data only. Intra-examiner reliability on 30 children. Scott's pi for dmfs 0.89

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " .... Salzgitter was divided into five geographical areas from which two kindergartens were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information
Blinding (performance bias and detection bias)	Unclear risk	Quotes: "Neither the kindergarten children nor the kindergarten staff were aware of the purpose of the study, nor were they told that a toothpaste containing different amount of fluoride was given to other kindergartens" and "At the time of the examinations the examiner was not aware if the child belonged to the study group or not" Comment: clinical assessors blinded, but unclear whether participants and kindergarten staff blinded. Participants very young children so knowledge of intervention unlikely to influence outcome
Incomplete outcome data (attrition bias)	High risk	83/155 available for examination in low fluoride group; 89/164 available in the high fluoride group. Total dropout rate of 46% Quote: "The majority of children who failed to complete the study either went to new kindergartens in the area or to a lesser extent change residence" Comment: high dropout rate, mainly due to change of kindergarten or change of residence. Although reasons for dropouts unlikely to be due to intervention, high rates could influence results
Selective reporting (reporting bias)	Low risk	Comment: routine caries diagnosis. No radiographs taken; clinical examination only. All possible caries indices are reported: ds, fs, dmfs, dt ft, dmft, caries free. Data on different surfaces also presented
Baseline characteristics balanced?	Unclear risk	Comment: baseline data only available for those assessed at 22 months. As a cluster-randomised trial more information about the individual clusters is required to evaluate this
Free of contamination/co-intervention?	Low risk	Comment: unlikely as cluster randomised. All children used 250 ppm F toothpaste at home but undertook supervised daily brushing with study toothpastes in kindergarten. Children using fluoride supplements were excluded from the study

Takeuchi 1968

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: Japan Number of centres: 1 Recruitment period: study began 1964
Participants	Inclusion criteria: unknown Exclusion criteria: unknown Baseline caries: reported at surface level only (Gp A: 121/3175 (3.8%) surfaces affected; Gp B: 111/3362 (3.3%) surfaces affected) Age at baseline (years): range 8 to 10 years (Gp A: range 8 to 10 years; Gp B: range 8 to 10 years) Sex: unknown Any other details of important prognostic factors: background exposure to fluoride: not reported Number randomised: 1230 (Gp A: 611; Gp B: 619) Number evaluated: 620 at 1 year (available at final examination) (total and group distribution unknown, data reported at a surface level) Attrition: 50% dropout after 3 years (study duration = 1 year)
Interventions	**Comparison: FT versus PL** Gp A (n = 611): SMFP 1000 ppm F; abrasive system: not reported; home use (unsupervised) with periodical brushing management by school teacher Gp B (n = 619): placebo; abrasive system: not reported; home use (unsupervised) with periodical brushing management by school teacher
Outcomes	Primary: newly developed caries surfaces - (CA) cl + DR (xr); caries onset rate (at 1 year) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1 year
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: not included in meta-analysis Other information of note: clinical (VT) and radiographic (DR) caries assessment by 2 examiners according to WHO criteria, diagnostic threshold = CA

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "By stratified random sampling in various degrees of caries ...." Comment: random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	High risk	Comment: overall dropout not calculable, as number of children present at final examination not reported
Selective reporting (reporting bias)	High risk	Outcomes reported: DMFS increment - (CA) cl (DR) xr, reported at 12 month follow-up caries rate numerical data reported at surface level only Comment: trial protocol not available. All outcomes listed in Methods section were reported (DFS)
Baseline characteristics balanced?	Low risk	Prognostic factors reported: caries Comment: baseline DMFS appears balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Thomas 1966

Methods	Trial design: 3-armed, double-blind, placebo-controlled, and head-to-head, stratified RCT Location: USA Number of centres: 1 mobile dental unit visiting 6 orphanages across South-Eastern states, USA Recruitment period: study began 1961
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 10.7 DFS (Gp A: 10.66 DFS (SE 0.69); Gp B: 10.57 DFS (SE 0.57); Gp C: 10.88 DFS (SE 0.60)). Baseline characteristics (DFS, DFT, TAR) "balanced" Age at baseline (years): range 7 to 16 years, mean 12 years (Gp A: 11.56 years (SE 0.19); Gp B: 11.37 years (SE 0.19); Gp C: 11.48 years (SE 0.19)) Sex: 227 F:237 M (Gp A: 71 F:80 M; Gp B: 75 F:83 M; Gp C: 81 F:74 M) (evaluated participants only) Any other details of important prognostic factors: background exposure to fluoride: none reported. Residents of "communities with only minor concentrations of fluoride in the communal water supply", levels not reported Number randomised: 679 (Gp A: 224; Gp B: 226; Gp C: 229) Number evaluated: 464 at 2 years (present during entire study period) (Gp A: 151; Gp B: 158; Gp C: 155) Attrition: 32% dropout after 2 years (study duration = 2 years). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = 224): SnF_2 1000 ppm F; abrasive system: IMP; institution use/supervised, twice a day Gp B (n = 226): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; institution use/supervised, twice a day Gp C (n = 229): placebo; abrasive system: IMP; institution use/supervised, twice a day
Outcomes	Primary: 2-year DFS increment - cl + xr; DFT (at 6 months, 1 year, 18 months, 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: not reported Data handling by review authors: Gps A + B versus C in analyses Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (10 BW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Check of diagnostic errors done

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were stratified according to age, DMF permanent teeth... before dentifrices were assigned randomly within strata. Each formulation of dentifrice was assigned 8 numbers at random. These numbers were arranged into random subsets of three; each subset contained a number for each of the three formulations. This sequence was continued across strata boundaries and repeated until all of the participating children had been allocated" Comment: still not enough information provided on the actual method of sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "The list of names and dentifrice numbers was forwarded to the grantor, who provided the dentifrices in plain white wax-lined tubes labelled with each child's name, home and cottage number... The code of dentofrice numbers... and the three formulations were placed in a sealed envelope and stored in the school safe.."
Blinding (performance bias and detection bias)	Low risk	Quotes: "The control and experimental dentifrices were identically formulated except for SnF_2 which was omitted in the control toothpaste. Both toothpastes were coloured blue" and "The participating subjects, as well as the examiner were unaware of the arrangement of numbers into dentifrice groups and the specific formulas throughout the study" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 32% in 2 years. Dropout by group: 73/224 FT 1, 68/226 FT 2, 74/229 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present for the entire study period
Selective reporting (reporting bias)	Low risk	Outcomes reported: DFS increment - cl + xr, reported at 6 months, 1, 1.5 and 2 years follow-ups DFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DFS: 10.66 FT 1, 10.57 FT 2, 10.88 PL DFT: 7.05 FT 1, 6.72 FT 2, 7.01 PL mean age: 11.56 FT 1, 11.37 FT 2, 11.48 PL TAR: 12.04 FT 1, 11.47 FT 2, 11.59 PL Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Low risk	Quote: "The tubes were readily identified by the child's name on the label. Thus it was easy for the housemothers to prevent the children from exchanging toothpaste during brushing" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Torell 1965

Methods	Trial design: 4-armed, double-blind, placebo-controlled, and head-to-head RCT Location: Sweden Number of centres: not reported. Elementary schools in Göteberg, Sweden Recruitment period: study began 1962
Participants	Inclusion criteria: not reported Exclusion criteria: mental disability; recipients of previous fluoride treatment; inhabitants of water supply area containing > 0.5 ppm F Baseline caries: 14.5 DMFS (from sample randomised) (Gp A: 14.2 DMFS (SE 0.53); Gp B: 14.7 DMFS (SE 0.58); Gp C: 14.5 DMFS (SE 0.54); Gp D: 14.6 DMFS (SE 0.56)). Baseline characteristics (DMFS, MD-DMFS) "balanced" Age at baseline (years): mean 10 years (group distribution not reported) Sex: distribution not reported numerically; "even distribution of girls and boys" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply naturally fluoridated < 0.3 ppm F Number randomised: 766 (Gp A: 196; Gp B: 196; Gp C: 198; Gp D: 176) Number evaluated: 668 at 2 years (available at final examination) (Gp A: 169; Gp B: 166; Gp C: 179; Gp D: 154) Attrition: 13% dropout rate after 2 years (study duration = 2 years). Reasons for attrition: natural losses mainly; no differential group losses
Interventions	**Comparison: FT (2 groups) versus PL (2 groups)** Gp A (n = 196): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed Gp B (n = 196): NaF 1100 ppm F; abrasive system: Na bicarbonate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed Gp C (n = 198): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed Gp D (n = 176): placebo; abrasive system: Na bicarbonate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed
Outcomes	Primary: 2-year DMFS increment - (CA) cl; MD-DMFS; FS; proportion of children with new carious lesions (U) xr (at 1, 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: Swedish Medical Research Council; City of Göteberg; [Swedish] National Board of Health. Toothpastes provided by Swedish Association of Manufacturers of Fluoride Toothpastes and Procter & Gamble Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: Gps A + B versus C + D in analyses Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA; radiographic assessment (BW) by 2 examiners, diagnostic threshold = DR. State of tooth eruption included not reported. Inter- and intra-examiner reproducibility checks done for clinical caries in 4% and 2% sample respectively; duplicate examination of x-rays records done and any discrepancies discussed before final diagnosis

Risk of bias table

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 statisticians..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The control dentifrice had the same composition with the exception of the fluoride" and "On the registration charts the different groups were referred to by their code numbers. The examiners did not have access to the code during the course of the investigation" and "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: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 13% in 2 years. Dropout by group: 27/196 FT 1, 29/198 PL 1, 30/196 FT 2, 22/176 PL 2. Reasons for losses: changing school, moving away, appearance of new caries, unpleasant taste (not reported by group) Comment: numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if 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, reported at 1 and 2 years follow-ups MD-DMFS FS proportion of children with new carious lesions (U) xr Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS (xr): 3.77 FT 1, 3.85 PL 1, 3.94 FT 2, 4.17 PL 2 DMFS (cl): 14.2 FT 1, 14.5 PL 1, 14.7 FT 2, 14.6 PL 2 Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Torell 1965a

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: Sweden Number of centres: not reported. Södertälje, Stockholm, Sweden Recruitment period: study began 1962
Participants	Inclusion criteria: not reported Exclusion criteria: mental disability; recipients of previous fluoride treatment; inhabitants of water supply area containing > 0.5 ppm F Baseline caries: 11.7 DMFS (from sample randomised) (Gp A: 11.30 DMFS (SE 0.55); Gp B: 12.02 DMFS (SE 0.44)). Baseline characteristics (DMFS, MD-DMFS) "balanced" Age at baseline (years): mean 10 years (group distribution not reported) Sex: distribution not reported numerically; "equal number of girls and boys" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply naturally fluoridated < 0.3 ppm F Number randomised: 357 (Gp A: 177; Gp B: 180) Number evaluated: 285 at 2 years (available at final examination) (Gp A: 148; Gp B: 137) Attrition: 20% dropout rate after 2 years (study duration = 2 years). Natural losses mainly; differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 177): SMFP 1000 ppm F; abrasive system: Ca carbonate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed Gp B (n = 180): placebo; abrasive system: Ca carbonate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed
Outcomes	Primary: 2-year DMFS increment - (CA) cl; MD-DMFS; FS (at 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: Swedish Medical Research Council; County of Stockholm; [Swedish] National Board of Health. Toothpastes provided by Swedish Association of Manufacturers of Fluoride Toothpastes and Procter & Gamble Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: study reports 2 age groups separately, see Torell 1965b for older age group Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; radiographic assessment (BW) by 2 examiners, diagnostic threshold = DR. State of tooth eruption included not reported. Intra-examiner reproducibility check done for clinical caries in a sample; duplicate examination of x-rays records done and any discrepancies discussed before final diagnosis

Risk of bias table

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 statisticians..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The control dentifrice had the same composition with the exception of the fluoride" and "On the registration charts the different groups were referred to by their code numbers. The examiners did not have access to the code during the course of the investigation" and "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: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 20% in 2 years. Dropout by group: 29/177 FT, 43/180 PL. Reasons for losses: changing school, moving away, appearance of new caries, unpleasant taste (not reported by group) Comment: numbers lost were not unduly high for the length of follow-up. Differential losses between groups (16.4% FT, 23.9% PL). It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations. Group losses unlikely to be related to intervention
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - (CA) cl, reported at 2 years follow-up MD-DMFS FS. Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS (cl): 11.30 FT, 12.02 PL DMFS (xr): 2.29 FT, 2.46 PL mean age: 10 years (both groups) Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	No information provided

Torell 1965b

Methods	Trial design: 2-armed, double-blind, placebo-controlled RCT Location: Sweden Number of centres: not reported. Södertälje, Stockholm, Sweden Recruitment period: study began 1962
Participants	Inclusion criteria: not reported Exclusion criteria: mental disability; recipients of previous fluoride treatment; inhabitants of water supply area containing > 0.5 ppm F Baseline caries: 15 DMFS (from sample randomised) (Gp A: 14.52 DMFS (SE 0.63); Gp B: 15.41 DMFS (SE 0.72)). Baseline characteristics (DMFS, MD-DMFS) "balanced" Age at baseline (years): mean 11 years (group distribution not reported) Sex: distribution not reported numerically; "equal number of girls and boys" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply naturally fluoridated < 0.3 ppm F Number randomised: 432 (Gp A: 215; Gp B: 217) Number evaluated: 368 at 2 years (available at final examination) (Gp A: 188; Gp B: 180) Attrition: 15% dropout rate after 2 years (study duration = 2 years). Reasons for attrition natural losses mainly; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 215): SMFP 1000 ppm F; abrasive system: Ca carbonate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed Gp B (n = 217): placebo; abrasive system: Ca carbonate; home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed
Outcomes	Primary: 2-year DMFS increment - (CA) cl; MD-DMFS; FS (at 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: Swedish Medical Research Council; County of Stockholm; [Swedish] National Board of Health. Toothpastes provided by Swedish Association of Manufacturers of Fluoride Toothpastes and Procter & Gamble Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: study reports 2 age groups separately, see Torell 1965a for younger age group. SDs imputed from SEs in analyses using standard Cochrane methods Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; radiographic assessment (BW) by 2 examiners, diagnostic threshold = DR. State of tooth eruption included not reported. Intra-examiner reproducibility check done for clinical caries in a sample; duplicate examination of x-rays records done and any discrepancies discussed before final diagnosis

Risk of bias table

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 statisticians..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "The control dentifrice had the same composition with the exception of the fluoride" and "On the registration charts the different groups were referred to by their code numbers. The examiners did not have access to the code during the course of the investigation" and "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: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 15% in 2 years. Dropout by group: 27/215 FT, 37/217 PL. Reasons for losses: changing school, moving away, appearance of new caries, unpleasant taste (not reported by group) Comment: numbers lost were not unduly high for the length of follow-up with no differential losses between groups (12.6% FT, 17.1% PL). It is unclear if 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, reported at 2 years follow-up MD-DMFS FS Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS (xr): 3.76 FT, 4.13 PL DMFS (cl): 14.52 FT, 15.41 PL mean age: 11 years (both groups) Comment: initial caries appears balanced between groups
Free of contamination/co-intervention?	Unclear risk	Comment: no information provided

Vilhena 2010

Methods	Trial design: 4-armed, single-blind, head-to-head, stratified RCT Location: Brazil Number of centres: 57 primary schools, São Jose dos Campos, São Paulo, Brazil Recruitment period: study began 2005
Participants	Inclusion criteria: participants with caries dmfs > 0 Exclusion criteria: schools located in slums (preventing researcher access); schools with few 4 year-olds; schools with highly-mobile student body; research participation in prior 3 months; orthodontic brackets Baseline caries: 5.04 dmfs (Gp A: 5.07 (SD 5.11); Gp B: 4.80 (SD 5.00); Gp C: 5.24 (SD 5.37); Gp D: 5.05 (SD 4.89)). Baseline characteristics similar according to dmfs Age at baseline (years): 4 years (Gp A: 4; Gp B: 4; Gp C: 4; Gp D: 4). Baseline characteristics similar according to age Sex: 527 F:526 M (Gp A: 133 F:138 M; Gp B: 134 F:128 M; Gp C: 123 F:127 M; Gp D: 137 F:133 M) (evaluated participants only). Baseline characteristics similar according to sex, and dmfs Any other details of important prognostic factors: background exposure to fluoride: community water supply fluoridated 0.6 to 0.8 ppm F Number randomised: 1402 in 57 school clusters/222 classrooms (Gp A: 345 (55 classrooms); Gp B: 343 (52 classrooms); Gp C: 354 (59 classrooms); Gp D: 360 (56 classrooms)) Number evaluated: 1053 children in 57 school clusters/222 classrooms at 20 months (available at final examination) (Gp A: 271 (55 classrooms); Gp B: 262 (52 classrooms); Gp C: 250 (59 classrooms); Gp D: 270 (56 classrooms)) Attrition: 25% dropout after 20 months years (study duration = 20 months). No reasons for dropout given. Dropout ranged from 19% to 29%
Interventions	**Comparison: FT versus FT** Gp A (n = 345): NaF 1100 ppm F, pH 4.5; liquid dentifrice formulation (reduced viscosity); abrasive system: not reported; home use (unsupervised) and school use (supervised), twice daily Gp B (n = 343): NaF 1100 ppm F, pH 7.0; liquid dentifrice formulation (reduced viscosity); abrasive system: not reported; home use (unsupervised) and school use (supervised), twice daily Gp C (n = 354): NaF 550 ppm F, pH 4.5; liquid dentifrice formulation (reduced viscosity); abrasive system: not reported; home use (unsupervised) and school use (supervised), twice daily Gp D (n = 360): NaF 1100 ppm F, pH 7.0; abrasive system: not reported; home use (unsupervised) and school use (supervised), twice daily
Outcomes	Primary: 20 months net dmfs increment - (CA) cl; dmfs (at 20 months) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1 year 8 months
Notes	Adverse effects: not reported Funding source: "This research was supported by FAPESP (grants 05/03975-6 and 05/04090-8)." FAPESP is São Paulo's state-funded research foundation Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: Gps A +B + D versus C in analyses Other information of note: data were analysed by GLM procedure using the classrooms (cluster) as unit of analysis. Clinical (VT) caries assessment by 2 examiners according to WHO criteria, at CA diagnostic threshold. No radiographic assessment. The intra-examiner agreement was tested by duplication of 107 examinations for examiner 1 (Kappa = 0.91) and 127 for examiner 2 (Kappa = 0.95). 20 children were examined twice by both dentists at baseline and follow-up. The related Kappa values were 0.85 and 0.87 for the 1st and 2nd examinations, respectively

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The software Excel 2003 (Micro- soft, Redmond, Wash., USA) generated random numbers ranging from 0 to 1" Comment: random sequence generation stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Assignment of the included children to the study groups was done by 1 of the re- searchers (J.R.P.L.), using a previously established algorithm, for each of the 3 categories of SES" Comment: unclear whether allocation was concealed
Blinding (performance bias and detection bias)	Low risk	Quote: "The study was blinded only for the examiner, since the commercial toothpaste [Group 4 only] was maintained in its original package" Comment: examiner blinded
Incomplete outcome data (attrition bias)	Low risk	Quotes: "The number of dropouts was 74, 81, 104 and 90, for groups 1–4, respectively" and "The dmfs index means ± SD at baseline and after 20 months for the subjects that remained in the whole study and the dmfs increment for each group were very similar for all the groups and no significant differences were detected among them" Comment: overall dropout for length of follow-up: 25% in 20 months. Dropout ranged from 19% to 29% per group. Reasons for losses not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported: dmfs Comment: trial protocol not available. All outcomes listed in Methods section were reported (dmfs)
Baseline characteristics balanced?	Low risk	Prognostic factors reported: age, sex, socio-economic status, dmfs Comment: all appear balanced
Free of contamination/co-intervention?	Low risk	Quotes: "Family kits containing 5 toothbrushes, 6 dentifrice tubes (120 g each) and 1 leaflet about oral hygiene care and compliance need were distributed for all participants every 4 months" and "... the classrooms were considered as units of draw, in order that only 1 type of dentifrice was distributed in each classroom" Comment: contamination not observed

Weisenstein 1972

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported, "several" elementary schools, suburban Columbus, Ohio, USA Recruitment period: study began in/before 1969
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 7.0 DMFS (Gp A: 7.01 DMFS (SE 0.387); Gp B: 6.99 DMFS (SE 0.357)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 5 to 15 years, mean 9.5 years (Gp A: 9.39 years; Gp B: 9.49 years). Baseline characteristic (age) "balanced" Sex: 357 F:337 M (Gp A: 177 F:169 M; Gp B: 180 F:168 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply fluoride "negligible", F level not reported Number randomised: 694 (Gp A: 346; Gp B: 348) Number evaluated: 402 at 1.8 years (available at final examination) (Gp A: 206; Gp B: 196) Attrition: 42% dropout after 1.8 years (study duration = 1.8 years). Reasons for high dropout described: change of residence, absent on examination day; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 346): NaF 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 348): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 1.8-year DMFS increment - cl + xr; DMFT (at 9 months, 1.4 years, 1.8 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1.8 years (21 months)
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: results of 1 examiner chosen (Examiner A) Other information of note: clinical (VT) caries assessment by 2 examiners, diagnostic threshold not reported. Radiographic assessment (7 BW) by 2 examiners, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... each child was assigned one of two dentifrices randomly within the strata of age, sex and visual-tactile DMFS exam results" Comment: not enough information presented
Allocation concealment (selection bias)	Unclear risk	No information presented
Blinding (performance bias and detection bias)	Low risk	Quotes: "The control and test dentifrices were similar in colour, flavour and other properties" and "The examiners had no knowledge of the dentifrice assigned to each child, and the children had no knowledge of the identities of the dentifrices assigned to them. All clinical exams and radiographic interpretations were made independent of previous exam records" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 42% in 1.8 years. Dropout by group: 117/348 FT, 113/329 PL. Reasons for losses: change of residence, absent on examination day Comment: numbers lost were unduly high for the length of follow-up. No differential losses between groups. It is unclear if 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: DMFS increment - cl + xr, reported at 9 months, 1.4 and 1.8 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 7.01 FT, 6.99 PL DMFT: 4.02 FT, 4.18 PL age: 9.39 FT, 9.49 PL gender: 169 M, 177 F FT; 168 M, 180 F PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The possible effect of a non-study dentifrice was minimized because enough dentifrice was given each child to supply the household for the duration of the study" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Winter 1989

Methods	Trial design: 2-armed, double-blind, head-to-head RCT Location: UK Number of centres: not reported. Pre-school children residing in Norwich Health District, UK Recruitment period: study began 1984
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 0 DMFS (assumed. No clinical examination undertaken). Baseline characteristics not reported Age at baseline (years): mean 2 years (group distribution not reported). Baseline characteristics not reported Sex: 442 F:463 M (full radiographic data sample only. n = 905) (group distribution not reported). Baseline characteristics not reported Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supplies fluoridated - ranging from 0.08 to 0.57 ppm F Number randomised: 3040 (group distribution not reported) Number evaluated: 2177 at 3 years available at final clinical examination (Gp A: 1073; Gp B: 1104); 905 available for final clinical and radiological examination (Gp A: 428; Gp B: 477) Attrition: 28% dropout after 3 years (study duration = 3 years). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT versus FT** Gp A (n = evaluated 1073): SMFP NaF 550 ppm; abrasive system: Ca glycerophosphate; home use/supervised, daily frequency assumed Gp B (n = evaluated 1104): SMFP 1055 ppm F; abrasive system: Ca glycerophosphate; home use/supervised, daily frequency assumed
Outcomes	Primary: 3-year dmfs increment - cl + xr; dmfs; dfmt; ds; fs; proportion developing new caries (at 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: ms; plaque; compliance Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: Beecham Products Declarations/conflicts of interest: not reported Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 3 calibrated examiners, radiographic assessment by single examiner. Clinical and radiographic reliability assessed by 10% re-examination of sample. Kappa scores inter-rater reliability 0.65 to 0.71. Radiographic assessment by 1 examiner. Kappa scores inter-rater reliability 0.92

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Quote: "... 12 assistants to visit the children's homes on a monthly basis for the next 3 years" Comment: probably done
Blinding (performance bias and detection bias)	Low risk	Quoted: ".. double-blind clinical trial" and "... toothpaste was supplied ..... group code"
Incomplete outcome data (attrition bias)	Unclear risk	Comment: 28% dropout after 3 years for clinical examination alone; 70% dropout for clinical and radiographic examination. Reasons for dropout not stated; no differential group losses. High dropout likely to effect study estimates of treatment effect
Selective reporting (reporting bias)	Low risk	Clinical and radiographic assessments, dmfs and dmft indices reported
Baseline characteristics balanced?	Unclear risk	Comment: age of participant at start of trial 2 years, no baseline caries assumed for all participants
Free of contamination/co-intervention?	Low risk	Quote: "Sufficient toothpaste was provided for the whole family to avoid mistaken use of another product for the child" Comment: contamination unlikely

Zacherl 1970

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported. Edmonton, Alberta, Canada Recruitment period: study began in/before 1963
Participants	Inclusion criteria: not reported Exclusion criteria: mental disability Baseline caries: 4.71 DMFS (Gp A: 4.88 (SE 0.24); Gp B: 4.53 (SE 0.23)). Baseline characteristics (DMFS, DMFT, oral hygiene) "balanced" Age at baseline (years): range 6 to 9 years (dental age Gp A: 6.99 (SE 0.17); Gp B: 6.78 (SE 0.17)). Baseline characteristic (dental age) "balanced" Sex: 417 F:485 M (Gp A: 204 F:257 M; Gp B: 213 F:228 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply naturally fluoridated < 0.1 ppm F Number randomised: 902 (Gp A: 461; Gp B: 441) Number evaluated: 512 at 2.5 years (available at final examination) (Gp A: 251; Gp B: 261) Attrition: 43% dropout after 2.5 years (study duration = 2.5 years). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 461): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 441): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2.5-year DMFS increment - cl + xr; DMFT (at 10 months, 1.5 years, 2.5 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2.5 years (30 months)
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: study reports 2 age groups separately, see Zacherl 1970a for older age group Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5 to 10 BW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "Only grades 1 and 2, and grade 7 were selected. Each of these 2 age groups were divided into 2 similar subgroups according to age, sex and caries history... Adjacent subjects within arrays were assigned by coin toss to one of two groups simply indicated D or H"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "The investigator did not know which was the control and which was the experimental group" and "The study was double blind" and "The control dentifrice lacked the tin compounds but was otherwise identical" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 43% in 2.5 years. Dropout by group: 210/461 FT, 180/441 PL. Reasons for losses: not reported Comment: numbers lost were somewhat high for the length of follow-up. No differential losses between groups. It is unclear if 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: DMFS increment - cl + xr, reported at 10 months, 1.5 and 2.5 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 5.06 FT, 4.69 PL DMFT: 2.69 FT, 2.51 PL dental age: 6.99 FT, 6.78 PL gender: 257 M, 204 F FT; 228 M, 213 F PL oral hygiene: 1.58 FT, 1.63 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "To minimize the possible effect of non-study dentifrice, enough dentifrice was provided monthly to each individual to supply the household for the test period" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Zacherl 1970a

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: USA Number of centres: not reported. Edmonton, Alberta, Canada Recruitment period: study began in/before 1963
Participants	Inclusion criteria: not reported Exclusion criteria: mental disability Baseline caries: 23.53 DMFS (Gp A: 23.46 (SE 0.77); Gp B: 23.60 (SE 0.77)). Baseline characteristics (DMFS, DMFT, oral hygiene) "balanced" Age at baseline (years): range 13 to 14 years (dental age Gp A: 25.12 (SE 0.18); Gp B: 25.17 (SE 0.18)). Baseline characteristic (dental age) "balanced" Sex: 404 F:407 M (Gp A: 201 F:207 M; Gp B: 203 F:200 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply naturally fluoridated < 0.1 ppm F Number randomised: 811 (Gp A: 408; Gp B: 403) Number evaluated: 528 at 2.5 years (available at final examination) (Gp A: 260; Gp B: 268) Attrition: 35% dropout after 2.5 years (study duration = 2.5 years). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 408): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 403): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2.5-year DMFS increment - cl + xr; DMFT (at 10 months, 1.5 years, 2.5 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2.5 years (30 months)
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: study reports 2 age groups separately, see Zacherl 1970 for younger age group Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5 to 10 BW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "Only grades 1 and 2, and grade 7 were selected. Each of these 2 age groups were divided into 2 similar subgroups according to age, sex and caries history... Adjacent subjects within arrays were assigned by coin toss to one of two groups simply indicated D or H"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias)	Low risk	Quotes: "The investigator did not know which was the control and which was the experimental group" and "The control dentifrice lacked the tin compounds but was otherwise identical" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 35% in 2.5 years. Dropout by group: 148/408 FT, 135/403 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if 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: DMFS increment - cl + xr, reported at 10 months, 1.5 and 2.5 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 24.55 FT, 23.97 PL DMFT: 12.21 FT, 12.03 PL dental age: 25.12 FT, 25.17 PL gender: 207 M, 201 F FT; 200 M, 203 F PL oral hygiene: 1.61 FT, 1.60 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "To minimize the possible effect of non-study dentifrice, enough dentifrice was provided monthly to each individual to supply the household for the test period" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Zacherl 1972

Methods	Trial design: 2-armed, double-blind, placebo-controlled, stratified RCT Location: Canada Number of centres: not reported. Elementary schools, Jasper Place, Alberta, Canada Recruitment period: study began in/before 1969
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 11.7 DMFS (Gp A: 11.40 (SE 0.682); Gp B: 12.09 (SE 0.733)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 6 to 15 years, mean 10 years (Gp A: 10.22 years; Gp B: 10.17 years). Baseline characteristic (age) "balanced" Sex: 321 F:356 M (Gp A: 163 F:185 M; Gp B: 158 F:171 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply fluoridated < 0.1ppm F Number randomised: 677 (Gp A: 348; Gp B: 329) Number evaluated: 447 at 2 years (available at final examination) (Gp A: 231; Gp B: 216) Attrition: 34% dropout after 2 years (study duration = 2 years). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT versus PL** Gp A (n = 348): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 329): placebo; abrasive system: not reported; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - cl + xr; DMFT (at 1 , 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: n/a Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5 to 10 BW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... subjects were classified by age, sex and DMFS. The subjects were then assigned by random number to one of the two dentifrices, identified only by code letter"
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "A double blind investigation..." and "The control dentifrice was the same as the test dentifrice except that it had no active ingredients..." Comment: use of placebo described but blind outcome assessment not clearly described, although it was probably done as earlier report by same author clearly described blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 34% in 2 years. Dropout by group: 117/348 FT, 113/329 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if 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 - cl + xr, reported at 1 and 2 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 12.10 FT, 12.44 PL DMFT: 6.27 FT, 6.33 PL age: 10.22 FT, 10.17 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Zacherl 1972a

Methods	Trial design: 5-armed, double-blind, placebo-controlled and head-to-head, stratified RCT Location: Canada Number of centres: not reported. Leduc County, Alberta, Canada Recruitment period: study began in/before 1969
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 7.3 DMFS (Gp A: 7.32 (SE 0.550); Gp B: 7.19 (SE 0.465); Gp C: 6.79 (SE 0.429); Gp D: 7.05 (SE 0.426); Gp E: 7.80 (SE 0.444)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 6 to 16 years, mean 9.3 years (Gp A: 9.27; Gp B: 9.30; Gp C: 9.40; Gp D: 9.30; Gp E: 9.19). Baseline characteristic (age) "balanced" Sex: 689 F:726 M (Gp A: 137 F:135 M; Gp B: 134 F:138 M; Gp C: 132 F:134 M; Gp D: 145 F:156 M; Gp E: 141 F:163 M). Baseline characteristic (sex) "balanced" Any other details of important prognostic factors: background exposure to fluoride: water. Naturally fluoridated community water supply, ranging from 1.5 to 3.8 ppm F Number randomised: 1405 (Gp A: 272; Gp B: 272; Gp C: 256; Gp D: 301; Gp E: 304) Number evaluated: 894 at 1.7 years (present for both follow-up examinations) (Gp A: 174; Gp B: 175; Gp C: 151; Gp D: 184; Gp E: 210) Attrition: 36% dropout after 1.7 years (study duration = 1.7 years). Reasons for high dropout not reported; exclusions based on presence in both examinations; no differential group losses
Interventions	**Comparison: FT (4 groups) versus PL** Gp A (n = 272): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate in all toothpastes; home use/unsupervised, daily frequency assumed Gp B (n = 272): NaF 1000 ppm F; abrasive system: Ca pyrophosphate in all toothpastes; home use/unsupervised, daily frequency assumed Gp C (n = 256): SMFP 1000 ppm F; abrasive system: Ca pyrophosphate in all toothpastes; home use/unsupervised, daily frequency assumed Gp D (n = 301): APF 1000 ppm F; abrasive system: Ca pyrophosphate in all toothpastes; home use/unsupervised, daily frequency assumed Gp E (n = 304): placebo; abrasive system: Ca pyrophosphate in all toothpastes; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 1.7-year DMFS increment - cl + xr; DMFT (at 1 year, 1.7 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 1.7 years (20 months)
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: Gps A + B + C + D versus E in analyses Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5 to 10 BW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were arrayed by sex, age and initial visual-tactile DMFT and then assigned by random number to one of five groups identified only by code letter"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "A double blind clinical investigation..." and "All dentifrices were similar in colour, flavour and other consumer properties" and "All examinations and interpretations were independent of previous records" Comment: use of placebo described but blind outcome assessment not clearly described, although it was probably done as earlier report by same author clearly described blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 36% in 1.7 years. Dropout by group: 98/272 FT, 94/304 PL. Reasons for losses: exclusion based on presence at all examinations Comment: numbers lost were somewhat high for the length of follow-up. No differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at all examinations
Selective reporting (reporting bias)	Low risk	Outcomes reported: DMFS increment - cl + xr, reported at 1 and 1.7 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 7.63 FT 1, 7.33 FT 2, 6.98 FT 3, 7.28 FT 4, 7.60 PL DMFT: 4.34 FT 1, 4.19 FT 2, 4.00 FT 3, 4.17 FT 4, 4.13 PL age: 9.31 FT 1, 9.28 FT 2, 9.37 FT 3, 9.25 FT 4, 9.17 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Unclear risk	No information provided

Zacherl 1973

Methods	Trial design: 3-armed, double-blind, placebo-controlled and head-to-head, stratified RCT Location: USA Number of centres: not reported. Parochial school population in urban Columbus, Ohio, USA Recruitment period: study began in/before 1970
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline caries: 8.45 DMFS (Gp A: 8.37 (SE 0.392); Gp B: 8.53 (SE 0.397)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 5 to 13 years, mean 8.95 (Gp A: 8.89 years; Gp B: 8.99 years). Baseline characteristic (age) "balanced" Sex: 334 F:343 M (Gp A: 167 F:177 M; Gp B: 167 F:166 M) Any other details of important prognostic factors: background exposure to fluoride: none reported. Community water supply fluoride level "negligible", F level not reported Number randomised: 1015 (groups relevant to review: 677) (Gp A: 344; Gp B: 333) Number evaluated: 649 (groups relevant to review: 444) at 2 years (available at final examination) (Gp A: 220; Gp B: 224) Attrition: 34% dropout after 2 years (study duration = 2 years). Reasons for attrition not reported; no differential group losses
Interventions	**Comparison: FT[a] versus PL** Gp A (n = 344): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 333): placebo; abrasive system: not reported; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 2-year DMFS increment - cl + xr; DMFT (at 1 year, 2 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 2 years
Notes	Adverse effects: not reported Funding source: not reported Declarations/conflicts of interest: institutional affiliations reported only Data handling by review authors: [a]Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only) Other information of note: clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5 to 10 BW) by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Sample was stratified by age, sex and DMFS, and assigned by random permutations to the 3 dentifrices identified only by code letter" Comment: probably done. Earlier reports by the same author clearly describe use of random sequeunces (Zacherl 1972)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quotes: "All examinations were independent of previous examination records" and "A third dentifrice containing no known caries inhibiting agents was used as control" and "The study was double blind..." Comment: use of placebo described but blind outcome assessment not clearly described, although it was probably done as earlier report by same author clearly described blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 34% in 2 years. Dropout by group: 124/344 FT, 109/333 PL. Reasons for losses: not reported Comment: numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if 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: DMFS increment - cl + xr, reported at 1 and 2 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 8.06 FT, 8.02 PL DMFT: 4.41 FT, 4.37 PL age: 8.78 FT, 8.76 PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Low risk	Quote: "The assigned dentifrice was supplied to the entire families of the study participants approximately every 2 months during the study" Comment: there is sufficient indication overall of prevention of contamination/co-intervention

Zacherl 1981

Methods	Trial design: 3-armed, double-blind, placebo-controlled and head-to-head, stratified RCT Location: USA Number of centres: not reported. Central Ohio, USA Recruitment period: study began in/before 1977
Participants	Inclusion criteria: not reported Exclusion criteria: orthodontic treatment; extensive prosthetic appliance use Baseline caries: 5.82 DMFS (Gp A: 6.06 (SE 0.0.223); Gp B: 5.65 (SE 0.206); Gp C: 5.59 (SE 0.315)). Baseline characteristics (DMFS, DMFT) "balanced" Age at baseline (years): range 6 to 14 years, mean 8.9 years (Gp A: 8.95 years; Gp B: 8.93 years; Gp C: 8.93 years) Sex: 1552 F:1541 M (Gp A: 669 F:659 M; Gp B: 667 F:660 M; Gp C: 216 F:222 M) Any other details of important prognostic factors: background exposure to fluoride: none reported. Naturally fluoridated community water supply, < 0.3 ppm F Number randomised: 3093 (Gp A: 1328; Gp B: 1327; Gp C: 438) Number evaluated: 1754 at 3 years (available at final examination) (Gp A: 760; Gp B: 740; Gp C: 254) Attrition: 43% dropout after 3 years (study duration = 3 years). Reasons for attrition described: change of residence, absent on examination day, poor quality of x-rays; no differential group losses
Interventions	**Comparison: FT (2 groups) versus PL** Gp A (n = 1328): SnF_2 1000 ppm F; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed Gp B (n = 1327): NaF 1100 ppm F; abrasive system: silica; home use/unsupervised, daily frequency assumed Gp C (n = 438): placebo; abrasive system: Ca pyrophosphate; home use/unsupervised, daily frequency assumed
Outcomes	Primary: 3-year DMFS increment - (CA) cl + (ER) xr; DMFT (at 1, 2, 3 years) Secondary: none assessed Assessments irrelevant to this review's scope: n/a Follow-up duration: 3 years
Notes	Adverse effects: not reported Funding source: Procter & Gamble, Cincinatti, Ohio Declarations/conflicts of interest: institutional affiliation reported only Data handling by review authors: Gps A + B versus C in analyses Other information of note: clinical (VT) caries assessment (FOTI used) by 1 examiner, diagnostic threshold = CA. Radiographic assessment (postBW) by 1 examiner, diagnostic threshold = ER. State of tooth eruption included not reported. Intra-examiner reproducibility checks for incremental clinical and radiographic caries data in 10% sample (ICC score 0.9). Reversal rate very low and similar among groups

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Following the baseline examinations, the subjects were separated by sex, age and DMFS. Within these strata, they were assigned to a treatment regimen by random permutations of seven in a 1:3:3 ratio.."
Allocation concealment (selection bias)	Unclear risk	Quote: "Following initial assignment of subjects to treatment groups, the investigator was supplied with a file of tamper proof, sealed opaque envelopes which contained the name and identification number of each subject. Within each envelope, the treatment identity for the subject was printed" Comment: allocation concealment should be dealt with prior to not after assignment
Blinding (performance bias and detection bias)	Low risk	Quotes: "No situations occurred during the study that required any of the envelopes to be opened. At no time during the course of the study did the examiner or the subjects know which dentifrice the subjects were assigned" and "The design used for this study is a modification of the classical double-blind placebo controlled clinical trial. In this study, three times as many subjects were assigned to the groups constituting the primary comparison, than were assigned to the placebo group" Comment: blind outcome assessment and use of placebo described
Incomplete outcome data (attrition bias)	Unclear risk	Overall dropout for length of follow-up: 43% in 3 years. Dropout by group: 568/1328 FT, 184/438 PL. Reasons for losses: changing of residence, poor quality radiographs, exclusion due to absence at final examination Comment: numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if 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: DMFS increment - (CA) cl + (ER) xr, reported at 1, 2 and 3 years follow-ups DMFT Comment: trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Low risk	Prognostic factors reported: DMFS: 6.06 (6.15) FT 1, 5.65 (5.60) FT 2, 5.59 (5.02) PL DMFT: 3.61 (3.31) FT 1, 3.49 (3.07) FT 2, 3.44 (2.77) PL Comment: initial caries appears balanced
Free of contamination/co-intervention?	Unclear risk	Quote: "Toothbrushes and dentifrice labelled with the subject's name and unique identification number were supplied by the study's sponsor in plain white tubes...." Comment: not enough information provided

Footnotes

Al = aluminium; AmF = amine fluoride; ANC = active non-cavitated caries lesions; APF = acidulated phosphate fluoride; BL = bucco and lingual; BW = bite-wing; Ca = calcium; $CaHPO_4$ $2H_2O$ = dicalcium phosphate; 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; CIR = caries incidence rate; cl = clinical examination; CPP = casein phosphopeptide; dfs = decayed and filled primary surface; DFS = decayed and filled permanent surface; DFT = decayed and filled permanent teeth; DMFS = decayed, missing, and filled permanet surface; DMFT = decayed, missing, and filled permanent teeth; dmft/s = decayed, missing (or extracted) and filled deciduous teeth or surface; DR = radiolucency into dentine; DSTM = Dundee selectable threshold method for caries diagnosis; D_1 = enamel/non-cavitated caries lesions; D_2 = enamel caries; D_3 = dentinal/cavitated caries lesions; D_4 = caries lesions extending into the pulp; E + U = all erupted and erupting teeth

combined; ECSI = Extrapolated Carious Surface Increment Index; ER = radiolucency in enamel/enamel-dentine junction; F = female; F = fluoride; FOTI = fiber-optic transillumination; FT = fluoride treatment; Gp = group; ICC = intra-class correlation coefficient; IMP = insoluble sodium metaphosphate; ITT = intention-to-treat; M = male; MD = mesio and distal; MFP = monofluorophosphate; n/a = not applicable; Na = sodium; NaF = sodium fluoride; NCA = non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures; NS = not significant; O = occlusal; OHI = oral hygiene index; postBW = posterior bite-wing X-ray assessment; PF = pit and fissure; PL = placebo; ppm = parts per million; RCT = randomised controlled trial; SAR = surfaces at risk; SD = standard deviation; SE = standard error; SEM = standard error of the mean; SMFP = sodium monofluorophosphate; SnF_2 = stannous fluoride; SnF_2-HMP = stannous fluoride with sodium hexametaphosphate; TAR = teeth at risk; TMP = trimetaphosphate; VT = visual/tactile methods; xr = radiographic examination.

Characteristics of excluded studies

Andlaw 1983

Reason for exclusion	Equivalent fluoride concentration SMFP 1000 ppm (2 groups). Additional potential anti-caries agent (3% trimetaphosphate) in placebo arm

Baysan 2001

Reason for exclusion	Inadequate follow-up period (6 months)

Beiswanger 1978

Reason for exclusion	Additional fluoride applied topically at baseline and annually

Beiswanger 1981

Reason for exclusion	Equivalent fluoride concentration (1000 ppm SnF_2, 1100 ppm NaF)

Bibby 1945

Reason for exclusion	Random allocation not stated or indicated

Bixler 1966

Reason for exclusion	Additional anti-calculus agent (stannous pyrophosphate) in active intervention arm only

Blinkhorn 1988

Reason for exclusion	Equivalent fluoride concentration (1400 ppm NaF, 1400 ppm SMFP, 1000 ppm SMFP + 450 ppm NaF)

Chedid 2012

Reason for exclusion	Intervention part of supervised programme. Additional measures included topical fluoride or chlorhexidine or both and fluoride drops/tablets. Not randomised (systematic allocation)

Curnow 2002

Reason for exclusion	Comparison of children receiving fluoridated toothpaste as part of a supervised toothbrushing programme with children receiving no intervention

Cutress 1992

Reason for exclusion	Post-trial evaluation. Data coding problems in original trial

Damle 2012

Reason for exclusion	Additional potential anti-caries agent (calcium glycerophosphate) added to 1000 ppm SMFP fluoride toothpaste only

De Paola 1993

Reason for exclusion	Equivalent fluoride concentration (1000 ppm SMFP, 1000 ppm NaF, 1000 ppm NaF)

Dolles 1980

Reason for exclusion	Additional non-fluoride active agent (chlorhexidine)

Downer 1976

Reason for exclusion	Non-random allocation. Additional topical fluoride-based intervention

Edlund 1977

Reason for exclusion	Equivalent fluoride concentration (1000 ppm SMFP, 1000 ppm NaF)

Edward 1978

Reason for exclusion	All participants given fortnightly fluoride rinses with NaF solution. Random allocation not stated or indicated. Conference abstract

Ennever 1980

Reason for exclusion	Random allocation not stated or indicated

Feng 2007

Reason for exclusion	Inadequate follow-up period (6 months)

Finn 1963

Reason for exclusion	Medically compromised institutionalised children

Fogels 1982

Reason for exclusion	Comparative study; not RCT

Frankl 1968

Reason for exclusion	Additional non-fluoride agent in placebo toothpaste (N-lauroyl sarcosinate). Equivalent fluoride concentration (1000 ppm SnF_2, 1000 ppm SMFP)

Freire 2016

Reason for exclusion	Additional (different) potential anti-caries agents (calcium glycerophosphate or trimetaphosphate) associated with 500 ppm NaF toothpastes only, not in 1000 ppm NaF comparator)

Gerdin 1972

Reason for exclusion	Non-random (systematic) allocation

Gish 1965

Reason for exclusion	Additional topical fluoride-based intervention

Hargreaves 1973

Reason for exclusion	Non-random (systematic) allocation

Heidmann 1997

Reason for exclusion	Aluminium-containing test toothpaste

Hill 1959

Reason for exclusion	Random allocation not stated or indicated

Horowitz 1966

Reason for exclusion	Non-random (systematic) allocation

Horowitz 1966a

Reason for exclusion	Toothpaste versus aqueous solution

Horowitz 1976

Reason for exclusion	Randomisation not stated or indicated

Jordan 1959

Reason for exclusion	Only 2 clusters (schools), each randomised to 1 of the 2 interventions compared

Kinkel 1968

Reason for exclusion	Additional potential agent (bromchlorophene) in SMFP arm

Koch 1967

Reason for exclusion	Non-random (systematic) allocation

Koch 1972

Reason for exclusion	Potassium fluoride and manganese chloride test toothpaste

Koch 1982

Reason for exclusion	Additional topical fluoride-based intervention

Kyes 1961

Reason for exclusion	Non-random allocation

Künzel 1977

Reason for exclusion	Additional fluoride-based intervention with fluoride toothpaste

Li 2015

Reason for exclusion	Equivalent fluoride concentration (1450 ppm F)

Lu 1985

Reason for exclusion	Additional non-fluoride agent in test toothpaste only

Mergele 1968a

Reason for exclusion	Medically compromised institutionalised young adults and children selected

Moller 1968

Reason for exclusion	Additional active agent added to fluoride in test toothpaste

Muhler 1958

Reason for exclusion	Random allocation not stated or indicated

Muhler 1960

Reason for exclusion	Non-random allocation

Muhler 1967

Reason for exclusion	Additional topical fluoride received. Non-random (systematic) allocation

Murray 1980

Reason for exclusion	Random allocation not stated or indicated

Nordström 2010

Reason for exclusion	Additional agent (fluoride varnish) every 12 months (or 6 months for children with very high caries risk)

Onisi 1970

Reason for exclusion	Random allocation not stated or indicated

Patz 1970

Reason for exclusion	Random allocation not stated or indicated

Peffley 1960

Reason for exclusion	Random allocation not stated. Inadequate follow-up period (10 months)

Ran 1991

Reason for exclusion	Placebo gel versus AmF gel or toothpaste (fortnightly application) in addition to usual toothbrushing practice

Riethe 1975

Reason for exclusion	Non-random allocation

Ripa 1990

Reason for exclusion	Equivalent fluoride concentration (1100 ppm NaF, 1000 ppm SMFP)

Saporito 2000

Reason for exclusion	Equivalent fluoride concentration (1100 ppm NaF, 1000 ppm SMFP)

Sjögren 1995

Reason for exclusion	Additional non-fluoride agent added to dentifrice A

Srisilapanan 2013

Reason for exclusion	Additional non-fluoride agent in test toothpaste only, and follow-up 6 months

Stookey 1975

Reason for exclusion	Random allocation not stated or indicated

Tavener 2006

Reason for exclusion	Prevalence and severity of fluorosis. No caries data

Thomas 1970

Reason for exclusion	Additional agent added (sodium N-lauroyl sarcosinate) in different concentrations 1000 ppm SMFP toothpastes but not to placebo toothpaste

Triol 1987

Reason for exclusion	Equivalent fluoride concentration (1000 ppm SMFP, 500 ppm SMFP + 500 ppm NaF)

Yin 2013

Reason for exclusion	Additional non-fluoride agent in test toothpaste only, and follow-up 6 months

You 2002

Reason for exclusion	Additional oral health programme for 1100 ppm NaF arm

Footnotes

AmF = amine fluoride, F = fluoride, NaF = sodium fluoride, ppm = parts per million, RCT = randomised controlled trial, SMFP = sodium monofluorophosphate, SnF_2 = stannous fluoride.

Characteristics of studies awaiting classification

NCT02016001

Methods	Trial design: 2-armed, double-blind, head-to-head RCT Location: USA Number of centres: not reported Setting: Pakistan Recruitment period: April 2013
Participants	Inclusion criteria: 1. regular school children of 12 to 15 years 2. presence of at least 4 molars Exclusion criteria: 1. non-consenting cases 2. medically/physically compromised children 3. children under any kind of parallel fluoride regimen (systemic or topical) 4. children consuming diet that is different from routine dietary practices 5. children using toothpaste with greater than 1100 ppm and less than 500 ppm of fluoride 6. children found with rampant caries 7. children found with all filled molars 8. children with any oral infection abscess, periodontitis, etc. 9. dentition with malocclusion 10. children undergoing orthodontic/prosthodontic treatment 11. children with temporomandibular joint disorder 12. children who missed the baseline examinations 13. loss to any follow-up cases
Interventions	**Comparison: FT versus FT** Group A: twice daily toothbrushing with fluoride concentration 1500 ppm Group B: twice daily toothbrushing with fluoride concentration 1000 ppm
Outcomes	Primary: 18-month DMFT increment Secondary: not reported Assessments irrelevant to this review's scope: not reported Follow-up duration: 18 months
Notes	

Footnotes

DMFT = decayed, missing, and filled permanent teeth; FT = fluoride treatment; ppm = parts per million; RCT = randomised controlled trial.

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in young children (primary dentition)

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in young children (primary dentition)
Population: young children between 1 and 6 years of age at the start of the study **Setting:** home, nursery, school **Intervention:** toothbrushing with higher fluoride concentration toothpaste **Comparison:** toothbrushing with lower fluoride concentration toothpaste **Outcomes:** primary dentition: d(m)fs, d(m)ft, proportion of children developing new caries, adverse effects of toothpaste

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in young children (primary dentition)							
Comparison	Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with lower fluoride concentration toothpaste	Risk with higher fluoride concentration toothpaste				
Caries increment (surface index $d_3$mfs)							
1500 ppm F compared with 0 ppm F	Caries increment (surface index $d_3$fs, adjusted for baseline value) Follow-up: 24 months	The mean caries increment with 0 ppm F was 4.73 $d_3$fs[a]	The mean caries increment in the higher fluoride group was on average MD 1.86 lower (95% CI 2.51 lower to 1.21 lower)	-	998 (1 RCT)	⊕⊕⊕⊖ moderate[b]	Mean caries increment in the higher fluoride group was on average SMD 0.40 lower (95% CI 0.53 lower to 0.27 lower)
1450 ppm F compared with 250 ppm F	Caries increment (surface index $d_3$mfs) Follow-up: 22 months	The mean caries increment with 250 ppm F was 2.90 dmfs[c]	The mean caries increment in the higher fluoridated group was on average MD 1.20 lower (95% CI 2.92 lower to 0.52 higher)	-	172 (1 RCT)	⊕⊕⊖⊖ low[d]	Effective sample size = 96 SMD 0.28 lower (95% CI 0.68 lower to 0.12 higher)
1055 to 1100 ppm F compared with 500 to 550 ppm F	Caries increment (surface index $d_3$mfs) Follow-up: range 20 to 36 months	The mean caries increment with 550 ppm F ranged from 2.05 to 2.52[e]	The mean caries increment in the higher fluoridated group was on average MD 0.05 dmfs lower (95% CI 0.38 lower to 0.28 higher)	-	1958 (2 RCTs)	⊕⊕⊕⊖ moderate[f]	SMD 0.02 lower (95% CI 0.12 lower to 0.07 higher) 2 additional studies (12-month follow-up) reporting caries increment at the active non-cavitated caries lesions (ANC) level with MD 0.31 lower (95% CI 0.93 lower to 0.32 higher) and SMD 0.20 lower (95% CI 0.67 lower to 0.27 higher)
Caries increment (tooth index $d_3$mft)							
1450 ppm F compared with 250 ppm F	Caries increment (tooth index $d_3$mft) Follow-up: 22 months	The mean caries increment with 250 ppm F was 1.20 dmft[g]	The mean caries increment in the higher fluoridated group was on average MD 0.40 lower (95% CI 1.14 lower to 0.34 higher)	-	172 (1 RCT)	⊕⊕⊖⊖ low[d]	Effective sample size = 96 SMD 0.22 lower (95% CI 0.62 lower to 0.18 higher)
1055 to 1100 ppm F compared with 500 to 550 ppm F	Caries increment (tooth index $d_3$mft) Follow-up: 36 months	The mean caries increment with 550 ppm F was 1.72[h]	The mean caries increment in the higher fluoridated group was on average MD 0.27 dmft lower (95% CI 0.60 lower to 0.06 higher)	-	905 (1 RCT)	⊕⊕⊖⊖ low[i]	SMD 0.11 lower (95% CI 0.24 lower to 0.02 higher)

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in young children (primary dentition)							
1450 F compared with 440 ppm F	Caries increment (tooth index $d_3$mft) Follow-up: 60 months	The mean caries increment with 450 ppm F was 2.49[j]	The mean caries increment in the higher fluoridated group was on average MD 0.34 dmft lower (95% CI 0.59 lower to 0.09 lower)	-	2362 (1 RCT)	⊕⊕⊕⊖ moderate[k]	SMD 0.11 lower (95% CI 0.19 lower to 0.03 lower)
Proportion of children developing new caries							
1450 ppm F compared with 250 ppm F	Proportion of children developing new caries Follow-up: 22 months	455 per 1000[l]	418 per 1000 (245 to 714)	RR 0.92 (0.54 to 1.57)	172 (1 RCT)	⊕⊕⊖⊖ low[d]	Effective sample size = 69
1055 to 1100 ppm F compared with 500 to 550 ppm F	Proportion of children developing new caries Follow-up: 36 months	484 per 1000[m]	416 per 1000 (358 to 479)	RR 0.86 (0.74 to 0.99)	905 (1 RCT)	⊕⊕⊖⊖ low[i]	
1450 F compared with 440 ppm F	Proportion developing new caries Follow-up: 60 months	577 per 1000[n]	502 per 1000 (467 to 542)	RR 0.87 (0.81 to 0.94)	2362 (1 RCT)	⊕⊕⊕⊖ moderate[k]	
Adverse effects of toothpaste							
1500 ppm F compared with 0 ppm F	Adverse effects of toothpaste Follow-up: 24 months			Not estimable	998 (1 RCT)	⊕⊕⊖⊖ low[o]	0 events reported
1450 ppm F compared with 250 ppm F	Adverse effects of toothpaste	No studies reported this outcome					
1055 to 1100 ppm F compared with 500 to 550 ppm F	Adverse effects of toothpaste Follow-up: 12 months			Not estimable	195 (1 RCT)	⊕⊕⊖⊖ low[p]	"There were no reports on adverse effects, but some children complained about the taste of the dentifrice"
1450 F compared with 440 ppm F	Adverse effects of toothpaste	No studies reported this outcome					

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **d(m)fs/t:** decayed, missing, filled primary surfaces/teeth; **d_3:** dentinal/cavitated caries lesions level; **F:** fluoride; **ppm:** parts per million; **RR:** risk ratio; **MD**: difference in means; **SMD**: standardised mean difference.

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in young children (primary dentition)
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** 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 substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Footnotes

[a]Reported mean caries increment $d_3$fs in the 0 ppm F group.

[b]Downgraded for study limitations (unclear overall risk of bias).
[c]Reported mean caries increment $d_3$mfs in the 250 ppm F group.

[d]Downgraded for study limitations (high risk of attrition bias) and imprecision.
[e]Reported mean caries increment $d_3$mfs in the 550 ppm F groups.

[f]Downgraded for imprecision. There were some study limitations in 1 study but we did not deem these to be sufficient for an additional downgrading of the certainty, as this study contributed only 27% to the overall estimate.
[g]Reported mean caries increment $d_3$ft in the 250 ppm F group.

[h]Reported mean caries increment $d_3$mft in the 550 ppm F group.

[i]Downgraded for study limitations (unclear overall risk of bias) and imprecision.
[j]Reported mean caries increment $d_3$mft in the 450 ppm F group.

[k]Downgraded for imprecision. Some concerns regarding study limitations (unclear risk of bias for performance bias and contamination) but not considered sufficient to merit additional downgrading.
[l]Reported proportion in the 250 ppm F group.
[m]Reported proportion in the 550 ppm F group.
[n]Reported proportion in the 440 ppm F group.
[o]Downgraded for imprecision (no events reported) and study limitations (unclear overall risk of bias).
[p]Downgraded for imprecision.

2 Fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in children and adolescents (immature permanent dentition) - NMA estimates

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in children and adolescents - NMA estimates

Population: children and adolescents between 5 and 15 years of age at the start of the study

Setting: home, school

Intervention: toothbrushing with higher fluoride concentration toothpaste

Comparison: toothbrushing with lower fluoride concentration toothpaste

Outcomes: immature permanent dentition: D(M)FS, D(M)FT (all follow-ups: closest to 36 months)

Comparison	Relative effect SMD (NMA estimate) (95% CI)	Studies*	Certainty of evidence (GRADE)	Relative effect SMD (NMA estimate) (95% CI)	Studies*	Certainty of evidence (GRADE)
	Caries increment (surface index D_3(M)FS)			Caries increment (tooth index D_3(M)FT)		
250 versus 0 ppm F	-0.15 (-0.25 to -0.05)	3	low[a, b, c]	-0.11 (-0.27 to 0.05)	1	low[a, b, c]
440 to 550 versus 0 ppm F	-0.12 (-0.31 to 0.07)	2	low[a, c, d]	-0.18 (-0.41 to 0.04)	2	low[a, c]
1000 to 1250 versus 0 ppm F	-0.28 (-0.32 to -0.25)	55	high[a, d]	-0.26 (-0.31 to -0.21)	41	high[a]
1450 to 1500 versus 0 ppm F	-0.36 (-0.43 to -0.29)	4	moderate[a, d]	-0.39 (-0.49 to -0.28)	4	moderate[a]
1700 to 2200 versus 0 ppm F	-0.32 (-0.41 to -0.22)	-	low[a, d]	-0.33 (-0.56 to -0.11)	-	low[d, e]

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in children and adolescents - NMA estimates						
2400 to 2800 versus 0 ppm F	-0.41 (-0.49 to -0.33)	3	low[a, b, c]	-0.39 (-0.52 to -0.25)	2	low[a, c, d]
440 to 550 versus 250 ppm F	0.03 (-0.17 to 0.23)	1	low[a, b, c]	-0.08 (-0.32 to 0.17)	1	low[a, c, d]
1000 to 1250 versus 250 ppm F	-0.14 (-0.24 to -0.04)	7	low[a, b, c]	-0.15 (-0.31 to 0)	3	low[a, c, d]
1450 to 1500 versus 250 ppm F	-0.21 (-0.33 to -0.10)	-	low[a, d]	-0.28 (-0.47 to -0.09)	-	low[a, d]
1700 to 2200 versus 250 ppm F	-0.17 (-0.30 to -0.04)	-	low[a, d]	-0.23 (-0.50 to 0.05)	-	low[d, e]
2400 to 2800 versus 250 ppm F	-0.26 (-0.38 to -0.14)	-	low[a, d]	-0.28 (-0.48 to -0.08)	-	low[a, d]
1000 to 1250 versus 440 to 550 ppm F	-0.16 (-0.35 to 0.03)	1	low[a, d]	-0.08 (-0.30 to 0.15)	1	low[a, c, d]
1450 to 1500 versus 440 to 550 ppm F	-0.24 (-0.44 to -0.04)	-	low[a, d]	-0.20 (-0.45 to 0.04)	-	low[a, d]
1700 to 2200 versus 440 to 550 ppm F	-0.20 (-0.41 to 0.01)	-	low[a, d]	-0.15 (-0.46 to 0.16)	-	low[a, d]
2400 to 2800 versus 440 to 550 ppm F	-0.29 (-0.49 to -0.08)	-	low[a, d]	-0.20 (-0.46 to 0.05)	-	low[a, d]
1450 to 1500 versus 1000 to 1250 ppm F	-0.08 (-0.14 to -0.01)	10	moderate[a]	-0.13 (-0.23 to -0.02)	4	low[a, b]
1700 to 2200 versus 1000 to 1250 ppm F	-0.03 (-0.12 to 0.06)	5	low[c, e]	-0.07 (-0.30 to 0.15)	1	very low[c, d, e]
2400 to 2800 versus 1000 to 1250 ppm F	-0.12 (-0.20 to -0.05)	6	low[a, b, c]	-0.12 (-0.25 to 0.01)	3	very low[b, c, e]
1700 to 2200 versus 1450 to 1500 ppm F	0.04 (-0.07 to 0.15)	-	moderate[a]	0.05 (-0.19 to 0.30)	-	low[a, b, d]
2400 to 2800 versus 1450 to 1500 ppm F	-0.05 (-0.14 to 0.05)	2	moderate[a]	0 (-0.16 to 0.17)	-	low[a, f]
2400 to 2800 versus 1700 to 2200 ppm F	-0.09 (-0.20 to 0.02)	1	low[a, e]	-0.05 (-0.27 to 0.17)	-	very low[b, e, g]

*Indirect evidence only is indicated by -

CI: confidence interval; **D(M)FS:** decayed, missing, filled surfaces (permanent dentition); **D(M)FT:** decayed, missing, filled teeth (permanent dentition); **D_3:** dentinal/cavitated caries lesions level; **F:** fluoride; **NMA:** network meta-analysis; **ppm:** parts per million; **SMD**: standardised mean difference.

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in children and adolescents - NMA estimates
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** 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 substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Footnotes

[a]Downgraded (some concerns) for within-study bias.
[b]Downgraded (some concerns) for heterogeneity: prediction interval extends into clinically important or unimportant effects.
[c]Downgraded (some concerns) for incoherence: lack of agreement of the direct and indirect estimates relative to the clinically important value (0.30 SMD).
[d]Downgraded (some concerns) for imprecision: 95% CI extends into clinically important effects (0.30 SMD).
[e]Downgraded (major concerns) for within-study bias.
[f]Downgraded (major concerns) for heterogeneity: prediction interval extends into clinically important or unimportant effects.
[g]Downgrade (major concerns) for incoherence: lack of agreement of the direct and indirect estimates relative to the clinically important value (0.30 SMD).

3 Fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in children and adolescents (immature permanent dentition)

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in children and adolescents

Population: children and adolescents between 5 and 15 years of age at the start of the study
Setting: home, school
Intervention: toothbrushing with higher fluoride concentration toothpaste
Comparison: toothbrushing with lower fluoride concentration toothpaste

Outcomes: immature permanent dentition: proportion of children developing new caries, adverse effects of toothpaste

Comparison	Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with lower fluoride concentration toothpaste	Risk with higher fluoride concentration toothpaste				
Proportion of children developing new caries							
250 ppm F compared with 0 ppm F	Proportion of children developing new caries Follow-up: 24 months	451 per 1000[a]	483 per 1000 (411 to 636)	RR 1.07 (0.91 to 1.27)	684 (2 RCTs)	⊕⊕⊖⊖ low[b]	
1000 to 1250 ppm F compared with 0 ppm F	Proportion of children developing new caries Follow-up: ranged from 12 to 60 months	596 per 1000[c]	536 per 1000 (459 to 632)	RR 0.90 (0.77 to 1.06)	1898 (7 RCTs)	⊕⊕⊖⊖ low[d]	6 studies had follow-up of 36 months or less
1500 ppm F compared with 0 ppm F	Proportion of children developing new caries Follow-up: 36 months	947 per 1000[e]	900 per 1000 (862 to 928)	RR 0.95 (0.91 to 0.98)	945 (1 RCT)	⊕⊕⊖⊖ low[b]	
1450 to 1500 ppm F compared with 1000 to 1250 ppm F	Proportion of children developing new caries Follow-up: 36 months	728 per 1000[f]	742 per 1000 (677 to 808)	RR 1.02 (0.93 to 1.11)	4328 (2 RCTs)	⊕⊕⊖⊖ low[g]	
Adverse effects of toothpaste							
All comparisons	Adverse effects of toothpaste Follow-up: closest to 36 months	16 studies assessed possible side effects arising from toothpaste use, principally in terms of oral (soft tissue) pathologies and tooth staining. 6 studies[h] reported either no untoward events or no untoward events which could be attributed to the use of the toothpaste on the soft tissue. 6 studies[i] reported a greater incidence of staining in the stannous fluoride group. 1 study[j] reported no differential in staining between the groups (2.5% fluoride group versus 1% placebo group) and no staining was found in another[k]. No side effects of toothpaste were observed or reported in 4 studies[l]					

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **F:** fluoride; **ppm:** parts per million; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Footnotes

[a]Reported proportion in the 0 ppm F groups.
[b]Downgraded for imprecision and study limitations (unclear risk of selection and attrition bias).
[c]Reported proportion in the 0 ppm F groups.
[d]Downgraded for imprecision, study limitations (6 studies at unclear risk of selection or attrition bias or both, 1 study at high risk of performance and detection bias), and inconsistency (I^2 = 80%).
[e]Reported proportion in the 0 ppm F group.
[f]Reported proportion in the 1000 ppm F, 1250 ppm F groups.
[g]Downgraded for imprecision, study limitations (unclear risk of selection and attrition bias and contamination/co-intervention), and inconsistency (I^2 = 82%).
[h]Conti 1988; Fogels 1979; Fogels 1988; Koch 1990; Rule 1984; Stephen 1994.
[i]Fanning 1968; James 1967; Naylor 1967; Slack 1964; Slack 1967; Slack 1967a.
[j]Jackson 1967.
[k]Fogels 1979.
[l]Fan 2008; Glass 1983; Kleber 1996; Rao 2009.

4 Fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in adults (mature permanent dentition)

The effects of fluoride toothpaste with higher versus lower concentration of fluoride for preventing caries in adults

Population: adults aged between 18 and 93 years of age at the start of the study
Setting: home
Intervention: toothbrushing with higher fluoride toothpaste concentration
Comparison: toothbrushing with lower fluoride toothpaste concentration

Outcomes: mature permanent dentition: D(M)FS, D(M)FT, proportion of adults developing new caries, adverse effects of toothpaste

Comparison	Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with lower fluoride concentration toothpaste	Risk with higher concentration toothpaste				
1000 or 1100 ppm F compared with 0 ppm F	Caries increment (surface index D_3MFS) Follow-up: 12 to 24 months	The mean caries increment with 0 ppm F ranged from 0.69 to 4.99 D_3MFS[a]	The mean caries increment in the higher fluoride group was on average MD 0.53 lower (95% CI 1.02 lower to 0.04 lower)	-	2162 (3 RCTs)	⊕⊕⊕⊖ moderate[b]	Mean caries increment in the higher fluoride group was on average SMD 0.17 lower (95% CI 0.29 lower to 0.06 lower)
1000 or 1100 ppm F compared with 0 ppm F	Caries increment (tooth index D_3MFT) Follow-up: 24 months	The mean value with 0 ppm F was 1.52 D_3MFT[c]	The mean caries increment in the higher fluoride group was on average MD 0.46 lower (95% CI 0.93 lower to 0.01 higher)	-	247 (1 RCT)	⊕⊕⊖⊖ low[d]	Mean caries increment in the higher fluoride group was on average SMD 0.24 lower (95% CI 0.49 lower to 0.01 higher)
1000 or 1100 ppm F compared with 0 ppm F	Proportion of adults developing new caries	No studies reported this outcome					
1000 or 1100 ppm F compared with 0 ppm F	Adverse effects of toothpaste	No studies reported this outcome					

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **D(M)FS:** decayed, missing, filled surfaces (permanent dentition); **D(M)FT:** decayed, missing, filled teeth (permanent dentition); **D_3:** dentinal/cavitated caries lesions level; **F:** fluoride; **MD**: difference in means; **ppm:** parts per million; **RCT:** randomised controlled trial; **SMD**: standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Footnotes

[a]Reported mean caries increment D_3MFS in the 0 ppm F groups. Caries increment D_3MFS values in 1 study were considerably higher than in the other 2 studies.
[b]Downgraded for study limitations (high overall risk of bias due to high levels of attrition in 1 study). Despite substantial heterogeneity (I^2 = 68%) being observed for this comparison we did not downgrade for inconsistency, as all studies were showing a beneficial effect of the higher fluoride concentration.
[c]Reported mean caries increment D_3MFT in the 0 ppm F group.
[d]Downgraded for study limitations (high overall risk of bias due to high levels of attrition) and imprecision.

Additional tables

1 Distribution of potential effect modifiers

Fluoride concentration	Supervised toothbrushing		Community water fluoridation > 0.5 ppm F	
	D(M)FS	D(M)FT	D(M)FS	D(M)FS
0 ppm F (placebo toothpaste)	15/61 (25%)	13/46 (28%)	6/41 (15%) (unreported 20 studies)	6/31 (unreported 15 studies)
250 ppm F	1/4 (25%)	1/2 (50%)	1/4 (25%)	1/2 (50%)
440 to 550 ppm F	No studies	No studies	No studies	No studies
1000 to 1250 ppm F	4/20 (20%)	3/7 (43%)	3/15 (20%) (unreported 5 studies)	2/7 (29%)
1450 to 1500 ppm F	2/8 (25%)	2/2 (100%)	1/4 (25%) (unreported 4 studies)	1/2 (50%)
1700 to 2200 ppm F	0/5 (0%)	0/1 (0%)	1/5 (20%)	0/1 (0%)
2400 to 2800 ppm F	1/6 (17%)	0/3 (0%)	0/3 (0%) (unreported 3 studies)	0/3 (0%)

Footnotes

D(M)FS = decayed, missing, filled permanent surfaces; D(M)FT = decayed, missing, filled permanent teeth; F = fluoride; ppm = parts per million.

2 Confidence intervals (CI) and predictive intervals (PI) for the D(M)FS NMA estimates in children and adolescents (immature permanent dentition)

Fluoride concentration comparison (ppm F)	NMA SMD (95% CI) NMA SMD (95% PI)	Direct SMD (95% CI) Indirect SMD (95% CI) Direct contribution
250 versus 0	-0.15 (-0.25 to -0.05) -0.15 (-0.37 to 0.07)	-0.09 (-0.25 to 0.07) -0.19 (-0.33 to -0.06) 42.9%
440 to 550 versus 0	-0.12 (-0.31 to 0.07) -0.12 (-0.40 to 0.15)	-0.06 (-0.29 to 0.17) -0.27 (-0.64 to 0.10) 71.9%
1000 to 1250 versus 0	-0.28 (-0.32 to -0.25) -0.28 (-0.48 to -0.09)	-0.28 (-0.32 to -0.24) -0.33 (-0.45 to -0.21) 91.5%
1450 to 1500 versus 0	-0.36 (-0.43 to -0.29) -0.36 (-0.57 to -0.15)	-0.34 (-0.46 to -0.22) -0.37 (-0.46 to -0.29) 33.8%
1700 to 2200 versus 0*	-0.32 (-0.41 to -0.22) -0.32 (-0.53 to -0.10)	- -0.32 (-0.53 to -0.10) -
2400 to 2800 versus 0	-0.41 (-0.49 to -0.33) -0.41 (-0.62 to -0.20)	-0.523 (-0.689 to -0.36) -0.372 (-0.47 to -0.28) 24.8%
440 to 550 versus 250	0.03 (-0.17 to 0.23) 0.03 (-0.25 to 0.31)	-0.01 (-0.25 to 0.23) 0.11 (-0.26 to 0.49) 70.2%
1000 to 1250 versus 250	-0.14 (-0.24 to -0.04) -0.14 (-0.36 to 0.08)	-0.10 (-0.21 to 0.01) -0.36 (-0.63 to -0.09) 86.1%

Fluoride concentration comparison (ppm F)	NMA SMD (95% CI) NMA SMD (95% PI)	Direct SMD (95% CI) Indirect SMD (95% CI) Direct contribution
1450 to 1500 versus 250*	-0.21 (-0.33 to -0.10) -0.21 (-0.44 to 0.02)	- -0.21 (-0.33 to -0.10) -
1700 to 2200 versus 250*	-0.17 (-0.30 to -0.04) -0.17 (-0.41 to 0.07)	- -0.17 (-0.30 to -0.04) -
2400 to 2800 versus 250*	-0.26 (-0.38 to -0.14) -0.26 (-0.49 to -0.03)	- -0.26 (-0.38 to -0.14) -
1000 to 1250 versus 440 to 550	-0.16 (-0.35 to 0.03) -0.16 (-0.44 to 0.11)	-0.11 (-0.35 to 0.14) -0.26 (-0.58 to 0.06) 63.5%
1450 to 1500 versus 440 to 550*	-0.24 (-0.44 to -0.04) -0.24 (-0.52 to 0.04)	- -0.24 (-0.44 to -0.04) -
1700 to 2200 versus 440 to 550*	-0.20 (-0.41 to 0.01) -0.20 (-0.48 to 0.09)	- -0.20 (-0.41 to 0.01) -
2400 to 2800 versus 440 to 550*	-0.29 (-0.49 to -0.08) -0.29 (-0.57 to 0.00)	- -0.29 (-0.49 to -0.08) -
1450 to 1500 versus 1000 to 1250	-0.08 (-0.14 to -0.01) -0.08 (-0.28 to 0.13)	-0.10 (-0.17 to -0.03) 0.02 (-0.12 to 0.15) 77.8%
1700 to 2200 versus 1000 to 1250	-0.03 (-0.12 to 0.06) -0.03 (-0.25 to 0.18)	-0.02 (-0.12 to 0.07) -0.19 (-0.58 to 0.20) 94.4%
2400 to 2800 versus 1000 to 1250	-0.12 (-0.20 to -0.05) -0.12 (-0.33 to 0.09)	-0.09 (-0.18 to 0.00) -0.20 (-0.35 to -0.06) 71.1%
1700 to 2200 versus 1450 to 1500*	0.04 (-0.07 to 0.15) 0.04 (-0.18 to 0.27)	- 0.04 (-0.07 to 0.15) -
2400 to 2800 versus 1450 to 1500	-0.05 (-0.14 to 0.05) -0.05 (-0.26 to 0.17)	-0.11 (-0.28 to 0.07) -0.03 (-0.14 to 0.09) 28.5%
2400 to 2800 versus 1700 to 2200	-0.09 (-0.20 to 0.02) -0.09 (-0.32 to 0.13)	-0.01 (-0.22 to 0.20) -0.13 (-0.26 to 0.01) 29.6%

Footnotes

*

Indirect evidence only. The caries preventive effects of these different fluoride comparisons were not directly evaluated in any study.
CI = confidence interval; D(M)FS = decayed, missing, filled permanent surfaces; F = fluoride; NMA = network meta-analysis; PI = predictive interval; ppm = parts per million; SMD = standardised mean difference.

3 D(M)FS caries increments not in meta-analysis (immature permanent dentition)

Comparison	**1000 to 1250**			**440 to 550**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Stookey 2004	6.27	4.58	174	6.24	4.49	168	0.01 (-0.21 to 0.22)
Comparison	**1450 to 1500**			**440 to 550**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Biesbrock 2003b	0.21	4.02	180	0.26	4.03	169	-0.05 (-0.90 to 0.80)
Comparison	**1450 to 1500**			**1000 to 1250**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	4.27	3.91	1116	4.33	3.91	1120	-0.02 (-0.10 to 0.07)
Comparison	**1700 to 2200**			**1000 to 1250**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	3.78	3.91	2126	4.33	3.91	1120	-0.14 (-0.21 to -0.07)
Comparison	**2400 to 2800**			**1000 to 1250**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Biesbrock 2003a	1.25	3.59	153	1.47	3.50	168	-0.06 (-0.28 to 0.16)
Marks 1994	3.46	3.91	1112	4.33	3.91	1120	-0.22 (-0.31 to -0.14)
Comparison	**1700 to 2200**			**1450 to 1500**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	3.78	3.91	2126	4.27	3.91	1116	-0.13 (-0.20 to -0.05)
Comparison	**2400 to 2800**			**1450 to 1500**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	3.46	3.91	112	4.27	3.91	1116	-0.21 (-0.40 to -0.01)
Comparison	**2400 to 2800**			**1700 to 2200**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	3.46	3.91	1112	3.78	3.91	2126	-0.08 (-0.15 to -0.01)

Footnotes

CI = confidence interval; D(M)FS = decayed, missing, filled permanent surfaces; n = number; SD = standard deviation; SMD = standardised mean difference.

4 Confidence intervals (CI) and predictive intervals (PI) for the D(M)FT NMA estimates in children and adolescents (immature permanent dentition)

Fluoride concentration comparison (ppm F)	**NMA SMD (95% CI)** **NMA SMD (95% PI)**	**Direct SMD (95% CI)** **Indirect SMD (95% CI)** **Direct contribution**
250 versus 0	-0.11 (-0.27 to 0.05) -0.11 (-0.40 to 0.19)	-0.16 (-0.44 to 0.12) -0.08 (-0.28 to 0.11) 32.7%

Fluoride concentration comparison (ppm F)	NMA SMD (95% CI) NMA SMD (95% PI)	Direct SMD (95% CI) Indirect SMD (95% CI) Direct contribution
440 to 550 versus 0	-0.18 (-0.41 to 0.04) -0.18 (-0.52 to 0.15)	-0.21 (-0.48 to 0.05) -0.11 (-0.55 to 0.34) 73.9%
1000 to 1250 versus 0	-0.26 (-0.31 to -0.21) -0.26 (-0.51 to -0.01)	-0.26 (-0.30 to -0.21) -0.36 (-0.55 to -0.17) 93.8%
1450 to 1500 versus 0	-0.39 (-0.49 to -0.28) -0.39 (-0.66 to -0.12)	-0.37 (-0.50 to -0.23) -0.43 (-0.60 to -0.26) 60.4%
1700 to 2200 versus 0*	-0.33 (-0.56 to -0.11) -0.33 (-0.67 to 0.01)	- -0.33 (-0.56 to -0.11) -
2400 to 2800 versus 0	-0.39 (-0.52 to -0.25) -0.39 (-0.67 to -0.11)	-0.59 (-0.85 to -0.33) -0.32 (-0.47 to -0.16) 26.7%
440 to 550 versus 250	-0.08 (-0.32 to 0.17) -0.08 (-0.43 to 0.27)	0.01 (-0.28 to 0.29) -0.35 (-0.85 to 0.16) 76.0%
1000 to 1250 versus 250	-0.15 (-0.31 to 0.00) -0.15 (-0.45 to 0.14)	-0.16 (-0.33 to 0.00) -0.06 (-0.54 to 0.43) 89.5%
1450 to 1500 versus 250*	-0.28 (-0.47 to -0.09) -0.28 (-0.59 to 0.03)	- -0.28 (-0.47 to -0.09) -
1700 to 2200 versus 250*	-0.23 (-0.50 to 0.05) -0.23 (-0.60 to 0.15)	- -0.23 (-0.50 to 0.05) -
2400 to 2800 versus 250*	-0.28 (-0.48 to -0.08) -0.28 (-0.60 to 0.04)	- -0.28 (-0.48 to -0.08) -
1000 to 1250 versus 440 to 550	-0.08 (-0.30 to 0.15) -0.08 (-0.41 to 0.26)	-0.09 (-0.37 to 0.19) -0.05 (-0.43 to 0.32) 64.0%
1450 to 1500 versus 440 to 550*	-0.20 (-0.45 to 0.04) -0.20 (-0.56 to 0.15)	- -0.20 (-0.45 to 0.04) -
1700 to 2200 versus 440 to 550*	-0.15 (-0.46 to 0.16) -0.15 (-0.56 to 0.26)	- -0.15 (-0.46 to 0.16) -

Fluoride concentration comparison (ppm F)	NMA SMD (95% CI) NMA SMD (95% PI)	Direct SMD (95% CI) Indirect SMD (95% CI) Direct contribution
2400 to 2800 versus 440 to 550*	-0.20 (-0.46 to 0.05) -0.20 (-0.56 to 0.16)	- -0.20 (-0.46 to 0.06) -
1450 to 1500 versus 1000 to 1250	-0.13 (-0.23 to -0.02) -0.13 (-0.40 to 0.14)	-0.17 (-0.31 to -0.04) -0.05 (-0.23 to 0.12) 62.5%
1700 to 2200 versus 1000 to 1250	-0.07 (-0.30 to 0.15) -0.07 (-0.41 to 0.26)	-0.06 (-0.32 to 0.19) -0.13 (-0.66 to 0.39) 80.9%
2400 to 2800 versus 1000 to 1250	-0.12 (-0.25 to 0.01) -0.12 (-0.4 to 0.16)	-0.06 (-0.21 to 0.09) -0.33 (-0.59 to -0.09) 75.7%
1700 to 2200 versus 1450 to 1500*	0.05 (-0.19 to 0.30) 0.05 (-0.30 to 0.41)	- 0.05 (-0.19 to 0.30) -
2400 to 2800 versus 1450 to 1500*	0.00 (-0.16 to 0.17) 0.00 (-0.29 to 0.30)	- 0.00 (-0.16 to 0.17) -
2400 to 2800 versus 1700 to 2200	-0.05 (-0.27 to 0.17) -0.05 (-0.39 to 0.29)	-0.04 (-0.29 to 0.22) -0.11 (-0.63 to 0.41) 80.8%

Footnotes

*Indirect evidence only. The caries preventive effects of these different fluoride comparisons were not directly evaluated in any study.

CI = confidence interval; D(M)FT = decayed, missing, filled permanent teeth; F = fluoride; NMA = network meta-analysis; PI = predictive interval; ppm = parts per million; SMD = standardised mean difference.

5 D(M)FT caries increments not in meta-analysis (immature permanent dentition)

Comparison	1450 to 1500			1000 to 1250			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	2.44	2.22	1116	2.43	2.22	1120	0.00 (-0.08 to 0.09)
Comparison	**1700 to 2200**			**1000 to 1250**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	2.195	2.22	2126	2.43	2.22	1120	-0.11 (-0.18 to -0.03)
Comparison	**2400 to 2800**			**1000 to 1250**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	2.13	2.22	1112	2.43	2.22	1120	-0.14 (-0.22 to -0.05)
Comparison	**1700 to 2200**			**1450 to 1500**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	2.195	2.22	2126	2.44	2.22	1116	-0.11 (-0.18 to -0.04)
Comparison	**2400 to 2800**			**1450 to 1500**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	2.13	2.22	1112	2.44	2.22	1116	-0.31 (-0.49 to -0.13)
Comparison	**2400 to 2800**			**1700 to 2200**			
Study	Mean	SD	n	Mean	SD	n	SMD (95% CI)
Marks 1994	2.13	2.22	1112	2.195	2.22	2126	-0.03 (-0.10 to 0.04)

Footnotes

CI = confidence interval; D(M)FT = decayed, missing, filled permanent teeth; n = number; SD = standard deviation; SMD = standardised mean difference.

References to studies

Included studies

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[CRSSTD: 3249374]

Abrams RG, Chambers DW. Caries-inhibiting effect of a stannous fluoride silica gel dentifrice: a three-year clinical study. Clinical Preventive Dentistry 1980;2:22-7. [CRSREF: 3249375]

Andlaw 1975

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* Andlaw RJ, Tucker GJ. A dentifrice containing 0.8 per cent sodium monofluorophosphate in an aluminium oxide trihydrate base. A 3-year clinical trial. British Dental Journal 1975;138:426-32. [CRSREF: 3249377]

Tucker GJ, Andlaw RJ, Burchell CK. The relationship between oral hygiene and dental caries incidence in 11-year-old children. A 3-year study. British Dental Journal 1976;141:75-9. [CRSREF: 3249378]

Ashley 1977

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Ashley FP, Mainwaring PJ, Emslie RD, Naylor MN. Clinical testing of a mouthrinse and a dentifrice containing fluoride. A two-year supervised study in school children. British Dental Journal 1977;143:333-8. [CRSREF: 3249380]

Beiswanger 1989

[CRSSTD: 3249381]

Beiswanger BB, Lehnhoff RW, Mallatt ME, Mau MS, Stookey GK. A clinical evaluation of the relative cariostatic effect of dentifrices containing sodium fluoride or sodium monofluorophosphate. Journal of Dentistry for Children 1989;56(4):270-6. [CRSREF: 3249382]

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[CRSSTD: 3249383]

Biesbrock AR, Gerlach RW, Bollmer BW, Faller RV, Jacobs SA, Bartizek RD. Relative anti-caries efficacy of 1100, 1700, 2200, and 2800 ppm fluoride ion in a sodium fluoride dentifrice over 1 year. Community Dentistry and Oral Epidemiology 2001;29:382-9. [CRSREF: 3249384]

Biesbrock 2003a

[CRSSTD: 3249385]

Biesbrock AR, Bartizek RD, Gerlach RW, Jacobs SA, Archila L. Dose response efficacy of sodium fluoride dentifrice at 9 and 21 months with supervised brushing. American Journal of Dentistry 2003;16(5):305-12. [CRSREF: 3249386]

Biesbrock 2003b

[CRSSTD: 3249387]

Biesbrock AR, Bartizek RD, Gerlach RW, Jacobs SA, Archila L. Effect of three concentrations of sodium fluoride dentifrices on clinical caries. American Journal of Dentistry 2003;16(2):99-104. [CRSREF: 3249388]

Blinkhorn 1983

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Blinkhorn AS, Holloway PJ, Davies TG. Combined effects of a fluoride dentifrice and mouthrinse on the incidence of dental caries. Community Dentistry and Oral Epidemiology 1983;11:7-11. [CRSREF: 3249390]

Brudevold 1966

[CRSSTD: 3249391]

Brudevold F, Chilton NW, Wellock WD. A preliminary comparison of a dentifrice containing fluoride and soluble phosphate and employing a calcium-free abrasive with other types of fluoride dentifrices. First year report of a clinical study. Journal of Oral Therapeutics and Pharmacology 1964;56:1-6. [CRSREF: 3249392]

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Buhe 1984

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Barlage B, Buhe H, Buttner W. A 3-year clinical dentifrice trial using different fluoride levels: 0.8 and 1.2% sodium monofluorophosphate. Caries Research 1981;15:185. [CRSREF: 3249395]

* Buhe H, Buttner W, Barlage B. 3-year clinical tooth cream test with toothpastes of varying fluoride content: 0.8% and 1.2% sodium monofluorophosphate [Uber einen dreijahrigen klinischen Zahncremetest mit Zahnpasten unterschiedlicher Fluoridkonzentration: 0,8% und 1,2% Natriummonofluorphosphat]. Quintessenza 1984;35:103-11. [CRSREF: 3249396]

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Cardoso 2014

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Chesters RK, Pitts NB, Matuliene G, Kvedariene A, Huntington E, Bendinskaite R, et al. An abbreviated caries clinical trial design validated over 24 months. Journal of Dental Research 2002;81(9):637-40. [CRSREF: 3249402]

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Data on file (CL-213). The Procter & Gamble Company 1983. [CRSREF: 10142723]

CL-216 1982

Published and unpublished data [CRSSTD: 10142724]

Data on file (CL-216). The Procter & Gamble Company 1982. [CRSREF: 10142725]

CL-220 1986

Published and unpublished data [CRSSTD: 10142726]

Data on file (CL-220). The Procter & Gamble Company 1986. [CRSREF: 10142727]

Conti 1988

[CRSSTD: 3249403]

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Davies 2002

[CRSSTD: 3249407]

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Classification pending references

Data and analyses

1 0 ppm F versus 1000 ppm F in adults (mature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 DMFS	3	2162	Mean Difference(IV, Random, 95% CI)	-0.53 [-1.02, -0.04]
1.2 DMFT	1		Mean Difference(IV, Random, 95% CI)	Subtotals only

2 0 ppm F versus 1500 ppm F in young children (primary dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 dfs	1		Mean Difference(IV, Random, 95% CI)	Subtotals only

3 250 ppm F versus 1450 ppm F in young children (primary dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 dmfs	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
3.2 dmft	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
3.3 Proportion developing new caries	1		Risk Ratio(M-H, Random, 95% CI)	Subtotals only

4 500 to 550 ppm F versus 1055 to 1100 ppm F in young children (primary dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 dmfs/ANC	4		Mean Difference(IV, Random, 95% CI)	Subtotals only
4.1.1 dmfs	2	1958	Mean Difference(IV, Random, 95% CI)	-0.05 [-0.38, 0.28]
4.1.2 ANC	2	285	Mean Difference(IV, Random, 95% CI)	-0.31 [-0.93, 0.32]
4.2 dmft	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
4.3 Proportion developing new caries	1		Risk Ratio(M-H, Random, 95% CI)	Subtotals only

5 440 ppm F versus 1450 ppm F in young children (primary dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 dmft	1		Mean Difference(IV, Random, 95% CI)	Subtotals only
5.2 Proportion developing new caries	1		Risk Ratio(M-H, Random, 95% CI)	Subtotals only

6 0 ppm F versus 250 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 D(M)FS closest to 3 years	3	1460	Std. Mean Difference(IV, Random, 95% CI)	-0.09 [-0.19, 0.02]
6.2 D(M)FT	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only
6.3 Proportion developing new caries	2	684	Risk Ratio(M-H, Random, 95% CI)	1.07 [0.91, 1.27]

7 0 ppm F versus 500 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 D(M)FS closest to 3 years	2	816	Std. Mean Difference(IV, Random, 95% CI)	-0.07 [-0.21, 0.06]
7.2 D(M)FT	2	816	Std. Mean Difference(IV, Random, 95% CI)	-0.28 [-0.72, 0.15]

8 0 ppm F versus 1000 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 D(M)FS	55	31819	Std. Mean Difference(IV, Random, 95% CI)	-0.28 [-0.33, -0.24]
8.2 D(M)FT	41	24837	Std. Mean Difference(IV, Random, 95% CI)	-0.26 [-0.31, -0.21]
8.3 Proportion developing new caries	7	1898	Risk Ratio(M-H, Random, 95% CI)	0.90 [0.77, 1.06]

9 0 ppm F versus 1450 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
9.1 D(M)FS	4	4406	Std. Mean Difference(IV, Random, 95% CI)	-0.34 [-0.51, -0.18]
9.2 D(M)FT	4	4406	Std. Mean Difference(IV, Random, 95% CI)	-0.37 [-0.50, -0.24]
9.3 Proportion developing new caries	1		Risk Ratio(M-H, Random, 95% CI)	Subtotals only

10 0 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
10.1 D(M)FS closest to 3 years	3	1989	Std. Mean Difference(IV, Random, 95% CI)	-0.84 [-1.29, -0.38]
10.2 D(M)FT	2	1209	Std. Mean Difference(IV, Random, 95% CI)	-1.57 [-3.96, 0.82]

11 250 ppm F versus 500 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
11.1 D(M)FS	1	766	Std. Mean Difference(IV, Random, 95% CI)	-0.01 [-0.15, 0.13]
11.2 D(M)FT	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only

12 250 ppm F versus 1000 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
12.1 D(M)FS	6	3047	Std. Mean Difference(IV, Random, 95% CI)	-0.11 [-0.20, -0.02]
12.2 D(M)FT	3	2087	Std. Mean Difference(IV, Random, 95% CI)	-0.16 [-0.27, -0.05]
12.3 Proportion developing new caries	2	676	Risk Ratio(M-H, Random, 95% CI)	1.00 [0.63, 1.59]

13 500 ppm F versus 1000 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
13.1 D(M)FS	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only
13.2 D(M)FT	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only

14 1000 ppm F versus 1450 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
14.1 D(M)FS	7	13094	Std. Mean Difference(IV, Random, 95% CI)	-0.10 [-0.14, -0.05]
14.2 D(M)FT	4		Std. Mean Difference(IV, Random, 95% CI)	No totals
14.3 Proportion developing new caries	2	4328	Risk Ratio(M-H, Random, 95% CI)	1.02 [0.93, 1.11]

15 1000 ppm F versus 1700 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

15.1 D(M)FS	5	14196	Std. Mean Difference(IV, Random, 95% CI)	-0.02 [-0.05, 0.01]
15.2 D(M)FT	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only

16 1000 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
16.1 D(M)FS	6	10553	Std. Mean Difference(IV, Random, 95% CI)	-0.08 [-0.12, -0.04]
16.2 D(M)FT	3	7044	Std. Mean Difference(IV, Random, 95% CI)	-0.06 [-0.12, 0.00]

17 1450 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

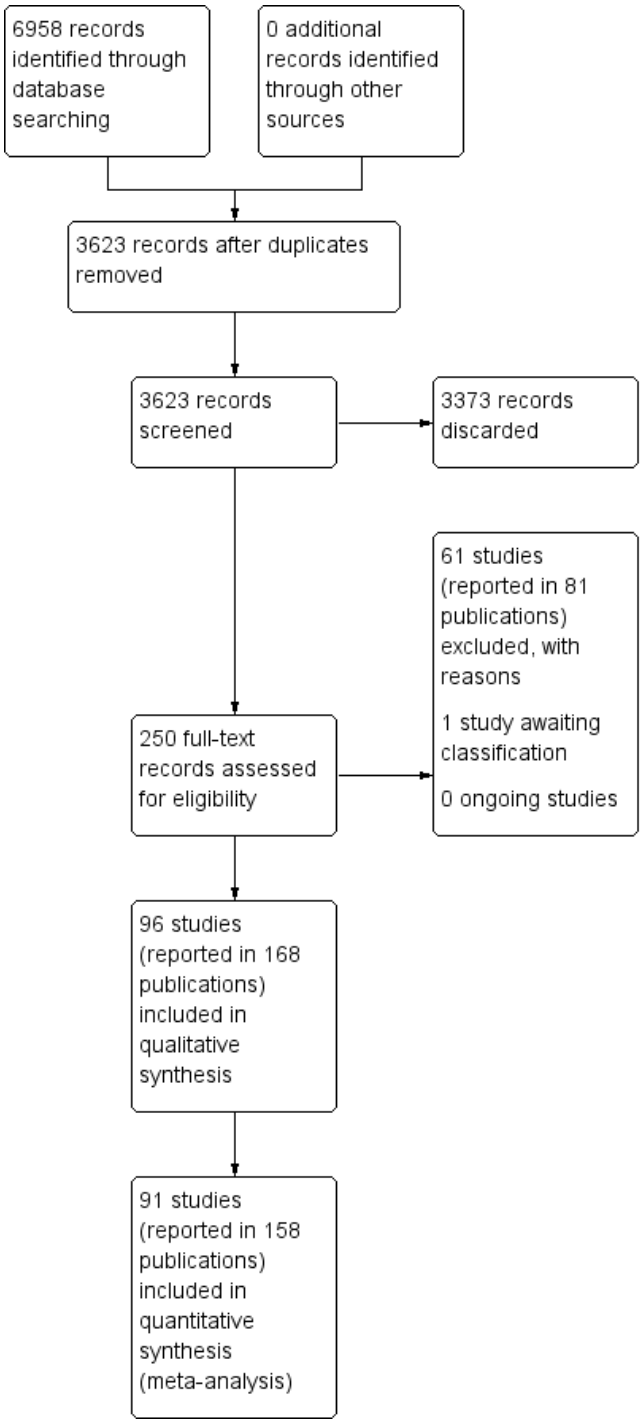
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
17.1 D(M)FS	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only

18 1700 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
18.1 D(M)FS	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only
18.2 D(M)FT	1		Std. Mean Difference(IV, Random, 95% CI)	Subtotals only

Figures

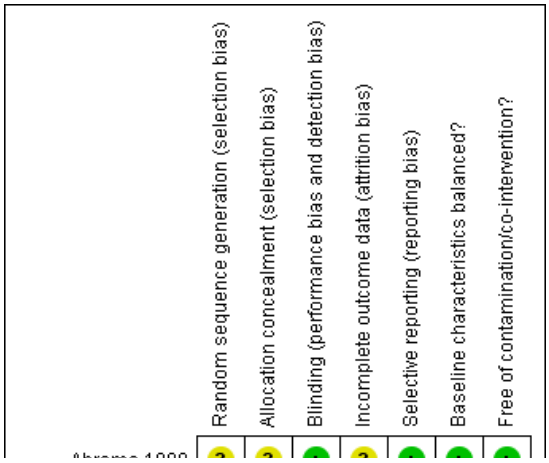
Figure 1

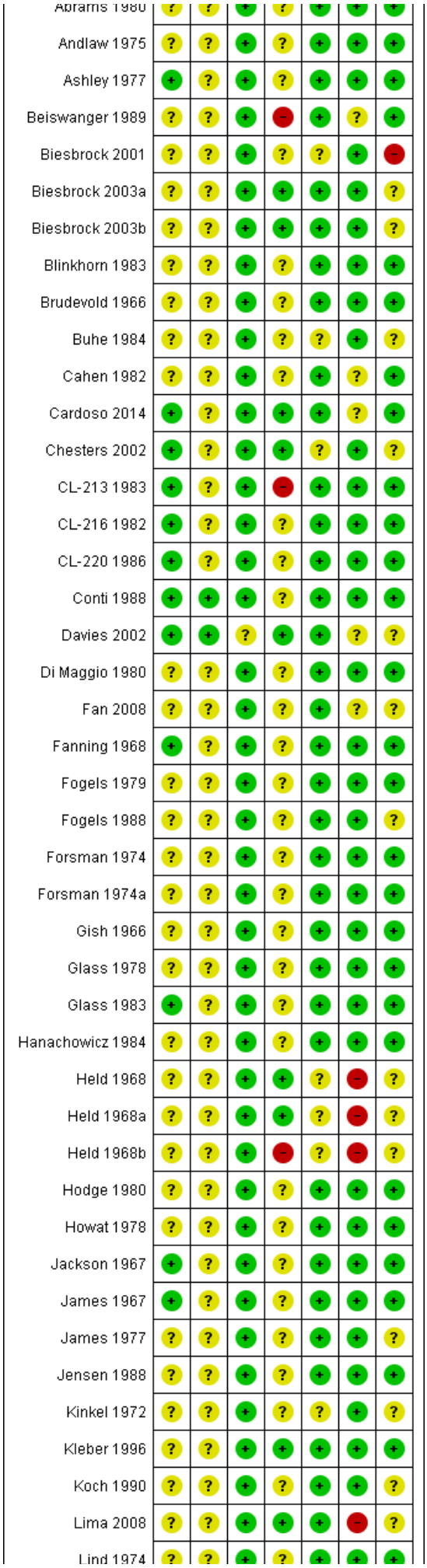


Caption

Study flow diagram.

Figure 2

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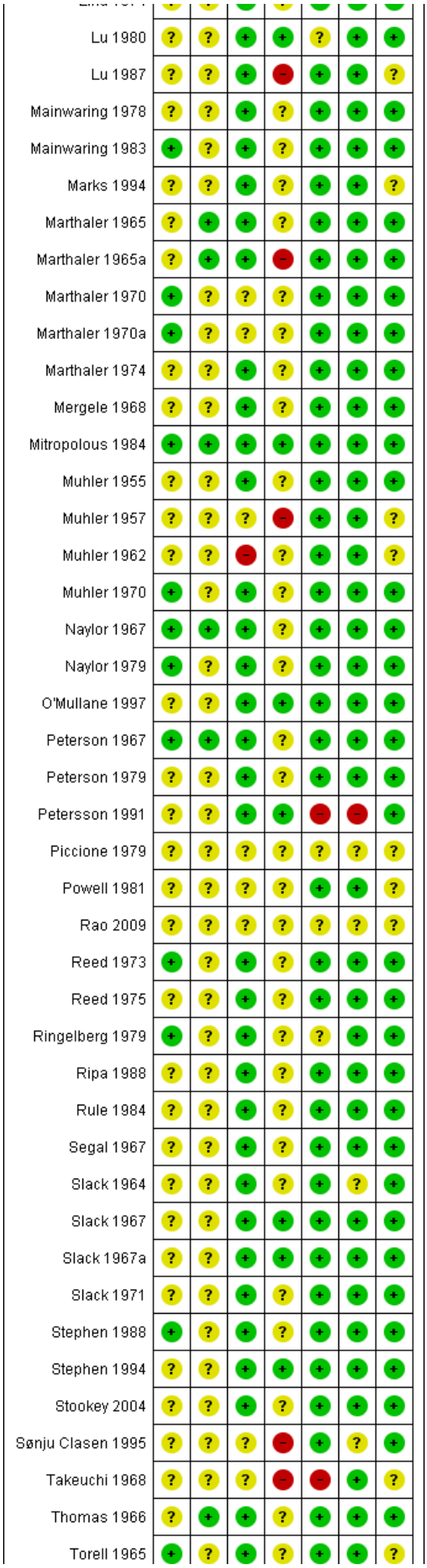
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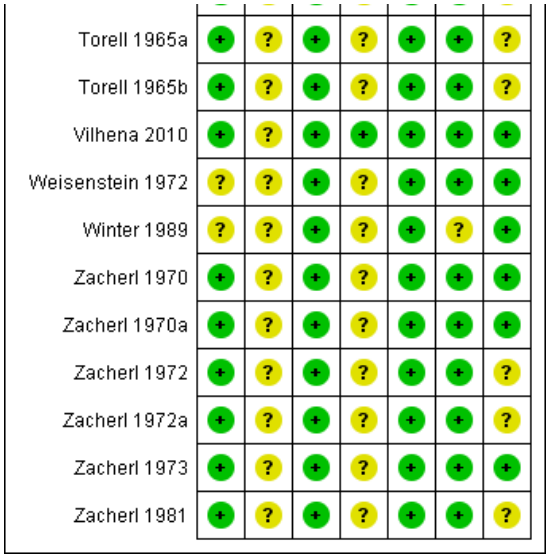
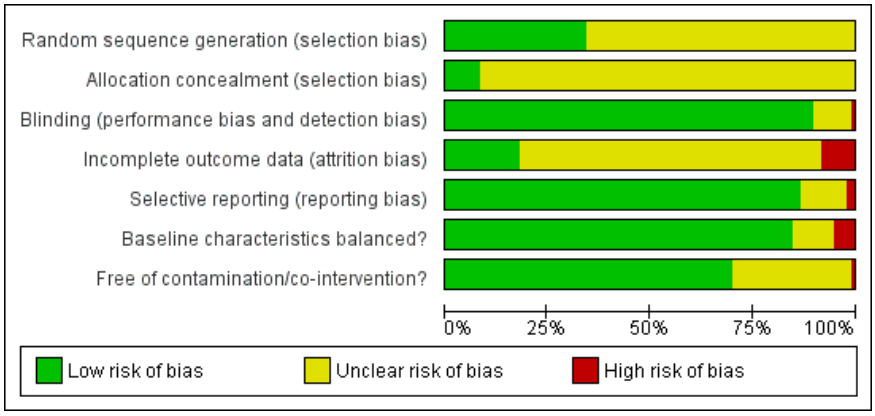
Stookey 2004
Sønju Clasen 1995
Takeuchi 1968
Thomas 1966
Torell 1965



Caption

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

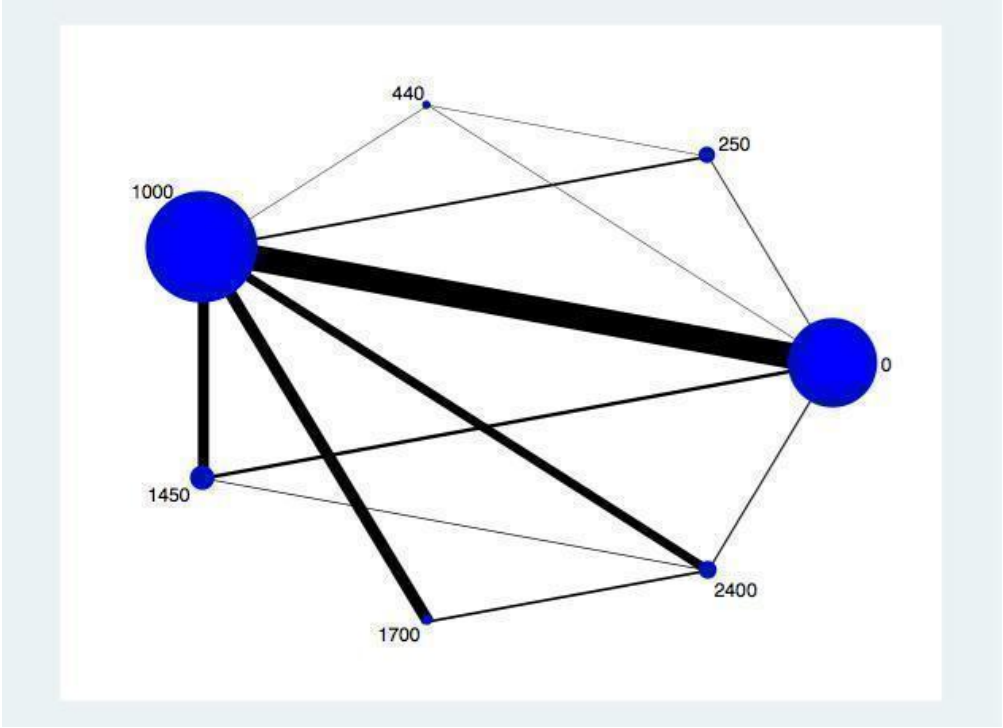
Figure 3



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

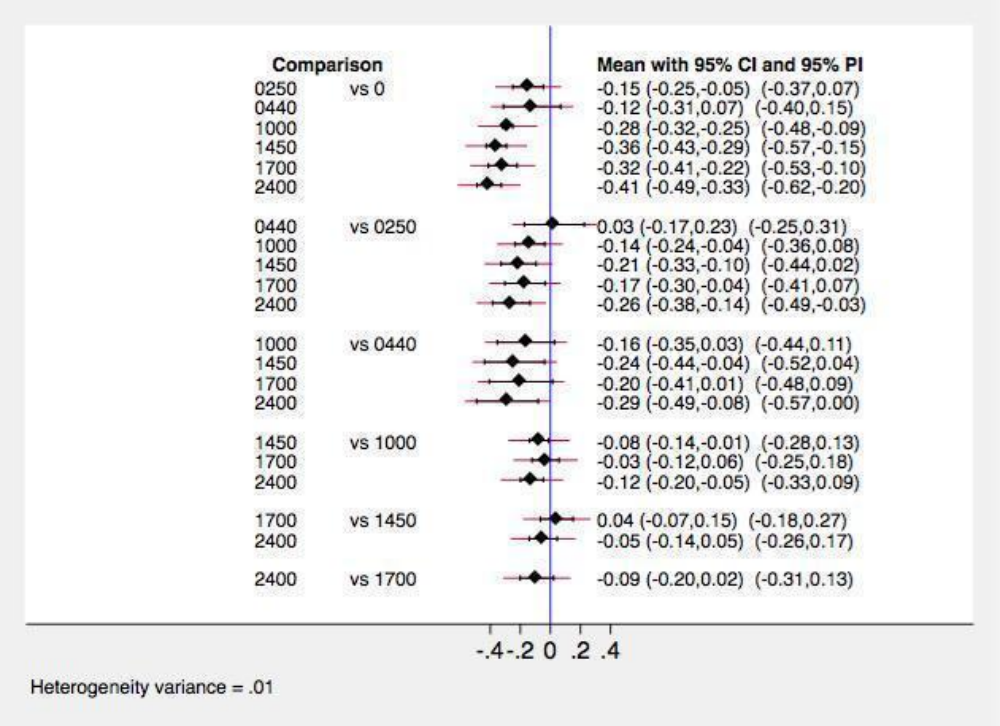
Figure 4



Caption

Plot of the decayed, missing, filled surfaces (D(M)FS) network in children and adolescents (immature permanent dentition).

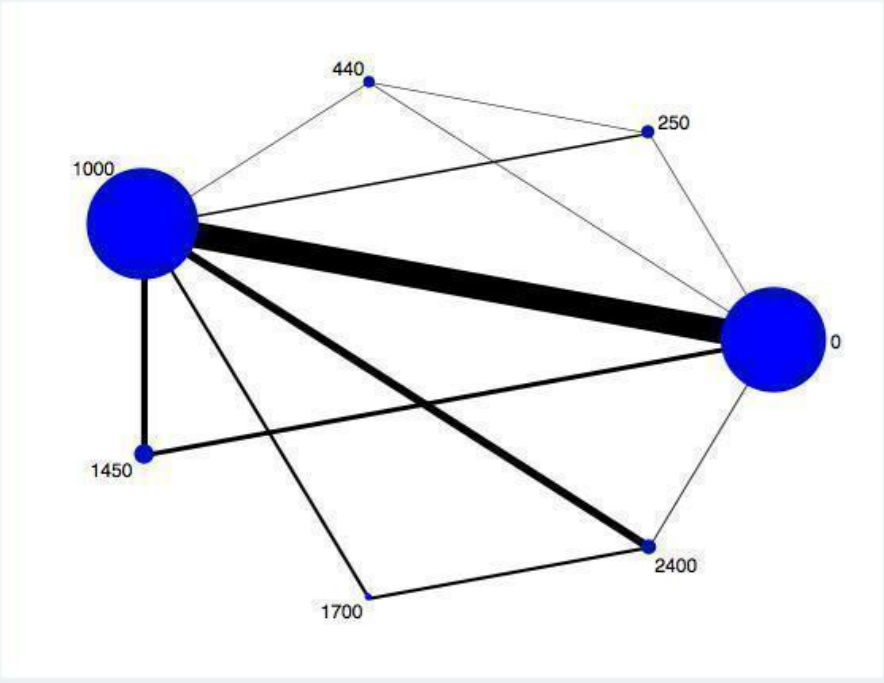
Figure 5



Caption

Forest plot of 95% confidence intervals (CI) and predictive intervals (PI) for the decayed, missing, filled surfaces (D(M)FS) network in children and adolescents (immature permanent dentition).

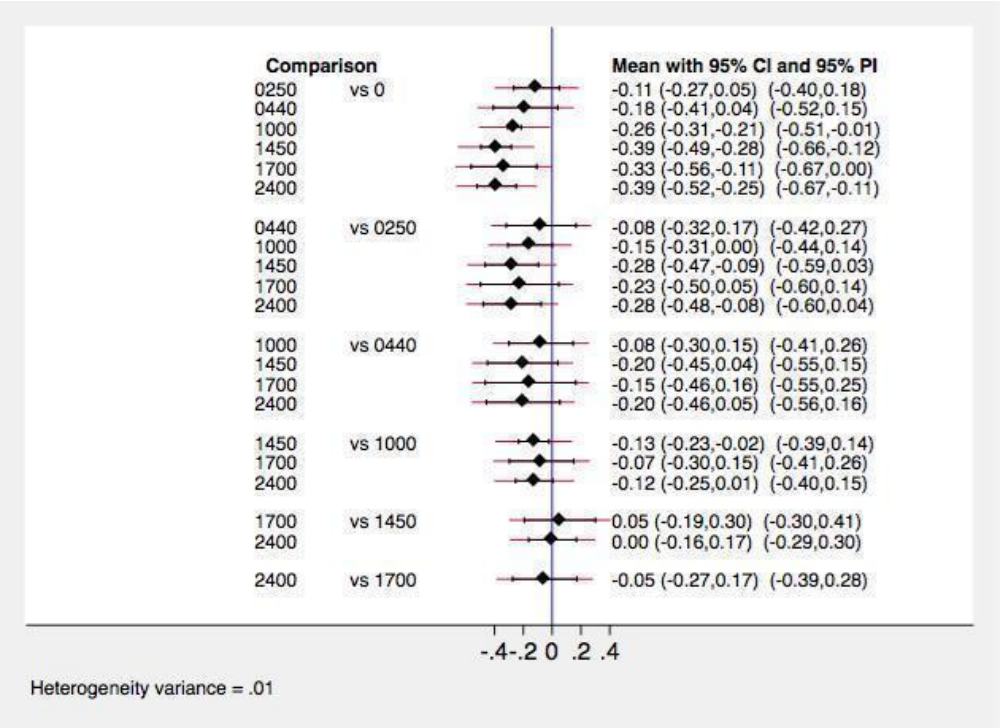
Figure 6



Caption

Plot of the decayed, missing, filled teeth (D(M)FT) network in children and adolescents (immature permanent dentition).

Figure 7



Caption

95% confidence intervals (CI) and predictive intervals (PI) for the decayed, missing, filled teeth (D(M)FT) network in children and adolescents (immature permanent dentition).

Sources of support

Internal sources

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- Cochrane Review Support Programme, UK
  Provided GBP 5000 to support review update.

Feedback

Appendices

1 Cochrane Oral Health's Trials Register search strategy

1 ((teeth and (cavit* or caries or carious or decay* or lesion* or demineral* or remineral* or defect*)):ti,ab) AND (INREGISTER)
2 ((tooth and (cavit* or caries or carious or decay* or lesion* or demineral* or remineral* or defect*)):ti,ab) AND (INREGISTER)
3 ((dental and (cavit* or caries or carious or decay* or lesion* or demineral* or remineral* or defect*)):ti,ab) AND (INREGISTER)

4 ((enamel and (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*)):ti,ab) AND (INREGISTER)
5 ((dentin and (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*)):ti,ab) AND (INREGISTER)
6 ((root* and (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*)):ti,ab) AND (INREGISTER)
7 (#1 or #2 or #3 or #4 or #5 or #6) AND (INREGISTER)
8 ((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) AND (INREGISTER)
9 (toothpast*:ti,ab) AND (INREGISTER)
10 (((tooth or teeth) and brush*):ti,ab) AND (INREGISTER)
11 (#9 or #10) AND (INREGISTER)
12 (#7 and #8 and #11) AND (INREGISTER)

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

#1 [mh "Tooth demineralization"]
#2 (teeth near/5 (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*))
#3 (tooth near/5 (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*))
#4 (dental near/5 (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*))
#5 (enamel near/5 (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*))
#6 (dentin near/5 (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*))
#7 (root* near/5 (cavit* or caries or carious or decay* or lesion* or deminerali* or reminerali* or defect*))
#8 [mh "Dental caries activity tests"]
#9 [mh "Dental health surveys"]
#10 {or #1-#9}
#11 [mh Fluorides]
#12 (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
#13 #11 or #12
#14 [mh Toothbrushing]
#15 [mh Dentifrices]
#16 toothpast*
#17 ((tooth or teeth) near/3 brush*)
#18 {or #14-#17}
#19 #10 and #13 and #18

3 MEDLINE Ovid search strategy

1. Dental Caries.mp. or exp Dental Caries/
2. Dental Caries Activity Tests/
3. Dental Caries Susceptibility/
4. carie$.mp.
5. DMF$.mp.
6. exp Fluorides/
7. exp Fluorides, Topical/
8. FLUOR$.mp.
9. AMF.mp.
10. AMINE F.mp.
11. SNF2.mp.
12. STANNOUS F.mp.
13. NAF.mp.
14. SODIUM F.mp.
16. SMFP.mp.
17. MFP.mp.
18. monofluor$.mp.
19. exp Cariostatic Agents/
20. exp Dentifrices/
21. toothpaste$.mp.
22. paste$.mp.
23. dentrifice$.mp.
24. 4 or 1 or 3 or 2 or 5
25. 6 or 11 or 7 or 9 or 17 or 12 or 15 or 14 or 8 or 18 or 19 or 16 or 10 or 13
26. 22 or 21 or 23 or 20
27. 25 and 24 and 26

4 Embase Ovid search strategy

1. Dental caries/
2. (teeth adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$ or defect$)).mp.
3. (tooth adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$ or defect$)).mp.
4. (dental adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$ or defect$)).mp.
5. (enamel adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$ or defect$)).mp.
6. (dentin adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$ or defect$)).mp.
7. (root adj5 (cavit$ or caries or carious or decay$ or lesion$ or demineral$ or remineral$)).mp.
8. or/1-7
9. exp Fluoride/
10. (fluorid$ 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$" or SMFP or MFP or monofluor$).mp.
11. 9 or 10
12. Tooth brushing/
13. Toothpaste/
14. toothpast$.mp.
15. ((tooth or teeth) adj3 brush$).mp.
16. or/12-15
17. 8 and 11 and 16

5 US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

caries and fluoride and toothpaste

6 World Health Organization International Clinical Trials Registry Platform search strategy

caries and fluoride and toothpaste

7 Dose-response analysis of caries increment D(M)FS in children and adolescents (immature permanent dentition)

Meta-regression to assess heterogeneity of network estimates in relation to dose

'A study' in meta-regression analysis was a particular comparison (i.e. 440 versus 1000 parts per million (ppm)), represented by the network effect size estimate. Such an approach was possible because the effect modifier: a comparison's maximal fluoride concentration (higher of the two fluoride concentrations), was the same for all the studies that were assigned to a particular estimate.

The effective sample size for each network comparison (aka study in meta-regression) was calculated by Thorlund and Mills 2012 (Thorlund 2012) method which takes into account both direct and indirect randomised controlled trial evidence. Heterogeneity-corrected effective sample size assuming 50% heterogeneity was used (Thorlund 2011).

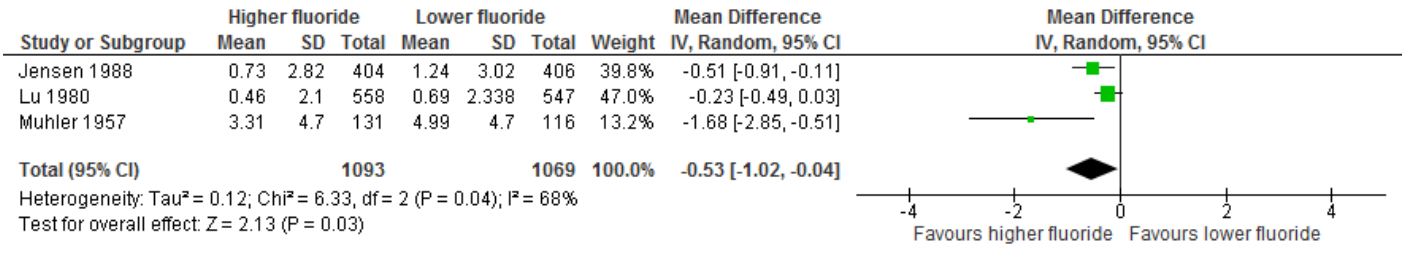
To be able to assess possible dose-effect relationship with meta-regression, it was necessary to express effect sizes of maximal fluoride concentration as effect sizes from placebo. We reconstructed these placebo-wise estimates by using the principle of transitivity. As an example the effect size for the comparison between 1700 and 2400 ppm was represented as the effect size for 2400 versus placebo comparison by adding two network effect size point estimates: 1700 versus 0 ppm, and 1700 versus 2400 ppm, while the corresponding 95% confidence interval was estimated by the root-sum-of-squares method.

The random-effects meta-regression based on the restricted maximum likelihood method was used to further assess fluoride dose-effect relationship. Maximal fluoride concentration, expressed on a log scale, was introduced in a meta-regression model as a covariate. Log transformation of a dose was important as it allowed for modelling of dose-effect relationship with the linear meta-regression analysis, given that doses possibly belonging to sigmoidal tails are excluded from analysis (Tallarida 2000). Therefore, we performed meta-regression analysis on different data sets: data set including effects of all doses, without the effect of 250 ppm dose, and without the effects of 250 and 440 ppm maximal doses.

Graphs

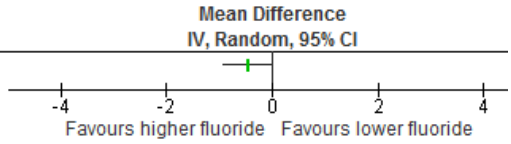
1 - 0 ppm F versus 1000 ppm F in adults (mature permanent dentition)

1.1 DMFS



1.2 DMFT

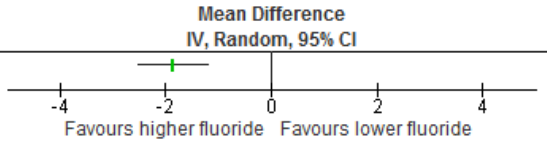
Study or Subgroup	Favours higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Muhler 1957	1.06	1.9	131	1.52	1.9	116		-0.46 [-0.93, 0.01]



2 - 0 ppm F versus 1500 ppm F in young children (primary dentition)

2.1 dfs

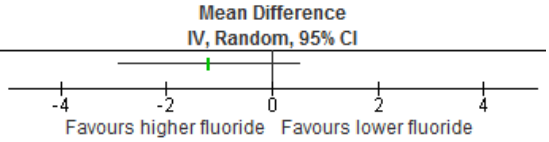
Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fan 2008	2.8671	4.3743	670	4.73	5.17	328		-1.86 [-2.51, -1.21]



3 - 250 ppm F versus 1450 ppm F in young children (primary dentition)

3.1 dmfs

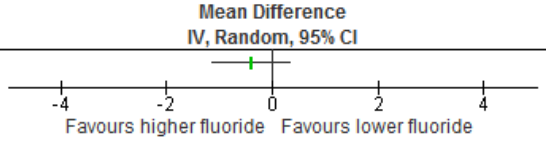
Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sønju Clasen 1995 (1)	1.7	3.2	50	2.9	5.1	46		-1.20 [-2.92, 0.52]



Footnotes
(1) Sample size adjusted by design effect (ICC 0.05) to account for cluster randomisation

3.2 dmft

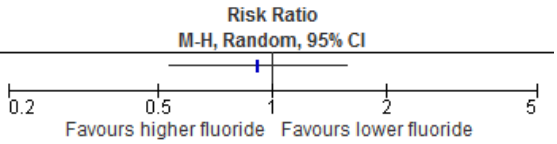
Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sønju Clasen 1995 (1)	0.8	1.4	50	1.2	2.2	46		-0.40 [-1.14, 0.34]



Footnotes
(1) Sample size adjusted by design effect (ICC 0.05) to account for cluster randomisation

3.3 Proportion developing new caries

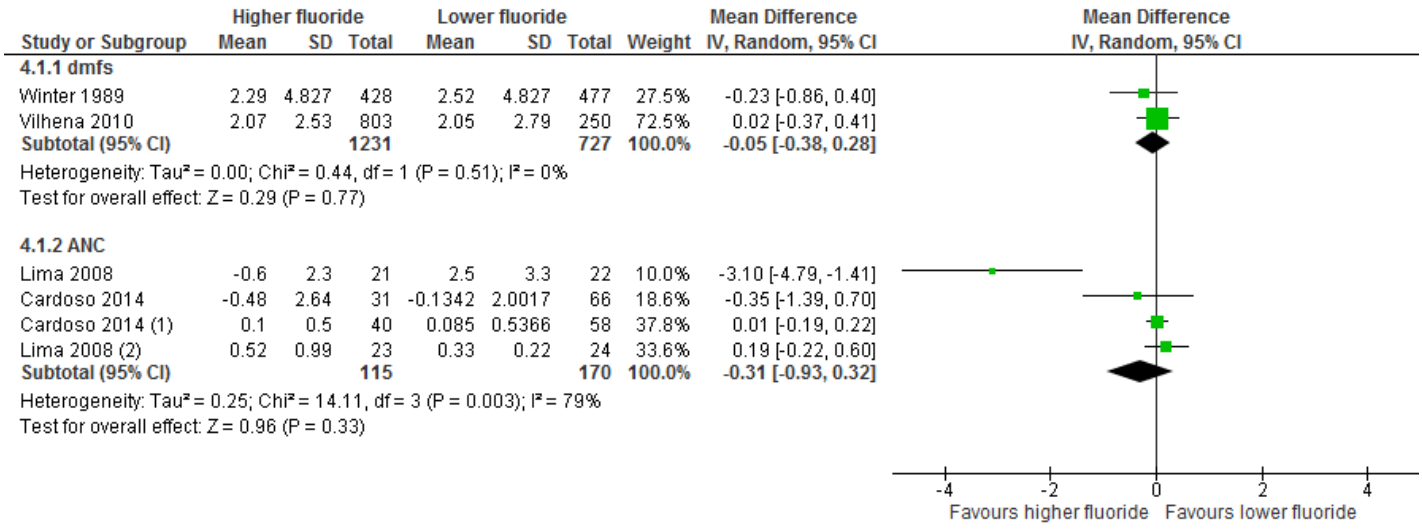
Study or Subgroup	Higher fluoride Events	Total	Lower fluoride Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Sønju Clasen 1995 (1)	15	36	15	33		0.92 [0.54, 1.57]



Footnotes
(1) Sample size and number of events adjusted by design effect (ICC 0.05) to account for cluster randomisation

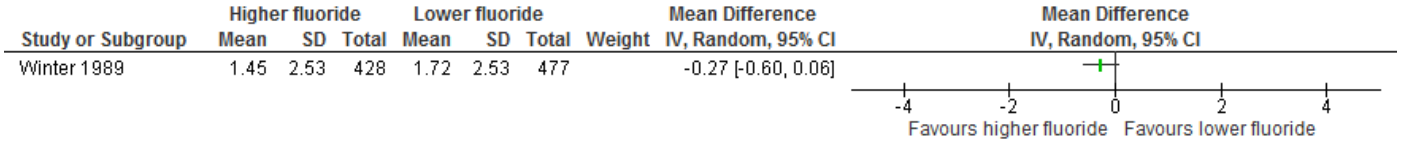
4 - 500 to 550 ppm F versus 1055 to 1100 ppm F in young children (primary dentition)

4.1 dmfs/ANC

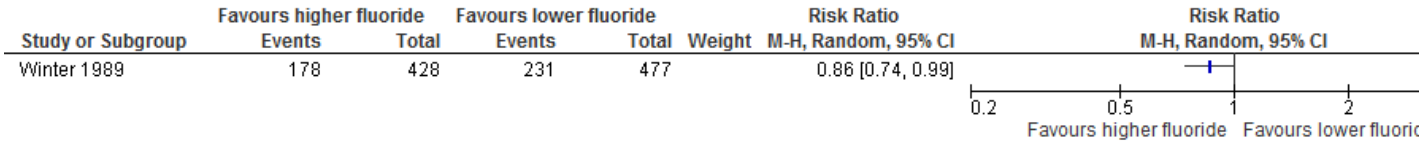


Footnotes
(1) Caries-inactive group
(2) Caries-inactive group

4.2 dmft

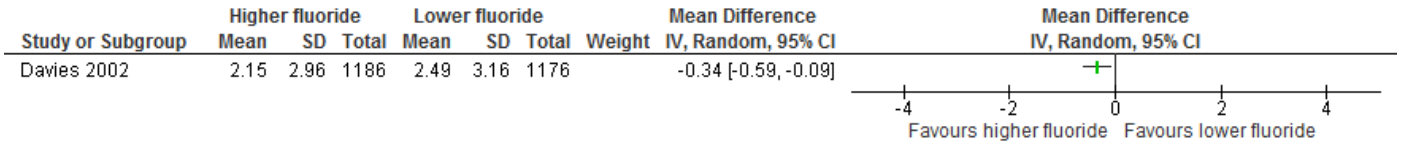


4.3 Proportion developing new caries

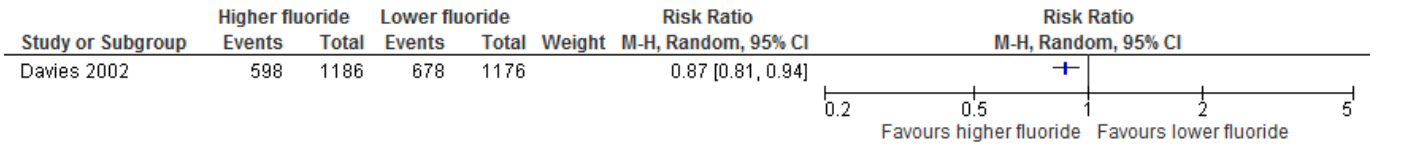


5 - 440 ppm F versus 1450 ppm F in young children (primary dentition)

5.1 dmft

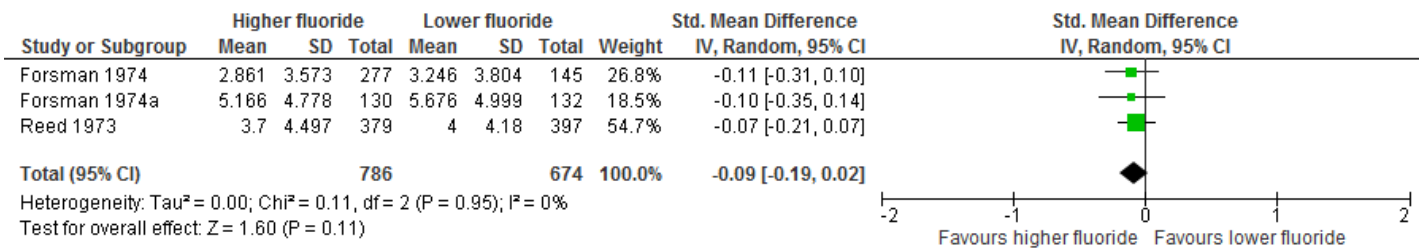


5.2 Proportion developing new caries



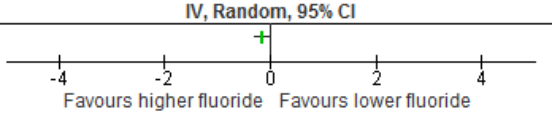
6 - 0 ppm F versus 250 ppm F in children and adolescents (immature permanent dentition)

6.1 D(M)FS closest to 3 years



6.2 D(M)FT

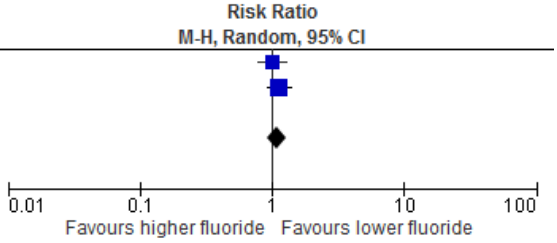
Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Reed 1973	2.14	2.55	379	2.54	2.45	397		-0.16 [-0.30, -0.02]



6.3 Proportion developing new caries

Study or Subgroup	Higher fluoride Events	Total	Lower fluoride Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Forsman 1974	107	277	56	145	42.2%	1.00 [0.78, 1.29]
Forsman 1974a	77	130	69	132	57.8%	1.13 [0.91, 1.41]
Total (95% CI)		**407**		**277**	**100.0%**	**1.07 [0.91, 1.27]**
Total events	184		125			

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)

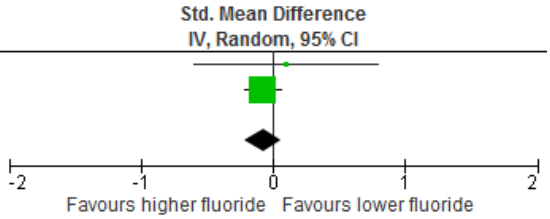


7 - 0 ppm F versus 500 ppm F in children and adolescents (immature permanent dentition)

7.1 D(M)FS closest to 3 years

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Held 1968b	6.1	5.182	14	5.6	4.969	18	3.9%	0.10 [-0.60, 0.80]
Reed 1973	3.66	4.25	387	4	4.18	397	96.1%	-0.08 [-0.22, 0.06]
Total (95% CI)			**401**			**415**	**100.0%**	**-0.07 [-0.21, 0.06]**

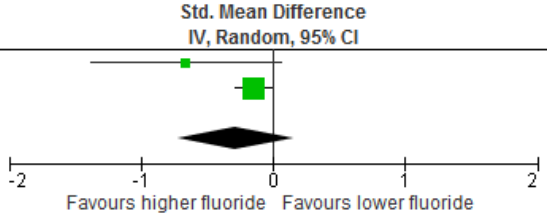
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)



7.2 D(M)FT

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Held 1968b	0.9	1.626	14	2.3	2.325	18	25.3%	-0.67 [-1.38, 0.05]
Reed 1973	2.16	2.52	387	2.54	2.45	397	74.7%	-0.15 [-0.29, -0.01]
Total (95% CI)			**401**			**415**	**100.0%**	**-0.28 [-0.72, 0.15]**

Heterogeneity: Tau² = 0.06; Chi² = 1.88, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 1.27 (P = 0.20)

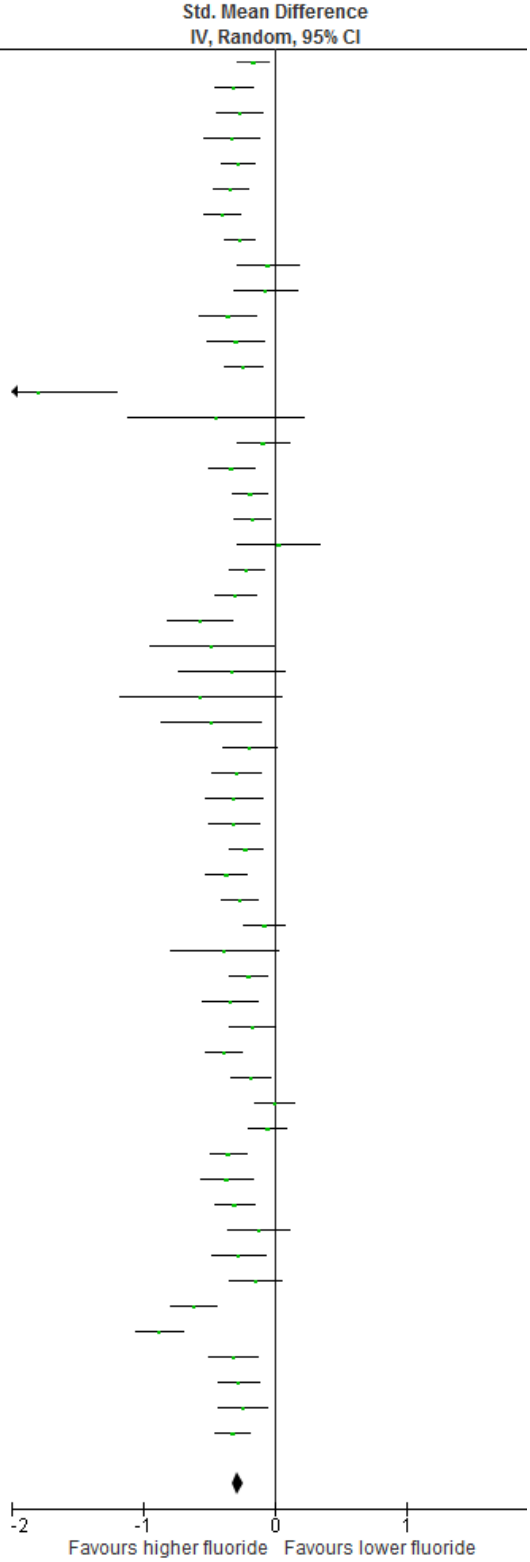


8 - 0 ppm F versus 1000 ppm F in children and adolescents (immature permanent dentition)

8.1 D(M)FS

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abrams 1980	6.42	5.314	761	7.33	5.672	380	2.4%	-0.17 [-0.29, -0.04]
Andlaw 1975	6.07	4.97	364	7.68	5.24	376	2.2%	-0.31 [-0.46, -0.17]
Ashley 1977	4.44	4.02	246	5.61	4.64	243	1.9%	-0.27 [-0.45, -0.09]
Blinkhorn 1983	4.6	4.33	184	6.25	5.55	184	1.7%	-0.33 [-0.54, -0.13]
Brudevold 1966	5.52	6.1	955	7.21	6.11	323	2.4%	-0.28 [-0.40, -0.15]
Buhe 1984	13.7	7.95	438	16.6	9.23	427	2.3%	-0.34 [-0.47, -0.20]
Fanning 1968	9.67	6.37	422	12.23	6.37	422	2.3%	-0.40 [-0.54, -0.27]
Fogels 1979	6.83	5.478	890	8.34	6.043	449	2.5%	-0.27 [-0.38, -0.15]
Forsman 1974	3.03	3.676	137	3.246	3.804	145	1.6%	-0.06 [-0.29, 0.18]
Forsman 1974a	5.31	4.841	132	5.676	4.999	132	1.5%	-0.07 [-0.32, 0.17]
Gish 1966	4.75	4.24	165	6.44	5.18	163	1.7%	-0.36 [-0.57, -0.14]
Glass 1978	5.31	5.95	178	7.36	7.68	168	1.7%	-0.30 [-0.51, -0.09]
Glass 1983	2.39	3	567	3.21	4.04	286	2.2%	-0.24 [-0.38, -0.10]
Held 1968	2.6	3.409	32	13.2	7.571	31	0.4%	-1.79 [-2.38, -1.20]
Held 1968a	5.5	4.926	19	8	5.92	17	0.4%	-0.45 [-1.11, 0.21]
Hodge 1980	7.31	5.68	194	7.83	5.49	202	1.8%	-0.09 [-0.29, 0.10]
Howat 1978	5.71	5.49	253	7.69	6.39	242	1.9%	-0.33 [-0.51, -0.15]
Jackson 1967	7.23	4.7	438	8.2	5.45	433	2.3%	-0.19 [-0.32, -0.06]
James 1967	4.26	5.2	406	5.19	5.42	397	2.3%	-0.17 [-0.31, -0.04]
Kleber 1996	1.66	2.8	77	1.59	2.13	79	1.1%	0.03 [-0.29, 0.34]
Mainwaring 1978	6.94	5.96	791	8.27	6.62	316	2.3%	-0.22 [-0.35, -0.09]
Mainwaring 1983	8.88	6.4	458	11	8.23	224	2.1%	-0.30 [-0.46, -0.14]
Marthaler 1965	5.31	3.75	145	7.71	4.7	124	1.5%	-0.57 [-0.81, -0.32]
Marthaler 1965a	11.33	7.59	42	15.25	8.55	32	0.6%	-0.48 [-0.95, -0.02]
Marthaler 1970	3.44	2.52	43	4.4	3.14	57	0.8%	-0.33 [-0.73, 0.07]
Marthaler 1970a	2.57	2.09	23	3.95	2.704	20	0.4%	-0.57 [-1.18, 0.05]
Marthaler 1974	5.62	5.5	50	8.39	5.77	59	0.9%	-0.49 [-0.87, -0.10]
Mergele 1968	4.83	3.28	197	5.57	4.3	190	1.8%	-0.19 [-0.39, 0.01]
Muhler 1955	1.55	2.645	219	2.42	3.291	225	1.9%	-0.29 [-0.48, -0.10]
Muhler 1962	8.28	6.2	174	10.45	7.54	169	1.7%	-0.31 [-0.53, -0.10]
Muhler 1970	2.87	3.47	201	4.05	3.99	235	1.9%	-0.31 [-0.50, -0.12]
Naylor 1967	7.94	5.09	494	9.22	6.2	479	2.4%	-0.23 [-0.35, -0.10]
Naylor 1979	8.09	6.09	319	10.42	6.47	306	2.1%	-0.37 [-0.53, -0.21]
Peterson 1967	7.63	5.59	634	9.19	6.12	320	2.3%	-0.27 [-0.40, -0.14]
Peterson 1979	2.87	3.66	467	3.18	3.86	245	2.1%	-0.08 [-0.24, 0.07]
Rao 2009	0.24	1.03	47	0.62	0.92	45	0.8%	-0.39 [-0.80, 0.03]
Reed 1973	3.2	3.786	362	4	4.184	397	2.2%	-0.20 [-0.34, -0.06]
Reed 1975	3.02	3.31	168	4.32	4.21	176	1.7%	-0.34 [-0.55, -0.13]
Ringelberg 1979	5.13	5.85	370	6.25	7.35	186	2.0%	-0.18 [-0.35, 0.00]
Rule 1984	4.56	4.7	460	6.39	4.69	416	2.3%	-0.39 [-0.52, -0.26]
Segal 1967	2.69	3.46	338	3.33	3.46	310	2.1%	-0.18 [-0.34, -0.03]
Slack 1967	5.59	5.34	356	5.62	5.62	340	2.2%	-0.01 [-0.15, 0.14]
Slack 1967a	5.64	4.83	376	5.95	5.68	381	2.2%	-0.06 [-0.20, 0.08]
Slack 1971	10.04	7.68	821	12.83	8.31	289	2.3%	-0.36 [-0.49, -0.22]
Thomas 1966	2.84	2.92	309	4.08	4.11	155	1.8%	-0.37 [-0.56, -0.17]
Torell 1965	8.09	6.86	335	10.16	6.59	333	2.1%	-0.31 [-0.46, -0.15]
Torell 1965a	10.11	5.11	148	10.81	6.2	137	1.6%	-0.12 [-0.36, 0.11]
Torell 1965b	10.25	6.03	188	12.12	7.24	180	1.7%	-0.28 [-0.49, -0.08]
Weisenstein 1972	4.98	4	206	5.6	4.34	196	1.8%	-0.15 [-0.34, 0.05]
Zacherl 1970	3.79	3.49	251	6.36	4.69	261	1.9%	-0.62 [-0.80, -0.44]
Zacherl 1970a	8.5	6.61	260	15.04	8.19	268	1.9%	-0.88 [-1.05, -0.70]
Zacherl 1972	6.51	5.21	231	8.39	6.58	216	1.9%	-0.32 [-0.50, -0.13]
Zacherl 1972a	5.08	5.21	684	6.62	6.25	210	2.1%	-0.28 [-0.44, -0.13]
Zacherl 1973	3.55	5.77	220	5.04	6.39	224	1.9%	-0.24 [-0.43, -0.06]
Zacherl 1981	4.1	5.63	1500	6.02	7.71	254	2.3%	-0.32 [-0.45, -0.19]
Total (95% CI)			**18745**			**13074**	**100.0%**	**-0.28 [-0.33, -0.24]**

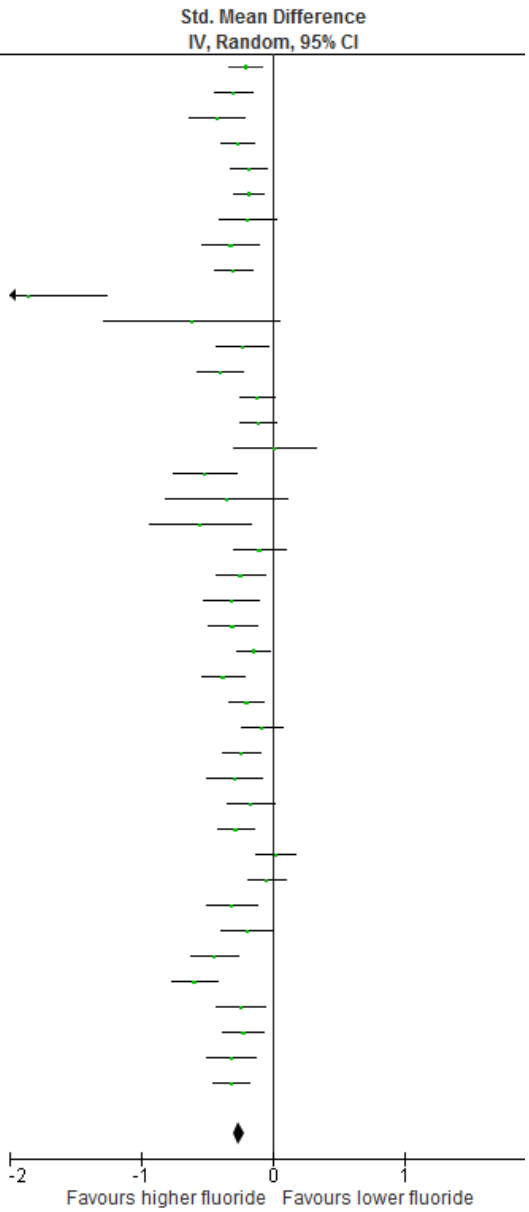
Heterogeneity: Tau² = 0.02; Chi² = 161.93, df = 54 (P < 0.00001); I² = 67%
Test for overall effect: Z = 13.23 (P < 0.00001)



8.2 D(M)FT

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abrams 1980	3.41	2.702	761	3.99	2.868	380	3.2%	-0.21 [-0.33, -0.09]
Andlaw 1975	3.73	2.8	364	4.56	2.72	376	2.9%	-0.30 [-0.45, -0.16]
Blinkhorn 1983	2.45	2.37	184	3.51	2.61	184	2.2%	-0.42 [-0.63, -0.22]
Brudevold 1966	2.59	2.75	955	3.32	2.75	323	3.1%	-0.27 [-0.39, -0.14]
Buhe 1984	5	3.21	438	5.6	3.25	427	3.0%	-0.19 [-0.32, -0.05]
Fogels 1979	4.22	2.93	890	4.77	3.07	449	3.3%	-0.18 [-0.30, -0.07]
Gish 1966	3.14	2.65	165	3.66	2.71	163	2.1%	-0.19 [-0.41, 0.02]
Glass 1978	3.19	3.07	178	4.27	3.61	168	2.2%	-0.32 [-0.53, -0.11]
Glass 1983	1.55	1.68	567	2.13	2.35	286	2.9%	-0.30 [-0.44, -0.16]
Held 1968	0.3	1.07	32	4.5	3.003	31	0.5%	-1.85 [-2.45, -1.26]
Held 1968a	2.6	2.436	19	4.3	2.951	17	0.4%	-0.62 [-1.29, 0.05]
Hodge 1980	4.07	2.68	194	4.72	2.9	202	2.3%	-0.23 [-0.43, -0.03]
Howat 1978	3.2	2.65	253	4.36	3.12	242	2.5%	-0.40 [-0.58, -0.22]
Jackson 1967	4.58	4.34	438	5.13	4.48	433	3.0%	-0.12 [-0.26, 0.01]
James 1967	2.252	2.55	406	2.53	2.47	397	3.0%	-0.11 [-0.25, 0.03]
Kleber 1996	1.06	1.67	77	1.04	1.51	79	1.4%	0.01 [-0.30, 0.33]
Marthaler 1965	2.57	2.13	145	3.81	2.65	124	1.9%	-0.52 [-0.76, -0.27]
Marthaler 1965a	5.12	3.04	42	6.22	3.18	32	0.8%	-0.35 [-0.81, 0.11]
Marthaler 1974	3.26	2.64	50	4.88	3.09	59	1.1%	-0.56 [-0.94, -0.17]
Mergele 1968	3.62	2.25	197	3.87	2.43	190	2.3%	-0.11 [-0.31, 0.09]
Muhler 1955	0.84	1.584	219	1.27	1.854	225	2.4%	-0.25 [-0.44, -0.06]
Muhler 1962	4.02	3.3	174	5.17	3.9	169	2.2%	-0.32 [-0.53, -0.10]
Muhler 1970	1.48	2.18	201	2.19	2.39	235	2.4%	-0.31 [-0.50, -0.12]
Naylor 1967	4.48	2.74	494	4.89	2.86	479	3.1%	-0.15 [-0.27, -0.02]
Naylor 1979	4.49	2.81	319	5.58	2.92	306	2.8%	-0.38 [-0.54, -0.22]
Peterson 1967	3.42	2.67	634	3.98	2.93	320	3.0%	-0.20 [-0.34, -0.07]
Peterson 1979	1.99	2.35	467	2.2	2.56	245	2.8%	-0.09 [-0.24, 0.07]
Reed 1973	1.94	2.47	362	2.54	2.45	397	2.9%	-0.24 [-0.39, -0.10]
Reed 1975	1.92	2.06	168	2.58	2.39	176	2.2%	-0.29 [-0.51, -0.08]
Ringelberg 1979	2.86	2.92	370	3.38	3.29	186	2.5%	-0.17 [-0.35, 0.01]
Rule 1984	2.78	3.22	460	3.67	3.06	416	3.0%	-0.28 [-0.42, -0.15]
Slack 1967	3.27	2.83	356	3.22	2.73	340	2.9%	0.02 [-0.13, 0.17]
Slack 1967a	3.64	2.75	376	3.78	3.08	381	2.9%	-0.05 [-0.19, 0.09]
Thomas 1966	1.61	2.06	309	2.32	2.61	155	2.4%	-0.31 [-0.51, -0.12]
Weisenstein 1972	2.9	2.31	206	3.4	2.77	196	2.3%	-0.20 [-0.39, -0.00]
Zacherl 1970	1.69	1.9	251	2.62	2.26	261	2.6%	-0.44 [-0.62, -0.27]
Zacherl 1970a	3.19	3.06	260	5.09	3.27	268	2.6%	-0.60 [-0.77, -0.42]
Zacherl 1972	2.89	2.72	231	3.62	3.28	216	2.4%	-0.24 [-0.43, -0.06]
Zacherl 1972a	2.51	2.68	684	3.15	3.22	210	2.8%	-0.23 [-0.38, -0.07]
Zacherl 1973	1.68	2.79	220	2.6	3.01	224	2.4%	-0.32 [-0.50, -0.13]
Zacherl 1981	2.25	3.03	1500	3.26	3.92	254	3.0%	-0.32 [-0.45, -0.18]
Total (95% CI)			**14616**			**10221**	**100.0%**	**-0.26 [-0.31, -0.21]**

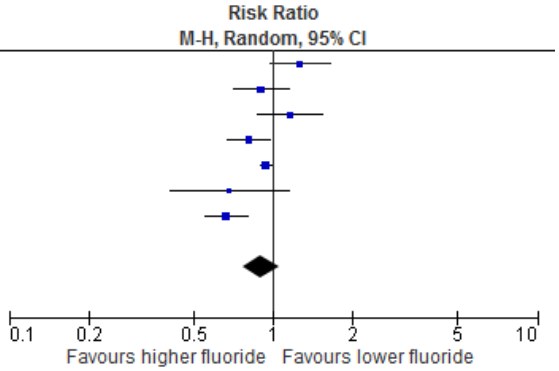
Heterogeneity: Tau² = 0.01; Chi² = 112.04, df = 40 (P < 0.00001); I² = 64%
Test for overall effect: Z = 11.16 (P < 0.00001)



8.3 Proportion developing new caries

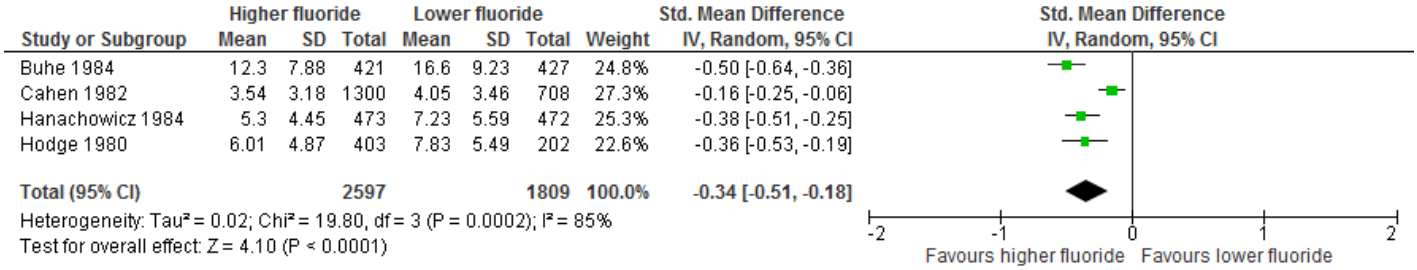
Study or Subgroup	Higher fluoride Events	Total	Lower fluoride Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Forsman 1974	67	137	56	145	13.3%	1.27 [0.97, 1.65]
Forsman 1974a	62	132	69	132	14.1%	0.90 [0.70, 1.15]
Kleber 1996	45	77	40	79	12.5%	1.15 [0.87, 1.54]
Marthaler 1974	37	50	54	59	16.5%	0.81 [0.67, 0.97]
Muhler 1962	153	165	160	162	20.5%	0.94 [0.90, 0.98]
Rao 2009	15	47	21	45	6.6%	0.68 [0.41, 1.15]
Torell 1965	113	335	169	333	16.4%	0.66 [0.55, 0.80]
Total (95% CI)		**943**		**955**	**100.0%**	**0.90 [0.77, 1.06]**
Total events	492		569			

Heterogeneity: Tau² = 0.03; Chi² = 29.57, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 1.29 (P = 0.20)

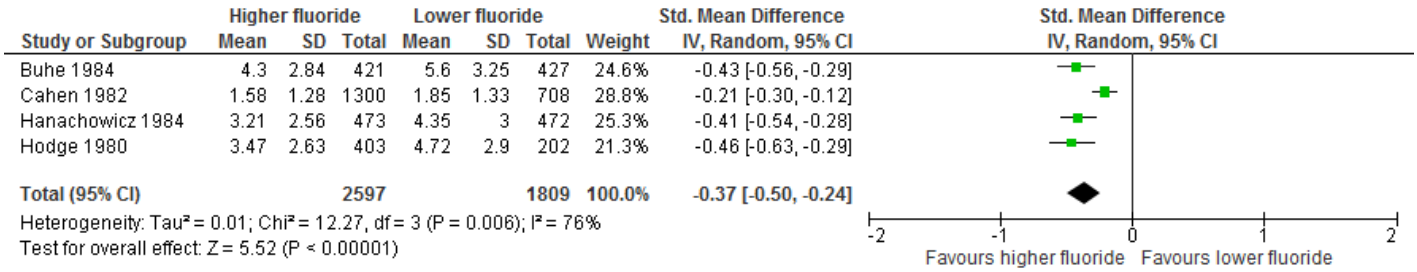


9 - 0 ppm F versus 1450 ppm F in children and adolescents (immature permanent dentition)

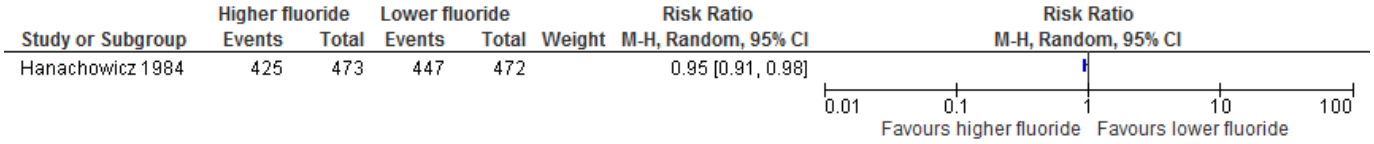
9.1 D(M)FS



9.2 D(M)FT

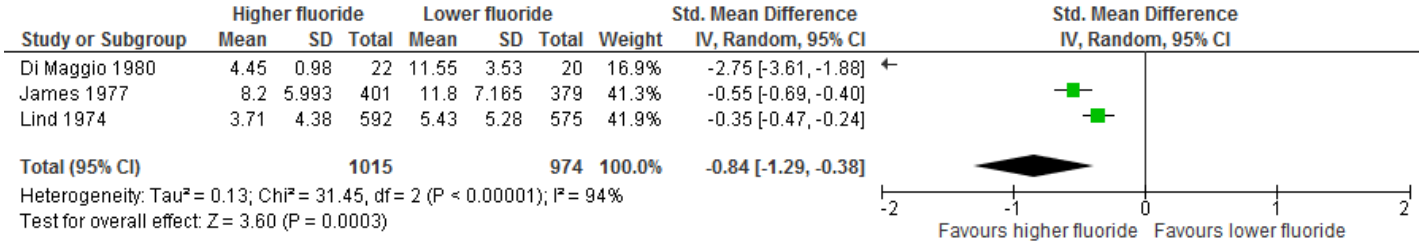


9.3 Proportion developing new caries

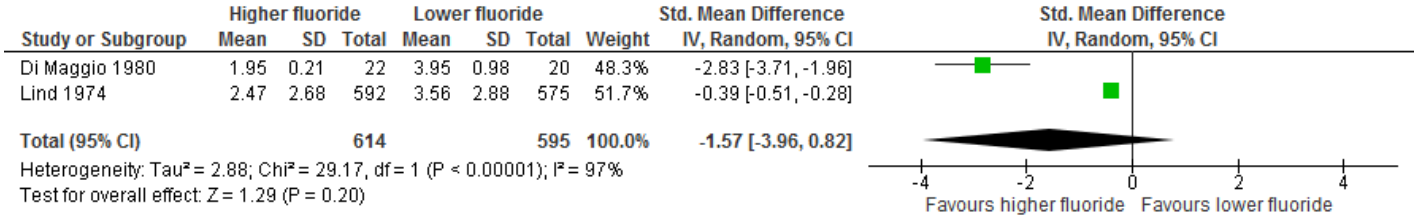


10 - 0 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

10.1 D(M)FS closest to 3 years

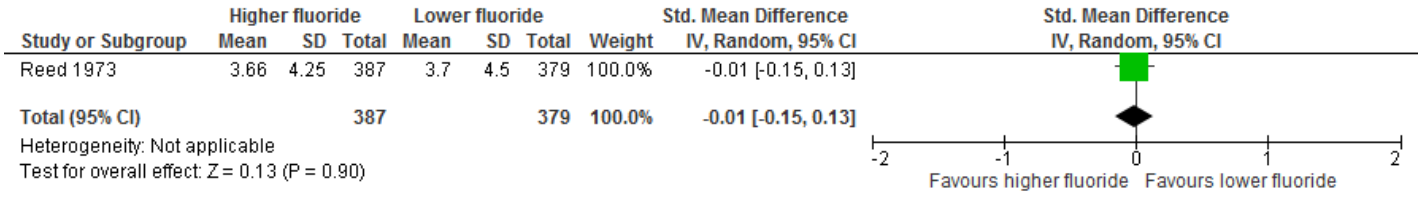


10.2 D(M)FT

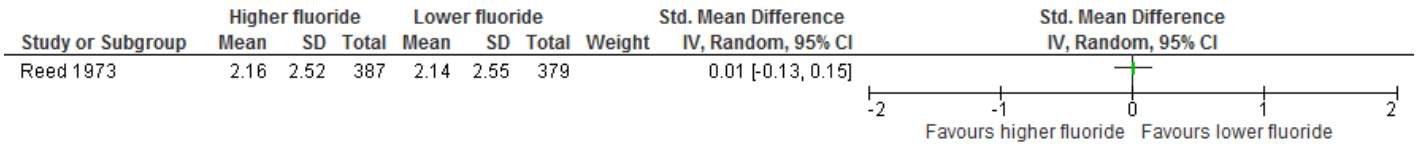


11 - 250 ppm F versus 500 ppm F in children and adolescents (immature permanent dentition)

11.1 D(M)FS

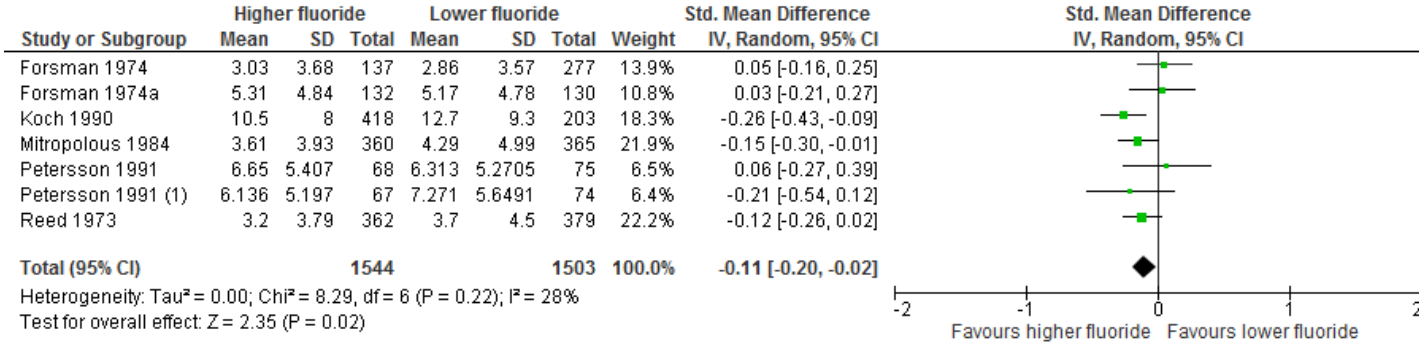


11.2 D(M)FT



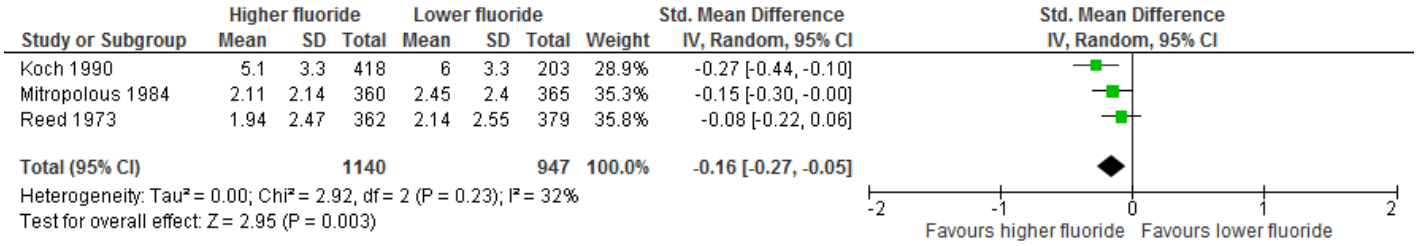
12 - 250 ppm F versus 1000 ppm F in children and adolescents (immature permanent dentition)

12.1 D(M)FS



Footnotes
(1) MFP / NaF plus 3% xylitol

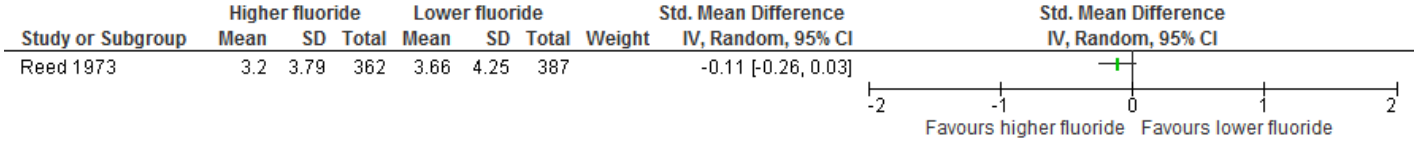
12.2 D(M)FT



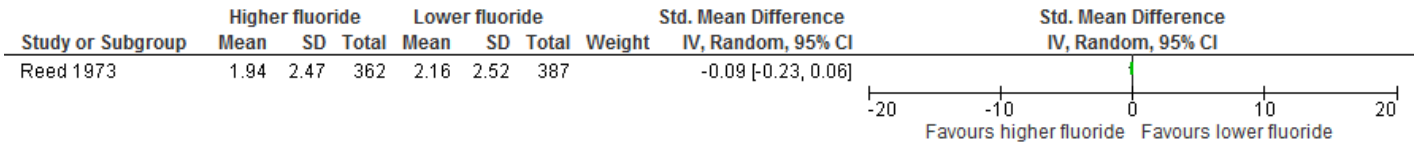
12.3 Proportion developing new caries

13 - 500 ppm F versus 1000 ppm F in children and adolescents (immature permanent dentition)

13.1 D(M)FS



13.2 D(M)FT

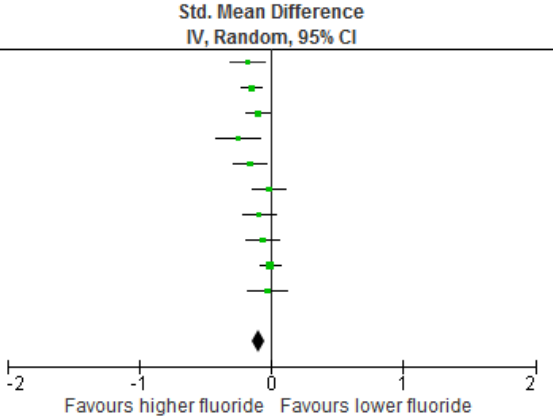


14 - 1000 ppm F versus 1450 ppm F in children and adolescents (immature permanent dentition)

14.1 D(M)FS

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Buhe 1984	12.3	7.88	421	13.7	7.95	438	8.2%	-0.18 [-0.31, -0.04]
Conti 1988	1.87	3.26	1187	2.39	3.73	1228	14.7%	-0.15 [-0.23, -0.07]
Fogels 1988	2.02	3.21	963	2.36	3.47	950	13.2%	-0.10 [-0.19, -0.01]
Hodge 1980	6.01	4.87	403	7.32	5.68	194	5.7%	-0.25 [-0.43, -0.08]
O'Mullane 1997	5.17	5.1	474	6.04	5.95	491	8.9%	-0.16 [-0.28, -0.03]
O'Mullane 1997 (1)	5.62	5.54	500	5.71	5.1	477	9.0%	-0.02 [-0.14, 0.11]
Stephen 1988	6.27	5.64	464	6.83	6.54	469	8.7%	-0.09 [-0.22, 0.04]
Stephen 1988 (2)	6.39	5.81	466	6.77	5.87	452	8.6%	-0.07 [-0.19, 0.06]
Stephen 1994	6.75	6.54	1401	6.8	6.36	1419	15.7%	-0.01 [-0.08, 0.07]
Stephen 1994 (3)	6.35	6.39	353	6.52	6.33	344	7.1%	-0.03 [-0.18, 0.12]
Total (95% CI)			**6632**			**6462**	**100.0%**	**-0.10 [-0.14, -0.05]**

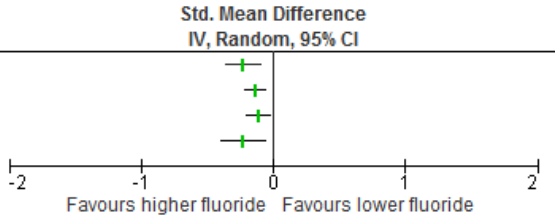
Heterogeneity: Tau² = 0.00; Chi² = 15.20, df = 9 (P = 0.09); I² = 41%
Test for overall effect: Z = 4.06 (P < 0.0001)



Footnotes
(1) NaF plus 3% trimetaphosphate
(2) SMFP plus 0.5% zinc citrate
(3) NaF plus 3% trimataphosphate

14.2 D(M)FT

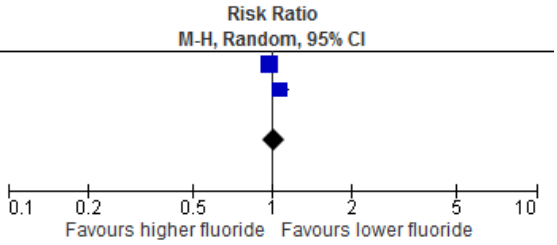
Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Buhe 1984	4.3	2.84	421	5	3.21	438	-0.23 [-0.36, -0.10]
Conti 1988	1.06	1.9	1187	1.34	2.13	1228	-0.14 [-0.22, -0.06]
Fogels 1988	1.22	1.86	963	1.44	2	950	-0.11 [-0.20, -0.02]
Hodge 1980	3.47	2.63	403	4.07	2.68	194	-0.23 [-0.40, -0.05]



14.3 Proportion developing new caries

Study or Subgroup	Higher fluoride Events	Total	Lower fluoride Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Conti 1988	943	1187	1001	1228	54.5%	0.97 [0.94, 1.01]
Fogels 1988	624	950	593	963	45.5%	1.07 [1.00, 1.14]
Total (95% CI)		**2137**		**2191**	**100.0%**	**1.02 [0.93, 1.11]**
Total events	1567		1594			

Heterogeneity: Tau² = 0.00; Chi² = 5.57, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.33 (P = 0.74)

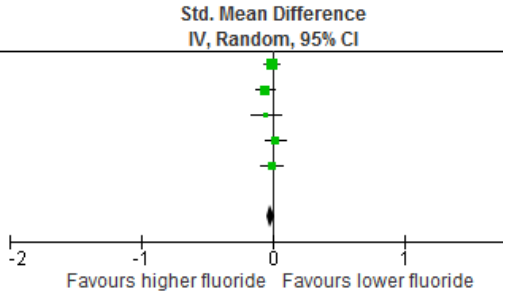


15 - 1000 ppm F versus 1700 ppm F in children and adolescents (immature permanent dentition)

15.1 D(M)FS

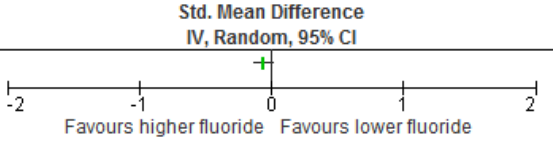
Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beiswanger 1989	2.8698	3.5	2185	2.9138	3.1885	2273	32.8%	-0.01 [-0.07, 0.05]
Biesbrock 2001	1.45	4.7	2211	1.71	3.36	1127	21.9%	-0.06 [-0.13, 0.01]
CL-213 1983	9.21	7.24	615	9.62	7.77	582	8.8%	-0.05 [-0.17, 0.06]
CL-216 1982	1.49	2.332	1387	1.45	2.337	1371	20.3%	0.02 [-0.06, 0.09]
CL-220 1986	4.7336	6.4893	1605	4.79	6.992	840	16.2%	-0.01 [-0.09, 0.08]
Total (95% CI)			**8003**			**6193**	**100.0%**	**-0.02 [-0.05, 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 2.66, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)



15.2 D(M)FT

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Biesbrock 2001	0.92	1.81	2211	1.03	1.81	1127		-0.06 [-0.13, 0.01]

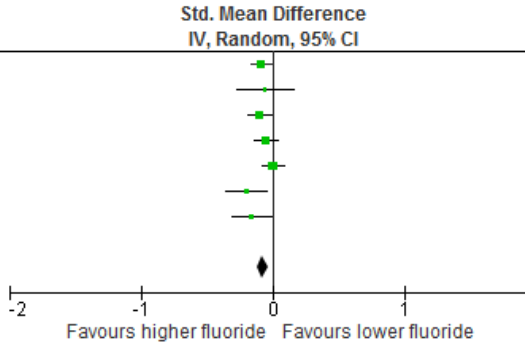


16 - 1000 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

16.1 D(M)FS

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Biesbrock 2001	1.41	3.31	1093	1.71	3.36	1127	21.1%	-0.09 [-0.17, -0.01]
Biesbrock 2003a	1.25	3.5871	153	1.47	3.4996	168	3.9%	-0.06 [-0.28, 0.16]
Chesters 2002	4.96	5.04	1017	5.47	5.08	994	19.6%	-0.10 [-0.19, -0.01]
Lu 1987	4.13	5.12	1352	4.4	5.17	703	18.4%	-0.05 [-0.14, 0.04]
Ripa 1988	3.67	4.59	858	3.69	4.78	1651	21.4%	-0.00 [-0.09, 0.08]
Stephen 1988	5.56	5.81	239	6.83	6.54	469	7.4%	-0.20 [-0.36, -0.05]
Stephen 1988 (1)	5.85	5.37	277	6.77	5.87	452	8.0%	-0.16 [-0.31, -0.01]
Total (95% CI)			**4989**			**5564**	**100.0%**	**-0.08 [-0.12, -0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 7.32, df = 6 (P = 0.29); I² = 18%
Test for overall effect: Z = 3.50 (P = 0.0005)

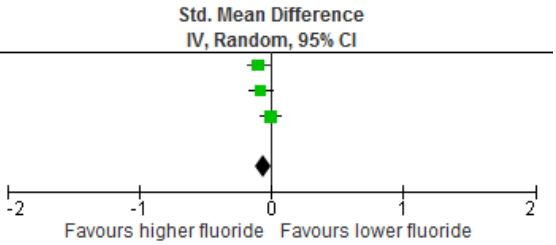


Footnotes
(1) SMFP plus 0.5% zinc citrate

16.2 D(M)FT

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Biesbrock 2001	0.85	1.82	1093	1.03	1.81	1127	33.7%	-0.10 [-0.18, -0.02]
Lu 1987	2.37	2.66	1352	2.58	2.86	703	29.8%	-0.08 [-0.17, 0.01]
Ripa 1988	1.62	2.01	955	1.63	3.5	1814	36.5%	-0.00 [-0.08, 0.08]
Total (95% CI)			**3400**			**3644**	**100.0%**	**-0.06 [-0.12, 0.00]**

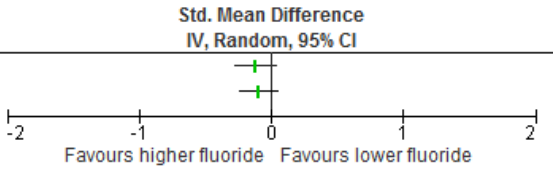
Heterogeneity: Tau² = 0.00; Chi² = 2.97, df = 2 (P = 0.23); I² = 33%
Test for overall effect: Z = 1.91 (P = 0.06)



17 - 1450 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

17.1 D(M)FS

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Stephen 1988	5.56	5.81	239	6.27	5.64	464		-0.12 [-0.28, 0.03]
Stephen 1988 (1)	5.85	5.37	277	6.39	5.81	466		-0.10 [-0.24, 0.05]

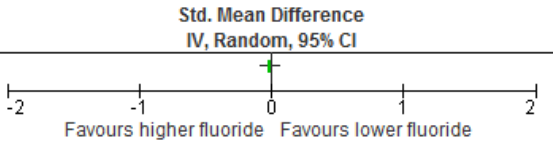


Footnotes
(1) SMFP plus 0.5% ZCT

18 - 1700 ppm F versus 2400 ppm F in children and adolescents (immature permanent dentition)

18.1 D(M)FS

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Biesbrock 2001	1.41	3.31	1093	1.45	4.7	2211		-0.01 [-0.08, 0.06]



18.2 D(M)FT

Study or Subgroup	Higher fluoride Mean	SD	Total	Lower fluoride Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Biesbrock 2001	0.85	1.82	1093	0.92	1.81	2211		-0.04 [-0.11, 0.03]