TOPICAL FLUORIDES FOR THE PREVENTION OF DENTAL CARIES IN CHILDREN – A SYSTEMATIC REVIEW

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ABSTRACT

The effectiveness of topical fluorides on dental caries has been extensively reviewed in a number of traditional narrative reviews which often provide different estimates of effectiveness based on selected published literature, and rarely explore the causes of variability in reported effectiveness in a formal way. Recent studies, focusing mainly on the evaluation of specific topical fluoride interventions, have used the meta-analytical approach to synthesize studies results. However, there has been no systematic investigation evaluating and comparing the effectiveness of the main forms of topical fluoride used for caries prevention and examining formally the main factors that may influence their effectiveness.

The aim of this thesis was to evaluate objectively and quantitatively the effectiveness and safety of topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels and varnishes in the prevention of dental caries in children. A secondary aim was to examine the sources of heterogeneity that may influence effectiveness, including the initial level of caries, background exposure to fluoride and intervention features. With regard to the clinical effectiveness of TFT three basic questions were asked: Is TFT effective for children and adolescents? Is one of the forms of TFT more effective than another? Are combinations of TFT more effective than one TFT used alone?

A comprehensive search was carried out, in order to identify all relevant studies for inclusion irrespective of language. It involved searching a wide range of databases and other sources for controlled trials. Study selection, data extraction and quality assessment were performed based on pre-designed and pilot tested forms and were duplicated in one third of studies. The main outcome measure was caries increment, as measured by the D(M)FS index. The primary measure of effect was the prevented fraction (PF) – the difference in mean caries increment between the treatment and control groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed throughout for estimation of treatment effects. Potential sources of heterogeneity were investigated in random effects metaregression analyses.
Regular toothbrushing with fluoride toothpaste, supervised regular use of mouthrinse, fluoride gels applied professionally or self-applied under supervision a few times a year, and fluoride varnishes applied two to four times a year were associated with clear reductions in caries increment. For fluoride varnishes, results were largely based on trials with no treatment controls, and for the other modalities results were based on a substantial body of evidence from placebo-controlled trials. Based on the direct evidence from the trials, no conclusion could be reached about any effects that fluoride toothpaste might have on fluorosis, or about any potential adverse effects of TFT. The caries preventive effect of TFT varied according to type of control group (DMFS PF being substantially higher in non-placebo controlled trials), and increased with supervised use of self-applied TFT, higher initial caries levels, higher fluoride concentration and frequency of application, but was not influenced by exposure to water fluoridation. In adjusted indirect comparisons, caries reductions were likely to be greater with the use of fluoride varnish; no significant differences in effectiveness were indicated for the other TFT modalities. Evidence from head to head comparisons did not indicate that fluoride varnish is more effective than other fluorides; compared with each other, fluoride toothpaste and mouthrinse, and toothpaste and gel appear to be effective to a similar degree. Topical fluorides (mouthrinses, gels, or varnishes) used in addition to fluoride toothpaste achieve a modest reduction in caries compared to toothpaste alone. It was concluded that the benefits of TFT are well established, but further research is needed on potential adverse effects.
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CHAPTER 1

INTRODUCTION AND GENERAL BACKGROUND

1.1 - Introduction

Following the original epidemiological work of Dean et al (1938) showing the link between fluoride levels in the drinking water and the prevalence of dental fluorosis and dental caries, different strategies aimed at maximising the benefits of fluorides in the prevention of dental caries for communities and for individuals have been developed during the last 60 years. A wide choice of interventions became available and the use of topical fluorides in the form of toothpastes, mouthrinses, gels and varnishes in particular has increased considerably in recent decades.

Decisions about the appropriate provision of preventive or therapeutic strategies should be informed by knowledge of the effects of the interventions, and require that this knowledge is quantitative. The synthesis of research evidence can help increase access to this knowledge base by ordering and summarising the evidence available and by increasing the precision of any estimates of effects. Systematic reviews locate, appraise and synthesize the evidence from relevant and valid primary studies in order to provide informative empirical answers to research
questions. Unlike other types of reviews that do not adhere to an explicit method, and tend to be based on only a selection of the literature and thereby may be open to substantial bias and error, systematic reviews aim to avoid these pitfalls by presenting an objective and transparent view and a comprehensive scientific summary of the available evidence. In addition, by including a quantitative synthesis of the results of individual experimental studies, a meta-analysis, in a systematic review this can provide valuable insights concerning the effectiveness of health care interventions through the epidemiological exploration and evaluation of the included studies. Systematic reviews are therefore increasingly well recognised as valuable sources of scientific information for rational decision-making, and a worldwide attempt is underway by The Cochrane Collaboration to disseminate the available evidence concerning important questions about the effects of health care interventions in the form of systematic reviews of randomized controlled trials (Chalmers, 1993; Chalmers et al, 1997; Oxman, 2001; Clarke, 2002).

Systematic reviews are widely used to compile the evidence on the effectiveness of therapeutic and preventive interventions in many areas of health care. They should be a powerful scientific tool to bring together and summarise the large body of knowledge from many experimental studies of topical fluoride therapy for the prevention of dental caries. If so, the present study has the potential to influence decisions about oral health care. It will be important because it may reliably answer the research question relating to the effectiveness of topical fluorides, provide the basis for the planning of future research, help in the formulation of evidence-based guidelines, and enhance estimation of probabilities needed for decision-trees and cost-effectiveness analysis.

A variety of study designs have been used to evaluate the effects of oral health care interventions such as topical fluorides, and a hierarchy of validity exists to grade such studies based on the rigour of their design and their ability to minimise bias (Woolf et al, 1990; CRD Report 4, 1996). This hierarchy relates to how confident one can be that the observed effects are attributable to the intervention and are not the result of other factors. The levels of research evidence range from simple descriptive studies (e.g. cross-sectional), through observational studies of individual based associations (e.g. case-control and cohort studies),
to formal experiments (e.g. randomized controlled trials). Large randomized trials are at the top of the hierarchy. These are regarded as the best type of evidence to be included in systematic reviews, because they are considered the best study design for prospective research into effectiveness.

The concept of caries prevention through topical fluoride treatments and the animal, laboratory research, and human trials which created the basis for the widespread use of fluoride in the form of toothpastes, mouthrinses, gels and varnishes have been extensively documented and discussed over the years since the potential usefulness of fluorides was first suggested in 1930s. While these various topical fluoride interventions have been subjected to intensive clinical testing in randomized controlled trials, the vast majority of reviews on the topic still use traditional narrative methods to evaluate this evidence. This double standard of combining the least biased evidence in a potentially biased way has been found in health care generally. Such narrative reviews often provide very different estimates of effectiveness due to differences in how the literature to be included was selected, and they rarely explore the causes of variability in reported effectiveness in a formal way. Nevertheless, a large number of these reviews have highlighted important issues relevant to the assessment of the effectiveness of topical fluorides in caries prevention.

Major issues that need to be considered when evaluating the effectiveness of topical fluoride interventions include: the potential benefits to be expected from topical fluorides, mainly in terms of reduced overall caries increment; whether the benefits differ among the various interventions and when these are used in combination; and how the benefits of topical fluoride therapy vary according to the influence of potentially important effect modifiers (including initial level of caries severity and background exposure to other fluoride sources). In addition, potential harmful effects (including symptoms of acute toxicity and dental fluorosis) require consideration. Unfortunately, these are rarely investigated or reported in conjunction with effectiveness estimates in experimental studies.

To date, some published reviews focusing mainly on the evaluation of specific topical fluoride active agents within specific delivery systems, have used a quantitative meta-analytical
approach to synthesize study results (Stamm et al, 1984; Clark et al, 1985; Johnson, 1993; Helfenstein and Steiner, 1994; Stamm, 1995; van Rijkom et al, 1998, Bartizek et al, 2001; Strohmenger and Brambilla, 2001; Chaves and Vieira da Silva, 2002, Ammari et al 2003). However, there has been no systematic investigation evaluating and comparing the overall effectiveness of the main forms of topical fluoride therapy currently used and examining formally the main factors that may influence their effectiveness. Moreover, none of the existing reviews have attempted to identify all relevant experimental research.

This is the gap that this thesis will fill. It will evaluate objectively and quantitatively the effectiveness of topical fluorides in caries prevention in children, and ascertain how widely the experimental approach, specifically randomized trials, has been utilised in assessing their effects. It will do so through a series of systematic reviews of all available evidence.

Following this introduction, a description of the potentials, concepts and principles of systematic reviews of controlled trials and of the current movement to disseminate them in general and oral health care is presented in Section 1.2. This section also discusses the developments of, and future prospects for, systematic reviews. Section 1.3 provides background information on the epidemiology of caries in children and on the patterns of use of topical fluoride therapy for caries prevention, and addresses relevant issues regarding the assessment of the effectiveness of these interventions, expanding on the rationale for undertaking the systematic review on the topic. The aims, objectives and the structure of the thesis are outlined in Section 1.4, and finally, Section 1.5 describes the focus of the thesis further in the criteria used for considering studies for inclusion in the systematic reviews.

1.2 – Systematic reviews of controlled trials in general and oral health care

The move towards evidence-based health care is a complex process. It requires reliable research findings to be made widely accessible and easily interpretable by those making decisions. In dentistry, as in other scientific disciplines, the exponential growth of the volume and complexity of health care information is making it increasingly difficult to keep abreast of all relevant research and to ensure that the best available evidence is used in delivering
care. Firstly, the volume of research currently produced is too vast, too dispersed across many types of publications and often too costly to access and compile. Secondly, most health care professionals, including members of the dental profession, have not been prepared academically to identify efficiently and appraise relevant research, which varies greatly in quality\(^1\). And thirdly, the time required to review the total body of research in a particular area or health care topic is much more than that which would be feasible for practising health care professionals.

In response to these difficulties, scientific methods have been developed to improve the ability to access, summarise, interpret and apply research evidence; foremost among them is the systematic review. Systematic reviews of the best available evidence regarding the effectiveness of health care interventions have come to occupy a key position between research evidence and better health care. Such reviews can efficiently identify, evaluate and synthesize valid research findings concerning important questions and provide ‘new’ information which may not be apparent from the individual studies to guide decisions and choices in the health services (Chalmers and Haynes, 1994; Mulrow, 1994; Bero and Jadad, 1997; Cook et al, 1997).

In direct contrast to the selective and subjective approach largely used in the traditional narrative review, the use of exhaustive search and pre-defined rigorous methods to conduct systematic reviews reduce chance effects and limit bias, thus providing more reliable results upon which to draw conclusions and make decisions. Moreover, because existing evidence is appraised thoroughly and its inadequacies uncovered in systematic reviews, they are a crucial first step before carrying out new research (Chalmers and Haynes, 1994) and are already making major contributions to the standards of research conduct and reporting (Chalmers, 2001).

Thus, systematic reviews aim not only to evaluate and summarise the reliable research evidence on any particular topic or question of interest, but also to highlight where such

\(^1\) Quality of a study is defined in this thesis as the confidence that its design, conduct and analysis has minimised or avoided biases.
evidence is lacking. In this way they fill a role at both ends of the research process: as ‘up-to-date’ summaries of accumulated knowledge and as stimuli for new work.

The specific issue of how to bring together quantitatively the evidence on the effectiveness of an intervention provided by individual studies is also guided by formal rules in systematic reviews. The appropriate and careful use of meta-analysis, with the statistical integration (and examination) of results of similar independent studies, increases the power and precision of estimated effects and “provides information that cannot be ascertained from any of the studies alone” (Whitehead and Whitehead, 1991). Consequently, small but potentially important effects may be detected with increased power, uncertainty may be resolved with improved estimates when individual reports disagree, generalisability may be improved, a priori hypothesis regarding treatment effects in subgroups of participants may be tested, and heterogeneity between study results may be explored and sometimes explained (Egger and Smith, 1997; Egger et al, 1997).

By performing cumulative meta-analyses in which each study is added sequentially to reflect the order that each new relevant study became available, the point in time when a treatment effect first reached conventional levels of statistical significance can be retrospectively identified (Lau et al, 1995). When compared to recommendations made by experts in traditional narrative reviews, the performance of continuously updated cumulative meta-analysis, as shown by Antman and collaborators (1992), can lead to earlier and more actionable conclusions both in confirming that a therapy is beneficial and in identifying one that is not beneficial or even harmful. In this way, systematic reviews can help prevent delays in both the provision of valid advice on effective forms of care and the cessation of promotion for other forms of care that are shown to be ineffective or harmful. Moreover, the conduct of unnecessary new studies addressing questions that have been already answered can be avoided.

A careful application of the meta-analytical approach in systematic reviews can, therefore, contribute importantly to health care. It can overcome not only the limitations of narrative reviews but also many of the limitations of using a single study as evidence for the
effectiveness of health care interventions, as single primary studies are almost never
definitive. Most individual studies provide preliminary evidence at best because of limited
scope, poor design or execution, or a sample size insufficient for important benefits or
adverse effects of an intervention to be detected. This is particularly applicable to
randomized controlled trials (RCTs), generally considered the most appropriate study design
for estimating the relative effects of different health care interventions. RCTs may have a
rigorous design and conduct, but often lack the required size to demonstrate a moderate,
albeit potentially important treatment effect, or are too limited in scope to allow the
applicability to other populations to be determined or to perform reliable subgroup analyses
(Peto et al, 1995). Thus, the appropriate combining of results from as much as possible of the
randomized evidence in systematic reviews has become a desirable and necessary strategy in
effectiveness evaluation.

Furthermore, because heterogeneity and bias can and should be carefully examined in every
meta-analysis (Greenland, 1994; Thompson, 1994; Egger et al, 1997), a systematic review of
RCTs is often the best strategy for appraising the evidence across trials. Investigations of
differences between studies (heterogeneity) in a meta-analysis increase the scientific
understanding of the studies reviewed and the clinical relevance of their results. If the meta-
analysis contains unexpected heterogeneity, metaregression (a powerful extension of a meta-
analysis where the influence of one or more characteristics of the studies on the size of
treatment effect is examined) and subgroup analyses can be performed, if a sufficiently large
number of studies is available (Higgins et al, 2002). In this way, sources of variability (and
bias) may be detected. However, results of such analyses should be interpreted with caution,
especially if these analyses were not determined a priori (Thompson, 2001). This is because
exploring sources of heterogeneity through multiple or post hoc analyses in systematic
reviews may result in false positive conclusions (Thompson and Higgins, 2002).

Individual participant data (IPD), rather than published summary statistics, are often required
for meaningful subgroup (Davey Smith et al, 1997) and metaregression analyses (Thompson
and Higgins, 2002). Despite this, systematic reviews that have performed meta-analysis
entirely based on summary data from published reports are much more common and have
provided robust indicators of treatment outcome. However, the resource intensive and time-consuming IPD reviews will overcome many of the problems associated with a reliance on published data only, and some of those associated with a reliance on aggregate data, and will add to the analysis that can be performed and increase the relevance of conclusions drawn (Clarke and Stewart, 2001).

Research into the numerous ways in which bias may be introduced in systematic reviews of clinical trials has contained important findings. Studies which show a statistically significant effect of treatment are more likely to be published (Easterbrook et al, 1991; Dickersin et al, 1992; Stern and Simes, 1997), more likely to be published without delay (Ioannidis, 1998), more likely to be published in English (Egger et al, 1997a), more likely to produce multiple publications (Tramer et al, 1997), and more likely to be cited by other authors (Gotzsche, 1987). Such ‘positive’ studies are therefore more likely to be located and included in systematic reviews, which may overestimate the beneficial effects of treatment (Egger et al, 2001). Study quality has also been shown to influence the size of treatment effect estimates in meta-analysis, because if poorly designed and executed studies may also overestimate the effects of healthcare (Sacks et al, 1982; Schulz et al, 1995; Moher et al, 1998). These biases (publication and location biases, and bias due to poor methodological quality of trials) are more likely to affect small rather than large studies, and may become evident in a systematic review through an association between treatment effect and study size (Sterne et al, 2001). With the progress that has been made in our understanding of how best to detect and deal with such biases in meta-analysis, using graphical (especially funnel plot analysis) and statistical methods, the scientific relevance of systematic reviews has increased considerably.

Nevertheless, although meta-analysis may reduce statistical imprecision and may take account of biases retrospectively, it cannot prevent biases. Greater efforts are required to reduce or avoid biases in the individual studies that will contribute to systematic reviews, such as registration of studies prior to their results being known, better conduct and reporting of studies, and reporting of findings of studies regardless of the results (Chalmers and Altman, 1999). More fundamentally, the pooling of trials in meta-analysis (and the quantitative exploration of study results) may not always be appropriate, particularly if the available data are too sparse, of too
low quality, or too varied to allow for the sensible pooling of results. Thus, sometimes the qualitative or descriptive synthesis of included studies is all that is possible in a systematic review. In such situations, the thorough consideration of heterogeneity between study results, in particular of possible sources of bias, can generally provide more insights than the mechanistic calculation of an overall measure of effect. It is therefore important to examine further the basic concepts and principles of systematic reviewing research.

1.2.1 – Definitions and terminology

What, then, is a ‘systematic review’, and why should this term (or its synonyms) be distinguished from the term ‘meta-analysis’? A useful definition of systematic review was given by Mulrow et al (1997): “Concise summaries of the best available evidence that address sharply defined questions”. The term ‘systematic review’ denotes a type of scientific investigation that seeks to assemble and examine all available evidence for a specific question in order to provide an unbiased summary of this evidence by following an objective, pre-defined and methodologically rigorous approach.

In contrast to narrative reviews which have widely recognised limitations in reliably summarising research evidence, a systematic review is focused on the question posed, comprehensive in the search for relevant studies, reproducible and impartial in the selection and critical evaluation of these studies, and objective in the formal integration and exploration of study results in order to meet the high methodological standards demanded of scientific enquiry. In addition, the conduct of systematic reviews will commonly require considerably more time, resources, skills and collaboration than that of narrative reviews, as demonstrated by a comparison of their main features (Table 1.1).
Table 1.1 – Systematic reviews and traditional narrative reviews compared (adapted from Cook et al, 1997 and Petticrew, 2001).

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<th>Feature</th>
<th>Systematic review</th>
<th>Narrative review</th>
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<td>Question</td>
<td>Often clear and focused question or hypothesis to be tested</td>
<td>Often general/broad in scope with no stated hypothesis</td>
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<tr>
<td>Search</td>
<td>Strive to locate all relevant published and unpublished studies to limit impact of publication and other biases</td>
<td>Not usually specified and potentially biased</td>
</tr>
<tr>
<td>Selection</td>
<td>Explicit description of inclusion criteria to limit selection bias</td>
<td>Not usually specified and potentially biased</td>
</tr>
<tr>
<td>Appraisal</td>
<td>Examine systematically the methods used in primary studies, and investigate potential biases in those studies</td>
<td>Often do not consider differences in study methods/quality</td>
</tr>
<tr>
<td>Data extraction</td>
<td>Duplicate data extraction in pre-tested forms. Strive to obtain relevant published and unpublished data</td>
<td>Often not an objective and reproducible process</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Systematic qualitative summary of the evidence and often quantitative summary, if appropriate</td>
<td>Often a qualitative summary</td>
</tr>
<tr>
<td>Inferences</td>
<td>Usually evidence-based</td>
<td>Sometimes evidence-based</td>
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In this way, a systematic review is a piece of research carried out to identify, appraise, synthesize “and communicate the results and implications of otherwise unmanageable quantities of research” (CRD Report 4, 1996a). If a review does not clearly describe all the stages of the review process, it cannot be considered a systematic review (Fig.1.1).
An alternative term for systematic reviews, which is sometimes used, is 'overview'. This is less specific, as it can be used to refer to narrative reviews (Oxman et al, 1994), and has been used to refer to individual patient data reviews that combined the raw results derived exclusively from randomized trials (Peto, 1987; Peto et al, 1995). Other alternative terms frequently used concurrently such as ‘research synthesis’ or ‘integrative review’ imply a broader definition for systematic reviews, as the principle of quantitative compilation of research results may actually be implicit on them. This is the case in the definition provided by Cooper and Hedges (1994) in
the ‘Handbook of Research Synthesis’. There, a systematic review is broadly defined as a fundamental scientific activity which attempts to integrate findings of empirical studies, the conjunction of a particular primary focus and goal, for the purposes of creating generalisations (which also involves seeking the limits and modifiers of generalisations), discovering the consistencies or inconsistencies of findings and accounting for the variability in similar-appearing studies. Expanding on this definition, the authors point out that with the perspective of seeking initially to provide neutral representation and the intention to be exhaustive in the coverage of the research base, “integrative research reviews also almost always (a) pay attention to relevant theories, (b) critically analyse the research they cover, (c) try to resolve conflicts in the literature, (d) and attempt to identify central issues for future research” (Cooper and Hedges, 1994, p.5).

A systematic review in which statistical techniques are employed to pool results from a set of studies is frequently also called a ‘meta-analysis’. However, this term actually describes a possible component of systematic reviews, albeit a particularly important one, as many systematic reviews include a meta-analysis. The classical definition for meta-analysis was given nearly thirty years ago, by the psychologist G.V. Glass (1976), who coined the term to refer to “the statistical analysis of a large collection of analysis results from individual studies for the purposes of integrating the findings”. Glass sought to distinguish meta-analysis from primary analysis – the original analysis of data from a research study – and secondary analysis – the reanalysis of the original data from either a different perspective or with different techniques to answer new research questions (Glass, 1976).

A meta-analysis, however, allows for extensions beyond the calculation of a combined effect estimate, such as the formal assessment of factors that may affect treatment effects. Moreover, because this quantitative technique can range from analysis which draws upon the summary statistics of a number of published studies alone to that based on raw individual patient data provided by the authors of published or unpublished studies, the acronym IPD MA is being used to denote the meta-analysis using raw individual data. In all instances, the principal argument in favour of the term ‘meta-analysis’ is its inherent suggestion of the involvement of numbers or
Thus, although expressions such as 'overview', 'research synthesis', 'integrative review' and 'meta-analysis' have been used interchangeably to refer to systematic reviews, the term 'meta-analysis' will be reserved in the present dissertation to describe specifically the use of statistical techniques to summarise the results of studies into a pooled estimate and to quantitatively identify and explore variations in the results of the studies, and not to the entire enterprise of research synthesis involving clearly defined methods to review a body of data. This will be referred to as a systematic review. Distinguishing between the two terms contributes to methodological clarity and minimises the tendency to place an inappropriately small emphasis on aspects other than the statistical analysis in systematic reviews, as they do not automatically involve quantitative synthesis.

This convention has now been adopted more widely. As pointed out by Chalmers (2001a) in his foreword to the second edition of the book 'Systematic Reviews in Health Care: Meta-Analysis in Context', “current discussions about ways of reducing biases and imprecision in reviews of research must not be allowed to be held hostage by ambiguous use of the term ’meta-analysis’”.

1.2.2 – Evolution and current status

The science of systematic reviewing is relatively young and is still developing. The concept of integration of scientific knowledge is not new however, and the need to synthesize research evidence has been recognised for well over two centuries. Explicit methods for this form of research were not developed until the 20th century, when the development of methods to reduce statistical imprecision using quantitative synthesis preceded the development of methods to reduce biases, the later only beginning to receive proper attention over recent decades (Chalmers et al, 2002).

Wider recognition of the science of research synthesis within academia and acknowledgement of the key role of reviews in summarising and disseminating the results of prior research to inform practice and policy has prompted considerations on their quality and on the deficiencies
in the existing strategies for research integration. This has also provided mechanisms to ‘force’ the necessary improvements in the conduct and reporting of primary research.

1.2.2.1 – Early developments

Several early conceptualisations of the systematic review as a research process in its own right occurred in the early 1970s in the social sciences, independently of the developments for meta-analysis (Cooper and Hedges, 1994). Light and Smith (1971) highlighted some of the pitfalls of the traditional approach and argued that if treated properly, the variations in results among related studies could be a valuable source of information, rather than a source of consternation, which it appeared to be when treated with traditional reviewing methods.

During the 1970s and early 1980s, the body of evidence identifying the biases and random errors which can compromise the validity of reviews and drawing attention to the systematic steps needed to minimise them was generated largely by researchers in psychology and education, who popularised meta-analysis and further developed the statistical methodology for its application (Glass, 1976; Rosenthal, 1979; Cooper, 1982; Light and Pillemer, 1984; Hedges and Olkin, 1985).

Systematic reviews employing meta-analysis were however rare in health care sciences until the second half of the 1980s, when considerable attention began to be devoted to their application in clinical trial research (Yusuf et al, 1987; L’Abbe et al, 1987; Sacks et al 1987; Bulpitt, 1988; O’Rourke and Detsky, 1989) and to the poor scientific quality and trustworthiness of health care review articles (Mulrow, 1987; Oxman and Guyatt, 1988).

In particular, attention was drawn to the fact that scientific principles are usually abandoned when moving from ‘primary’ research, such as properly conducted randomized controlled trials, to integrative research, the process of reviewing that research, a double standard shown to be manifest in some of the world’s leading medical journals (Mulrow, 1987). In a systematic assessment of 50 reviews published in four major American medical journals in 1985 and 1986, Mulrow (1987) found out that none of the reviews met all of eight criteria for scientifically
sound summaries of evidence, and most distressingly, “only one had clearly specified methods of identifying, selecting, and validating included information”.

This double standard which still operates in the biomedical field, where the style of the vast majority of reviews tends to be largely narrative, is no exception in dentistry. Systematic reviews of randomized controlled trials are only recently beginning to proliferate in dentistry despite the fact that thousands of RCTs of oral health care interventions have been published in the past five decades, and reviews employing meta-analyses of controlled trials of caries preventive measures started to appear in the mid 1980s (Stamm et al, 1984; Clark et al, 1985), coinciding with the growth in their availability in medicine.

By the late 1980s, as a result of the progress in adopting scientific methods of research synthesis in medicine, international collaboration had led to the completion of landmark systematic review projects in pregnancy and childbirth (Chalmers et al, 1989) and in cancer and cardiovascular disease (Antiplatelet Trialists' Collaboration, 1988; Early Breast Cancer Trialists' Collaborative Group, 1988). The latter endeavours, which involved collaborative reanalyses of individual patient data derived from almost all relevant randomized trials, became yardsticks against which the scientific quality of other systematic reviews in the field of health care would be judged.

In the early 1990s, the practical importance of improving the scientific quality of reviews was given great impetus by a study conducted by Antman and collaborators (1992) which compared textbook advice on the treatment for myocardial infarction with results of systematic reviews of relevant RCTs, and showed that valid advice on some lifesaving treatments had been delayed for more than a decade, and other forms of care had been promoted long after they had been shown to be harmful.

1.2.2.2 – Recent developments

Over the last decade, recognition of the importance of systematic reviews in the accumulation and dissemination of knowledge about the effects of health care in all
specialties grew rapidly, and continues to grow. Guides have been created (and updated) to aid in the conduct (Mulrow and Oxman, 1994; CRD Report 4, 1996a), reporting and critical appraisal (Oxman et al, 1994; Cook et al; 1995; Moher et al, 1999; Stroup et al, 2000) of reviews, and numerous articles have been produced about systematic reviewing methods and empirical studies of these methods (CMR, 2002). This is not least because of the work of The Cochrane Collaboration (www.cochrane.org), the primary purpose of which is to generate and make accessible high-quality systematic reviews of health care interventions in all areas of health care, in an international collaborative effort (Clarke and Langborne, 2001).

The appreciable methodological developments that have arisen from the recent, intense activity in reviews of health care interventions have not only facilitated understanding of systematic reviews in the context of the full scientific research process but also prompted their consideration as original research by journal editors and within the academic community (Egger et al, 2002). In addition, common myths and misconceptions about the methods and utility of systematic reviews have been exposed (Petticrew, 2001), in order to dispel criticism aimed at them from those still doubtful about their wider role.

There have also been important initiatives to facilitate the identification of published and unpublished trials and to improve the quality of reporting of trials, in order to reduce imprecision and biases when these are located and included in systematic reviews. A major development for trial finding is The Cochrane Central Register of Controlled Trials (CENTRAL), which regularly incorporates records of reports of trials identified through handsearching of thousands of journals and other sources around the world (Lefebvre and Clarke, 2001). Another important development that should improve the reporting of clinical trials is the adoption of the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Begg et al, 1996; Moher et al, 2001) by an increasing number of biomedical journals, including dental journals. These and various other recent developments in turn can further enhance the role of systematic reviews of controlled trials in helping clinicians, dentists, patients, policy makers and researchers answer relevant questions about the effects of health care interventions.
1.2.3 – Availability, production and dissemination

The number of systematic reviews that can be found nowadays in biomedical journals, including dental journals, is a reflection of their increased importance. Indeed, a considerable increase in the availability of systematic reviews has occurred since the late 1980s, when Sacks and colleagues (1987) could find less than one hundred reports of meta-analysis of randomized controlled trials in the English-language literature. The number of systematic reviews published annually increased greatly in the years that followed. A search of MEDLINE (an electronic bibliographic database which covers all areas of medicine, nursery, dentistry, and basic clinical sciences) for the text word ‘meta-analysis’ to assess the growth in the publication of systematic reviews employing meta-analytical methods and interest in quantitative methods of research synthesis, indicates that the increase has been substantial over the past twenty years in health care, with hundreds of such publications being produced each year since the late 1980s (Fig. 1.2).

![Graph showing the number of publications of/about systematic reviews using meta-analysis, published in each two-years period (non-cumulative), 1983-2002 (results from a MEDLINE search using the text word ‘meta-analysis’, limited to the dates of publication above).](image)

Fig 1.2 – Number of publications of/about systematic reviews using meta-analysis, published in each two-years period (non-cumulative), 1983-2002 (results from a MEDLINE search using the text word ‘meta-analysis’, limited to the dates of publication above).
When the same electronic search strategy is restricted to the dental subset alone in MEDLINE, a modest pattern of increase in dentistry is shown (Fig. 1.3).

![Graph showing number of publications of/about systematic reviews using meta-analysis, published in each two-years period (non-cumulative), in the dental subset of MEDLINE, 1983-2002.](image)

Fig 1.3 – Number of publications of/about systematic reviews using meta-analysis, published in each two-years period (non-cumulative), in the dental subset of MEDLINE, 1983-2002 (results from a MEDLINE search using the text word ‘meta-analysis’ limited to the dental subset and to the dates of publication above).

The first publications in the dental literature lagged behind, only starting to appear when the burst of growth in health care as a whole was well under way in the late 1980s and early 1990s. Nevertheless, the publication rate has risen since the mid 1990s, and it is envisaged that it will continue to rise as the support for systematic reviews from those who are trying to assemble existing evidence to make more effective use of limited resources increases in the dental field. With this regard, two organisations are playing a major role. The NHS Centre for Reviews and Dissemination at the University of York, in Britain, established to locate and disseminate the results of good quality existing reviews, and to prepare, commission and disseminate systematic reviews in areas of priority to the NHS in the United Kingdom; and, at an international level, The Cochrane Collaboration (with the evolving Cochrane Oral Health Group) (Tavender and Glenny, 2003), established to prepare, maintain and promote the accessibility to systematic reviews on the effects of all forms of health care.

In fact, many, if not the majority of, existing systematic reviews in dentistry should be found in specialised databases maintained by these two organisations, and available in *The Cochrane*
Library. This electronic source of reliable and continuously updated information includes, among several databases, a database with all full text Cochrane reviews, the Cochrane Database of Systematic Reviews (CDSR), and a database with structured abstracts of systematic reviews published elsewhere and critically appraised by the NHS Centre for Reviews and Dissemination, the Database of Abstracts of Reviews of Effects (DARE). DARE is also available through the NHS Centre for Reviews and Dissemination homepage at www.york.ac.uk/Inst/crd. Since 2000, Cochrane reviews are indexed in MEDLINE. Structured abstracts that convey essential information in a standardised format are included in the MEDLINE file without modification, and this has made it easier to identify these maintained systematic reviews and to keep track of them, whenever a Cochrane review is updated substantively a record for the new version is added to MEDLINE with a reference to the earlier record (Clarke and Oxman, 1999). Free online access to MEDLINE is available through PubMed at http://www.ncbi.nlm.nih.gov/PubMed/.

In addition, recent initiatives have made the full text of all Cochrane reviews available free of charge to an increasing number of countries where access to The Cochrane Library online is provided to everybody (national provision): Australia, England, Wales, Ireland, Finland and Norway (http://www.update-software.com/cochrane/provisions.htm; accessed on January 11, 2003). In South Africa, free access to The Cochrane Library is available for registered members of SA HealthInfo. In Brazil, BIREME provides online access to The Cochrane Library through the BIREME interface (in English, Spanish or Portuguese) free of charge, upon registration, and this has now been extended to all countries in Latin and Central America and the Caribbean. Through a partnership led by WHO, free online access to The Cochrane Library is also provided for at least 100 low-income countries (http://www.update-software.com/cochrane/LowIncome.htm; accessed on January 11, 2003). People elsewhere can access The Cochrane Library, through subscriptions to the CD-ROMs or online version from subscription agents and 3rd-party publishers (http://www.update-software.com/cochrane/order.htm, http://www.wileyeurope.com/WileyCDA/Section/id-101093.html).

1.2.3.1. – The Cochrane Collaboration
Much of the impetus for the increasing accessibility and adoption of sound reviewing strategies has arrived due to the work of The Cochrane Collaboration, which has accompanied the increasing influence of the evidence-based approach in general and oral health care. Since 1993, this worldwide initiative has sought to help people make well-informed decisions about health care through the preparation and maintenance of up-to-date systematic reviews of health care interventions. Its main focus is on systematic reviews of RCTs but this does not imply that information from other study designs is ignored within the Collaboration, but rather that in order to achieve a stable state in respect of its primary objectives, a choice had to be made as to the best type of research evidence about effectiveness to cover first (Chalmers et al, 1997).

This international network of clinicians, epidemiologists, and other health professionals (including those from oral health), researchers and consumers was named after Archie Cochrane, a British epidemiologist pioneer in the field of evaluation of medical interventions. In ‘Effectiveness and Efficiency’, his influential book published in 1972 he drew attention to the collective ignorance about the effects of health care, made a strong case for the evaluation of new and existing forms of care in controlled trials (especially in the usual case when the effects of care are not dramatic, but nevertheless important), and explained how evidence from such trials could help in a more rational use of resources (Cochrane, 1972).

The Cochrane Collaboration has evolved in response to Cochrane’s criticism of the health professions, for not having organised systematic, periodically updated reviews, by specialty or subspecialty, of all relevant randomized controlled trials (Cochrane, 1979; Clarke and Langhorne, 2001). Since the establishment of the first Cochrane Centre in Oxford, UK, in October 1992 (Chalmers et al, 1992), this initiative has been growing rapidly, with the foundation of 11 further centres in Europe (5), North America (2), Australasia (1), Brazil (1), South Africa (1) and China (1), and over nine thousand individuals from over 80 countries collaborating in review groups. Cochrane centres and collaborative review groups (CRGs) are the two main types of organisational units in The Cochrane Collaboration. In addition, there are Methods Groups, with expertise in relevant areas of methodology; Fields or Networks,
with broad areas of coverage spanning the scope of many review groups; and a consumer
Network helping to promote the interest of users of health care (Clarke, personal
communication).

The activities of Cochrane centres tend to reflect the interests of individuals associated with
them and the resources made available to them. The Cochrane centres throughout the world
share the responsibility for helping to co-ordinate and support the work of The Cochrane
Collaboration in various aspects. Collaborative review groups focus on particular health
problems or clinical specialties and subspecialties. Within each of these groups, an editorial
team helps to ensure that relevant controlled trials are identified and that Cochrane reviews
(the principal output of the Collaboration) are prepared and maintained to a high standard.

By mid 2003, 50 collaborative review groups covering various areas of health care had
registered as components of the Collaboration, and over 3000 Cochrane reviews were
available, 1754 of which as full systematic reviews and 1304 as protocols for reviews in
progress (CDSR, 2003). Although several hundred reviews and protocols are added each
year, there are many areas of health care still to be covered by Cochrane reviews, and the
number of reviews needed to do this is likely to be at least 10,000 (Mallett and Clarke, 2003).
Achieving this level of coverage while keeping all reviews up to date is perhaps the biggest
challenge for The Cochrane Collaboration in the years to come (Clarke and Langhorne,
2001).

The Cochrane Oral Health Group based in Manchester, UK, since 1998, is one of the specialty-
based review groups contributing to this international work across one area of health care. The
scope of systematic reviews within the Cochrane Oral Health Group (COHG) covers all
randomized controlled trials relevant to prevention, treatment, and rehabilitation across the
complete range of oral health care interventions. The group works closely with the Cochrane
Ear, Nose and Throat Group to avoid any duplication of effort. Where RCTs are not appropriate
or possible, rather than unavailable (such as in the area of oral health promotion, for example),
other levels of evidence may be considered for inclusion in a COHG systematic review. As of
mid 2003, 62 Cochrane reviews were available in oral health, 30 of which as full systematic reviews and 32 as protocols (CDSR, 2003).

The COHG editorial base maintains a Specialized Register of Trials, which contains thousands of records of clinical trials relating to oral health in an electronic database. The foundation for its on-going development is The Cochrane Central Register of Controlled Trials (CENTRAL), supplemented by the COHG’s programme of handsearching journals. The register provides a valuable starting point for reviewers and others searching for controlled trials on oral health topics (Bickley, 2002)

1.2.3.2 – Preparation, publication and maintenance of Cochrane reviews and others

The preparation and maintenance of Cochrane reviews, which is based on the guidelines provided in the Cochrane Reviewers’ Handbook (Clarke and Oxman, 2002), is dependent on the flow of information between a large number of people and places, and The Cochrane Collaboration has adopted electronic media as a primary means of assembling and disseminating these reviews. Several tools and systems to help with their preparation and to facilitate their electronic publication and updating, as well as that of other relevant material have been developed and are maintained by the Collaboration. These tools and systems make up the Cochrane Information Management System. This currently covers the review preparation software (RevMan, with RevMan Analyses as its statistical component), the software used to compile information in modules for electronic publication (ModMan), a contacts database, and a comments and criticisms process (Clarke et al, 2002).

All protocols and complete systematic reviews produced by collaborative review groups as well as information about these review groups, together with information from all the other entities of the Collaboration (centres, fields, methods working groups, and the consumer network) are submitted periodically for electronic publication, in full, in The Cochrane Library (Fig. 4).
Fig 1.4 – The Cochrane Collaboration’s organisational and analytical framework for assembling Cochrane reviews electronically in The Cochrane Library.

Besides all reviews prepared by contributors to The Cochrane Collaboration, The Cochrane Library also includes structured abstracts and references of systematic reviews produced outside the Collaboration; citations and abstracts of all relevant controlled trials identified as part of the Collaboration’s international effort to systematically search the world’s health
care journals published in English and other languages, and other sources; all methodology reviews prepared by the contributors to the Cochrane Methodology Review Group; as well as studies on the methodology of evaluating health care and social interventions. This information is distributed in five key components of The Cochrane Library:

(a) The Cochrane Database of Systematic Reviews (CDSR).
(b) The Database of Abstracts of Reviews of Effects (DARE).
(c) The Cochrane Central Register of Controlled Trials (CENTRAL).
(d) The Cochrane Database of Methodology Reviews (CDMR).
(e) The Cochrane Methodology Register (CMR).

As pointed out before, the highly structured Cochrane reviews in the CDSR, represent a distillation of the latest evidence in an easily accessible single source and the structured abstracts of good quality reviews in the DARE, provide critical commentaries which highlight the factors to take into account when interpreting and using the evidence presented.

Making systematic reviews available in an electronic form has clear advantages over more traditional methods. In the CDSR for example, the reviews can be updated as new evidence emerges and mistakes can be corrected in response to comments and criticisms, a special feature of Cochrane reviews. However, neither the highly structured format nor the medium through which Cochrane reviews are published in the CDSR will be acceptable to everyone whose health care decisions could be better informed by access to research knowledge. As a result, other formats and media are also used to disseminate key messages from Cochrane reviews and other systematic reviews to professional and lay people, and for evaluating the impact of these in controlled experiments (Chalmers et al, 1997).

In dentistry, the journals of secondary publication Evidence-Based Dentistry, a supplement of the British Dental Journal, and Evidence-Based Dental Practice are examples of a strategy to disseminate systematic reviews in another format. These are similar to other publications in medicine, such as ACP Journal Club and Evidence-Based Medicine, and present structured abstracts of good quality published studies which are considered important to oral health care decision-makers. These studies include systematic reviews on therapy, diagnosis and
prognosis, chosen and appraised according to explicit methodological criteria. A
commentary is provided for each study, discussing the appropriate application of the findings
in relevant settings (Lawrence, 1998).

All these new sources of evidence reveal the dearth of reliable evidence to inform choices,
expose gaps in past research, and highlight priorities for new research in dentistry.

1.2.4 – Quality and critical appraisal of systematic reviews

Various assessments carried out in recent years indicate not only that there is considerable
room for improvement in the quality of reports of RCTs, but that this also applies to reports
of systematic reviews of RCTs. As pointed out before, steps have been taken to develop
reliable methods to help improve the quality of reporting of randomized trials in order to
reduce bias when controlled trials are included in systematic reviews (Begg et al, 1996;
Moher et al, 2001). Similar efforts are underway for reports of systematic reviews of
controlled trials (Moher et al, 1999). The CONSORT and QUORUM guidelines for
improving the quality of reports of RCTs and systematic reviews of RCTs respectively can
also be used to critically appraise these types of reports.

Although only a few dental journals have adopted these guidelines as of mid 2003, it is
important that this is done more widely, for as the number of systematic reviews increases in
dentistry we are increasingly seeing reported in their findings that the quality of the primary
research is poor (NHS CRD, 2000; Montenegro et al, 2002; Sjögren and Halling, 2002). Similar findings were reported over a decade ago, following the publication of the first
systematic reviews in dentistry, conducted by Antczak-Bouckoms and collaborators (Tulloch
et al, 1989; Antczak-Bouckoms et al, 1990; Antczak-Bouckoms et al, 1993; Antczak-
Bouckoms, 1995).

Moreover, in spite of the relatively small number of systematic reviews currently available in
dentistry, a recent study indicates that their quality can be improved (Glenny et al, 2003).
This assessment of systematic reviews in dentistry highlighted key areas of weakness: the
search strategies employed, the quality assessment of the studies included, the statistical analyses, and the interpretation of findings. Clearly, if we are to use systematic reviews of RCTs to inform practice, policy, and research agendas, more emphasis needs to be placed on the use of clear guidelines for reporting studies, such as those presented in CONSORT and QUOROM.

Empirical studies have shown that Cochrane reviews are, on average, more systematic and less biased than systematic reviews published in high-profile paper journals (Egger et al, 1997; Jadad et al, 1998; Jadad et al, 2000), although they can also contain some problems in their conduct and reporting (Olsen et al, 2001). Several medical and dental journals are now eager to publish versions of Cochrane reviews, having recognised the importance of providing high-quality, up-to-date summaries of evidence to their readers (Clarke, 2002; Alvares, personal communication).

Nevertheless, regardless of the source of publication, systematic reviews (like all types of research evidence) require critical appraisal to determine their validity and to establish whether and how their results will be used in practice (Hunt and McKibbon, 1997). If a review is systematic, the methods used should be described in sufficient detail to allow the assessment of its quality and importance. In addition, different systematic reviews on the same topic may produce conflicting conclusions due to bias. Their critical appraisal may help to clarify why they may conflict with each other, and to increase confidence in their results, if these are valid.

It should be noted, however, that many of the new information sources described before, which are being produced to encourage the use of reliable evidence from systematic reviews, make the tasks of finding and critically appraising the relevant evidence much simpler, by partially incorporating these steps into their production processes.

1.2.5 – Future prospects and challenges

As the science of reviewing research develops and insights, showing how it can be pursued more effectively and critically, continue to emerge from empirical research, sustained
complacency about the scientific quality of most of the textbooks and other conventional 
narrative reviews upon which health professionals have had to depend for information on 
treatment effectiveness in the past will become a clear disadvantage in any area of health care. 
Systematic reviews of controlled trials will play an increasing role in the evolution of health 
services by providing a strong guide for practice; in the design and reporting of, and 
justification for controlled trials; and in the education of health professionals in both general 
and oral health care. Such reviews are likely to change some current notions about the effects 
of health care, as forms of care believed to be ineffective can be shown to be effective; forms 
of care thought to be useful can be shown to be either useless or even harmful; and the 
uncertainty about the effects of many other forms of care can be made explicit.

By undertaking systematic reviews and highlighting the high quality evidence that does – or 
does not – exist in a given topic, dentists, policy-makers and patients will be better able to 
make well informed decisions, and can cooperate in addressing important questions and in 
investigating outcomes that really matter. The increasing availability of systematic reviews in 
dentistry, should not only facilitate the further adoption by oral health care professionals of an 
evidence-based approach to decision making, but also a more sensible use of limited resources 
by dental researchers, who will then be able to propose new research that is the most necessary 
and which is designed appropriately.

The Cochrane Collaboration is helping to promote the development of systematic reviews in 
all areas of health care at an international level by its commitment to addressing questions of 
relevance to people using the health services; by setting explicit standards for reviews and 
through continual peer review of its processes to minimise bias; by providing a framework 
within which people can collaborate in areas of mutual interest; by helping to mobilise 
resources for reviewers; and by providing better means for producing, maintaining and 
disseminating high quality systematic reviews (Chalmers and Haynes, 1994; Chalmers et al, 
1997). The Cochrane Collaboration’s potential derives, in part, from its openness to 
challenge.
However, the magnitude of the task of systematic reviewing the existing experimental
evidence about the effects of health care and making the findings readily available to people
who need them to take better decisions about their own health care or that of other people,
and about research, should not be underestimated. In oral health, even if the attention is to be
focused on RCTs alone, thousands of studies conducted during the second half of the 20th
century may need to be considered. Moreover, the demand for systematic reviews still vastly
exceeds the capacity of those who are prepared to commit themselves to preparing and
maintaining reviews of an acceptable scientific standard. Although a growing number of
contributors are already collaborating in the Cochrane Oral Health Group and getting to grips
with Cochrane’s daunting agenda, it is likely that it will take many years for a stable state to
be reached of prompt incorporation of new primary research into an existing body of
systematic reviews of previous research on the effects of health care interventions (Clarke
and Langhorne, 2001).

Meanwhile, individual studies of research evidence will continue to be used as a single
source of evidence about effectiveness until systematic reviews or further integrative studies
based on them have been conducted, because they are still more likely to be the only source
of scientific evidence available in most areas of health care. At the same time, when the
relation between ‘new’ and ‘old facts’ is assessed in the Discussion sections of reports of
trials, it is still rare for the new results to be set in the context of existing evidence (Clarke et
al, 2002a). However, unless new trials are placed in the context of available systematic
reviews of relevant earlier research, they exist as islands of information, and not as a
continuum in the process of research integration (Clarke and Chalmers, 1998). In
acknowledgement of the cumulative nature of scientific evidence, some journals (such as the
BMJ) have started to publish a summary of what is already known on an addressed topic with
each report of new research, along with details of what the new study has added, but more
developments are expected with the increasing realisation that research findings should not
be interpreted in isolation.

Finally, as Archie Cochrane made clear in ‘Effectiveness and Efficiency’ (Cochrane, 1972),
reliable evidence on the effects of specific elements of health care, although essential, is only
part of what is needed for improving decisions about health care and further research. Starting with issues surrounding the interpretation and applicability of results, systematic reviews should show what the data are in ways that cater for the different perspectives of the people who will use them – including service providers, service users, purchasers, researchers and funders. The interpretations of the data will usually differ between these various perspectives, depending on the perceived needs, the availability of resources, and priorities. As a consequence, effective mechanisms are required to applying the results from systematic reviews efficiently. By selecting implementation strategies which have been shown to be useful by well-controlled research, the likelihood of people benefiting from evidence derived from systematic reviews will be greater.

1.3 – Topical fluoride therapy for caries prevention

Dental caries is a highly prevalent chronic disease afflicting a significant proportion of the world population (Burt, 1998). Its peak activity occurs during childhood and may extend into and beyond adolescence with a slow increase in the number of caries/fillings with age. The condition is the major cause of tooth loss at all ages, and poses important and uncomfortable problems in all industrialised societies and in a large number of developing countries. If untreated, dental caries causes progressive destruction of the crowns of the teeth, often accompanied by severe pain and suffering. The repair and replacement of carious teeth is excessively time consuming and costly, representing a major drain of resources for health care systems. On a population basis dental caries is the most expensive human disease to treat in terms of direct costs (Sheiham, 2001).

Fluoride therapy has been the cornerstone of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray et al, 1991). The ability of fluoride to control the initiation and progression of dental caries is well known. Intensive laboratory and epidemiological research on the mechanism of action of fluoride in preventing caries indicates that fluoride's predominant effect is topical, which occurs mainly through promotion of demineralisation of early caries lesions and by reducing sound tooth enamel demineralisation (Featherstone and ten Cate, 1988; Featherstone, 1999).
Various modalities of fluoride use have been developed and tested in clinical trials over the past five decades, each with its own recommended concentrations, frequencies and dosage schedules. The use of topically applied fluorides in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades, and fluoride containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most widely used at present, either alone or in different combinations. By definition, the term 'topically applied fluoride' describes those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect and are therefore not intended for ingestion.

The various topical fluoride modalities can either be applied by professionals or self applied at home or in other settings. Products designed for professional use generally have higher concentrations and are used at less frequent intervals than those designed for self-application. Fluoride gels and varnishes are typical methods of professional application and both delivery systems have been used in school-based programmes. Fluoride gels have also been used as a self applied intervention in such programmes. Fluoride mouthrinses and toothpastes are the main forms of self applied fluoride therapy. The intensive use of fluoride mouthrinsing in school programmes has been discontinued in many developed countries because of doubts regarding its cost-effectiveness at a low prevalence of dental caries, and are being replaced by selective fluoride therapy directed to high risk children. Such procedures usually involve the combined use of fluoride toothpastes with gels or varnishes. Toothpastes are by far the most widespread form of fluoride usage (Murray et al, 1991a; Ripa, 1991), and the decline in the prevalence of dental caries in developed countries in the last decades has been mainly attributed to their increased use (Glass, 1982; Rolla et al 1991; Marthaler et al, 1994; O'Mullane, 1995; Marthaler et al, 1996).

However, there is currently a debate regarding the appropriate use of fluorides. The questions being asked relate mainly to the actual effectiveness and the potential risks (especially in terms of fluorosis) that may be expected from the various fluoride-based caries preventive measures in an era of decreased caries prevalence and widespread availability of fluoride
from multiple sources (Ripa, 1991). In this context, even the need for selective professional fluoride applications has been questioned (Seppa et al, 1998). This is particularly important as nearly all child populations are exposed to some source of fluoride, and adverse effects may be rare (such as acute fluoride toxicity) or more subtle (such as mild dental fluorosis). The persistence of this debate and the variations in the use of the main forms of topically applied fluorides suggest the need to search for meaningful ways to summarise the empirical findings on this topic systematically.

If topical fluorides remain effective it will then become relevant to assess which form is best by comparing the various treatments currently used, since no consensus on which one, if any, is the most effective can be found in the literature. In addition, it will be important to reliably assess how much extra benefits topical fluoride treatments used in combinations may actually have, and whether the likely benefits are worth the effort, considering potential negative effects and acceptability. For example, the unanswered question today, of how much extra benefit comes from a professionally-applied fluoride or a fluoride rinsing programme on top of that provided from the regular use of fluoride toothpaste is of obvious importance and needs to be investigated formally.

Hundreds of reports of randomized trials published since 1940s have helped to bring about a situation in which the effectiveness of topical fluorides in preventing caries has been widely recognised. Yet, systematic reviews of the body of evidence available on the effects of topical fluorides are lacking. These are clearly required in order to answer the relevant questions in a reliable, objective and consistent way.

1.3.1 – Caries prevention and the changed prevalence, severity and distribution of dental caries

The use of fluoride in a variety of ways is usually the centrepiece of caries preventive strategies, among other crucially important measures such as the control of sugar consumption, which involves behavioural changes and the implementation of food policies, the use of fissure sealants, and improved oral hygiene. These strategies are complementary
and their use in combination has the potential of virtually eliminating dental caries in children. From a public health perspective, it is important that caries prevention strategies and policies are constantly and critically examined in the light of changes in the prevalence, severity and distribution of dental caries in order to establish a rational basis for caries prevention.

As pointed out before, the prevalence and severity of dental caries in child populations in most industrialised countries have decreased substantially in the past two decades, reaching averages as low as 1.1 decayed, missing and filled teeth (DMFT) in 12 year olds, nearly half of whom have no tooth decay or fillings (Marthaler et al, 1996). Although the reasons for this large-scale decline in caries continue to be debated, most authorities attribute it to the various uses of fluoride, particularly fluoride in toothpaste (Brathall et al, 1996). However, this largely preventable disease is still common, increases significantly with age (even where millions of people are exposed to fluoridated toothpaste), and remains a public health problem for a considerable proportion of the world population. In the United Kingdom, 30% of 3.5 to 4.5 year olds (Moynihan and Holt, 1996), and 50% of 12 year olds (Downer, 1995) had experienced caries in 1993. In 2000, the figures were 40% for 5 year olds in Great Britain (Pitts et al, 2001) and 38% for 12 year olds in England and Wales (Pitts et al, 2002). These findings demonstrate the continuing need for effective caries preventive strategies and treatment services for these age groups in a country that has experienced a substantial caries decline.

At low levels of caries prevalence and severity, the majority of caries lesions are concentrated in a minority of children. This polarised distribution is seen in many countries where overall caries experience is low. However, it has been demonstrated that as the average DMF scores increase beyond DMFT of 1 with age, for any age group, the development of new caries lesions is not confined to the group who would be defined as ‘high risk’ (that is, the caries susceptible minority) (Batchelor, 1998). A high proportion of new caries occurs in the group defined as ‘low risk’, in spite of the average lower caries increment in this group at an initial low DMF score; and any changes in caries levels are distributed throughout the population. Thus, although the distribution of caries within
populations is skewed to the left (most children have few/no caries lesions and relatively few children have high levels of caries), both the caries susceptible minority and the majority with low levels of caries develop new caries (Batchelor, 1998). This challenges the frequently stated concept that there is either a subgroup of the population that is at either ‘high- or low-risk’ of developing dental caries, and highlights the fact that an approach for caries prevention limited to the small proportion of individuals at ‘high risk’ may fail to deal with the majority of the new caries (Batchelor and Sheiham, 2002).

As with other chronic diseases, prevention ideally should stop or delay progression of caries for long enough for the severe manifestations of the condition not to manifest. The majority of approximal caries lesions in children’s permanent teeth progress slowly, with an average lesion taking at least 3 years to progress through enamel to dentine. In addition, differing types of surfaces of the teeth are affected as the severity of caries increases. At levels of DMFS below 10, the main parts of the teeth attacked are the pits and fissures. As the caries attack increases, the disease extends to involve the approximal and smooth surfaces. Thus, caries prevalence increases with increasing age and so does the extension of the disease to more surfaces (Sheiham, 2001). Conversely, it has been demonstrated that as overall caries experience declines in populations, it does so first in the least susceptible surfaces (that is, approximal and smooth surfaces) and last in the most susceptible surfaces (pits and fissures on first and second molars) (McDonald and Sheiham, 1992; Sheiham, 1998).

Thus, with the decline in caries prevalence and severity in child populations, and its changed distribution within the population, the rate of progression of carious lesions through enamel and dentin has slowed (Pitts and Renson, 1987; Ekanaiake and Sheiham, 1987), and the distribution of caries among affected tooth surfaces has also changed (Ripa, 1991). The greatest change in prevalence has occurred in approximal tooth surfaces resulting in many children having caries confined to the pit and fissured surfaces of first molars. Approximal lesions have become a much smaller proportion of the total caries burden. While the clinical significance of a decrease in the rate of lesion progression is to extend the period of peak caries activity into late adolescence, and to allow longer intervals between screening and dental check-ups, the changing pattern of intraoral distribution of the disease has direct
implications for the appropriate choice of caries preventive measures since it may determine which preventive procedure or combinations of procedures will be more effective, safe and cost-effective.

1.3.2 – The caries protective effect of fluoride

General strategies for the prevention of dental caries may be divided into two categories with regard to their mechanism of action: decreasing the carious attack and increasing the resistance of the tooth surfaces. The first category essentially involves measures to reduce the cariogenicity of the diet (control of sugar consumption), and to control dental plaque (oral hygiene and use of antimicrobial agents). Increasing the resistance of the tooth surface to carious attack involves the use of pit-and-fissure sealants and fluoride.

Fluoride concentrated in plaque and saliva inhibits the demineralization of sound enamel and enhances the remineralization of demineralized enamel (Koulourides, 1990; Featherstone, 1999). The view on the mechanism by which fluoride exercises its cariostatic action has changed from that of being a systemic pre-eruptive effect, with a partial substitution of fluoride into apatite during tooth enamel formation, to a post-eruptive direct effect of fluoride in the saliva/plaque/tooth surface interfaces. It is now well accepted that the primary caries-protective effects of fluoride occur through promoting remineralization of early caries lesions and by reducing tooth enamel demineralization, topically, during and after tooth eruption (Thylstrup, 1990). On the other hand, the level of fluoride incorporated into dental mineral during tooth formation by systemic ingestion is insufficient to play a significant role in caries prevention (Featherstone, 1999). Thus, any pre-eruptive benefit from ingestion of fluoride during tooth development is relatively unimportant.

Dental caries occurs when cariogenic bacteria in dental plaque metabolize a substrate from the diet (sugars and other fermentable carbohydrates) and the acid produced as a metabolic by-product demineralizes the adjacent enamel surface. Demineralization involves the loss of calcium, phosphate, and carbonate. These minerals can be captured by surrounding plaque and be available for reuptake by the enamel surface. Fluoride, when present in the mouth, is
also retained and concentrated in plaque. Saliva is capable of depositing mineral in porous enamel areas demineralized by the acids (remineralization). The deposit of impure hydroxyapatite crystallites is an important protective property of human saliva. Saliva is always supersaturated with calcium as well as phosphate at pH 7. If a porous lesion is formed in enamel, repair by remineralization always takes place. However, remineralization is a slow process and has to compete with factors causing demineralization. If the remineralization process can effectively compete, repair of the enamel takes place. On the other hand, if the challenge is too great, it is below the critical pH, and demineralization dominates, porosity of enamel increases with lesion progression until finally a carious cavity forms (Arends and ten Bosch, 1985). The rate of demineralization is affected by the concentration of hydrogen ions (pH) at the tooth surface and the length of time, which is related to the frequency that the pH of the plaque is reduced below the critical pH (Arens, 1998). Cycles of demineralization and remineralization continue throughout the lifetime of the tooth.

Sugars, particularly sucrose, are the most important dietary aetiological cause of caries, and fluoride is the main factor altering the resistance of teeth to acid attack. Fluoride reduces caries in several ways. As cariogenic bacteria metabolize carbohydrates and produce acid, fluoride is released from dental plaque in response to lowered pH at the tooth-plaque interface. The released fluoride and the fluoride present in saliva are then taken up, along with calcium and phosphate, by de-mineralized enamel to establish an improved enamel crystal structure. This improved structure is more acid resistant and contains more fluoride and less carbonate (Featherstone, 1999). Fluoride is more readily taken up by demineralized enamel than by sound enamel (White and Nancollas, 1990). Fluoride also inhibits dental caries by affecting the activity of cariogenic bacteria as it concentrates in dental plaque (Hamilton, 1990). At relatively high concentrations in dental plaque, it inhibits the process by which bacteria metabolize sugars (acid production) stabilizing the microflora in plaque during the routine oscillation of sugar concentration and pH change, and, calcium fluoride (CaF2) is formed on the tooth surface, providing a source of low concentration ambient fluoride while gradually dissolved (Hamilton, 1990; Marsh, 1995).

Fluoride in drinking water and in fluoride-containing products reduces tooth decay via these
mechanisms. Fluoride is usually applied in low concentration and high frequency or high concentration and low frequency for the prevention of caries. When the impact of the effect of topical fluoride is considered it is important to make the following distinctions:

(1) The effect of continuous (frequent use) low concentrations of fluoride present in the remineralizing fluid pertains to drinking water (± 1 ppm F), and during the periods in between toothbrushing or fluoride mouthrinising.

(2) The effect of high concentrations of fluoride of short duration pertains to topical applications of fluoride varnishes (7000 or 22,600 ppm F), gels (± 12,300 ppm F), toothpastes (250 to 2800 ppm F) or mouthrinses (100 to 910 ppm F).

1.3.3 – Adverse effects of fluoride

There has been growing concern about the increasing problem of dental fluorosis, a defect of the tooth enamel caused by fluoride's interference with the growing tooth, which results in a range of visually detectable changes in enamel opacity. In the severe form, the compromised enamel might break away, resulting in excessive wear of the teeth. Although most enamel fluorosis seen today is of the mildest form (Horowtiz, 1999), severe dental fluorosis can be a public health problem in communities with naturally high levels of fluoride in the drinking water or households with well water.

Cosmetically objectionable enamel fluorosis can occur when young children ingest excessive amounts of fluoride, from any source, while tooth enamel is forming (up to age 6). Its occurrence appears to be most strongly associated with the total cumulative fluoride intake during the period of enamel development, but the condition's severity depends on the dose, duration, and timing of fluoride intake. Although the amount of fluoride ingested beyond which fluorosis may occur is not known accurately, a threshold of 0.05 to 0.07 mgF/kg body weight has been suggested (Burt, 1992). The transition and early maturation stages of enamel development appear to be most susceptible to the effects of fluoride (DenBesten and

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2 In measuring fluoride concentrations in drinking water, part per million (ppm) is exactly equal to mg/L; mg/L refers to a measurement of liquid that has a specific gravity of 1. For materials that do not have a specific gravity of 1 (like toothpaste) mg/kg equals ppm. Thus, the standard fluoridated toothpaste has a concentration of 1000 mg kg of fluoride.
These stages occur at varying times for different tooth types. For central incisors of the upper jaw, for example, the most sensitive period is estimated at age 15 to 30 months (Evans and Darvell, 1995).

There is a clear dose-response relationship between water fluoride level and the prevalence of fluorosis. Results from the NHS Centre for Reviews and Dissemination’s systematic review of the effects of water fluoridation (NHS CRD, 2000; McDonagh et al, 2000) confirm that fluorosis appears to occur frequently at fluoride levels typically used in artificial fluoridation schemes (about 1 ppm F, i.e. 1 mg/L). The proportion of fluorosis that is aesthetically concerning is lower: the pooled estimate of the prevalence of fluorosis at a water fluoride concentration of 1.0 ppm was 48% (95% confidence interval 40% to 57%) and for fluorosis of aesthetic concern 12.5% (95% confidence interval 7.0% to 21.5%). The review also concludes that the quality of the research is too poor to rule out important adverse effects of fluoride in addition to the high levels of fluorosis.

With the increase in the availability of fluoride from multiple sources, the total intake of fluoride has increased for some children, and increases in the prevalence of fluorosis have been noted in fluoridated as well as low/non-fluoridated communities (Szpunar and Burt, 1987; Ismail et al, 1990; Clark, 1994; Jackson et al, 1995; Pendrys et al, 1996; Holloway and Ellwood, 1997; Selwitz et al, 1998). Epidemiological surveys in industrialised countries have shown that main factors associated with the increase in fluorosis in both fluoridated and non-fluoridated communities are dietary fluoride supplements and early use of fluoride toothpaste (Osuji et al, 1988; Pendrys et al, 1996; Wang et al, 1997; Pendrys and Katz, 1989; Mascarenhas and Burt, 1998). The need to reduce excessive fluoride intake from all the often unintended systemic fluoride sources have not only prompted worldwide downward revision of fluoride supplements dosage regimens but also elimination of fluoride supplements in some countries recently. The use of small quantities of toothpaste and of low fluoride toothpaste for young children has also been widely advocated. However, it appears that the effectiveness of fluoride toothpastes in which concentrations range from 250 to 500 ppm F has yet to be established.
Acute toxicity, due to the ingestion by children of large doses of fluoride in products for topical application, can also be of concern. Information on the toxicity of fluoride in humans is gathered from recorded cases of deliberate or accidental overdose (Joyston-Bechal and Kidd, 1994). The ingestion of potentially life-threatening doses by young children depends on the amount of fluoride ingested and the body-weight of the child. For this reason the toxicity of fluoride is usually expressed as the amount per kilogram of body weight.

The probable toxic dose (PTD) of fluoride, defined as 'the minimum dose that could cause toxic signs and symptoms, including death, and that should trigger immediate therapeutic intervention and hospitalisation', is thought to be around 5 mg/kg body weight (Whitford, 1992). A 1 year old child weighs about 10 kg and thus the PTD is approximately 50 mg; for a child of 5 or 6 weighing approximately 20 kg, the PTD is nearer 100 mg.

The excessive ingestion of fluoride during topical applications is not an uncommon occurrence (Whitford, 1992), and the greatest health hazard is associated with the use of 12,300 ppm F APF gels. The probable toxic dose of 100 mg of fluoride for a 20 kg (5 to 6 year old) child is contained in only 8 ml volumes of these gels. Approximately 5 ml of gel is used in a topical application of APF gel in a tray, representing a potential exposure of 61.5 mg of fluoride ion. There is therefore a significant risk of overexposure which can result in acute toxicity (Ripa, 1990). On the other hand, fluoride varnishes are considered safe despite their high fluoride concentration (22,600 ppm F in Duraphat and Durafluor), because the amount of varnish usually applied to treat one child is only 0.5 ml on average (Ripa, 1990; Petersson, 1993), which delivers 3-11 mg of fluoride ion, an amount far below the probable toxic dose. Unlike gels, varnishes need only be applied to vulnerable tooth surfaces and not to the whole dentition, and their setting time is rapid.

Young children are particularly at risk of ingesting toxic doses of fluoride from a standard toothpaste tube of 125 g, generally containing 1100 ppm F. The accidental swallowing of one-third of a toothpaste tube (45 g) or two-thirds of it (90 g) is potentially life-threatening for a 1 year old (10 kg) or for a 5 to 6 year old (20 kg) respectively (Ellwood et al, 1998). Accidental swallowing of the usual 10 ml rinse volume of a 0.05% (230 ppm F) NaF solution
for daily use by a five to 6 year old child will result in ingestion of 2.3 mg of fluoride (equivalent to the ingestion of twice the optimum level of fluoride in a fluoridated area). Although this dose is far below the probable toxic dose, this amount would be available in just 434 ml of the standard daily rinsing solution. Therefore, it is generally recommended that fluoride toothpaste and mouthrinse should be kept out of the reach of young children.

Furthermore, gels and mouthrinses are not generally recommended for children under 6 years of age due to the risk of acute fluoride toxicity if gels are swallowed during application, and the risks of chronic fluoride overexposure if rinsing solutions are swallowed.

1.3.4 – Patterns of use of topical fluorides

The first use of fluoride for caries prevention was in 1945 in the United States and Canada, when the fluoride concentration was adjusted in the drinking water supplying four communities. This public health approach followed a long period of epidemiological studies of the effects of naturally occurring fluoride in drinking water (Burt and Eklund, 1999). These studies first showed that mottled enamel (fluorosis) was caused by fluoride in drinking water and later confirmed the association between fluoride water content and caries reductions. In light of this evidence, major public health programmes around the world were initiated to raise fluoride levels in drinking water (fluoridation) where it was considered deficient. Historically, 1 ppm has been taken as the optimal fluoride level, in which the risk of fluorosis does not outweigh the benefits of dental protection against caries. However, there has always been scientific controversy over the (positive and negative) effects of water fluoridation (NHS CRD, 2000; McDonagh et al, 2000).

Due to a slow progress, or opposition, towards fluoridation of water supplies in many countries, and the view that, where this public health measure has actually been implemented, many children, particularly those at higher risk of developing caries, could still benefit from non-systemic methods of preventing dental caries based on the use of fluorides, several other modalities have been developed and utilised. In particular, consideration has increasingly been paid to the appropriate use of topical fluoride treatments. Topical fluorides have become the
most widely adopted strategy for the prevention of dental caries, and the modalities utilised and recommended most often (whether deliberately adopted at home, or in public health programmes, or professionally-applied in clinical practice) are in the form of toothpastes, mouthrinses, gels and varnishes. This thesis focuses on these forms of topical fluoride intervention.

Various forms of fluoridation strategies have been developed and are currently in use in some countries, but will not be considered in this thesis. These approaches include fluoridated salt, fluoridated milk and paediatric fluoride supplements/tablets. As pointed out before, dietary fluoride supplements were formerly considered a practical alternative for children living in non-fluoridated areas. However, studies conducted since the 1980s indicated that supplements were a significant risk factor in the development of dental fluorosis due primarily to prescription errors related to improper dosages. Because the prevalence of fluorosis has been increasing and the use of other forms of fluoride is widespread, the continued use of fluoride supplements is being questioned; reduced dosages have been proposed and some countries (such as Belgium) have started to abolish the use of fluoride supplements.

The home-use of topical fluorides has increased mainly as a consequence of the dominance of the market by toothpastes containing fluorides. The highly competitive nature of the toothpaste market has resulted in improvements in dentifrice formulations over the years, and the intensive promotion of fluoride toothpastes by the oral health care industry has been a major factor in their increased use. Since the 1980s, nearly all commercially available toothpaste formulations contain fluoride. Consensus among researchers and public health authorities places fluoride toothpaste as the method of choice for preventing caries, as it is convenient and culturally approved, widespread, and it is commonly linked to the decline in caries prevalence in many countries (Rolla et al, 1991; Marthaler et al, 1994; O’Mullane, 1995; Marthaler et al, 1996). The usual concentration of fluoride in toothpastes is 1000/1100 ppm F, but toothpastes with higher (1500 ppm F or above) and lower than conventional fluoride levels (around 500 ppm F) are available in many countries.
The use of mouthrinses was especially widespread in organized school-based programmes in countries experiencing high caries prevalence in the 1970s and 1980s. Doubts about the effectiveness of fluoride mouthrinse as a population strategy began in the mid 1980s in view of the decline in dental caries, and their presumed cost-effectiveness was challenged (Stamm et al 1984; Disney et al, 1990). The current view is that fluoride mouthrinising programmes are only appropriate for high caries groups of children. While supervised, school-based, weekly rinsing programmes using 900 ppm F solutions remain a popular procedure in the United States of America in non-fluoridated communities (Horowitz and Ismail, 1996), in Scandinavia and in several other countries these have been discontinued based on the above noted caries decline and the almost ubiquitous use of fluoride toothpastes (Seppa, 1989). Mouthrinses containing 230 ppm F are available commercially for daily home use in many countries, and mouthrinses containing 100 ppm F are also available for over the counter (OTC) sales and recommended for twice daily use.

Fluoride gels and varnishes have traditionally been used as professionally-applied methods in clinical practice, usually at semi-annual intervals, but their use are also reported in large-scale community programmes in populations experiencing higher caries rates (Murray et al, 1991b; Olivier et al, 1992; Seppa et al, 1995). Fluoride gels have been the most popular method of professional application of fluoride in North America (Ripa, 1990), and these are extensively used in other countries. Although currently recommended only for children with moderate and high caries levels the cost-effectiveness of fluoride gels has been questioned even for these populations (van Rijkom et al, 1998). Fluoride gels can also be self applied under supervision. In general, operator-applied fluoride gels use trays and self applied gels use either a tray or a toothbrush. Typically, acidulated phosphate fluoride (APF) gels in the concentration of 12,300 ppm F are professionally-applied twice a year. Fluoride varnishes have been extensively used in Europe, Scandinavia and Canada and their use in other countries, such as the United States of America, seems to be increasing in recent years (WHO, 1994; Bawden, 1998; Kallestal et al, 1999; Beltran-Aguilar et al, 2000). The use of fluoride varnishes is considered appropriate for at-risk tooth-surfaces in caries susceptible individuals and for moderate and high caries prevalence child populations (Petersson et al, 1997). Although different formulations of fluoride varnishes are available commercially, the
two main preparations (Duraphat and Fluor Protector) contain fluoride in concentration of 22,600 ppm F and 7000 ppm F respectively. Varnishes are usually applied at the frequency of two to four times a year.

Variations in the patterns of use from country to country and within a country, and from practice to practice thus exist for all types of fluoride-based measures. One important, if not the most important determinant of variations in preventive practice in relation to topical fluorides is the uncertainty that exists among those who make decisions in oral health care about the effectiveness and safety of the main treatments.

1.3.5 – Evaluation of the effectiveness of topical fluorides

The experimental research which created the basis for the widespread use of fluoride in the form of toothpastes, mouthrinses, gels and varnishes have been extensively discussed by others, and important issues relevant to the assessment of the effectiveness of topical fluorides have been explored.

It has frequently been pointed out that, with the decline in caries prevalence in many developed countries, an overall decrease in the effectiveness of fluoride therapy in preventing caries has occurred. Naturally, the reduction in caries increment brought about through fluoride usage would be expected to translate into benefits most readily among individuals at particularly high risk of caries, who experience high disease levels. In line with this expectation, the caries increment outcome of topical fluoride therapy has been found to be actually more favourable in early clinical trials recruiting participants with high pre-existing caries levels than in recent trials largely involving participants with low or even without the disease (Glass et al, 1983; Mainwaring et al, 1983; Burchell et al, 1991). Accordingly, guidelines for caries clinical trials have changed during the last twenty years (FDI, 1982; CDT, 1988; ICWCCT, 2002). This was in recognition of the fact that with the caries prevalence decline (which occurred where the great majority of reported studies were conducted), and the need, for ethical reasons, to use a positive control instead of a placebo (in fluoride toothpaste trials in particular), differences between treatments have become smaller in both absolute and percentage terms. In order to overcome the
problem of small group differences study design approaches have been modified, and the main strategies have focused on increasing sample size and power, reducing measurement error, and conducting studies with high risk subjects, mainly defined on the basis of initial caries scores.

A review (Volpe et al, 1993) of ten clinical trials included in a meta-analysis comparing the anticaries efficacy of two fluoride dentifrice formulations (Johnson, 1993) pointed out that studies were conducted in different locations that "reflected different caries challenges...". It can be argued that as the participants included in different fluoride trials carried out in different locations over a large timespan are highly heterogeneous with respect to the broad range of underlying caries scores – which actually represent the measurable effect of different past caries challenges – the potential absolute benefits of fluoride therapy are expected to vary widely between studies. It may render the results of meta-analyses, which are pooled average estimates of efficacy, difficult to interpret if this important source of heterogeneity is not carefully investigated.

According to the 1994 Report of a WHO Expert Committee on Oral Health Status and Fluoride Use (WHO, 1994), in addition to considerations on availability of resources, the most cost effective means of administering fluoride will depend on the caries status of the community in question and existing environmental sources of fluoride exposure. Thus, in establishing the current best evidence with regard to the effectiveness of topical fluorides in the prevention of dental caries it is necessary to take into account the different levels of disease severity and exposure to fluorides, given that decisions regarding public health policy are usually determined on this basis (of populations caries risks).

Also, according to the Centers for Disease Control (CDC) 2001 Report on ‘Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States’ (CDC, 2001), the increasing availability of multiple fluoride modalities and the lower caries prevalence indicate a need for current studies of logical combinations of fluoride regimens in populations with different caries risks. Such research should be in the form of systematic reviews of the body of evidence, to allow both more objective and reliable assessment of the effects of single and combined fluoride modalities and a more efficient use of resources.
Indeed, it is becoming increasingly clear that the information from rigorous systematic reviews that now exists should inform decisions about population-wide use of fluoride to prevent caries and further research in dentistry. For example, The U.S. Preventive Services Task Force (Greene et al 1989; USPSTF, 1996) and the Canadian Task Force on Periodic Health Examination (Lewis and Ismail, 1995) affirm that there is strong evidence to support the major methods for providing fluoride to prevent dental caries. The following preventive measures are recommended: fluoridation of drinking water, fluoride toothpaste, professionally-applied topical fluorides, and use of fluoride mouthrinses for those at risk of dental caries. Yet, the NHS Centre for Reviews and Dissemination's systematic review of the effects of water fluoridation (NHS CRD, 2000), the first systematic review undertaken on the subject, shows that because research conducted over the past half century has been of a much lower quality than had previously been reported, as far as the effects (positive and negative) of water fluoridation are concerned, there will continue to be legitimate scientific controversy until high quality studies are undertaken providing more definite evidence. The results of this study reinforce the need to review systematically the evidence available for the use of topical fluorides.

1.4 – Aims, objectives and outline of the thesis

The aim of this thesis is to evaluate objectively and quantitatively the evidence on the effectiveness and safety of topical fluorides in caries prevention in children. A secondary aim is to investigate potentially important factors that may influence effectiveness.

Six objectives have been identified to achieve these aims:

(1) To determine the effectiveness and safety topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels and varnishes in preventing dental caries in the child/adolescent population.

(2) To examine whether the effect of each form of TFT is influenced by the initial level of caries severity.
(3) To examine whether the effect of each form of TFT is influenced by the background exposure to ambient levels of fluoride in water (or salt), or reported fluoride sources other than the study option(s).

(4) To examine whether the effect of each form of TFT is influenced by fluoride concentration or application features, such as frequency of use.

(5) To examine whether the effect of TFT is influenced by the form of TFT used (toothpastes, mouthrinses, gels and varnishes), mode/setting of use (self applied supervised use of TFT in preventive programmes, self applied ‘unsupervised’ use of TFT at home, and operator-applied use of TFT), initial caries level, background exposure of fluoride.

(6) To determine whether there are differences in the effects of the various forms of TFT either singly (one compared with another) or in combination with each other (primarily fluoride toothpaste plus another topical fluoride modality compared with fluoride toothpaste alone).

Answers to these objectives will be given through a systematic review of all available experimental evidence. This has been structured into a series of component reviews based on the following comparisons:

(1) Fluoride varnishes versus placebo/no treatment.

(2) Fluoride gels versus placebo/no treatment.

(3) Fluoride mouthrinses versus placebo/no treatment.

(4) Fluoride toothpaste versus placebo.

(5) Any of the four modalities of TFT versus placebo/no treatment, where differences between the above sets of placebo controlled trials will be examined (indirect comparisons), with additional investigation of covariates across all TFTs.

(6) Head to head comparisons of fluoride gels/varnishes/rinses/dentifrices (one TFT versus another).

(7) Head-to-head comparisons of TFT used in combination versus one form of TFT used alone (primarily any TFT plus fluoride toothpaste versus fluoride toothpaste only).

The thesis is divided into ten main chapters. Chapter 1 provides an introduction to the work developed in this thesis, covers relevant information related to the present study and sets the scene for the research described in later chapters. Chapter 2 focuses on the main steps taken
during the planning stage of this study and on the methods used for the topical fluoride reviews, which are reported in detail and in sequence in the subsequent chapters. Chapters 3 to 6 are each devoted to a separate systematic review on the effects of the individual topical fluoride modalities. Chapter 7 is a systematic review on the effectiveness of the four types of TFT compared to placebo or no treatment, which exploits power with additional investigation of covariates across all TFTs and indirect comparisons of the different forms TFTs. Chapter 8 compares different topical fluorides with each other, and Chapter 9 primarily compares TFTs used in combination with fluoride toothpaste used alone. As each review stands on its own and follows the fixed Cochrane format (i.e. is directly output from the Cochrane Review Manager software), a review is presented in full with tables, figures and references in chapters 3 to 9. Each one of these chapters is automatically page numbered, and the seven chapters are bound together in a separate thesis volume. The final chapter, Chapter 10, contains a discussion and a summary of the main findings of the reviews, implications for current practice and implications for future research. It follows Chapter 2 in this volume.

1.5 – Inclusion Criteria

The following general criteria were used when assessing studies for inclusion in the systematic reviews. These were defined on the basis of the design characteristics of the studies, types of participants, topical fluoride interventions, and relevant outcomes.

1.5.1 – Types of studies

Studies were included if they were randomized or quasi-randomized controlled trials using or indicating blind outcome assessment, in which TFT used singly or in combination (in the form of toothpaste, mouthrinse, gel or varnish) is compared concurrently to placebo, no treatment, or TFT in one of the forms described above, during at least one calendar or school year.
Randomized or quasi-randomized controlled trials using within-group paired comparison
designs (e.g. split-mouth trials)\(^3\), or with open outcome assessment or no indication of blind
assessment, or lasting less than one calendar or school year were excluded. Controlled trials
where random or quasi-random allocation was not used or indicated were excluded.

1.5.2 – Types of participants

Participants had to be children aged 16 or less at the start of the study (irrespective of initial
level of dental caries, background exposure to fluorides, dental treatment level, nationality,
setting where intervention is received or time when it started).

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

1.5.3 – Types of interventions

The types of intervention included in the reviews are fluoride toothpastes, mouthrinses, gels
(professionally- or self applied) or varnishes only, using any fluoride agent (which may be
formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any
concentration (ppm F), amount or duration of application, and with any technique or method of
application, provided the frequency of application is at least once a year. The control group is
placebo (for any method of fluoride application), no treatment (except for brushing or flossing
methods of application), or any TFT modality described above resulting in the following
comparisons: Any single TFT compared with a placebo or no TFT, any single TFT compared
with another TFT, any TFT combined with fluoride toothpaste compared with fluoride
toothpaste alone.

\(^3\) It was anticipated that many fluoride varnish trials would use a split-mouth design. The major
drawback in using the within-subject paired design in a topical fluoride study is that the
possibility of contamination of control sites cannot be excluded, regardless of the adhesiveness
of the material in the first hours after application. Thus, due to the possibility of fluoride
spreading across the mouth, such trials were not considered.
Studies where the intervention/comparison consisted of any caries preventive agent/procedure in addition to the forms of TFT considered above were excluded (e.g. other fluoride-based measures, anti-plaque or anti-calculus agents, sealants, oral hygiene interventions, xylitol chewing gums, glass ionomers).

1.5.4 – Types of outcome measures

The primary outcome measure is caries increment, as measured by change from baseline in the decayed, (missing) and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. For studies in younger children the outcome of interest is caries increment in deciduous tooth surfaces, as measured by change in the decayed, (missing/extraction indicated), and filled surface d(e/m)f’s index. Dental caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis.

The following outcome measures were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions; tooth loss; proportion of children developing new caries; dental pain/discomfort; specific side effects (fluorosis, tooth staining/dyscoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting); unacceptability of preventive treatment as measured by dropouts during the trial (in non-placebo controlled studies); use of health service resources (such as visits to dental care units, length of dental treatment time).

Studies reporting only on changes in plaque/calculus formation, plaque regrowth/vitality, plaque/salivary bacterial counts, or gingival bleeding/gingivitis, dentin hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc) were excluded.

The identification and appraisal of available reviews, the liaison with The Cochrane Collaboration, and all other general methods utilised for the development of the protocol and the preparation of the systematic reviews are presented in the following chapter.
CHAPTER 2

METHODS

This is a systematic review that consists of a series of component reviews assessing the effects of topical fluoride therapy (TFT) in the prevention of dental caries in children.

This research was conducted in accordance with the guidelines for systematic reviews produced by the NHS Centre for Reviews and Dissemination and The Cochrane Collaboration, supported by the Department of Epidemiology and Public Health and the Systematic Reviews Training Unit (the host organisations, at UCL), and sponsored by CAPES (Brazil). A review team was formed and an advisory panel of experts in the field was recruited to provide relevant advice. The systematic reviews were conducted under the auspices of the Cochrane Oral Health Group, who provide on-going editorial support.

2. 1 – Checking for existing and on-going reviews

A preliminary literature search was undertaken to provide information on available systematic reviews of topical fluoride interventions and on the scope of the literature in the field. It had to be ascertained first whether a review on the same topic of sufficient quality was available (or
being prepared) which had not become outdated. Checks for existing and on-going reviews were made in 1997 and 2000 with the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluation Database (NHS EED), MEDLINE and EMBASE. These searches were performed without any date limits, and were supplemented by contact with key research groups in the field.

The search strategy used to locate reviews in MEDLINE (searched using WinSpirs/SilverPlatter software) is given in Appendix A, Section 1. The ‘controlled vocabulary’ terms “Fluorides” and “Dental caries” + “DMF index” (and corresponding ‘free text’ terms) were used ‘exploded’ (and truncated) for the subject search phrase in this strategy. This strategy was adapted to search EMBASE. At this preliminary stage, with the exclusive aim of identifying existing systematic reviews, only the methodological terms most likely to retrieve systematic reviews/meta-analyses were used from this search strategy. With the aim of collecting further background information for defining the scope of the systematic review and identifying relevant trials (by checking references in the bibliographies of the review articles), at a subsequent stage, the full MEDLINE search strategy was used for retrieval of review articles (as it included the broader/less specific methodological terms to locate reviews).

Six relevant reviews employing quantitative synthesis were identified by mid 2000. The first two studies to use a meta-analytical approach were published nearly two decades ago. One is a review of US fluoride mouthrinses studies in non-fluoridated areas (Stamm et al, 1984) and the other is a study by Clark et al (1985) on the comparative effectiveness of acidulated phosphate fluoride (APF) gels and solutions and fluoride varnishes. However, these reviews were not considered further due to several methodological limitations that characterised these early attempts at quantitative synthesis in the dental field.

A few reviews employing meta-analysis were published in the 1990s. Two of these address the comparative efficacy of two commercially available active forms of fluoride in toothpaste (Johnson 1993; Stamm 1995). Another is a systematic review on the effectiveness of one commercially available fluoride varnish system, Duraphat (Helfenstein and Steiner, 1994; 1994a) and the other is a systematic review on the effectiveness of fluoride gels (van Rijkom,
1998). A common feature present in the first three is a greater focus on the statistical aspects of the investigation, rather than on the clinical and public health implications.

Table 2.1 shows the main features and the results of the four studies.
Table 2.1 – Main features and results of review articles employing meta-analyses published in the 1990s on the effects of topical fluoride interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Focus</th>
<th>Inclusion criteria</th>
<th>Search/Selection/Quality assessment/Data extraction</th>
<th>Statistical analysis/ Investigation of heterogeneity / Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Rijkom 1998</td>
<td>An investigation on the caries-inhibiting effect of fluoride gel treatment in children and on factors potentially modifying this effect.</td>
<td>Randomized studies on fluoride gels (versus placebo or no treatment), applied to permanent teeth of children in the general population aged 6 to 15 years. Outcome measure: caries increment</td>
<td>MEDLINE (1965 to 1995) search for English and German language papers. Studies selected independently by 2 examiners, but no report on method for assessing validity, or on how many data extraction.</td>
<td>17 studies analyzed (8263 participants) – caries reduction was 22% (95% CI: 18, 25%) favouring fluoride gels. Differences in caries increment expressed as Prevented Fractions (PF). Model used for MA not reported. Multiple regression analysis showed no significant influence on the PF for the variables &quot;baseline caries prevalence,&quot; &quot;general fluoride regimen,&quot; &quot;application method&quot; (tray/brush), and &quot;application frequency&quot;.</td>
</tr>
<tr>
<td>Stamm 1995</td>
<td>Comparative efficacy of two formulations of fluoride dentifrices: sodium fluoride (NAF) and sodium monofluorophosphate (SMFP).</td>
<td>Not specified in terms of participants. Study design/interventions: RCTs reporting direct comparison of the two agents, and &quot;appropriateness&quot; of the test agents. Outcome measure: caries increment</td>
<td>Not reported.</td>
<td>12 studies analyzed (14,257 participants) – difference in efficacy was 7% favouring NaF toothpaste. Differences in caries increment expressed as standardized mean differences in D(M)FS. Fixed effects model used for conventional and cumulative meta-analysis. Heterogeneity not investigated.</td>
</tr>
<tr>
<td>Johnson 1993</td>
<td>Comparative efficacy of two formulations of fluoride dentifrices: sodium fluoride (NAF) and sodium monofluorophosphate (SMFP).</td>
<td>Not specified in terms of participants. Study design/interventions: RCTs reporting direct comparison of the two agents, and anticalculus studies, and dual-active studies. Outcome measure: caries increment</td>
<td>Published studies searched. (&quot;Design&quot; rating used but in another publication). Study identification and selection processes not reported. Quality assessment and data extraction methods not reported.</td>
<td>9 head-to-head studies (over 7000 participants) – overall weighted mean difference of 0.28 (95% CI: 0.10, 0.46) favouring NaF toothpaste (representing a 6.4% reduction in the rate of caries development). Differences in caries increment expressed as weighted absolute mean differences in D(M)FS. Fixed effects and random effects models used for meta-analyses performed. Tests of heterogeneity performed. Sensitivity analyses performed.</td>
</tr>
<tr>
<td>Helfenstein and Steiner 1994</td>
<td>An investigation on the caries preventive effects of Duraphat (fluoride varnish).</td>
<td>Specified in Terms of participants (children aged 6-15), intervention (Duraphat), outcome measures (caries increment) and study design (not restricted to RCTs).</td>
<td>Searched Index to Dental Literature 1985-91 and references from review articles. Study identification and study selection processes not described. Judgments on validity and data extraction method not reported.</td>
<td>9 studies analyzed (1851 participants) – caries reduction was 38% (95% CI: 19, 57%) favouring fluoride varnish. Differences in caries increment expressed as weighted mean differences in D(M)FS. Random effects model used for meta-analysis. Test of heterogeneity significant. Influence of study duration observed (effect decreased with time). Sensitivity analyses performed (fixed effects model).</td>
</tr>
</tbody>
</table>
This general assessment of the available literature indicated an absence of systematic reviews addressing the main questions for this study.

2.2 – Protocol development process

An external advisory group of experts in the field was recruited early in the process to help refine the review questions. Advisory group members were trialists, experts in the subject area (Ruth Holt, Kenneth Stephens, and Helen Worthington), and were selected to reflect different views and perspectives. The advisory panel was chosen by a review team member, Aubrey Sheiham, in consultation with the others: Valeria Marinho (principal researcher), Stuart Logan, and Julian Higgins. The review team members had a range of expertise including the methodology of systematic reviews, epidemiology, statistics, and subject area. Expertise in information sciences was provided within the Systematic Reviews Training Unit.

A standard letter was sent to consultants inviting them to take part in the panel and explaining their possible role in the process (Appendix B, Section 1). All agreed to participate as advisors and a second letter was sent to each consultant, with a draft protocol attached, specifically asking for their comments on the questions to be addressed by the study (Appendix B, Section 2). When their comments had been received, it was deemed relevant to convene a joint meeting of the review team and the advisory group in order to clarify and incorporate any further comments into the protocol. The meeting took place in London, at the Department of Epidemiology and Public Health (UCL), in July 1997, when the main issues that had been raised with regard to the relevance of the review questions /scope of the review were discussed. In addition, advice was provided about dissemination of review findings.

Liaison with The Cochrane Collaboration was also established early in the process and both workshops held for Cochrane reviewers, “Developing a protocol” and “Getting a review into Rev Man”, were attended by this investigator, a trainee within the Systematic Reviews Training Unit at the time. When all the issues discussed with the advisory group were satisfactorily incorporated into the original protocol, it was submitted to the Cochrane Oral Health Group for the internal and external peer review process.
The protocol published in 1998, in The Cochrane Library, Issue 2, was intended to be the first of three addressing the main research questions. The original protocol is available in Appendix C, Section 1. However, although every effort had been made to adhere to the original plan, it was recognised that this was not always appropriate. As a greater understanding of the problem was developed during the course of the study, following a meeting of the review team in October 1999, it was decided that the study should be re-structured into a series of seven systematic reviews (instead of three) and the range of analyses undertaken should be broader. The re-structuring of the original protocol into five protocols, with the changes documented in each subsequent protocol, were not made on the basis of how they could affect the results of the reviews. The decisions/changes made, with agreement from the advisory panel and the Cochrane Oral Health Group, are documented in Appendix C, Section 2.

All seven protocols for the series of Cochrane reviews were submitted and published during 2000 (The Cochrane Library, Issues 3 and 4). The members of the advisory group were among those who refereed the drafts of the protocols (and later of the reviews), through the Cochrane Oral Health Group editorial process.

2.3 – Search strategies for identification of primary studies

A comprehensive search was carried out, in order to identify all relevant studies for inclusion in the systematic reviews irrespective of language. It involved searching a wide range of databases and other sources for the identification of controlled trials.

2.3.1 – Electronic searching

Each database was searched from its starting date to July/August 1997, in the first stage of the review process, and additional/updating searches were undertaken until January/February 2000.

2.3.1.1 – The preliminary multiple database search process
The following databases were searched in July 1997: MEDLINE (1966 to 1997), EMBASE (1980 to 1997), SCISEARCH (1981 to 1997), SSCISEARCH (1981 to 1997), ISTP (1982 to 1997), BIOSIS (1982 to 1997), CINAHL (1982 to 1997), ERIC (1966 to 1996), DISSERTATION ABSTRACTS (1981 to 1997) and LILACS/BBO (1982 to 1997). Two overlapping but complementary subject search phrases with very low specificity (but high sensitivity)\(^4\), using 'free text' and 'controlled vocabulary' terms, were formulated within Silverplatter MEDLINE around two main concepts, fluoride and caries, and combined with all three levels of the Cochrane Optimal Search Strategy for Randomized Controlled Trials (RCT filters), described in Appendix A, Section 2. The software RCT Filter for MEDLINE SilverPlater (windows version), particularly useful to run the Cochrane search strategy on very large files downloaded from MEDLINE, was used to run the Cochrane search strategy (all 3 levels) in the downloaded set of records from the second subject search strategy. The subject search phrases were customised for searching EMBASE and the other databases, and the RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISSERTATION ABSTRACTS, and LILACS/BBO. Full details of the search strategies used according to database searched are described in Appendix A, Section 3 (subject search strategies and modified methodological filters). The Cochrane Controlled Trials Register (CCTR) (The Cochrane Library Issue 1, 1997), and the System for Information on Grey Literature in Europe (SIGLE) database (1980 to 1997), were also searched using the terms 'fluor' and 'carie' truncated.

This preliminary database search was used for the development of a register of topical fluoride trials for the systematic reviews, as the Cochrane Oral Health Group's Trials Register was not

\(^4\) In the context of a systematic review, the attributes of a search strategy can be described in terms of sensitivity or recall (ability to identify relevant articles), and specificity or precision (ability to exclude irrelevant articles). Thus, sensitivity is the proportion of relevant citations identified by a search strategy expressed as a percentage of all relevant citations on a given topic, and specificity is the proportion of relevant citations identified expressed as a percentage of all citations (relevant and irrelevant) retrieved by the search strategy. Highly sensitive 'subject search strategies' and 'methodological filters' tend to have a very low specificity and vice-versa. The ability to identify all relevant articles (high recall) was more important for the systematic review than achieving high precision, i.e. the comprehensiveness of the search was increased.
yet developed in 1997/98. These searches had low specificity and were used to refine and direct further searches.

The preliminary searches produced the following total number of records, according to database searched: MEDLINE, 4599; EMBASE, 5052; BIOSIS, 421; SCISEARCH 514; SSCISEARCH, 169; ISTP, 66; CINAHL, 133; ERIC, 60; DISSESTATION ABSTRACTS, 95; LILACS, 48; BBO, 47; CCTR, 86; SIGLE, 6. These numbers include those records that were retrieved in more than one database. The downloaded set of records from each database was imported to the bibliographic package Reference Manager in separate databases (records from LILACS, BBO, CCTR, and SIGLE were not imported but were inspected separately and cross-checked with those in Reference Manager). Starting with MEDLINE, the records were then merged into one core database to eliminate duplicates (around 7500, after the merging process plus those not merged), retrieved according to database, and checked for relevance on the basis of title first, then by keywords and abstract (where available). Records were considered relevant if it could be determined that they were a controlled trial of at least 6 to 8 months duration, involving children, and assessing at least one relevant type of topical fluoride therapy (TFT). Appropriate keywords had been added during the importation process to optimise retrieval for subsequent classification of eligible records by database, in order to identify the most useful databases.

When these records were screened, 403 potentially eligible reports were identified, 368 (91%) of which had come from MEDLINE. There was overlap between MEDLINE and EMBASE (28 records); MEDLINE and BIOSIS (37); MEDLINE and SCISEARCH, (28); MEDLINE and SSCISEARCH (3); MEDLINE and DISSESTATION ABSTRACTS (1); MEDLINE and LILACS/BBO (2); MEDLINE and CCTR (35). No potentially eligible reports were identified in ISTP, ERIC, CINAHL, or SIGLE. There were 294 potentially eligible reports (90%) unique to MEDLINE, 14 to EMBASE, 6 to BIOSIS, 3 to SCISEARCH, 1 to SSCISEARCH, 1 to DISSESTATION ABSTRACTS, and 8 to LILACS/BBO.

Of the 403 reports initially identified as potentially eligible, 304 (75%) were English articles, 35 (9%) German articles and 64 (16%) were published in other languages.
The journals with the highest yield of potentially eligible reports (based on 383 records identified as such from MEDLINE and EMBASE) were Community Dentistry and Oral Epidemiology, 59; Caries Research, 33; Journal of the American Dental Association, 25; British Dental Journal, 16; Journal of Dental Research, 12; Journal of Public Health Dentistry, 14; and European Journal of Oral Sciences (former Scandinavian Journal of Dental Research), 12.

2.3.1.2 - Additional database searching

Both OLD MEDLINE (1963 to 1965), which covers citations from 1958 through 1965, and the Community of Science database, which included ongoing trials funded by the National Institute of Dental Research (NIDR), were searched in 1998 using the two terms 'fluor*' and 'carie'.

LILACS/BBO were searched for the second time in January 1999, where ‘free text’ subject search terms were combined with a methodological filter for RCTs. This strategy is described in Appendix A, Section 4.

As described above, MEDLINE yielded by far the highest number of eligible studies. It was therefore considered the most useful database for the development of supplementary more specific subject search phrases (including ‘free text’ and ‘controlled vocabulary’ terms), refined for the systematic reviews of the individual topical fluoride modalities (but utilised for all reviews). Four separate searches were formulated around three main concepts each (the relevant type of TFT, fluoride and caries) and were used to search Silverplatter MEDLINE up to January 2000 without any study design filters. These subject search strategies are also described in Appendix A, Section 4.

These specific search strategies were adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and have also been run on CCTR (The Cochrane Library Issue 2, 2000) to double check.

Finally, the metaRegister of Current Controlled Trials was searched in October 2001 for ongoing RCTs using the terms 'fluoride' and 'caries'.
2.3.2 – Reference searching

All relevant reports retrieved from the searches, meta-analyses and review articles located up to January 2000 were checked for relevant references. As described before, review articles had been identified mainly by the searches specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic. Reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions were also consulted.

2.3.3 – Hand searching

Prospective hand searching of the seven journals identified as having the highest yield of potentially eligible RCTs/controlled trials (CCTs) was carried out, from January 1999 until January 2000 (each journal was searched prospectively, at the time, throughout this single year): British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (1990 to December 1999), as this was the journal with the highest yield of potentially eligible reports (see section 2.3.1.1).

2.3.4 – Other searches

Searching for unpublished studies (or 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published from 1980 onwards in order to obtain information on unpublished studies possibly eligible for inclusion. All the authors of studies who had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies (there was no date limit for this). A standard letter is available in Appendix D.
Based on information extracted mainly from included studies, a list of manufacturers of fluoride toothpastes, mouthrinses, gels and varnishes was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group, in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Fourteen manufacturers were contacted (October 2000) and information on any unpublished trials requested: Bristol-Myers Co, Colgate-Palmolive, Davies Rose-Hoyt Pharmaceutical Division, Gaba AG, Ivoclar North America, John O Butler Company, Johnson & Johnson, Oral-B Laboratories, Pharmascience, Procter & Gamble, Smithkline Beecham, Synthelabo, Unilever/Gibbs, Warner-Lambert. However, reports that might be identified by contacting manufacturers are not referred to in this thesis (but should feature in updates of the Cochrane reviews).

2.4 – General management of references

As for the preliminary multiple database search process, the downloaded set of records from each database searched was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS/BBO, CENTRAL, SIGLE, and NIDR databases were not imported to Reference Manager and were checked without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filters were imported to Reference Manager for inspection, in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register and the metaRegister of Current Controlled Trials were also checked outside Reference Manager.

All the references identified when searching other (non-electronic) sources (reference lists of located relevant studies, review articles and book chapters, journal handsearching, personal contact) were searched for in MEDLINE afterwards. The references that could be found in MEDLINE were imported to Reference Manager for inspection, and the others were entered manually.
2.5 – Relevance assessment (identification of eligible reports)

All records identified by all the searches performed (in the preliminary stage and subsequently) were printed off and checked on the basis of title first, then by abstract (when this was available in English or in languages known by this reviewer). Records that were obviously irrelevant were discarded and the full text of all remaining articles were obtained. Records were considered irrelevant according to study design/duration, participants, or interventions/comparisons (if it could be determined that the article was not a report of a controlled trial; or the trial was of less than 6 to 8 months duration; or the trial was exclusively in adults; or the trial did not address the relevant TFTs, compared to placebo, no treatment, or with each other (singly or in combination)).

The process of tracking down eligible articles was carried out in UCL libraries (Clinical Sciences Library and The Eastman Dental Institute Library), The London Hospital Library and The British Dental Association Library. Interlibrary loans were ordered if an article could not be found in such libraries.

2.6 – Selection of studies for inclusion

The inclusion criteria form had been previously prepared and pilot tested (on a sample of 20 articles), and was used by one reviewer (VM) to assess all studies for inclusion in the review. A second reviewer, Julian Higgins (JH), independently duplicated the process for a sample of those (approximately 30%). In addition, any study that could not be classified by the first reviewer was independently assessed by the second. A third reviewer was consulted, Stuart Logan (SL) or Aubrey Sheiham (AS), to resolve any disagreement. Trial reports thought to be potentially relevant in languages not known by the reviewers were assessed for inclusion with reference to the translator. Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met. The inclusion criteria form is available in Appendix E.
It was considered essential to identify all reports related to the same study, since in many instances crucial information for study selection and/or data extraction was not reported in similar detail in all publications; in case of any important discrepancy between reports, authors were contacted.

2.7 – Quality assessment

The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Reviewers' Handbook (Clarke and Oxman, 2002). Allocation concealment for each trial was rated as belonging to one of three categories:

A. Adequately concealed (an adequate method to conceal allocation is described).
B. Concealment unclear ('random' allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
C. Inadequately concealed (an inadequate method of allocation concealment is described).

Excluded: random (or quasi-random) allocation clearly not used in the trial, or 'random' allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:

A. Double-blind (blind outcome assessment and use of placebo/blinding of participants described).
B. Single-blind (blind outcome assessment stated and no placebo used/participants not blind).
C. Blinding indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment, e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind outcome assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).
Excluded: clearly open outcome assessment used or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, of x-rays registered independently of clinical examination, of use of a placebo, and of examiners clearly not involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated the process for a random sample of approximately one third. Any disagreement was discussed and where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not be resolved an effort was made to contact authors directly to clarify the method used to conceal allocation or whether assessment of the main outcome had been carried out blind.

Checking of interobserver reliability was limited to these validity assessments. Based on 28 studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, interrater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73).

Table 2.2 – Number of concordant and discordant assessments for (a) allocation concealment and (b) blinding in main outcome assessment, independently performed by two reviewers (VM and JH) on 28 included studies.

<table>
<thead>
<tr>
<th>JHV/VM</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>JHV/VM</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>C</td>
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<td>D</td>
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</table>

Further quality assessment was carried out to assess completeness of follow up and handling of exclusions (extent to which reasons for attrition are explicitly reported, or losses are independent of treatment allocated), and other methodological features, but these were not used as thresholds.
for inclusion. However, all such assessments were coded for possible use in metaregression or sensitivity analyses.

2.8 – Data extraction

Data from each included study were extracted by one reviewer (VM) using a pre-designed pilot tested data extraction form. The data extraction form is available in Appendix F. A second reviewer (JH) extracted data from a random sample of approximately one third of included studies. Again, data that could not be coded by the first reviewer were independently coded by the second, any disagreements were discussed and a third reviewer consulted to achieve consensus where necessary. Papers in languages not known by the reviewers were data extracted with help from appropriate translators. Attempts were made to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. Justifications for excluding studies were also documented at this stage.

Additional information related to study methodology or quality that was extracted included: study duration (years of follow up); comparability of baseline characteristics: methods used pre-randomization in sizing/balancing (stratification based on relevant variables) or used post-randomization in analysing/adjusting for possible differences in prognostic factors between groups; objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors); any co-intervention and/or contamination. Information on sponsoring institutions and manufacturers involved was also recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries severity at start (average DMFS, DFS, or other measure), background exposure to fluoride sources other than the study option(s) (in water, topical applications, etc), year study began, place where study was conducted (country), setting where participants were recruited, and

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5 Sensitivity analyses are used to determine how sensitive (robust) the results of a systematic review are to changes in how it was carried out (it is analyzed whether decisions or assumptions made about the data and/or the methods that were used may have an impact on the overall results).
dental treatment level (F/DMF). Characteristics of the interventions that were extracted included: fluoride modality(s), mode of application (how the intervention was delivered), methods (technique/device) of application, prior- and post-application, fluoride active agents and concentrations used, frequency and duration of application, and amount applied.

Different ways of assessing or reporting caries increment in the trials (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units of measurement (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (permanent/deciduous teeth/surfaces, first molar teeth, approximal surfaces, etc), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiographic), and approaches to account or not for reversals in caries increment adopted (in a net or observed/crude caries increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow ups), and where assessments of caries increments were made during a post-intervention follow up period, the length of time over which outcomes were measured after the intervention ended was noted.

Because caries increment could be reported differently in different trials a set of a priori rules were developed to choose the primary outcome data for analysis from each study: data on permanent teeth would be chosen over data on deciduous teeth; data on surface level would be chosen over data on tooth level; DFS data would be chosen over DMFS data, and this would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted' only, and this over data for 'erupting' only; data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological' only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated lesions; net caries increment data would be chosen over crude (observed) increment data; and follow up nearest to 3 years (often the one at the end of the treatment period) would be chosen over all other lengths of follow up, unless otherwise stated. When no specification was provided with regard to the methods of examination adopted, diagnostic
thresholds used, groups of teeth and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices described above were assumed.

All other relevant outcomes assessed/reported in the trials were also recorded/listed. The data were extracted into MS Excel spreadsheets (Microsoft Corporation, 1989-96).

2.9 – Data Analysis

2.9.1 – Handling of missing main outcome data

It was decided that missing standard deviations for caries increments that were not obtained by contacting the original researchers would be imputed through linear regression of log standard deviations on log mean caries increments. To impute missing standard deviations the approach of van Rijkom et al (1998) was followed, and a regression of available standard deviations on means was performed, irrespective of treatment group. After the omission of three influential points (out of 182 available at the time of analysis) a linear relationship was identified between log(SD) and log(mean) (Fig. 2.1).
The resulting regression equation was $\log(\text{SD}) = 0.64 + 0.55 \times \log(\text{mean})$ where log indicates natural logarithm (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses.

This is a suitable approach for caries prevention studies since, as they follow an approximate Poisson distribution, caries increments are closely related (similar) to their standard deviations.

2.9.2 – Handling of results (main outcome) of studies with more than one treatment arm

Following external statistical advice it was also decided to combine the numbers, mean caries increments and standard deviations of two or more relevant experimental or control arms in multitreatment trials in order to obtain a measure of treatment effect.
Multitreatment trial can be defined as

\[ E_1 \text{ vs } E_2 \text{ vs } \ldots \text{ vs } E_i \text{ vs } C, \]

or,

\[ E_1 \text{ vs } E_2 \text{ vs } \ldots \text{ vs } C_1 \text{ vs } C_2 \text{ vs } \ldots \text{ vs } C_i. \]

For that as given in the (above) table the following formula was used in order to combine results from the relevant experimental or control arms in a trial:

\[ E_1 \text{ & } E_2 \text{ combined } = \frac{N_1 \times \bar{X}_1 + N_2 \times \bar{X}_2}{N_1 + N_2}. \]

Thus, in the studies with more than one relevant intervention group (of the same modality of TFT) and a common control group (such as those comparing different concentrations of fluoride ions in a mouthrinse to a control group for example), raw results from all relevant experimental groups were combined. This enables the inclusion of all relevant data in the primary meta-analysis, although may slightly compromise any secondary investigations of dose response.

In the studies comparing two or more relevant modalities of TFT to a common control group, the control group was divided into approximately equally sized smaller groups to provide a pairwise comparison for each modality. Means and standard deviations were unchanged.

2.9.3 - Choice of measure of effect and meta-analyses of main outcome

The chosen measure of treatment effect was the prevented fraction (PF).
For data as given in the (above) table, preventive fraction is defined as

\[ \text{PF} = \frac{\bar{X}_C - \bar{X}_E}{\bar{X}_C}, \]

or, equivalently,

\[ 1 - \frac{\bar{X}_E}{\bar{X}_C}. \]

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

Meta-analyses were performed using an inverse-variance-weighted average. Variances were estimated using the following formula (Dubey et al, 1965):

\[ \text{Var}(\text{PF}) = \frac{\bar{X}_E^2}{\bar{X}_C^4} \frac{S_c^2}{N_c} + \frac{S_e^2}{\bar{X}_C^2 N_E}. \]

This is based on a delta method approximation to the variance rather than the confidence interval derived through Fieller’s theorem (Buonaccorsi, 1998). This is more suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable.

Random effects meta-analyses were performed throughout. The random effects model assumes a different underlying effect for each study in a meta-analysis, and takes this additional between-study variation into account in calculating the average treatment effect (DerSimonian and Laird, 1986).
Deciduous and permanent teeth were analysed separately throughout.

Statistical analysis was carried out using RevMan versions 4.1 and 4.2 – Metaview and RevMan Analyses (The Cochrane Collaboration, England) and Stata version 6.0 (Stata Corporation, USA).

For illustrative purposes, when overall results were significant, the results were also presented as the number of children needed to treat (NNT) to prevent one carious teeth/surface. These were calculated by combining the overall prevented fraction with an estimate of the caries increment in the control groups of the individual studies.

2.9.4 – Assessment of heterogeneity and investigation of reasons for heterogeneity

Heterogeneity in the results of the trials was assessed by inspection of a graphical display of the plotted estimates of treatment effect from the trials along with their 95% confidence intervals, and by formal tests of homogeneity (Thompson and Sharp, 1999).

Statistically significant heterogeneity was investigated using metaregression when a meta-analysis included a sufficiently large number of studies. In addition to aspects of study quality, potential sources of heterogeneity investigated in metaregression included factors specified a priori (such as baseline levels of caries severity, exposure to fluoride sources other than the study options, and application features) and others that were not. The association of potential effect modifiers with estimated effects (D(M)FS PFs) were examined by performing random effects metaregression analyses in Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp, 1998). The random effects regression model described in detail elsewhere (Thompson and Sharp, 1999) relates treatment effect to study characteristics assuming a normal distribution for the residual errors with both a within- and an additive between-study component of variance. The between-studies variance was estimated by an iterative procedure, using an estimate that is based on a restricted maximum likelihood method.

To allow investigation of heterogeneity, relevant data were dealt with as follows: data on
'baseline levels of caries' were calculated from the study sample analysed (final sample) and in connection with the caries increment index chosen, unless otherwise stated, and were averaged between all relevant study groups. Data on 'background exposure to other fluoride sources' combined data on the use of any fluoride other than the study option(s) and the consumption of fluoridated water (or salt) and were grouped into two categories: one for studies which were based on samples provided with non-fluoride toothpaste/ reporting no/low use of other fluorides and which were from non-fluoridated areas (non exposed), and another for studies based on samples using any fluoride other than the study option(s) or studies in fluoridated communities or both. When background exposure to fluoride toothpaste was not clearly indicated in studies carried out in developed countries, it was assumed that fluoride toothpaste was widely used from the middle of the 1970s (Ripa 1989); this information was sought from authors (or obtained from other sources) when missing from studies carried out in other locations. When data on the year a study had begun was not provided this was calculated as a 'probable date' by subtracting the duration of the study (in years) plus one extra year, from the publication date of the study. Background exposure to fluoride rinses, gels, tablets, etc should be reported to have involved the majority of participants in the study to be considered as such, otherwise it was assumed that these had not been used. Exposure to water fluoridation should be above 0.3 ppm F; when information on the fluoridation status of a site was not available/obtainable, no assumptions were made.

Data on the 'fluoride application mode of use and forms of TFT' were classified as self applied unsupervised use (of toothpaste or mouthrinse at home), self applied supervised use (of gel, mouthrinse or toothpaste in school-based programmes), and operator-applied use (of gel or varnish). The four modalities of TFT were categorised as such.

Further potential sources of heterogeneity investigated by metaregression included the potential influence of fluoride concentration and frequency of use. Data on 'concentration applied' and 'frequency of use' have not been categorised, but a 'total intensity of application per year' covariate was produced by multiplying frequency of application (per year) by fluoride concentration (in ppm F). In multiple arm studies this intensity score was averaged over fluoride treatment groups. Any 'post hoc' analysis was clearly identified.
Sensitivity analyses were performed as appropriate. A few meta-analysis of D(M)FS PF were to be repeated to account for the cluster randomized design of a trial(s), for example. This was achieved by replacing the variance of the prevented fraction estimate with an 'inflation factor', that describes how much additional uncertainty one should have about the result for the trial knowing it was cluster randomized. The variance of the prevented fraction estimate was inflated by an amount equal to \((1 + (m-1) \times \text{ICC})\), where \(m\) is the average cluster size and ICC the intraclass correlation coefficient. A conservative value of 0.1 for the ICC was used if an ICC could not be found from the trial(s).

2.9.5 – Investigation of publication and other biases

A funnel plot (plots of treatment effect estimates versus the inverse of their standard errors) was drawn for the main meta-analyses. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, though may also represent a true relationship between trial size and effect size. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger et al (1997b), a (weighted) regression asymmetry test. It was carried out in Stata version 6.0 (Stata Corporation, USA) using the program Metabias (Steichen, 1998).

2.9.6 – Measures of effect and meta-analysis of other outcomes

For outcomes other than caries increment, dichotomous data were analysed by calculating risk ratios (RR) or, for adverse effects of fluoride treatment, risk differences (RD). RevMan 4.1 and 4.2 (Metaview and RevMan Analyses) was used for estimation of overall treatment effects. Again, a random effects model was used to calculate a pooled estimate of effect. NNT was calculated when overall results were significant. As a general rule only (relevant) outcomes with useable data were shown in the analyses tables.

Full details of specific objectives and inclusion criteria used in the separate reviews, as well as details of specific methods used in their analyses, including the factors investigated in
metaregressions, can be found in Chapters 3 to 9 (see second thesis volume), each comprising a full systematic review (including results, discussion and conclusions). The next chapter (in this thesis volume) is Chapter 10, which presents the final discussion and conclusions of the study.

2.10 – Dissemination strategies

It has been proposed that the systematic reviews’ findings should be disseminated (beyond the routine dissemination activities of The Cochrane Collaboration and The Centre for Reviews and Dissemination) through:

- BASCD - British Association for the Study of Community Dentistry Conference;
- ORCA - European Organization for Caries Research Congress;
- Chief Dental Officers (Europe);
- Relevant peer-reviewed journals indexed in major databases.
CHAPTER 10

DISCUSSION AND CONCLUSIONS

10.1 – Introduction

The effectiveness of topical fluorides for caries prevention has been extensively researched. There are, however, few published systematic reviews mainly assessing specific topical fluoride active agents within specific delivery systems, and no systematic investigation evaluating the relative effectiveness of the most widely used forms of topical fluoride therapy and examining formally the main factors that may influence their effectiveness.

The research outlined in this thesis assessed objectively and quantitatively the relative effectiveness of the main forms of topical fluoride interventions currently used for the prevention of dental caries in children and adolescents. The study also explored formally the main factors that may influence their effectiveness. In an attempt to identify all relevant experimental research, it was ascertained how widely the experimental approach has been utilised in assessing the effectiveness and safety of topical fluorides through a series of systematic reviews of all available evidence.
This final chapter contains a general discussion of the most important findings of the thesis and a summary of the conclusions with practical implications, which have been already addressed in detail in the discussion and conclusion sections concerned with each systematic review (Chapters 3 to 9). The discussion of the main results providing the context of previous knowledge highlights the amount and quality of the evidence found and the ability to answer the objectives with this evidence. The methodological strengths and weaknesses of the study are also highlighted. The chapter will conclude with an outline of the conclusions and the steps taken for the dissemination of the findings.

10.2 – Discussion of main results

10.2.1 – Is Topical Fluoride Therapy (TFT) in the form of toothpaste, mouthrinse, gel and varnish effective for caries prevention in children?

The selection of a professionally-applied topical fluoride intervention should be based on three general considerations. First, the intervention should be effective in preventing dental caries. Second, it should be safe and, lastly, it should be easy to use and acceptable to the user/recipient of care. The first question addressed by this thesis is how effective the use of topical fluorides in the form of toothpaste, mouthrinse, gel and varnish for the prevention of caries in children is when compared to placebo or no treatment. The study as a whole contains information from over 66,000 children included in the trials comparing a topical fluoride intervention with a placebo or no treatment, and confirms that the use of topical fluorides is associated with a clear reduction in caries increment in both the permanent (for all forms of topical fluorides examined) and the deciduous dentition (for fluoride gels and varnishes). For the great majority of children in these trials (approximately two thirds) the topical fluoride modality they used was toothpaste, followed by mouthrinse, gel and varnish applications.

With average D(M)FS preventive fractions ranging from 24% (95% CI, 21% to 28%) for fluoride toothpaste, through 26% (95% CI, 23% to 30%) for mouthrinses and 28% (95% CI, 19% to 37%) for gels, to 46% (95% CI, 30% to 63%) for fluoride varnishes, all topical fluorides were shown to be effective. These conclusions were made on a clearer basis in placebo...
controlled trials, as indicated by the results of the 5th review in the series, which examined extensively the influence of potential sources of heterogeneity between studies across all four types of topical fluoride interventions and suggested that caries reductions are overestimated in no treatment control trials, conceivably of lesser methodological quality. Indeed, in the review which focused specifically on the effectiveness of fluoride gels, the pooled D(M)FS PF was 21% (95% CI, 14% to 28%) based exclusively on 14 placebo-controlled studies (significantly different from the 38% D(M)FS PF for the nine studies which compared the gel with a no treatment control group). The lack of significant differences between these two groups of studies in the other individual reviews is likely to be due to an insufficient volume of data for the varnish review (which included only seven studies) and the high preponderance of placebo-controlled mouthrinse trials and total preponderance of toothpaste trials in these reviews respectively. Nevertheless, when restricting the analyses to placebo-controlled trials in the varnish and mouthrinse reviews, consistently lower pooled estimates of effect were shown in comparison with their no treatment subsets.

Previous systematic reviews have concluded that there is evidence for the effectiveness of fluoride varnishes (Helfenstein and Steiner, 1994; 1994a) and fluoride gels (van Rijkom et al, 1998) in preventing dental caries. The caries reductions suggested for the permanent dentition for fluoride varnishes and gels in the systematic reviews in this study are very similar to those reported in the previous meta-analyses, in spite of substantial differences in selection criteria and methods between the reviews. The meta-analysis on the caries preventive effect of fluoride varnishes in permanent tooth surfaces (Helfenstein and Steiner, 1994) had found a 38% (95% CI, 19% to 57%) reduction in caries increment, and the meta-analysis on the caries preventive effect of fluoride gels (van Rijkom et al, 1998) reported a pooled D(M)FS estimate of a 22% (95% CI, 18% to 25%).

In terms of absolute caries reductions per year in D(M)FS increments (in populations with caries increments of around 2 D(M)FS per year), these ranged from 0.46 for fluoride gels to 0.74 for fluoride varnishes (mouthrinses 0.56, toothpaste 0.62). The magnitude of the effect of each topical fluoride was well illustrated in the reviews by presenting numbers of children needed to treat (NNT) to prevent one D(M)FS (based on the pooled D(M)FS PF and on the caries
increments in the control groups of the trials that contributed data to the meta-analysis). However, NNT may reinforce the rationale for targeting preventive care to high-risk populations leading to a failure to deal with those at lower risk in which the majority of new caries is likely to occur, and the interpretation and application of these absolute results need to be made with that caveat.

Further, based on the pooled results from all included studies comparing a topical fluoride with a placebo or no treatment, there is strong evidence of a generalizable beneficial effect of topical fluoride therapy (TFT). The random effects meta-analysis of the 133 trials combined assessing the effect of all topical fluoride modalities on the permanent dentition suggests a caries inhibiting effect of 26% on average; an approximate, though anti-conservative, interval in which at most 95% of underlying effects might lie is from 0% to 53%. There was substantial heterogeneity, but the direction of effect was consistent. The random effects meta-analysis of the five studies combined assessing the effect of topical fluorides on the deciduous dentition suggests that the use of topical fluoride applications is associated on average with a 33% (95% CI, 22% to 44%) reduction in decayed, missing and filled tooth surfaces. However, only five studies reported the effects of topical fluoride therapy on caries increment in deciduous tooth surfaces, two of these tested self applications of fluoride gel with a toothbrush and three studies tested fluoride varnish applications. It is still unclear whether the cariostatic effectiveness of topical fluoride differs in permanent and primary teeth (confidence intervals do overlap).

The conclusion that fluoride varnish, in particular, is effective for caries prevention in primary teeth may be unique (33% d(e/m)fhs PF; 95% CI, 19% to 48%), it has not been advanced in previous reviews. However, although the results are moderately consistent (I squared = 49%) (Higgins et al, 2003), the confidence intervals around the effects estimates are relatively wide, since few trials (some of lesser quality) were included in the meta-analysis. In fact, the suggestion of a substantial caries-inhibiting effect of fluoride varnish in the permanent dentition is based largely on a small number of trials that used no treatment controls. In addition, a relatively large number of fluoride varnish studies, many published in the 1990s, were excluded from the reviews due to poor methodological quality (in particular, due to absence of
randomized or quasi-randomized allocation to treatment and absence of blind outcome assessment), including those which were primarily excluded due to the use of a split-mouth design. With the increasing interest in evidence-based dentistry over the past decade, one would have hoped that more attention had been given to controlling threats to the internal validity of the clinical trials that comprise that evidence.

Whilst robust evidence is available on effectiveness (which has confirmed the relative effectiveness of topical fluorides), there was a general inability of the reviews to examine the safety of the various topical fluoride interventions, as the trials rarely provided information on adverse effects. Although disappointing, because safety issues should be important determinants in both public health decisions and individual clinical decisions regarding their use, the lack of direct evidence from topical fluoride trials on the risk of adverse effects is not totally unexpected. Randomised controlled trials are the best way to evaluate small to moderate effects of healthcare interventions, and much of the evidence for benefits from treatment comes from such studies. However, problems with using randomised trials to assess and report harms have been found in health care generally (Cuervo and Clarke, 2003). Some of these problems affect systematic reviews directly. For example, identifying harms is difficult when the delay between the intervention and the onset of side effects is long or when a cumulative exposure is necessary to trigger the harms. The lack of data on enamel fluorosis in the toothpaste trials illustrates this problem, and is likely, in part, to reflect the type of studies considered (RCTs), the age ranges of the participants in such trials (5 year olds and above), and their usual duration (2 to 3 years). Nevertheless, insufficient data from the trials on potential harms associated with toothpaste, varnishes, gels and mouthrinses is unfortunate. The selection of appropriate concentrations of fluoride in toothpaste for young children, for example, requires evaluation of how they may affect fluorosis as well as caries in young children. Gels and mouthrinses are not generally recommended for young children due to the risk of acute and chronic over ingestion respectively, and even though varnishes are generally perceived to be safe and well accepted (since relatively less fluoride needs to be applied, and in a relatively reduced time), there is still a lack of evidence on safety and unclear evidence on acceptance. Patient acceptance of the different topical fluorides was also scarcely assessed in the trials included in the reviews.
This general scarcity of reliable evidence on relevant outcomes other than caries increment on permanent teeth from experimental research makes it more difficult to weigh the benefits of topical fluorides in preventing caries against potential harms. Although other sources of evidence of harms such as observational studies might have been considered, these have problems of their own, as it is difficult to know how many people have been exposed and the susceptibility to bias is considerably greater. The reporting of adverse effects however might be improved through initiatives such as CONSORT for randomised trials, and QUOROM for reviews (Moher et al, 1999; Moher et al, 2001).

10.2.2 – Is the effect of TFT influenced by initial level of caries, background exposure to other fluoride sources, mode/setting of use, fluoride concentration and frequency of use, and the form of TFT used?

A secondary objective of this thesis was to exploit power to look at potential sources of heterogeneity between studies across all four types of topical fluoride modalities and at indirect comparisons of the different TFT types (Chapter 7). It was examined extensively whether there was any relationship between the caries-preventive effectiveness of topical fluoride therapy (compared to placebo/no treatment) and a number of factors, including initial level of caries, background exposure to extraneous fluoride sources, mode/setting of TFT use and type of topical fluoride intervention used. A significant influence of the pre-specified factors initial level of caries, mode of use, and type of topical fluoride on the prevented fraction (PF) was shown in the metaregression analyses performed. Among the other potential sources of heterogeneity investigated, a significant influence of type of control group was shown.

A constant relative increase in the PF was detected as trials involved children with higher initial D(M)FS scores. Although the magnitude of the effect of initial caries levels (baseline risk of the study population) on the PF was small, this does imply that as the caries levels of a community decline, the percentage caries reductions will decrease. It may be noted that baseline caries prevalence, traditionally considered as the most useful stratifying variable or covariable in caries trials (Downer et al, 1977), has also been used in the pre-selection of high risk subjects to increase the sensitivity of caries trials for decades (Downer and Mitropoulos, 1984; Burchell et
al, 1991). The complete reporting of these data in virtually all trials made it possible to investigate the influence of baseline caries on the size of treatment effect reliably across all topical fluorides. However, although the indication of a lower caries reduction at lower levels of caries prevalence with the use of TFT may also represent the marginal percent reduction added to existing fluoride sources, estimates that have emerged with this regard from this investigation are at best approximate, since such data (on background exposure to other fluoride sources) were not fully and consistently reported in all the trials (except for water fluoridation). A clear relationship between background exposure to other fluoride sources and the magnitude of the treatment effect could not be detected in any of the reviews. Although this may have been partly influenced by potential misclassification, especially due to the incomplete reporting of data on exposure to fluorides other than water (forcing a number of assumptions to classify the use of toothpaste, for example), the lack of association between background exposure to water fluoridation and treatment effect, based on analysis including 116 trials (20 of which were in fluoridated areas), implies that estimates of treatment effect were similar between trials conducted in fluoridated and non-fluoridated areas.

There was a significant decrease in the PF with the unsupervised home use of self applied topical fluoride interventions (basically toothpaste) compared with self applied supervised and with operator-applied use in the adjusted metaregression analysis. In addition, the effect of self applied supervised use of TFT appeared to be greater than that of operator-applied and unsupervised home use of TFT. These differences in treatment effect between trials of supervised use and both unsupervised use and operator-applied use are perhaps unsurprising. They are likely to reflect the more intensive use of topical fluoride interventions under supervised schemes. As regards the suggested greater treatment effect with increased frequency and intensity of topical fluoride application across topical fluoride treatments, this had been indicated in most of the component reviews and should probably be more relevant in the context of each, as discussed later in this section.

Treatment effects estimates from the trials that employed a no treatment control group were on average 14% more beneficial than from those with a placebo control group. The strong evidence on differences in effect estimates by type of control group shown in the 'summary' review
(which included 116 placebo-controlled comparisons and 17 no-treatment control comparisons in the analysis) had been clearly indicated in the fluoride gel review (which included 14 placebo-controlled studies and nine no-treatment control studies). As pointed out before, the lack of significant differences between these two groups of studies in the other reviews may be explained by an insufficient volume of data for the varnish review (which included only seven studies) and the high preponderance of placebo-controlled mouthrinse trials and a total preponderance of toothpaste trials in these separate reviews. Nevertheless, when restricting the analyses to placebo-controlled trials in the varnish and mouthrinse reviews, consistently lower pooled estimates of effect were shown in comparisons with their no treatment subsets. This invigorates the discussion of the influence of study methods on effect estimates. Blind assessment of outcome was an inclusion criterion used across all reviews but clearly participants could not have been blinded in trials with no treatment controls. Although it is unclear why this should have been associated with differences in outcome in these particular circumstances, type of control group can be considered a useful 'proxy' for the use or not of double-blinding in included studies, a key methodological feature that may represent the best indicator of study quality in these reviews. Previous research has shown that lack of double-blinding is associated on average with larger treatment effects (Schulz et al, 1995). With regard to the key quality domain of allocation concealment, no association with treatment effect could be demonstrated for this in any of the reviews, possibly due to the fact that the randomization process was poorly described in the studies included and information on this aspect could only rarely be obtained from trialists.

Most of the potential sources of heterogeneity were formally examined in the individual reviews of topical fluorides (Chapters 3 to 6). As pointed out before, none of the reviews found a significant association between treatment effect and exposure to fluorides from other sources. Higher preventive fractions were significantly associated with higher initial levels of caries, higher fluoride concentration and supervised toothbrushing in the fluoride toothpaste review, and a significant effect of type of control group was indicated in the fluoride gel review. There was also some evidence that frequency of use and/or fluoride concentration were associated with a greater PF with fluoride gel, fluoride toothpaste, and fluoride mouthrinse, in each relevant review. It should be noted, however, that in a few multiarm studies investigating combinations
of concentrations-frequencies or testing two fluoride concentrations of the same TFT type, these values were averaged over fluoride treatment groups to combine study results, a decision that may have slightly affected these particular investigations of heterogeneity. Although metaregression analyses including a large number of trials, like in the toothpaste review (and in the mouthrinse and gel reviews to some extent), had sufficient power to detect such relationships, more robust investigations of these aspects of the interventions require direct, head to head comparisons of different fluoride concentrations and frequencies of application for each relevant TFT, which were not within the scope of this thesis.

A significant influence of type of topical fluoride on the prevented fraction was shown from adjusted indirect comparisons of all four TFT types (Chapter 7). Results suggested no significant differences in treatment effects between fluoride gel, mouthrinse and toothpaste, but significantly lower D(M)FS prevented fractions for fluoride gel, mouthrinse or toothpaste in comparison with fluoride varnish. However, relatively few fluoride varnish trials were included and very few among these were placebo-controlled trials, making it difficult to rule out the possibility of an overestimation of the size of the differential effect (14% on average), due to the preponderance of no treatment control fluoride varnish studies of lower methodological quality. Moreover, these results should be interpreted with caution since the investigation of differences between subgroups is effectively a non-randomized comparison, and is prone to all the difficulties in inferring causality in observational studies. Nevertheless, the adjusted indirect comparisons had the advantage that other possible explanations for heterogeneity in different trials, including prognostic factors of participants (such as baseline caries levels and background exposure to fluorides), intervention and actual trial characteristics, could be partially taken into account. Another advantage was that uncertainty could be incorporated in the analyses’ results by providing wider confidence intervals.

Although visual inspection of the funnel plots in the individual reviews (Chapters 3 to 6) and in the ‘summary’ review (Chapter 7) may suggest a degree of asymmetry, the Egger formal test for asymmetry (1997) provided no evidence of a significant relationship between trial size and effect estimate. Publication bias is usually reported to result in a lower probability of publication of small studies with negative effects, and there is no evidence that the smaller studies in the
meta-analyses of D(M)FS PFs tend to show larger treatment effects. It should be noted however that although no clear relationship between prevented fraction and precision could be observed in the funnel plot of the seven studies in the meta-analysis of fluoride varnishes, power is limited when only a few trials are included.

10.2.3 – Are there differences in the effects of the various forms of TFT either used singly or in combination with each other?

The main question addressed by the 6th review in this thesis (Chapter 8) is how effective the use of one type of topical fluoride therapy (TFT) for the prevention of caries in children is compared to another. The 15 studies included in the meta-analyses in this review covered nearly all the range of direct head to head comparisons of possible practical value between fluoride toothpastes, mouthrinses, gels and varnishes. Yet, there is a relatively small number of trials in each main comparison/meta-analysis. The randomized evidence that was brought together is, as far as one can ensure, the totality of the available randomized evidence comparing the relevant topical fluoride modalities directly. There is a general lack of statistical significance for virtually all meta-analyses’ results in this review. Further, for the great majority of comparisons, the confidence intervals are relatively wide and the variation among the results of the studies can be substantial. This calls for a cautious interpretation of the data.

Thus, based on the results from the single trial comparing professionally-applied fluoride varnish and gel directly, there is insufficient evidence to confirm or refute a differential effect in caries reduction between these two interventions (analysis of this trial showed a non-significant effect in favour of fluoride varnish and a wide confidence interval for the estimate of effect).

The question of whether there was a beneficial effect from the use of fluoride mouthrinses compared with professionally-applied TFTs (varnishes or gels) is addressed exclusively by the meta-analysis of five trials of fluoride mouthrinse versus varnish (the only comparison of fluoride gel and mouthrinse available, involved self-application of fluoride gel, and showed a non-significant effect in favour of fluoride mouthrinse, and a wide confidence interval for the estimate of effect). Although the random effects meta-analysis of the five trials produced a non-
significant result (of small magnitude) in favour of varnishes, when the analysis was restricted to
the subset of two double-blind trials (both cluster randomized trials comparing the same fluoride
varnish product used semi-annually with the same fluoride mouthrinse used fortnightly), the
difference in effect was reverted in favour of mouthrinses, but still not statistically significant.

It is interesting to compare these results with those of Strohmenger and Brambilla (2001). The
authors carried a systematic review on the anti-caries efficacy of fluoride varnishes using a
different and restrictive set of inclusion criteria, which resulted in the analysis of only three
studies. All three of these studies were comparisons of fluoride varnishes with fortnightly
fluoride mouthrinses at school, and were included in the present study. Again, although the
pooled estimate of the treatment effect in the meta-analyses by Strohmenger and Brambilla
favoured fluoride varnish, the results were not statistically significant.

The final objective of the review was a comparison between fluoride toothpastes and any other
modality of TFT (mouthrinses, gels or varnishes). Results for the separate subsets and for all the
data combined comparing toothpaste with either gel or mouthrinse are consistent with no
evidence of an important differential effect (relevant comparisons with useable data of fluoride
toothpaste and varnish were lacking).

These results, based on head to head comparisons, are generally in line with those from the
adjusted indirect comparisons, although significantly lower D(M)FS prevented fractions for
fluoride gel, mouthrinse or toothpaste in comparison with fluoride varnish were shown in the
adjusted analyses. Empirical evidence indicates that in most cases results of adjusted indirect
comparisons are not significantly different from those from direct comparisons (Song et al,
2003), and when direct evidence is available but insufficient, the adjusted indirect comparison
may provide supplementary information (Higgins and Whitehead, 1996). With new methods
being developed to formally combine data from direct and indirect evidence (Higgins, personal
communication), these could usefully strengthen conclusions based on the pooled results from
the direct comparisons in future updates of the Cochrane reviews (especially since there are
concerns about the methodological quality of a few fluoride varnish trials).
The main question addressed by the last review in this thesis (Chapter 9) is how effective the simultaneous use of combined topical fluoride therapy (TFT) for the prevention of caries in children is compared to one topical fluoride treatment used alone. The 11 studies included in the seven meta-analyses (or in the nine comparisons) have not tested all combinations of possible practical value, and there is a small number of trials in each relevant comparison/meta-analysis. Again, the randomized evidence brought together is likely to be the totality of the available randomized evidence comparing the combined use of any two topical fluoride modalities with one of them used alone. Although there is a suggestion of a modest caries inhibiting effect with the combined use of topical fluorides in the permanent dentition for most of the comparisons, a general lack of statistical significance is apparent. This calls for a cautious interpretation of the data.

Thus, for the primary objective of the review, there is evidence showing that simultaneous use of a topical fluoride treatment with fluoride toothpaste results in an enhanced caries inhibiting effect compared with the use of toothpaste alone. Over 4000 children were included in the trials, and for the majority of children the combined topical fluoride regimen they used at the same time was toothpaste and mouthrinse, followed by toothpaste and gel, and toothpaste and varnish. The random effects meta-analysis of the nine studies assessing the effect of fluoride mouthrinses, gels or varnishes used in combination with fluoride toothpaste on the permanent dentition suggests that their combined use is associated on average with a 10% (95% CI, 2% to 17%) reduction in decayed, missing and filled tooth surfaces. It may be noted that whilst there is evidence that additional caries protection accrues from their combined use, the size of the estimated benefit, of the order of 10%, is not substantial. Further, in populations with a caries increment of 2.5 D(M)FS per year (at the highest range of the results seen in the included studies), this implies an absolute caries reduction of 0.25 D(M)FS per year. At lower levels of caries in children using fluoride toothpaste, the preventiveness of combinations of fluorides is even lower. There was only one trial assessing the effect of the combined use of topical fluorides with toothpaste on the deciduous dentition. This compared varnish plus toothpaste versus toothpaste alone and suggests a 15% reduction in decayed and filled tooth surfaces in favour of the combined therapy, but it is unclear whether the effect was significant.
To what extent statistically significant caries reductions in the order of 10% should be considered important? Some authorities have advocated the use of arbitrary thresholds that indirectly define clinical significance for anticaries products. For example, the American Dental Association produced guidelines proposing that a toothpaste cannot be claimed to be superior to another unless it provides a 10% difference in effect (just the size of the difference for the simultaneous use of TFT and fluoride toothpaste in this review) (CDT, 1988). The trials in a review may give a power calculation that specifies the size of effect the trialists considered being important, which may be preferred to the use of arbitrary thresholds. In this review this was provided in the trial by Blinkhorn et al (1983), which had an 80% power to detect a 25% difference between the combined TFT group (toothpaste and mouthrinse in this trial) and the fluoride toothpaste group. Taking this as the clinically important difference indicates that the combined use of toothpaste with other TFTs had no greater effect than toothpaste used alone.

A secondary objective of the review was to examine whether there was a beneficial effect in terms of caries prevention from the addition of each TFT modality to toothpaste separately compared to toothpaste alone or from the combined use of any other two TFT modalities separately compared to one of them alone. A differential effect could only be detected from two of the seven available comparisons. However, the evidence from one single small trial, which was not carried out double-blind, of a significant differential effect in caries reduction favouring the combined use of fluoride varnish and toothpaste over toothpaste alone should be viewed with caution, as this is far from definite. Further, there is evidence of an increased benefit with the use of fluoride gel and mouthrinse compared to fluoride gel alone, and no suggestion of a significant beneficial effect with the use of fluoride mouthrinse and gel compared to mouthrinse alone. This finding may in fact indirectly suggest that larger caries reductions may be achieved with fluoride mouthrinse used singly, as opposed to the single use of fluoride gel.

As was generally the case for all other reviews in this thesis, we found no useful information in the trials included in these last two reviews about potential adverse effects. However, if children are allocated to fluoride toothpaste they appear to be more likely to stay in the study than if they are given single alternative forms of topical fluoride therapy.
Finally, it should be pointed out that when two methods of applying topical fluoride are already in use in a population, additional benefits may, indeed, be small, especially when the measures act identically or by similar mechanisms (it is conceivable that the combined effect is not proportionally larger than that of one or the other measure alone). Thus, even with additional caries protection accruing from some of the combined preventive regimens, the additional cariostatic effect may be slight and not worth the extra effort with the use of a second intervention.

10.3 – Further methodological considerations

The findings of the present study should be considered in relation to its methodological strengths and weaknesses, many of which have already been highlighted.

This study is an improvement on most previous systematic reviews on the effectiveness of topical fluorides for three main reasons. First, essentially identical methodological approaches have been used to conduct every review in this thesis. One of the advantages of the preparation of a series of reviews on the effects of topical fluorides in this manner, beyond the ability to bring all the evidence together in a consistent way, is that the various interventions can be sensibly compared with each other as similar methodology and outcome measures have been used throughout, and results are not interpreted in isolation. Second, the attempt to identify all (or nearly all) of the relevant trials with a comprehensive search strategy (covering at least 13 databases) meant that as much as possible of the randomized evidence was considered in both the qualitative and quantitative analyses in order to minimise bias and improve precision and generalisability. It also meant that because a sufficiently large number of studies of acceptable quality were considered, the use of a powerful extension of meta-analyses, univariate and multivariate metaregression analyses, could be generally performed to investigate the separate and simultaneous effects of several important covariates on treatment effect. Third, being prepared and published as Cochrane reviews ensures per se methodological rigour in the process, and the unique advantage that one can be confident in having access to reliable evidence that will be updated regularly as new evidence emerges and in response to comments and criticisms.
The study does have limitations. One obvious weakness of the study relates to the inability to independently assess inclusion criteria and perform all data extraction from all studies in duplicate. Due to the considerable amount of data involved, such step proved very difficult in practical terms. However, approximately one third of studies in the various reviews were independently selected, data extracted and quality assessed in duplicate, and although checking of interobserver reliability was limited to validity assessments, agreement between reviewers was good. In addition, any study that could not be classified by the first reviewer or that posed doubts during quality assessment or data extraction was independently assessed by a second reviewer (and a third reviewer was consulted where necessary to resolve any uncertainty). Moreover, one should not forget that because Cochrane reviews are frequently updated, it is possible that data extraction is performed in duplicate in the future.

Another possible weakness of the study relates to the absence of a consumer’s perspective centred around the appropriate interpretation of results and conclusions drawn from the reviews (and indeed on the selection of relevant outcomes, had the general lack of outcome measures other than caries increment not represented an inherent limitation). Members of the review team, advisory panel and in the external peer review process for the Cochrane reviews have been selected because of their knowledge in the field and because of their previous experience with clinical trials and/or systematic reviews. In order to make the study more open to relevant views, there is the approach to encourage the use of the ‘comments and criticisms’ function for Cochrane reviews, which is, nevertheless, a later possibility to accommodate a greater diversity of relevant views.

A set of *a priori* rules to choose the primary outcome data for analysis from each study meant that some important data that had actually been coded had to be given a lower priority. For example, data for 'all surface types combined' were chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' were chosen over data for 'erupted' or 'erupting' teeth only, and so on. In the context of the toothpaste review in particular, it can be argued that data on ‘teeth erupting only’ are given low priority, as these data might provide insight into the ‘real life’ effect of fluoride toothpastes which are used, in the main, during the
time the dentitions are erupting. In order to answer the main questions of the thesis as objectively as possible these data were not analysed separately (in general, data on the state of tooth eruption considered in the trials were not clearly specified in many trials). Nevertheless, extended analyses of relevant specific data sets, where these are reliably reported, can still be considered in future updates of the Cochrane reviews.

Finally, one should not forget that associations between the various sources of heterogeneity investigated and treatment effects are subject to the potential biases of observational studies. Confounding could thus exist between the factors investigated and other characteristics of the trials (such as the characteristics of participants or interventions). Therefore, even though an unusually large number of studies were included in most analyses, all metaregression results should be interpreted with a degree of caution given the observational nature of the comparisons and the large number of comparisons made, and, of course, no causal inferences should be made.

10.4 – Conclusions

The main conclusions of the present study with implications for practice and research are now briefly outlined:

• The benefits of fluoride toothpastes are firmly established. Taken together, the trials are of relatively high quality, and provide clear evidence that fluoride toothpastes are efficacious in preventing caries. Regular toothbrushing with a fluoride toothpaste reduces the incidence of dental caries in children by about 24% (95% CI, 21% to 28%). The effect of fluoride toothpaste increased with higher baseline levels of D(M)FS, higher fluoride concentration, and supervised brushing, but was not influenced by exposure to water fluoridation. Based on the direct evidence from clinical trials, the review was unable to reach any conclusion about any effects that fluoride toothpastes might have on fluorosis (data on fluorosis was not recorded in the trials). Further research to identify the appropriate concentrations of fluoride in toothpaste for pre-school children must include assessments of potential benefits and harms, as young children often ingest toothpaste during toothbrushing.
- Supervised regular use of fluoride mouthrinse at two main strengths and rinsing frequencies is associated with a clear reduction in caries increment in children (26% D(M)FS PF; 95% CI, 23% to 30%). Based on the direct evidence from clinical trials, the review does not provide useful information on the likelihood of significant side effects with the use of fluoride mouthrinse, and inconclusive information on acceptability. Further research is needed on adverse effects and acceptability of mouthrinses.

- There is clear evidence of a caries-inhibiting effect of fluoride gel. The best estimate of the magnitude of this effect, based on the 14 placebo-controlled trials, is a 21% reduction (95% CI, 14% to 28%) in D(M)FS. Further research is needed to identify and quantify potential harmful effects and acceptability of fluoride gels.

- A substantial caries-inhibiting effect of fluoride varnish in both the permanent (46% D(M)FS PF; 95% CI, 30% to 63%) and the deciduous dentitions (33% d(e/m)fs PF; 95% CI, 19% to 48%) is suggested, based largely on trials with no treatment controls. Given the relatively poor quality of most of the included studies and the wide confidence intervals around the estimates of effect, there remains a need for further trials. It is important that these trials should be of high quality and include assessments of potential adverse effects and acceptability.

- There is strong evidence of a generalizable beneficial effect of topical fluoride therapy (TFT). A caries inhibiting effect of 26% on average is suggested based on a sizeable body of evidence from randomized controlled trials. There was substantial heterogeneity, confirmed statistically, but the direction of effect was consistent. D(M)FS PF was on average 14% (95% CI, 5% to 23%) higher in non-placebo controlled trials, 14% (95% CI, 2% to 26%) higher in fluoride varnish trials compared with all others, and - 10% (95% CI, -17% to -3%) lower in trials of unsupervised home use compared with self applied supervised and operator-applied. There was a 0.7% increase in the PF per unit increase in baseline caries (95% CI, 0.2% to 1.2%), but the effect was not influenced by exposure to water fluoridation or other fluoride sources. While the formal examination of sources of heterogeneity between studies has been important in the overall conclusions reached, these should be interpreted with caution. The
evaluation of possible differences in effect associated to topical fluoride application features, such as application frequency or fluoride concentration, should be based on trials that directly address the comparison of such features. No definite conclusions about any adverse effects that might result from the use of topical fluorides could be reached, because data reported in the trials are scarce.

- Few trials are included in each main comparison/meta-analysis estimating the effects of competing topical fluoride interventions. Fluoride toothpastes in comparison to mouthrinses or gels appear to have a similar degree of effectiveness for the prevention of dental caries in children. There is no clear suggestion that fluoride varnish is more effective than mouthrinses from the direct comparisons in the meta-analysis, and the evidence for the comparative effectiveness of fluoride varnishes and gels, and mouthrinses and gels is inconclusive. No conclusions about adverse effects could be reached, because no data were reported on in the trials. Acceptance is likely to be greater for fluoride toothpaste. Taking the available results from indirect evidence into account as well, there may be a suggestion for the performance of additional larger studies of higher methodological quality to determine whether fluoride varnishes are more effective in caries prevention than other topical fluorides. Such trials should include assessments of potential adverse effects and acceptability.

- There is a general lack of randomized trial evidence evaluating the use of different combinations of topical fluorides for the prevention of dental caries in children, and, therefore, a modest treatment effect may have been missed for most relevant comparisons available. Fluoride mouthrinses, gels, or varnishes used in addition to fluoride toothpaste achieve a 10% average reduction in caries compared to toothpaste used alone. Not all other combinations of possible practical value were tested in the trials and no other combinations of TFT were consistently superior to a single TFT. The only other significant result was in favour of the combined use of fluoride gel and mouthrinse in comparison to gel alone, based on two trials only. No conclusions about any adverse effects could be reached, because data are scarcely reported in the trials. The lack of a clear suggestion of significant benefits from the data analysed in the majority of the comparisons may not indicate priority for the performance of new studies.
10.5 – Dissemination of findings

Thus far the findings of the first systematic review that was published in 2002 in The Cochrane Database of Systematic Reviews (CDSR) – Fluoride gels for preventing dental caries in children and adolescents – have been presented at a Conference in Brazil:

- Marinho, V. An introduction to Evidence-Based Dentistry. 2nd Annual Oral Health Promotion Seminar, Axelsson Center, São Paulo, Brazil – 26 April 2002.

There are five reviews published in The Cochrane Library (CDSR) and two reviews, the 6th and the 7th, going through external peer review to be published in Issue 1, 2004. Citation details for all reviews and protocols published in the Cochrane Library, Issue 4, 2003 are as follows:

Published Reviews (The Cochrane Library, Issue 4, 2003):

Published Protocols (The Cochrane Library, Issue 4, 2003):


There is one paper from the systematic review on the effectiveness of fluoride gels:


There is one book chapter (book in press) where the findings of the four individual Cochrane reviews on the effects of fluoride gels, varnishes, mouthrinses and toothpastes are reported and discussed:


Discussions on which Journal(s) to publish the series of reviews and on the best approaches to achieve this effectively are currently taking place.
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APPENDIX A

Electronic Searches

A.1- Search strategy used to retrieve reviews/meta-analyses

A.2- Cochrane Optimal Search Strategy for Randomized Controlled Trials (RCTs)

A.3- Search phrases used according to database searched in the preliminary stage (1997)

A.4- Search phrases used according to database searched from 1998 onwards
Appendix A. Section 1: MEDLINE search strategy for reviews/meta-analyses
(using Silverplatter software)

SilverPlatterASCII 3.0DOS
Selected Databases
(explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPICAL/ ALL SUBHEADINGS) or (FLUOR*)
(explode "DENTAL-CARIES" / ALL SUBHEADINGS) or (CARI*) or (explode "DMF INDEX" / ALL SUBHEADINGS) or (DMF*)
(explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*)
(TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
#2 or #3
#1 and #5
#6 not #4
REVIEW-ACADEMIC in PT
REVIEW-TUTORIAL in PT
META-ANALYSIS in PT
SYSTEMATIC* near REVIEW*
SYSTEMATIC* near OVERVIEW*
METAANALI* or META ANALI*
METAANALY* or META ANALY*
METANALY*
METANALI*
#8 or #9
#17 and #7
#10 or #11 or #12 or #13 or #14 or #15 or #16
#19 and #7

115
Appendix A. Section 2: Search strategy for RCTs

[(TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))] = #6
[#5 (subject search) not #6]
RANDOMIZED-CONTROLLED-TRIAL in PT
CONTROLLED-CLINICAL-TRIAL in PT
RANDOMIZED-CONTROLLED-TRIALS
RANDOM-ALLOCATION/ ALL SUBHEADINGS
DOUBLE-BLIND-METHOD/ALL SUBHEADINGS
SINGLE-BLIND-METHOD
#8 or #9 or #10 or #11 or #12 or #13
#7 and #14
CLINICAL-TRIAL in PT
explode CLINICAL-TRIALS/ all subheadings
(CLIN* near TRIAL*) in TI
(CLIN* near TRIAL*) in AB
((SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*)) in TI
((SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*)) in AB
PLACEBOS
PLACEBO* in TI
PLACEBO* in AB
RANDOM* in TI
RANDOM* in AB
RESEARCH-DESIGN/ ALL SUBHEADINGS
#16 or #17 or #18 or #19
#20 or #21 or #22 or #23 or #24
#25 or #26 or #27
#28 or #29 or #30
#7 and #31
TG=COMPARATIVE-STUDY
explode EVALUATION-STUDIES/ all subheadings
FOLLOW-UP-STUDIES
PROSPECTIVE-STUDIES
(CONTROL* or PROSPECTIVE* or VOLUNTEER*) in TI
(CONTROL* or PROSPECTIVE* or VOLUNTEER*) in AB
#33 or #34 or #35 or #36 or #37 or #38
#7 and #39
Appendix A. Section 3: Subject search phrases and modified methodological filters according to database searched in 1997 (all databases searched from date of inception)

**MEDLINE** - searched (from 1966 to 1997) using two overlapping but complementary subject search phrases (which included 'free text' and 'controlled vocabulary' terms):

(a) \[(["DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS" all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or DMF*) and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR SMFP OR MFP OR MONOFLUOR*) or ("CARIOSTATIC-AGENTS" explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or "DENTIFRICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or CARIOSTA* or PROPHYLA* or ANTICARI* or ANTI CARI* or VARNISH* or LACQUER* or DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRIC* or MOUTHMRINS* or MOUTH RINS* or RINS* or MOUTHWASH* or MOUTH WASH*)].

(b) \[([(explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPOCAL/ ALL SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT)) and ((CARI*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT* in TI, in AB, in MESH)) or (explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or (explode MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or (MOUTHMRINS* or MOUTH RINS*) or (VARNISH* or LACQUER*)].

**EMBASE** - searched (from 1980 to 1997) using two overlapping but complementary subject search phrases (which included 'free text' and 'controlled vocabulary' terms):

(a) \[(((dental caries in thesaurus) or (tooth disease in thesaurus - all subheadings) or (tooth infection in thesaurus - all subheadings) or (tooth pain in thesaurus - all subheadings) or (cari* or dmf*)) and (((fluoride in thesaurus) or (fluoride varnish in thesaurus) or (acidulated fluorophosphate in thesaurus) or (fluoride sodium in thesaurus) or (fluor*) or (amf) or (amine f) or (snf2) or (stannous f) or (naf) or (sodium f) or (smfp) or (mfp) or (monofluor*) or (duraphat*)) or (anticaries agent in thesaurus) or (preventive dentistry in thesaurus - all subheadings) or (caries prevention in thesaurus) or (fluoridation in thesaurus) or (mouth hygiene in thesaurus) or (tooth brushing in thesaurus) or (toothpaste in thesaurus) or (cariosta*) or (prophyla*) or (anticari*) or (anti cari*) or (gel*) or (varnish*) or (preventive dentistry in thesaurus) or (caries prevention in thesaurus) or (fluoridation in thesaurus) or (mouth hygiene in thesaurus) or (tooth brushing in thesaurus) or (toothpaste in thesaurus) or (cariosta*) or (prophyla*) or (anticari*) or (anti cari*) or (gel*) or (varnish*) or]
(lacquer*) or (dentifric*) or (toothpaste*) or (tooth paste*) or (mouthrins*) or (mouth rins*) or (rins*) or (mouthwash*) or (mouth wash*)])

(b) [((fluoride in thesaurus) or (fluoride sodium in thesaurus) or (fluor*) or (amf) or (amine f) or (snf2) or (stannous f) or (naf) or (sodium f) or (smfp) or (mfp) or (monofluor*) or (duraphat*)) and (((dental caries in thesaurus) or (tooth disease in thesaurus - all subheadings) or (tooth infection in thesaurus - all subheadings) or (tooth pain in thesaurus - all subheadings) or (cari*) or (dmf*) or (tooth*) or (teeth*) or (dent*)) or ((anticaries agent in thesaurus) or (preventive dentistry in thesaurus - all subheadings) or (caries prevention in thesaurus) or (fluoridation in thesaurus) or (mouth hygiene in thesaurus) or (tooth brushing in thesaurus) or (toothpaste in thesaurus) or (anticari*) or (anti cari*) or (mouthrins*) or (mouth rins*) or (mouthwash*) or (mouth wash*)))].

These phrases were combined with the following methodological filter for RCTs (which included 'controlled vocabulary' and 'free text' terms):
[(random*) or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask*)) or (clinical trial in thesaurus - all subheadings) or (controlled study in thesaurus - all subheadings) or (drug comparison in thesaurus - all subheadings) or (placebo in thesaurus - all subheadings) or (clin* trial*) or (control* trial*) or (control* stud*) or (placebo*) or (comparison in thesaurus) or (comparati* or evaluati* or volunteer*)].

BIOSIS (Biological Abstracts) – searched (from 1982 to 1997) using a subject search phrase which included ‘free text’ terms only:
[(fluor* or ppmf or ppm f or amf or amine f or snf2 or stannous f or naf or sodium f or apf or smfp or mfp or monofluor* or duraphat*) and (cari* or dmf* or tooth* or teeth* or dent* or prevent* or anticari* or anti cari* or mouthwash* or mouth wash* or mouthrins* or mouth rins* or lacquer* or varnish*)].

This was combined with the following methodological filter:
[(random*) or (clin* trial*) or ((singl* or doubl* or tripl* or trebl*) and (blind*, mask*)) or (placebo*) or (control* trial*)].

SCI (Science Citation Index) – searched (from 1981 to 1997) using the same subject search phrase described for BIOSIS:
[(fluor* or ppmf or ppm f or amf or amine f or snf2 or stannous f or naf or sodium f or apf or smfp or mfp or monofluor* or duraphat*) and (cari* or dmf* or tooth* or teeth* or dent* or prevent* or anticari* or anti cari* or mouthwash* or mouth wash* or mouthrins* or mouth rins* or lacquer* or varnish*)].

This was combined with the following methodological filter:
[random* or blind* or mask* or (clin* and trial*) or (control* and trial*) or placebo*].

SSCI (Social Science Citation Index) and ISTP (Index to Scientific and Technical Proceedings) - both also searched (from 1981 to 1997 and from 1982 to 1997 respectively) using the same subject search phrase described for BIOSIS, without a methodological filter.

DISSERTATION ABSTRACTS - searched (from 1981 to 1997) using the subject search phrase (which included ‘free text’ and ‘controlled vocabulary’ terms):

[((FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT)) and ((explode "HEALTH-SCIENCES,-DENTISTRY") or (explode "HEALTH-SCIENCES,-PUBLIC-HEALTH") or (CARI*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT*)or PREVENT* or (ANTICARI* or ANTI CARI*) OR (MOUTHWASH* OR MOUTH WASH*) OR (MOUTHRINS* OR MOUTH RINS*) OR (VARNISH* OR LACQUER*))].

This was combined with the following methodological filter for RCTs:

[[CLIN* and TRIAL*) or (CONTROL* and TRIAL*) or (RANDOM*) or (PLACEBO*) or (BLIND*) or (MASK*) or (PROSPECTIV* or VOLUNTEER* or COMPARATIV*) or ( FOLLOW-UP*)].

CINAHL - searched (from 1982 to 1997) using subject search phrase only (which included ‘free text’ and ‘controlled vocabulary’ terms):

[((explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPOCAL/ ALL SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT)) and (explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or (explode MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or (MOUTHRINS* or MOUTH RINS*) or (VARNISH* or LACQUER*) or (CARI*) or (DMF*) or (TOOTH*) or
(TEETH*) or (DENT*) or (explode "PREVENTIVE-DENTISTRY"/ all subheadings or "PREVENTIVE-TRIALS"/ all subheadings or explode "CENTERS-FOR-DISEASE-CONTROL-AND-PREVENTION-(U.S.)"/ all subheadings or "PREVENTIVE-HEALTH-CARE"))

ERIC - searched (from 1966 to 1996) using subject search phrase only (which included ‘free text’ and ‘controlled vocabulary’ terms):
[((FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT)) and ((explode "DENTAL-EVALUATION") or (explode "DENTAL-ASSISTANTS") or (explode "DENTISTRY") or (explode "DENTAL-CLINICS") or (explode "DENTAL-HEALTH") or (explode "DENTAL-HYGIENISTS") or (explode "DENTAL-TECHNICIANS") or (explode "DENTAL-SCHOOLS") or (explode "DENTAL-STUDENTS") or (explode "DENTISTS") or (explode "HEALTH-PROMOTION") or (explode "PREVENTION") or (explode "PREVENTIVE-MEDICINE") or (explode "EFFECT-SIZE") or (explode "COST-EFFECTIVENESS") or (explode "COST-EFFECTIVENESS") or (explode "ECONOMIC-IMPACT") or (explode "EFFICIENCY") or explode "PUBLIC-HEALTH" or (CARI*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT*) or PREVENT* or (ANTICARI* or ANTI CARI*) OR (MOUTHWASH* OR MOUTH WASH*) OR (MOUTH RINS*) OR (VARNISH* OR LACQUER*))].

LILACS/BBO (Latin American and Caribbean Health Sciences Literature/ Brazilian Bibliography of Dentistry) – searched (from 1982 to 1997) using the subject search phrase (‘free text’ subject terms only):
[(fluor* or ppmf or ppm f or amf or snf2 or naf or apf or mfp or monofluor* or duraphat*) and (carie* or dmf* or cpo* or tooth* or teeth* or dent* or anticari* or cario* or (mouthrins*) or (mouth rins*) or (mouthwash*) or (mouth wash* or bochecho* or enjuagatorio* or varnish* or verniz*)].

This was combined with a methodological filter for RCTs:
[random* or aleatori* or acaso* or azar* or blind* or mask* or cego* or cega* or ciego* or placebo* or ((clinical* or clinico*) and (trial* or ensaio* or stud*)) or ((control*) and (trial* or ensaio* or estud*))].
Appendix A. Section 4: Search phrases according to database searched from 1998 to 2000
(databases searched from date of inception)

LILACS/BBO – searched in 1999 (from 1982 to 1998) using subject search terms from the previous
search and additional subject search terms (‘free text’ only), combined with a methodological filter
for RCTs:
[(fluor$ or ppmf or ppm f or amf or snf or naf or apf or mfp or smfp or monofluor$ or duraphat$) and
(caric$ or dmf$ or cpo$ or tooth$ or teeth$ or dent$ or dient$ or anticarie$ or cario$ or mouthrin$ or
mouth rin$ or rinse$ or bochech$ or enjuag$ or verniz$ or varnish$ or barniz$ or laca$ or gel or
gels) and [random$ or aleator$ or acaso$ or azar$ or blind$ or mask$ or cego$ or cega$ or ciego$ or
ciego$ or placebo$ or (clinical$ and (trial$ or ensaio$ or estud$)) or (control$ and (trial$ or ensaio$ or
estud$))].

MEDLINE – searched (from 1966 to January 2000) using four supplementary subject search phrases
(including ‘free text’ and ‘controlled vocabulary’ terms), formulated around three concepts each (the
relevant topical fluoride therapy (TFT), fluoride and caries), and without methodological filters:
[(CARIE* or (DENT* near CAVIT*) or TOOTH* DECAY* or DMF* or (explode "DENTAL-
CARIES"/ ALL SUBHEADINGS)) and (FLUOR* or APF* or NAF* or AMINE F OR SNF* or
ACIDULATED* PHOSPHATE* FLUORID* or ACIDULATED* FLUORID* or PHOSPHATE*
FLUORID* or SODIUM* FLUORID* or AMINE* FLUORID* or STANNOUS* FLUORID* or
(explode "FLUORIDES"/ ALL SUBHEADINGS))
and
(1) (TOOTHPASTE* or TOOTH* PASTE* or DENTIFRICE* or PASTE*) or (explode
"DENTIFRICES"/ all subheadings)).
(2) ((RINS* or MOUTH* RINS* or WASH* or MOUTH* WASH*) or (MOUTH RINS* or
MOUTH WASH*)) or (explode "MOUTHWASHES"/ all subheadings)).
(3) (FLUOR* or ...or ELMEX* or (explode "FLUORIDES"/ ALL SUBHEADINGS))
and (GEL* or TRAY*).
(4) (FLUOR* or (DURAPHAT* or FLUOR PROTECTOR*) or (explode "FLUORIDES"/ ALL
SUBHEADINGS)) and (VARNISH*) or (LACQUER* or LAQUER*) or (VERNIZ*) or
(LACKER*) or (LAKK*) or (SILANE* or POLYURETHANE*)].
APPENDIX B

Recruitment of Panel of Consultants

B.1- First standard letter

B.2- Second standard letter
Appendix B. Section 1: First standard letter sent to advisory panel members

Professor Ken Stephen
Department of Adult Dental Care
University of Glasgow Dental School
378 Sauchiehall Street
Glasgow G2 3JZ, UK

London, 2nd December 1996

Dear Professor Stephen,

The NHS has recently established the Systematic Reviews Training Unit (SRTU) to train health professionals in the conduct of systematic reviews.

As a trainee in the Unit, working in conjunction with Professor Aubrey Sheiham (UCL), I am undertaking a systematic review of the effect of topical fluorides on preventing caries in children and adolescents.

The protocol for the review has been developed according to the standards of the Cochrane Collaboration Handbook and CRD guidelines, and it has been accepted, by the Cochrane Oral Health Group Coordination, to be entered in the Cochrane Database of Systematic Reviews (CDSR) as a title.

At our last meeting with Dr Stuart Logan, SRTU Director, he suggested recruiting an external advisory group basically to help to fine-tune the review. I do not think the work will be very time consuming. Members of the advisory group will discuss the specific questions the review is/should be addressing, help clarify the appropriate comparisons to set up, and provide advice about the content of the report and its dissemination later in the process. In practical terms this would mean reading and commenting on the review protocol and reading an early draft of the final report. If members of the panel felt it would be useful we would
convene a meeting in London where the panel could meet with the researchers. We would be able to pay travel expenses if this was arranged.

Being very active in the field of caries-preventive clinical trials, with an invaluable contribution to the field, we would like to invite you to join the panel. Other potential contributors are Dr Ruth Holt (Eastman Dental Hospital, London) and Dr Helen Worthington (Turner Dental School, Manchester).

Hoping you will accept our invitation, I look forward to hearing from you.

With kind regards,

Yours sincerely,

Valeria Marinho
Department of Epidemiology and Public Health
University College London
1-19 Torrington Place
London WC1E 6BT
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Professor Aubrey Sheiham
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1-19 Torrington Place
London WC1E 6BT
e-mail: Valeria@public-health.ucl.ac.uk
Appendix B. Section 2: Second standard letter sent to advisory panel members

Professor Kenneth Stephen
Department of Adult Dental Care
University of Glasgow Dental School
378 Sauchiehall Street
Glasgow G2 3JZ, UK

London, 21st January 1997

Dear Professor Stephen,

Thank you very much for offering to help in the systematic review on the effectiveness of topical fluorides. We will be able to have a range of views while clarifying the relevant issues on this topic since Dr Worthington and Dr Holt have also agreed to assist.

I have attached the review aims/objectives/hypotheses and inclusion criteria for your information and comments.

As mentioned in my previous letter, we would like to discuss the main questions the review should address and set up the appropriate comparisons (with respective outcomes and categories which should be measured to determine effectiveness). We have tried to identify "effect modifiers" prior to data extraction/analysis, to set up the appropriate hypotheses/comparisons. Because this review has multiple objectives, protocol development was more complex than we had thought initially.

The inclusion criteria need to be carefully discussed as well to ensure a reliable relevance assessment. The set of possible relevant outcomes that can be used in the review were defined first based on the range of possible outcomes that have been/should have been used in primary studies (clinical trials).
I look forward to having your comments on the draft protocol.

Yours sincerely,

Valeria Marinho
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APPENDIX C

1998 Cochrane protocol and subsequent changes to it

C.1- Original Cochrane protocol published in 1998
C.2- Protocol changes
Appendix C. Section 1: First protocol published in The Cochrane Library issue 2, 1998

Cover sheet

Title
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents

Reviewers
Marinho VCC, Sheiham A, Logan S, Higgins JPT

Dates
Date edited: 11/02/1998
Date of last substantive update: 11/02/1998
Date of last minor update: //
Date next stage expected 01/11/1999
Review first published:

Contact reviewer
Mrs Valeria CC Marinho
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Secondary contact person's name: Professor Aubrey Sheiham

Intramural sources of support
CAPES - Ministry of Education, Brazil, BRAZIL

Extramural sources of support
None

What's new

Dates
Date review re-formatted: 20/07/1999
Date new studies sought but none found: //
Date new studies found but not yet included/excluded: //
Date new studies found and included/excluded: //
Date reviewers' conclusions section amended: //
Date comment/criticism added: //
Date response to comment/criticisms added: //
Background

Dental caries and its consequences pose important and uncomfortable problems in all industrialized societies and in an increasing number of developing countries. Although dental caries rates in industrialized countries have decreased dramatically in the past 2 decades (Sheiham 1991), particularly among children in North American and Western European countries (Anderson 1982; Brunelle 1982; Downer 1982; Feierskov 1982; Kalsbeek 1982; Koch 1982), it remains a major public health and social problem. Thirty per cent of 3 1/2 - 4 1/2 year olds (Owenniann 1996) and fifty per cent of 12 year olds in UK (Downer 1995; Marthaler 1996) had experienced caries in 1993. There are consistent differences in dental caries levels by socio-economic status in industrialized countries and in urbanized developing countries; low-SES children have higher dental caries rates than those in the upper SES groups (Chen 1995).

Fluoride therapy has been the cornerstone of any caries-preventive strategy since the introduction of water fluoridation schemes five decades ago (Murray 1991). The primary caries-protective effects of fluorides occur through promotion of remineralization of early caries lesions and by reducing tooth enamel demineralization (Ericson 1995). The use of topical fluoride therapy (TFT) in particular, has increased during the past two decades and fluoride containing dentifrices, mouthrinses, gels and varnishes are the topical forms most commonly used at present either alone or in different combinations. Dentifrices (toothpastes) are the most widespread form of fluoride usage (Murray 1991a) and the decline in the prevalence of dental caries in developed countries has been mainly attributed to its increased use (Rolla 1991; Marthaler 1994; O’Mullane 1995; Marthaler 1996). However, there is currently a vigorous debate regarding the appropriate use of fluorides in terms of their actual effectiveness and the potential risks (and costs) that may be expected from the various fluoride-based caries preventive measures in an era of decreased caries prevalence and widespread availability of fluorides (Ripa 1991). The persistence of this debate and the variations in the use of topical fluoride therapy in its various forms suggest the need to search for meaningful ways to summarize the empirical findings on this topic systematically.

Historically, the effect of TFT on the prevention of dental caries has been extensively reviewed and synthesised in a number of narrative reviews which generally provide a broad range of effect estimates, based on selected published literature, and in which the causes of differences in reported effectiveness are not formally explored. A small but growing number of recent studies, focusing on the evaluation of specific topical fluoride active agents within specific delivery systems, have used the quantitative meta-analytical approach to synthesise studies results (Stamm 1984; Clark 1985; Johnson 1993; Helfenstein 1994). However, none of the existing meta-analyses have evaluated or compared the main forms of topical fluoride treatments currently used in caries prevention; none were comprehensive in their searches for primary studies or explored systematically the main factors that may influence the outcomes measured. The present investigation examines all these issues.

Objectives

The primary objective of this review is to determine the effect of topical fluoride therapy (TFT) in the form of dentifrices, mouthrinses, gels and varnishes in the prevention of dental caries in children and adolescents. The secondary objective is to examine whether the effect of TFT is influenced by the level of caries severity, the background exposure to other fluoride sources, the mode/setting and form of delivery.

With regard to the clinical effectiveness of TFT in the forms above described three basic questions can be asked:
1- Is TFT effective for children and adolescents?
2- Is one of these forms of TFT more effective than another?
3- Are combinations of these TFT forms more effective than one form used alone?

This review concentrates on answering the first question and the other two questions will be addressed in future reviews. The specific objectives are:
1 - To determine the effectiveness and safety of topical fluoride therapy in the form of dentifrices, mouthrinses, gels and varnishes in preventing dental caries in the child/adolescent population.
2 - To examine whether the effect of TFT is influenced by the level of caries severity.
3 - To examine whether the effect of TFT is influenced by the background exposure to ambient levels of fluorides in water (or salt), and in dentifrices (for fluoride mouthrinse and fluoride gel/varnish studies).
4 - To examine whether the effect of TFT is influenced by mode/setting of delivery (self-applied supervised use of TFT in preventive programmes, self-applied supervised/unsupervised use of TFT at home, and operator-
applied use of TFT in the clinic), and if this does occur, whether there is a differential effect on caries prevention among the different forms of TFT used in each mode-setting of delivery.

Criteria for considering studies for this review

Types of studies
Randomized or quasi-randomized controlled trials, with at least one element of blinding in outcome assessment (such as clinical and/or radiographical assessment) in which treatment with topical fluorides in the delivery forms of dentifrices, mouthrinses, gels and varnishes, used single or combined was administered for at least one year and compared to placebo or no treatment. Studies employing the split-mouth design are not considered in this review in order to exclude the possibility of contamination of control sites.

Types of participants
Children and adolescents (aged 16 or less) from the general population, irrespective of nationality or background exposure to fluorides. Studies which have recruited only children or adolescents with special medical conditions are not considered in the review.

Types of interventions
Topical fluoride therapies in the following forms/vehicles of delivery are considered: fluoride dentifrices, mouthrinses, gels and varnishes (at any dose, frequency, duration or mode of administration, which, for gels and varnishes, may be used with prior prophylaxis or not, and with any of the following active agents/ingredients: NaF (sodium fluoride), SMFP (sodium monofluorophosphate), SnF2 (stannous fluoride), APF (acidulated phosphate fluoride), amine F (amine fluoride), which, in the case of dentifrices, may be formulated with any compatible abrasive system.

Studies that tested non-fluoride active agents in the same fluoride formulation (such as anti-plaque, anti-calculus agents in toothpastes) or studies that tested any other non-fluoride caries preventive treatments (such as sealants, oral hygiene procedures, xylitol chewing gum, glass ionomers) concurrently with (in the same group of) the TFT forms above-described are considered as long as such preventive treatments are equally applied to the groups being compared in the study (only unconfounded trials).

Studies that tested other forms of TFT only (such as solutions/topical paintings of the teeth and prophylactic pastes) are not considered in this review.

The control groups considered in this review are placebo or no treatment, which makes the following as the relevant comparison: Any of the forms of TFT described above compared with a placebo or no treatment control group.

Types of outcome measures
Dental status is usually measured by the DMF index, DMFT/S and dmft/s scores, which indicate the numbers of decayed, missing and filled teeth or surfaces in the permanent and primary dentitions at various ages. With regard to the various ways that caries increment as measured by this index is reported, the main form considered in this review is the average change in caries experience in all (whole mouth) permanent teeth or surfaces in terms of net (reversals counted as negative increments) mean caries increment from baseline during the trial period (usually of around 2/3 years) measured clinically and radiographically and/or clinically only, where the "D" component of the index is recorded at the cavitation level of diagnosis. (See "Methods of the review" section for the different ways of reporting the DMFT/S scores in clinical trials of caries preventives). However, studies reporting final mean DMF scores (usually for teeth not yet erupted at the baseline examination) or reporting separate components of the DMF index are also considered, irrespective of dentition.

Other outcomes considered in this review are the numbers% of caries-free children during the trial period, incidence of dental pain/discomfort during the trial period, safety of the treatment as measured by the incidence of any adverse effect during the trial (such as fluorosis, including any side-effect, such as extrinsic staining of teeth, etching of composite restorations which compromises appearance, allergic reactions...) and acceptability of the treatment as measured by numbers% of participants dropping out during the trial period.

Studies which measured physiological outcomes such as fluoride uptake by enamel or dentin, fluoride retention, salivary secretion levels, or the process of re/de-mineralization of enamel, or changes in dentin hypersensitivity, or changes in plaque/calculus formation, plaque regrowth/vitality, plaque/salivary bacterial counts, or gingival bleeding/gingivitis, are not considered in this review (unless an outcome of interest is also measured in the study in question).
In summary, the outcomes of interest are:

1- Changes in caries experience
   a- average change in the number of Decayed, Filled, (and Missing) Teeth or Surfaces [D(M)FT/S];
   b- final average number of Decayed, Filled, (and Missing) teeth or surfaces [D(M)FT/S] (the measure used for teeth erupting during the trial period);
   c- average change in the number of Decayed permanent teeth/surfaces or final average number of Decayed permanent teeth/surfaces;
   d- average change in the number of Filled permanent teeth/surfaces or final average number of Filled permanent teeth/surfaces;
   e- average change in the number of Missing permanent teeth or final average number of Missing permanent teeth;
   f- average change in the number of decayed, filled (and extracted) deciduous teeth/surfaces [df(e)t/s];
   g- the number of participants per treatment group with no D(M)FT/S increment during the trial period, as opposed to any caries increment [D(M)FT/S of 1 or more];
   h- the number of participants per group reporting no dental pain/discomfort, as opposed to any dental pain/discomfort.

2- Safety of the treatment
   a- Safety of the intervention as measured by the incidence of any adverse effect (such as fluorosis, including any side-effect, such as extrinsic staining of teeth, etching of composite restorations which compromises appearance, allergic reactions...) during the trial period.

3- Acceptability of the treatment
   a- acceptability of the intervention to the participant as measured by numbers/% of participants dropping out during the trial.

Clinical efficacy for placebo control studies is defined as a relative reduction (%) of 20% or a reduction in caries increment (DMFT/S scores) of at least *. Clinical efficacy for active topical fluoride treatment control studies is defined as a relative caries reduction (%) of 10%, according to the American Dental Association (ADA) guidelines definition of clinical superiority (CDT, 19881. or as a reduction in caries increment of at least * . (* The pre-determined minimal important difference, which should be reported in sample size calculations of primary studies, may be used in order to reach a consensus with regard to defining clinical efficacy in terms of absolute caries reduction).

When appropriate, the outcomes will be grouped into age groups (6/7-9/10, >11/12) and into experimental time periods (12-20 months, 21-36 months, > 36 months).

Search strategy for identification of studies

See: Collaborative Review Group search strategy
With a comprehensive search, we attempt to identify all relevant studies irrespective of language. Papers outside the English language are considered if they can be translated.

Electronic searching
Relevant trials are identified by searching several electronic databases from date of inception: MEDLINE, EMBASE, SCISEARCH, SSCISEARCH, ISTP, BIOSIS, CINAHL, DISSERTATION ABSTRACTS, ERIC and LILACS/BBDO. Studies pre-dating 1966 are not searched for. The downloaded set of records from each of these databases are imported to the bibliographic package Reference Manager and merged into one core database. The Cochrane Controlled Trials Register (CCTR) in the Cochrane Library, the grey literature database SIGLE and the Community of Science database which includes ongoing trials funded by the National Institute of Dental Research are also searched for additional relevant trials and references are cross checked with those in the core database.

Reference searching
The references of eligible trials are checked for more relevant studies and each included study is sought as a citation on the SCISEARCH database. Reference lists from meta-analyses and review articles, identified in the searches performed previously or by searching The Cochrane Library databases (CDSR, DARE) and the CRD database (NEED), are scanned for relevant studies. Reference lists from preventive dentistry textbooks on topical fluorides are also consulted.

Personal contact
Searching for unpublished or unlisted studies has started by contacting manufacturers and experts in the field of preventive dentistry. A letter with a list of included studies will be sent to the first author of each study (and/or manufacturer involved, if any, such as Procter & Gamble, SmithKline Beecham, Colgate-Palmolive, Unilever)
asking them for information on published or unpublished studies potentially eligible for inclusion which are not included in the list.

Full-text searching


Methods of the review

Study selection

All reports electronically identified by the search are printed off and scanned on the basis of title, keywords and abstract (when this is available) by one reviewer to see if the study is likely to be relevant. The full report is obtained of all relevant articles. Where it is not possible to classify an article, the full article is obtained.

With the inclusion criteria form previously prepared for this review, one reviewer (VM) will select all full reports to be included in the review independently and unblinded, and a second reviewer (JH) will select a sample of those. Disagreements will be resolved by discussion. Any report that cannot be classified by the first reviewer will be independently assessed by the second. Where resolving disagreement by discussion is not possible a third reviewer will be consulted. If agreement cannot be reached, the trial is excluded.

Quality assessment

The methodological quality of the trials to be included will be assessed according to the criteria described in the Cochrane Collaboration Handbook (Mulrow 1997), when each trial is rated according to three quality of allocation concealment categories:

Category A: adequate concealment
Category B: "random" allocation reported but the actual method used to conceal it is not known
Category C: inadequate concealment

Excluded: no random/quasi random allocation or "random" not stated.

Where uncertainty cannot be resolved an effort will be made to contact authors directly to clarify the method used to conceal allocation. Sensitivity analysis will be performed to test the effect of the quality of allocation concealment, since quasi randomized studies, such as those using alternate allocation and record numbers (in category C), are included in this review.

Blinding of main outcomes assessment will be rated according to the following criteria:

A. Double blind (blind outcome assessment and use of placebo)
B. Single blind (blind outcome assessment but no placebo used)
C. Blinding not clearly stated but likely in any element of outcome assessment (such as radiographical examinations independently performed with results reported separately).

Excluded: no blinding or blinding not stated.

Other methodological characteristics of the trials such as completeness of follow-up (numbers/% excluded) and handling of exclusions (differential losses or extent to which outcomes of those who withdrew are described) are not used as methodological thresholds for inclusion, but will be coded in the data collection form, and sensitivity analyses will be performed when indicated.

Data extraction

Data will be extracted by one reviewer (VM) using a previously prepared data extraction form. A second reviewer (JH) will extract data on a sample of included studies. Checking of reliability will be limited to the coding of outcomes and for validity assessments. Data presented in graphs and figures will be extracted whenever possible, but will only be included if two reviewers independently have the same result. Again, any disagreement will be discussed and where necessary, a third reviewer will be consulted (or authors will be contacted for clarification/missing information whenever possible). Data will be excluded until further clarification is available if agreement cannot be reached.

Characteristics that are coded from each study in addition to those described for participants, interventions, outcome measures and methodological quality include: the disease severity scores, previous exposure to other fluorides, mode and setting of delivery, year study started, place of study, duration of study, dental treatment level (F/DF). An exploratory analysis, using sub-group analysis, will be done on those not specified a priori after the main meta-analysis.
For studies with more than two-arms, where the same TFT form may be compared in two or more experimental groups (but with different active agents, or doses, or frequency of use) decisions on which test group to be coded for the relevant comparison (with the placebo/no treatment group) will be made by choosing the standard/commercially available formulation wherever possible (not to favour the "new" test TFT). In case of only standard or new treatments in the test groups the decision will be made by flipping a coin.

Among the relevant studies, caries increment, as measured by the DMF index, is reported in various ways (separately/combined) according to different units of measure used (all teeth or surfaces/whole mouth, specific tooth or surface type - erupted, erupting, unerupted, first molars, approximal surfaces,...), diagnostic thresholds used for caries (cavitation/dentin lesions, pre-cavitation/white-spot lesions,...), methods of examination adopted (clinical only, radiological only, clin + radiol, clin + FOTI,...), approaches to account or not for reversals (in a Net Caries Increment where reversals are included, or in a Crude Caries Increment where they are excluded). Each of these ways of reporting are considered in this review. Thereafter, the types of outcomes which can best answer the review questions are chosen (see "Types of outcome measures" section).

In addition, outcomes may be assessed at more than one period of follow-up. All such assessments will be recorded and decisions on which outcome assessment timing to use from each study (presenting results at more than one follow-up time) will be based on the most commonly reported timing of assessment among all included studies (usually the last follow-up, after around 2 to 3 years). Study duration has been shown to influence treatment effect in a recent meta-analysis of the effectiveness of fluoride varnishes on caries prevention (Helfenstein and Steiner, 1994).

In studies where assessments of outcomes were also made during a post-intervention follow-up period, the length of time outcomes were measured after the intervention ended will be noted, and the effect (or possible lack of it) will be examined (outcomes will be recorded).

Data synthesis
The primary measure of treatment effect that will represent the within study comparison of test and control groups is mean caries reduction, in terms of differences in mean D(M)FS/T increments between control and test groups. Thus, absolute caries reduction (DMF teeth/surfaces saved per year) will be calculated for each trial. It will be treated as continuous data (approximately normally distributed/analysed originally by parametric tests in primary studies).

Continuous outcomes will be analyzed according to their difference in mean treatment effects and its standard errors. Dichotomous outcomes will be analyzed by calculating odds ratios. The uncertainty in each result will be expressed using confidence intervals.

The Cochrane Review Manager software RevMan will be used for estimation of overall treatment effects/meta-analysis of results. Both fixed and random effects models will be used to calculate a weighted average of the treatment effects across the studies under review.

Investigation of heterogeneity
Heterogeneity in the results of the trials will be assessed by inspection of graphical display of results and by formal tests of heterogeneity. Three possible reasons for heterogeneity were specified a priori: (1) that the effect of TFT differs according to the levels of caries severity; (2) that the effect of TFT differs according to exposure to other fluoride sources (in water, in dentifrices); (3) that the effect of TFT differs according to mode/setting of delivery (and form of delivery - TFT type, within each). The second and third reasons for heterogeneity will be assessed by looking at separate subgroups of trials. The first reason will be investigated by performing Bayesian analyses, in order to avoid the "regression to the mean phenomenon" (Senn 1994) and misrepresentation of a true effect, where BUGS statistical package (Thomas 1992) will be used.

Potential conflict of interest
None known

Additional references

Anderson 1982
Brunelle 1982

133
Rolla 1991

Senn 1994

Sheiham 1991

Stamm 1984

Thomas 1992
Appendix C. Section 2: Protocol changes

Changes to the protocol were made with the consultation of and agreement from the advisory panel and the Cochrane Oral Health Group. The original protocol became in effect protocol/review 5, and four new protocols were developed to evaluate the effects of each topical fluoride modality separately, in order to keep each review at a manageable length. However, protocol 5 still included the four placebo comparisons, examinations of differences between them, and investigations of covariates across all four types of topical fluorides (although the range of analyses to be undertaken would be broader), with cross-references to the more detailed component reviews.

Thus, the main changes/additions to the original protocol, which were incorporated in all others (new protocols), as appropriate, related to data analyses:

1. Change in the measure of treatment effect (for the primary outcome measure).
   The new measure of treatment effect (summary statistic) was the preventive fraction (PF), that is the difference in mean caries increments between the ‘treatment’ and ‘control’ groups expressed as a percentage of the mean increment in the ‘control’ group. This measure was considered more appropriate than the one chosen originally (mean difference between mean caries increment in the ‘experimental’ and ‘control’ groups), since it should allow both, the combination of different ways of measuring caries increment by the DMF index and a meaningful investigation of heterogeneity between trials; it was also considered simple to interpret.

2. Change in the meta-analysis method, model and software (for the primary outcome measure)
   When the change to the new measure of effect was made (and incorporated into all the protocols), analyses could not be performed in RevMan/MetaView as originally planned. It was decided that the raw results of the studies (mean/SD/n) could be entered in RevMan, and mean differences could be presented without meta-analyses. If meta-analyses using standardised mean differences (SMD) yielded materially similar results to those using preventive fractions, we would consider presenting these within MetaView. The meta-
analyses using preventive fractions were going to be carried out using Stata (Stata Corporation, USA) and calculated as inverse variance weighted averages. Variances would be estimated using the formula presented in Dubey et al (1965), which is suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable. Various statistical methods are available for pooling study results, but the usual approach associated with meta-analysis is the idea of combining treatment effects by calculating a weighted average of individual effect sizes together with a relevant confidence interval, in which the larger trials have more influence (weight) than the smaller ones.

In the new protocol, random effects meta-analyses were going to be performed throughout (instead of both, fixed and random effects meta-analyses, as described in the original protocol).

Meta-analytical techniques can be broadly classified into two models, the key difference being the way the variability between the results of the studies is dealt with. The 'fixed effects' model assumes an identical treatment effect underlying all studies and considers that the variability between studies is exclusively due to random variation (individual studies are simply weighted by their precision) (Yusuf et al, 1985). The 'random effects' model assumes a different underlying effect for each study, and that studies are a random sample taken from some hypothetical universe of trials; the central point of the distribution is the focus of the combined effect estimate (it takes this additional between-study variation into account in calculating the average treatment effect, which leads to a more even weighting of individual studies, although giving relatively more weight to small studies than they receive in the fixed effects model, and somewhat wider confidence interval for the random effects estimate) (DerSimonian and Laird, 1986). A substantial difference in the combined effect calculated by each model can be seen only if studies are markedly heterogeneous.

3. Change in the primary methods and software for investigations of heterogeneity
The new method to perform formal investigations of heterogeneity (in review 5, as well as in the four component reviews, if appropriate) involved metaregression analyses. As stated in the new protocol, metaregressions were thus going to be carried out for investigations of heterogeneity, using Stata software. In the original protocol, reasons for heterogeneity would be investigated by performing subgroup analyses in RevMan; Bayesian analyses, using
BUGS statistical package, would be performed specifically for evaluating the potential impact of baseline caries levels on treatment effect (however, it was recognised that more methodological research was required to define the appropriate place of Bayesian methods in meta-analyses).

Heterogeneity may be accounted for in a random effects meta-analysis which incorporates between-study variability into the overall estimate. It may be scrutinised and explained in random effects metaregression, a powerful extension of a traditional meta-analysis where the impact of characteristics of the studies on the size of treatment effect is examined (if there is a large number of studies). It may be possible to explain and effectively eliminate heterogeneity from the analyses by performing stratified analysis of subsets of studies, but it is more important to use pre-specified groupings as subgroups than it is in metaregression, due to an increased chance of a false positive result when many subgroup analyses are performed.

4. Change in the handling of results (main outcome) of multitreatment studies
In the new protocol, for studies with more than two-arms, where the same topical fluoride modality was compared in two or more experimental groups, caries increment of all relevant experimental arms were to be combined for the main meta-analysis. In the original protocol, one group only would to be chosen for analysis, but the criteria were considered arbitrary and would not allow the use of all relevant data.

Other changes to the protocol included:
The additional subject search strategies performed in MEDLINE were added to the section ‘Search strategy for identification of studies’.
Each subsection in the section ‘Criteria for considering studies for this review’ were re-written into clearer and more condensed subsections (‘Types of studies’, ‘Types of participants’, etc). (Many parts of the protocol were re-phrased, some parts were expanded and others were condensed, but these alterations were minor protocol changes.)

References

APPENDIX D

Standard letter to trialists
Dear Dr DePaola,

The Cochrane Collaboration is an international consortium that aims to prepare, maintain and disseminate systematic reviews of the effects of health care. The Cochrane Oral Health Group was established in 1994, and is currently undertaking a range of systematic reviews. Together with Dr Julian Higgins, Dr Stuart Logan and Prof Aubrey Sheiham I am undertaking a systematic review of the effects of Topical Fluoride Therapy on dental caries. Your paper [DePaola et al, 1980 – The anticaries effect of single and combined topical fluoride systems in school children] has been identified as a relevant clinical trial for inclusion in the review. In order to include relevant studies, we need to be able to extract the data in a standard manner. In some cases we require data that is not provided in the article assessed.

We are wondering whether you could help us by providing any of the information described below.

1- The method used to allocate children to groups: was it a quasi-random method such as alternation, or a random process was used to conceal treatment allocation? Could you please describe the method?

2- The number of participants present in each of the 4 groups at baseline, their mean DFS scores (and SD or se if possible).
3- Any data that may have been collected on reported regular use of F dentifrices or any information on availability of F dentifrices in the market at the time the trial begin (plus year of baseline examination).

I appreciate that locating these data may be a nuisance after so many years. Nevertheless, if you yourself do not have the original data, would it be possible to pass this letter on to the appropriate author?

Please feel free to contact me on the address/e-mail below.

I look forward to receiving the additional information and any information you may have on unpublished clinical trials using the same intervention(s).

With kind regards and many thanks for your co-operation,

Sincerely,

Valeria Marinho
Department of Epidemiology and Public Health
University College London
1-19 Torrington Place
London WC1E 6BT
e-mail: valeria@public-health.ucl.ac.uk or vcmarinho@yahoo.com
APPENDIX E

Inclusion Criteria Template
Inclusion-Exclusion criteria template - Topical fluoride therapy (TFT) for children and adolescents in the prevention of dental caries
(Single TFT vs placebo/no treatment, single TFT vs another TFT, combined TFT vs any single TFT in the combination)

**REVIEWER:**

<table>
<thead>
<tr>
<th>ID (Au 1. pub year)</th>
<th>Design/allocation</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes assessed</th>
<th>Blind assessment of main outcome</th>
<th>Length of follow-up</th>
<th>Notes (other potential reasons for exclusion and/or comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IN - experimental studies = Clinical trials (RCTs/CCTs)</strong></td>
<td><strong>EXCLUDE - but not parallel group design RCT/CCT (e.g. - within-group paired comparison used = split mouth) or clearly not randomised IRRELEVANT - observational studies: cohort (concurrent controls, historical controls), before-after, case-control, and descriptive studies</strong></td>
<td><strong>IN - children/adolescents (&lt; 17)</strong></td>
<td><strong>TFT = u/tr/g/v only (applied at least once a year). Controls = NT/PL/TFT. Comparisons: IN - 1 TFT type x placebo/NT, 1 TFT type x another TFT type, 2 TFT types x 1 of the TFT types. EXCLUDE - but with any association in the direct comparison (in test, control or both groups) of TFT other than u/tr/g/v, or with a differential association (either in test or control group) of any active agent or preventive measure other than TFT. IRRELEVANT (at present) - 2 or &gt;TFT types x placebo/NT, TFT in complex measures x placebo/NT, 1 (or &gt;) TFT type x same TFT type(s) (Other agent/concentr/frequency/mode, etc), 1 or &gt;TFT type x any intervention other than the TFT/control (comb or not to TFT).</strong></td>
<td><strong>IN - caries increment as measured by the DMF index/its components, dental pain/discomfort, side effects, dropouts, visits to dental care units, length of treatment. But do not code if essential clinical data in each group are not reported. EXCLUDE - only outcomes not clearly dependent on F action/ not related to caries only (e.g. - plaque/gingivitis, calculus, F physiological measures) IRRELEVANT - only outcomes not clinically useful (e.g. - those from in vitro, in vivo, in situ studies)</strong></td>
<td><strong>EXCLUDE - blind assessment clearly not attempted/ not used IRRELEVANT - impossibility of blind assessment for a particular design</strong></td>
<td><strong>Length of follow-up</strong></td>
<td></td>
</tr>
<tr>
<td><strong>EXCLUDE - but with special medical/dental conditions</strong></td>
<td><strong>IRRELEVANT - adults (&gt;16)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Dramatic drop-out rate (&gt;40% at 2 years), unit of allocation (cluster)/unit of analysis relationship...</strong></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX F

Data Extraction Template
Data extraction template for topical fluoride therapy (TFT) for children and adolescents in the prevention of dental caries

<table>
<thead>
<tr>
<th>A - MAIN DETAILS OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Title (of main publication):</td>
</tr>
<tr>
<td>2. Country of origin (and region/city), year started (of baseline examination):</td>
</tr>
<tr>
<td>3. Duration (in m/y): (at start) = n age group(s) =</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B - SET-UP/DESIGN OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study site (industrialized: large towns/small villages/...; or developing: urban/semi-urban/semi-rural/rural/...): number of sites:</td>
</tr>
<tr>
<td>a. Fluoridation status (water/salt): ppm F:</td>
</tr>
<tr>
<td>b. Fluoride toothpaste availability (production/promotion/consumption):</td>
</tr>
<tr>
<td>c. Sugar availability (production/promotion/consumption)/nutritional policy/dental service delivery type/...:</td>
</tr>
<tr>
<td>2. Center for recruitment (community/schools or institution/primary care or referral centre/private or institutional practice/...): number of centers:</td>
</tr>
<tr>
<td>a. Implementation of (school-/institution-/community-based) caries preventive treatment (F/non-F based) other than the clinical trial option(s):</td>
</tr>
<tr>
<td>3. Exclusions from eligibility criteria (previous exposure to fluoride/orthodontically treated/gender/ethnicity/...):</td>
</tr>
<tr>
<td>4. Intervention groups: 1 vs 2 vs 3 vs 4 vs 5</td>
</tr>
<tr>
<td>[indicate relevant comparison(s)]:</td>
</tr>
<tr>
<td>5. Characteristics of interventions, frequency, mode and setting of delivery,... - in each group (fill table 1): stratifying variables (age, sex, caries experience, dental age,...)</td>
</tr>
<tr>
<td>6. Randomization type (simple/stratified - with blocking used, ...):</td>
</tr>
<tr>
<td>7. Unit of randomization allocated to study groups (persons/person-siblings/school-classes, ...): number of units randomized:</td>
</tr>
<tr>
<td>8. Method of generating the allocation schedule (random number tables/computer/random arrangement/alternation/...):</td>
</tr>
</tbody>
</table>

| 9. Method of allocation concealment - control of selection bias at entry: |
| (+ any info on method to separate the generator from the executor of assignment) |
| A= adequate method described (centralised by a central office or pharmacy, pre-numbered or coded identical containers administered serially to participants, numbered sealed opaque envelopes, locked computer file...) |
| B= indication of random method (words such as random, randomization,...) |
| C= quasi method described (alternation, dates of birth, open list of random numbers) |

| 10. Blinding of main outcome assessment to treatment allocated - control of detection bias: |
| (Blinding at clinical examination/ radiographic/ both clinical + X-ray examinations/ all assessments /...): |
| A= double-blind (blind outcome assessment and use of placebo described) |
| B= single-blind (blind outcome assessment but no placebo described) |
| C= indication of blind assessment (likely in any element of outcome assessment such as x-rays assessed independently) |

| 11. Blinding of participants – control of performance bias (Y/N/NC/NR): |
| 12. Blinding of study personnel – control of performance bias (Y/N/NC/NR): |
| 13. Groups treated equally (Y/N/NC/NR): Co-interventions (Y/N/NC/NR): Contamination (Y/N/NC/NR): |

| 14. Main outcome(s): as measured by index/score Unit of measurement Minimum important difference of power calculation (Y/N/NC/NR): |
| 15. Secondary outcome(s): as measured by index/score Unit of measurement Full results reported (Y/N) |
### CONDUCT OF EXAMINATIONS

16. Standardized set of methods for dental caries assessment (Y/N/NC/NR): Overall Criteria (WHO/......):
   - a. Clinical caries examination (use of probe only, visual only, both combined): criteria: Diagnostic level: Number examiners doing all examinations:
   - b. Radiographic caries examination (bitewing, ...): criteria: Diagnostic level: Number examiners doing all X-rays diagnoses:
   - c. Other technique(s) for caries diagnosis (transillumination-FOTI, ...): criteria: Diagnostic level: Nos doing all diagnoses:

17. Standardized methods for assessment of other outcomes (Y/N/NC/NR):
   - a. Clinical caries examination (use of probe only, visual only, both combined): criteria: Diagnostic level: Number examiners doing all examinations:
   - b. Radiographic caries examination (bitewing, ...): criteria: Diagnostic level: Number examiners doing all X-rays diagnoses:
   - c. Other technique(s) for caries diagnosis (transillumination-FOTI, ...): criteria: Diagnostic level: Nos doing all diagnoses:

18. Detection of systematic errors in caries diagnosis (Y/N/NC/NR):
   - clinical recordings - inter-examiner, intra-examiner variability/kappa values
   - radiographic recordings - inter-examiner, intra-examiner variability/kappa values
   - Duplicate initial and final examinations (Y/N/NC/NR):
     - % of children seen for inter/intra examiner variability
     - % children seen for inter/intra examiner variability

19. Measurement of random errors in clinical/radiological caries diagnosis – reliability coefficient, reversal rates, … (Y/N/NC/NR)

20. Timing of examinations (m/y): bas = time 0, 1st follow-up = , 2nd follow-up = , 3rd follow-up = Frequency of examinations:

### ANALYSIS OF RESULTS

21. Completeness of follow-up – Overall attrition rate (<9.9%/10%-20%/>20%) after ..........m/y:

22. Reasons for attrition and respective numbers (n) by randomized group when explicitly reported (fill table 2) Any threshold chosen for “compliance” (Y/N/NC/NR):

23. Handling of exclusions – Main analysis of primary outcome based on intention-to-treat/ on few losses to follow-up and/or on losses independent of treatment allocated (no differential losses)/...-control of attrition/selection bias after entry (Y/N/NC/NR):

24. Participants initial/prognostic characteristics/measurements by randomized group - presented for original/randomized /final/analyzed/... sample (fill table 3)

25. Estimated effect of intervention on primary (any relevant) outcomes (point estimate + measure of precision) for those present at each follow-up (fill table 4)

26. Results (in absolute and relative numbers) of main analyses for those present at each follow-up (fill table 4)

27. Unit of analysis: Account for unit of randomization (Y/N/NC/NR):

28. Adjusted analysis presented (in case of baseline imbalances,..) (Y/N/NR): Unchanged results (Y/N/NC/NR):

29. Subgroup analysis performed (Y/N/NR): Unchanged results (Y/N/NC/NR):

### FINAL DECISION - INCLUDED: missing info on

- EXCLUDED: reasons

Author’s contact address / Institution (for missing info): Sponsoring manufacturer, if any (for missing info):

Any other report(s) of the same study (e.g. report of results at different follow-up times) used/to be used for data extraction (author 1, title, journal, year, volume: pages):

References of other potentially relevant trials cited in this study (author 1, title, journal, year, volume and pages):
Data extraction tables for topical fluoride therapy (TFT) for children and adolescents in the prevention of dental caries

Trial ID (author 1, year of main publication):   Paper reference number:   Reviewer:

Table 1
Characteristics of intervention(s) in each group - relevant comparison(s)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFT form (TP/MR/G/V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F agent/trade name (+ CAS reg number)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F concentration (ppm F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abrasive (for Toothpaste)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior-application procedure (for Gel/Varnish/Rinse)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application material/method (e.g. tray system/ cotton pellets ...)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount applied (e.g. pea-sized/ ... ml/ ... drops)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of application (min/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-application method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of application (times a year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of use (operator-applied/self-applied supervised/unsupervised)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting of use (clinic/school/home)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Reasons for withdrawals/drop-outs with respective numbers in each group/both groups/overall (e.g. moved away, side effects, lack of cooperation, poor “compliance”, ...)

<table>
<thead>
<tr>
<th></th>
<th>group 1</th>
<th>group 2</th>
<th>overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data extraction tables for topical fluoride therapy (TFT) for children and adolescents in the prevention of dental caries

Trial ID (author 1, year of main publication): Paper reference number: Reviewer:

**Table 3**

*Initial measurements of participants characteristics* (for original, randomized /final, analyzed sample)

Continuous variables: mean age, number of unerupted/erupted sound at risk deciduous/permanent teeth/surfaces, ID(M)FT/S score, id(e)ft/s scores, Plaque/Gingival index scores, fluorosis/enamel opacities indices scores, brushing/sugar intake frequency, length of previous exposure to fluoridation, ....

Categorical variables: %/n caries-free/with caries, %/n using F toothpaste regularly/not using, taking fluoride tablets/not taking, M/F, ....

(Other socio-demographic variables and oral health behaviour variables/proxies for them, such as D/DF ratios and F/DF ratios as proxies for utilization of dental services/level of dental care,...)

<table>
<thead>
<tr>
<th>Characteristics measured</th>
<th>Participants at baseline</th>
<th>Participants at follow-up (at ... m/y)</th>
<th>Participants at follow-up (at... m/y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>group 1</td>
<td>group 1</td>
<td>group 1</td>
</tr>
<tr>
<td></td>
<td>n=</td>
<td>n=</td>
<td>n=</td>
</tr>
<tr>
<td>“Continuous” variables</td>
<td>Estimate (measure)</td>
<td>estimate (measure)</td>
<td>estimate (measure)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categorical variables</td>
<td>n in categories</td>
<td>n in categories</td>
<td>n in categories</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data extraction tables for topical fluoride therapy (TFT) for children and adolescents in the prevention of dental caries

Trial ID (author 1, year of main publication):  

Reviewer:  

Table 4  
Treatment effect on relevant ("continuous"/dichotomous) outcomes (point estimate + measure of precision) for those present at various follow-ups.  
"Continuous" outcomes: caries indices scores (DFT, DFS, DMFT, DMFS, DT, DS, FT, FS, MT, MS, DFTU, DFSU, DMFSU, DMFTU, df, dfs, dft, dfs, etc.), caries progression scores, enamel defects/fluorosis indices scores, others (extrinsic staining scores, ...).  
Differences control-experimental in average change (increment from baseline) after ... months/years (calculate Surfaces Saved per year whenever possible), PF (Prevented Fractions).  
Categorical/dichotomous outcomes: numbers with 0 caries increment/1 or >D(M)FT/S, number of carious lesions remineralising/arresting/progressing, presence of pain, discomfort, others.  
Odds ratios, risk ratios and absolute risk reductions as measures of treatment effect (calculate Numbers Needed To Treat whenever appropriate).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>At........ Follow-up/examination</th>
<th>at........ Follow-up/examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Continuous&quot;</td>
<td>group 1 n=</td>
<td>group 2 n=</td>
</tr>
<tr>
<td>n final score/change (sd/se/CI)</td>
<td>n final score/change (sd/se/CI)</td>
<td>mean diff % reduc P</td>
</tr>
<tr>
<td>Categorical/ dichotomous</td>
<td>n events/total number</td>
<td>n events/total number</td>
</tr>
</tbody>
</table>

Record (for caries increment) if data for each outcome are presented combined and/or separately for different units measured (partial/full mouth recording - of all erupted/erupting teeth/surfaces, specific groups of teeth/surfaces in deciduous/permanent dentition), methods of examination used (clinical only/radiography only/clin + radi/o + FOI/...), types of statistical analysis (main analysis/adjusted analysis), diagnostic thresholds chosen for caries (pre-cavitation/cavitation level/...), approaches for reversals (accounting for them in Net Caries Increment, where reversals are included or Crude Caries Increment, where reversals are excluded), etc.
TOPICAL FLUORIDES FOR THE PREVENTION OF DENTAL CARIES IN CHILDREN – A SYSTEMATIC REVIEW

Valéria Coelho Catão Marinho

A thesis submitted for the degree of PhD

September 2003

The University of London

Department of Epidemiology and Public Health
Royal Free and University College Medical School
University College London
CHAPTER 3

FLUORIDE GELS FOR PREVENTING DENTAL CARIES IN CHILDREN AND ADOLESCENTS
Fluoride gels for preventing dental caries in children and adolescents

Cover sheet

Title
Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

Reviewers
Marinho VCC, Higgins JPT, Logan S, Sheiham A

Dates
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Fluoride gels for preventing dental caries in children and adolescents

Internal sources of support
Department of Epidemiology and Public Health (UCL), UK
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Medical Research Council, UK

External sources of support
CAPES - Ministry of Education, BRAZIL

Contribution of reviewers
All authors contributed to the development of the protocol. Valeria Marinho (VM) wrote the protocol, conducted searches, selected studies and extracted data. Julian Higgins (JH) duplicated study selection and data extraction in a sample of studies, and Stuart Logan (SL) or Aubrey Sheiham (AS) were consulted where necessary. VM entered and analysed the data in consultation with JH. VM prepared the full review and all authors were active in its revision and approval.

Acknowledgements
We gratefully acknowledge the help of the following investigators who provided additional information about their trials: H Gisselsson (Eslov Public Dental Service), M Olivier (University of Montreal), H D Mestrinho (University of Brasilia), H Horowitz (NIDR, Bethesda), A Treide (University of Leipzig), M Kukleva (Plovdiv Higher Medical Institute); thanks to B Kiene (GABA, Switzerland) who supplied reports of trials. The help and expertise of the following is also gratefully acknowledged: R Wents, A Schreiber, H Pikhart, K Turai (German, Russian, Bulgarian and Hungarian translations); B Anagnostelys and L Jones (Systematic Reviews Training Unit, London), E Tavender and S Bickley (Cochrane Oral Health Group, Manchester). We would also like to thank those who have provided comments and editorial input to this review: R Holt (UCL), M Lennon (University of Liverpool), S Poulsen (University of Aarhus), A Rugg-Gunn (Newcastle University Dental School), L Hooper (Cochrane Oral Health Group), H Worthington (Cochrane Oral Health Group), A-M Glenny (Cochrane Oral Health Group).

Potential conflict of interest
None known
Abstract

Background
Topically applied fluoride gels have been used as a caries-preventive intervention in dental surgeries and school-based programs for over three decades.

Objectives
To determine the effectiveness and safety of fluoride gels in the prevention of dental caries in children and to examine factors potentially modifying their effect.

Search strategy
We searched the Cochrane Oral Health Group's Trials Register (May 2000), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2000), MEDLINE (1966 to January 2000), plus several other databases. We handsearched journals, reference lists of articles and contacted selected authors and manufacturers.

Selection criteria
Randomized or quasi-randomized controlled trials with blind outcome assessment, comparing fluoride gel with placebo or no treatment in children up to 16 years during at least one year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS).

Data collection & analysis
Inclusion decisions, quality assessment and data extraction were duplicated in a random sample of one third of studies, and consensus achieved by discussion or a third party. Study authors were contacted for missing data. The primary measure of effect was the prevented fraction (PF), that is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed where data could be pooled. Potential sources of heterogeneity were examined in random effects meta-regression analyses.

Main results
Twenty-five studies were included, involving 7747 children. For the 23 that contributed data for meta-analysis, the D(M)FS pooled prevented fraction estimate was 28% (95% CI, 19% to 37%; p<0.0001). There was clear heterogeneity, confirmed statistically (p<0.0001). The effect of fluoride gel varied according to type of control group used, with D(M)FS PF on average being 19% (95% CI, 5% to 33%; p<0.009) higher in non-placebo controlled trials. A funnel plot of the 23 studies indicated a relationship between prevented fraction and study precision. Only two trials reported on adverse events.

Reviewers' conclusions
There is clear evidence of a caries-inhibiting effect of fluoride gel. The best estimate of the magnitude of this effect, based on the 14 placebo-controlled trials, is a 21% reduction (95% CI, 14% to 28%) in D(M)FS. This corresponds to an NNT of 2 (95% CI, 1 to 3) to avoid 1 D(M)FS in a population with a caries increment of 2.2 D(M)FS/year, or an NNT of 24 (95% CI, 18 to 36) based on an increment of 0.2 D(M)FS/year. There is little information concerning the deciduous dentition, on adverse effects or on acceptability of treatment. Future trials should include assessment of potential adverse effects.
Background

The prevention of dental caries in children and adolescents is generally regarded as a priority for dental services and considered more cost-effective than its treatment (Burt 1998). Fluoride therapy has been the centrepiece of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray 1991). These were introduced when caries was highly prevalent and severe, and when even modest prevention activities led to considerable reductions in disease levels. In the last twenty years, with the substantial decline in dental caries rates in many western countries, an increase in dental fluorosis levels in some countries, and intensive research on the mechanism of action of fluoride highlighting the primary importance of its topical effect, greater attention has been paid to the appropriate use of other fluoride-based interventions (Glass 1982; Featherstone 1988; Ripa 1991; O'Mullane 1994; Marthaler 1996; Featherstone 1999).

The use of topically applied fluoride products in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades. By definition, the term 'topically applied fluoride' is used to describe those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect, and are therefore not intended for ingestion. The most important anti-caries effect of fluoride is considered to result from its action on the tooth/plaque interface, through promotion of remineralization of early caries lesions and by reducing tooth enamel solubility (Featherstone 1988). Fluoride containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most commonly used at present, either alone or in combination. Various products are marketed in different countries and a variety of caries preventative programs based on these have been implemented. Toothpastes are by far the most widespread form of fluoride usage (Murray 1991a; Ripa 1991) and although the reasons for the decline in the prevalence of dental caries in children from different countries continues to be debated (Nadanovsky 1995; Krasse 1996; Marthaler 1996; de Liefde 1998), it has been mainly attributed to the gradual increase in, and regular home use of fluoride in toothpaste (Glass 1982; Ripa 1991; Rolla 1991; Marthaler 1994; O'Mullane 1994; Bratthall 1996).

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

The evidence on the effect of topical fluorides on the prevention of dental caries in children has been extensively reviewed in a number of traditional narrative reviews. A small number of reviews focusing on the evaluation of specific fluoride active agents within specific delivery systems have used a quantitative meta-analytical approach to synthesise studies results (Clark 1985; Johnson 1993; Helfenstein 1994; Stamm 1995; van Rijkom 1998). A systematic quantitative evaluation of the available evidence on the effect of the main modalities of topically applied fluoride has never been undertaken.

This review is one in a series of systematic reviews of topical fluoride interventions and assesses the effectiveness of fluoride gels in the prevention of dental caries in children.

FLUORIDE GELS
Fluoride gels have been widely used in dental surgeries and school-based caries preventive programs in many countries during recent decades. Although currently recommended only for children with moderate and high caries levels the cost-effectiveness of gels has been questioned recently even for these populations (van Rijkom 1998). Fluoride gels are either administered by a professional or are self-applied under supervision. In general, operator-applied fluoride gels use trays and self-applied gels use either a tray or a toothbrush. Fluoride gels must be differentiated from some fluoride toothpastes, which are also available in the form of gels. The 'classical' fluoride gels do not contain abrasives, their fluoride concentration is usually much higher than that of a fluoride toothpaste, and they are applied at relatively infrequent intervals. Various methods, concentrations and frequencies of gel applications have been tested, with or without prior dental prophylaxis, and different fluoride compounds have been used. Typically, acidulated phosphate fluoride (APF) gels in the concentration of 12,300 parts per million of fluoride (ppm F) are professionally-applied twice a year. The excessive ingestion of fluoride during topical application is not an uncommon occurrence (Whitford 1992) and the greatest health hazard is associated with the use of 12,300 ppm F APF gels. The probable toxic dose (PTD) of 100mg of fluoride for a 20kg (5-6 year-old) child is contained in only 8ml volumes of these gels. Approximately 5ml of gel is used in a topical application of APF gel in a tray, representing a potential exposure of 61.5mg of fluoride ion. There is a significant risk of over exposure which can result in acute toxicity (Ripa 1990). Nausea, vomiting, headache and abdominal pain are symptoms that have been reported in young people receiving fluoride gel applications. Because of the risk of over ingestion the use of gels in young children is not recommended.

Numerous clinical trials evaluating the caries preventive effect of fluoride gels have been reported, and these have been the subject of narrative reviews (Ripa 1989; Ripa 1991) and of two meta-analyses (Clark 1985; van Rijkom 1998). Although the most recent meta-analysis has addressed the same question this systematic review addresses it did not include a comprehensive search for individual studies or a formal evaluation of the internal validity of included studies. In addition, the meta-analysis included four studies of the effects of toothpaste (with fluoride concentrations much lower than those used in gels but a higher frequency of application) which may have biased the estimates of effect.

Objectives

1. To determine the effectiveness and safety of fluoride gels in preventing dental caries in the child/adolescent population.
2. To examine whether the effect of fluoride gels is influenced by the initial level of caries severity.
3. To examine whether the effect of fluoride gels is influenced by the background exposure to fluoride in water (or salt), toothpastes, or reported fluoride sources other than the study option(s).
4. To examine whether the effect of fluoride gels is influenced by the mode of use (self-applied supervised or operator-applied), and whether there is a differential effect between the tray and toothbrush methods of application in the self-applied mode of use.
5. To examine whether the effect of fluoride gels is influenced by the frequency of use (times/year) or fluoride concentration.

Criteria for considering studies for this review
Types of studies

Randomized or quasi-randomized controlled trials using or indicating blind outcome assessment, in which fluoride gel is compared concurrently to a placebo or no treatment group during at least one year/school year. Randomized or quasi-randomized controlled trials with open outcome assessment or no indication of blind assessment, or lasting less than one year/one school year, or controlled trials where random or quasi-random allocation is not used or indicated were excluded.

Types of participants

Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started). Studies where participants were selected on the basis of special (general or oral) health conditions were excluded.

Types of interventions

Topical fluoride in the form of gels only, operator- or self-applied, using any fluoride agent, at any concentration (ppm F), amount or duration of application, and with any technique of application, prior- or post-application. However, frequency of application should be at least once a year. The control group is placebo (for any method of gel application) or no treatment (for tray or cotton tips methods of gel application, but not for brushing or flossing methods), resulting in the following comparison:

Fluoride gel compared with a placebo or no treatment.

Studies where the intervention consisted of any other caries preventive agent or procedure (eg other fluoride-based measures, chlorhexidine, sealants, oral hygiene interventions, xylitol chewing gums, glass ionomers) used in addition to fluoride gel were excluded.

Types of outcome measures

The primary outcome measure in this review is caries increment, as measured by change from baseline in the decayed, missing and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. Dental caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis. (See 'Methods of the review' for the different ways of reporting the D(M)FT/S scores in clinical trials of caries preventives).

The following outcomes were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions, tooth loss, dental pain/discomfort, specific side effects (fluorosis, tooth staining/discoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting), unacceptability of preventive treatment as measured by dropouts during the trial/post-randomization exclusions (in non-placebo controlled studies), use of health service resources (such as visits to dental care units, length of dental treatment time).

Studies reporting only on plaque/gingivitis, calculus, dentin hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc) were excluded.
Search strategy for identification of studies

With a comprehensive search, we attempted to identify all relevant studies irrespective of language, from 1965 onwards.

ELECTRONIC SEARCHING (databases and registers)

Up to 1998

(a) ["DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS" all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or DMF*) and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR SMFP OR MFP OR MONOFLUOR*) or ("CARIOSTATIC-AGENTS" explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or "DENTIFRICICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or CARIOSTA* or PROPHYL* or ANTICARI* or ANTI CARI* or VARNISH* or LACQUER* or DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRIC* or MOUTHRINS* or MOUTH RINS* or RINS* or MOUTHWASH* or MOUTH WASH*)].

(b) [((explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPICAL/ ALL SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT)) and ((CARI*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT* in TI, in AB, in MESH)) or ((explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or (explode MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or (MOUTHRINS* or MOUTH RINS*) or (VARNISH* or LACQUER*)]].

These subject search phrases were customised for searching EMBASE and other databases. RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISSERTATION ABSTRACTS, and LILACS/BBO. All the strategies (subject search and methodological filters) developed to search each database are fully described in a report produced for the Systematic Reviews Training Unit (Marinho 1997), and are available on request. These were used for the development of a register of topical fluoride clinical trials for the systematic reviews, as the Cochrane Oral Health Group's Specialised Register was not yet developed in 1997/98.

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1,1997), the Community of Science database (1998), which included ongoing trials funded by the National Institute of Dental Research (NIDR), the System for Information on Grey Literature in Europe (SIGLE) database (1980-1997), and OLD MEDLINE (1963-1965) were searched using

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the terms 'fluor' and 'carie' truncated. (Grey literature search had also been carried out by searching the Index to Scientific and Technical Proceedings (ISTP) and DISSERTATION ABSTRACTS).

From 1999 to 2000
The following strategy was used to search LILACS/BBO in 1999 (1982-98), where free-text subject search terms were combined with a methodological filter for RCTs:

\[
(\text{fluor$ or ppmf or ppm f or amf or snf or naf or afp or mfp or smfp or monofluor$ or duraphat$}) \text{ and } (\text{carie$ or dmf$ or cpo$ or tooth$ or teeth$ or dent$ or dient$ or anticarie$ or cario$ or mouthrin$ or mouth rins$ or rinse$ or bochech$ or enjuag$ or verniz$ or varnish$ or barniz$ or laca$ or gel or gels}) \text{ and } (\text{random$ or aleatori$ or acaso$ or azar$ or blind$ or mask$ or cego$ or cega$ or ciego$ or ciega$ or placebo$ or(clinic$ and (trial$ or ensaio$ or estud$)) or (control$ and (trial$ or ensaio$ or estud$))).
\]

A supplementary and more specific subject search phrase (including 'free-text' and 'controlled vocabulary' terms), refined exclusively for this review, formulated around three concepts (gel, fluoride and caries) was used to search Silverplatter MEDLINE (up to January 2000) without methodological filters:

\[
(\text{CARIE* or (DENT* near CAVIT*) or TOOTH* DECAY* or DMF* or (explode "DENTAL-CARIES"/ ALL SUBHEADINGS)) and (FLUOR* or APF* or NAF* or AMINE F OR SNF* or ACIDULATED* PHOSPHATE* FLUORID* or ACIDULATED* FLUORID* or PHOSPHATE* FLUORID* or SODIUM* FLUORID* or AMINE* FLUORID* or STANNOUS* FLUORID* or ELMEX* or (explode "FLUORIDES"/ ALL SUBHEADINGS)) and (GEL* or TRAY*)].
\]

This strategy was adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and has also been run on CENTRAL (The Cochrane Library Issue 2, 2000) to double-check.

REFERENCE SEARCHING

All eligible trials retrieved from the searches, meta-analyses and review articles were scanned for relevant references. Reviews had been identified mainly by a MEDLINE search strategy specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic, when the Cochrane Library database - Cochrane Database of Systematic Reviews (CDSR), and the CRD databases - Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED), were also searched. Reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions were also consulted.

FULL-TEXT SEARCHING

Prospective handsearching of those journals (seven) identified as having the highest yield of eligible RCTs/CCTs were carried out, from January 1999 until January 2000: British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (1990-December 1999), as this was the journal with the highest yield of eligible reports.

PERSONAL CONTACT
Searching for unpublished studies (including 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published during the last two decades, in order to obtain information on possible unpublished studies eligible for inclusion. All the authors of studies who had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies.

Based on information extracted mainly from included studies, a list of manufacturers of fluoride gels was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group (COHG), in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Six fluoride gel manufacturers were contacted by the group (October 2000) and information on any unpublished trials requested from: GABA AG, Johnson & Johnson, Davies Rose-Hoyt Pharmaceutical Division, John O Butler Company, Oral-B Laboratories, Colgate Oral Pharmaceuticals.

Methods of the review

IDENTIFICATION OF RELEVANT REPORTS

Because multiple databases were searched, the downloaded set of records from each database, starting with MEDLINE, was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS, BBO, CCTR, SIGLE and NIDR databases were not imported to Reference Manager and were scanned without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filter were imported to Reference Manager for inspection but in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register were also checked outside Reference Manager.

All records electronically identified by the searches were printed off and scanned on the basis of title first, then by abstract (when this was available in English or in languages known by the reviewer) and/or keywords by one reviewer (VM). Irrelevant reports were discarded and the full-text of all remaining were obtained.

All potentially relevant articles identified when conducting other types of search (reference lists, journal handsearch, and personal contact) were also obtained.

It was considered essential to identify and check all reports related to the same study; and in case of any discrepancy, authors were contacted.

STUDY SELECTION

With the inclusion criteria form previously prepared and pilot tested, one reviewer (VM) assessed all studies for inclusion in the review, and a second reviewer (JH) independently duplicated the process for a sample of those (approximately 30%). In addition, any study that could not be classified by the first reviewer was independently assessed by the second. A third reviewer was consulted (SL or AS) to resolve any disagreement. It was decided in advance to exclude any trial
where agreement could not be reached but this did not occur. Trial reports thought to be potentially relevant in languages not known by the reviewers were translated and the reviewer (VM) completed the inclusion form with reference to the translator. Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met.

QUALITY ASSESSMENT

The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Collaboration Reviewers' Handbook (Clarke 2000) used in RevMan. Allocation concealment for each trial was rated as belonging to one of three categories:

A. Adequately concealed (an adequate method to conceal allocation is described).
B. Concealment unclear ("random" allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
C. Inadequately concealed (an inadequate method of allocation concealment is described).

Excluded: random (or quasi-random) allocation clearly not used in the trial, or "random" allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:

A. Double-blind (blind outcome assessment and use of placebo described).
B. Single-blind (blind outcome assessment stated and no placebo used).
C. Blinding indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment - e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).

Excluded: clearly open outcome assessment used or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, of x-rays registered independently of clinical examination, of use of a placebo, and of examiners clearly not involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated the process for a random sample of approximately one third of those. Any disagreement was discussed and where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not be resolved an effort was made to contact authors directly to clarify the method used to conceal allocation or whether assessment of the main outcome had been carried out blind.

Other methodological characteristics of the trials such as blinding of participants (placebo or no treatment control), completeness of follow-up (proportion excluded) and handling of exclusions (extent to which reasons for attrition are explicitly reported, or losses are independent of treatment allocated) were not used as thresholds for inclusion. However, all assessments of study quality are described in the table of included studies, and were coded for possible use in meta-regression/sensitivity analyses.

DATA EXTRACTION
Data from all included studies were extracted by one reviewer (VM) using a pilot tested data extraction form. A second reviewer (JH) extracted data from a random sample of approximately one third of included studies. However, in future updates all reports will be data extracted and quality assessed in duplicate. Checking of interobserver reliability was limited to validity assessments. Again, data that could not be coded by the first reviewer were independently coded by the second, any disagreement was discussed and a third reviewer consulted to achieve consensus where necessary. Provision was made to exclude data where agreement could not be reached but this situation did not occur. Data presented only in graphs and figures were extracted whenever possible, but were included only if two reviewers independently had the same result. Attempts were made to contact authors through an open-ended request to obtain missing information or for clarification whenever necessary.

Additional information related to study methodology or quality that was extracted included: study duration (years of follow-up), comparability of baseline characteristics - methods used pre-randomization in sizing/balancing (stratification based on relevant variables) or used post-randomization in analysing/adjusting for possible differences in prognostic factors between groups, objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors), any co-intervention and/or contamination. Information on sponsoring institutions and manufacturers involved was also recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries severity at start (average DMFS, DFS, or other measure), background exposure to other fluoride sources (toothpaste, water/salt), year study began, location where study was conducted (country), setting where participants were recruited, and dental treatment level (F/DMF). Characteristics of the intervention that were extracted included: mode of application (who delivered the intervention), methods (technique/device) of application, prior- and post-application, fluoride active agents and concentrations used, frequency and duration of application, and amount applied.

Different ways of reporting caries increment (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units measured (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (deciduous teeth/surfaces, first molar permanent teeth/surfaces, approximal surfaces, etc), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiographical), and approaches to account or not for reversals in caries increment adopted (in a net or observed increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow-ups).

As we were aware that caries increment would be recorded differently in different trials we developed a set of a priori rules to choose the primary outcome data for analysis from each study: data on permanent teeth would be chosen over data on deciduous teeth, data on surface level would be chosen over data on tooth level, DFS data would be chosen over DMFS data and this would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted only', and this over data for 'erupting only'; data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological' only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated lesions; net caries increment data would be chosen over crude (observed) increment data; and
follow-up nearest to three years (often the one at the end of the treatment period) would be chosen over all other lengths of follow-up, unless otherwise stated. When no specification was provided with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices described above were assumed.

The table of included studies provides a description of all the main outcome data reported from each study with the primary measure featuring at the top. Where assessments of caries increments were made during a post-intervention follow-up period, the length of time over which outcomes were measured after the intervention ended was noted. All other relevant outcomes identified as being assessed in the trials are also listed in this table.

ANALYSES

Handling of results (main outcome data) of studies with more than one treatment arm.
In the studies with more than one relevant intervention group and a common (or more than one relevant) control group, such as those comparing different active fluoride agents or concentrations of fluoride ions to a placebo group, results (the numbers, mean caries increments and standard deviations) from all relevant experimental groups (and control groups) were combined in order to obtain a measure of treatment effect. This enables the inclusion of all relevant data in the primary meta-analysis, although may slightly compromise the secondary investigations of dose response.

Handling of missing main outcome data.
It was decided that missing standard deviations for caries increments that were not revealed by contacting the original researchers would be imputed through linear regression of log standard deviations on log mean caries increments. This is a suitable approach for caries prevention studies since, as they follow an approximate Poisson distribution, caries increments are closely related (similar) to their standard deviations (van Rijkom 1998).

Choice of measure of effect and meta-analyses of main outcome.
The chosen measure of treatment effect was the prevented fraction (PF), that is (mean increment in the controls minus mean increment in the treated group) divided by mean increment in the controls. For an outcome such as caries increment (where discrete counts are considered to approximate to a continuous scale and are treated as continuous outcome), this measure was considered more appropriate than the mean difference or standardised mean difference since it allows combination of different ways of measuring caries increment and a meaningful investigation of heterogeneity between trials. It is also simple to interpret. The meta-analyses were conducted as inverse variance weighted averages. Variances were estimated using the formula presented in Dubey 1965 which was more suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable. Random effects meta-analyses were performed throughout.

For illustrative purposes the results were also presented as the number of children needed to treat (NNT) to prevent one carious teeth/surface. These were calculated by combining the overall prevented fraction with an estimate of the caries increment in the control groups of the individual studies.

With the use of prevented fraction, it was not possible to perform the main outcome analyses in RevMan/MetaView (when the review was published). However, the raw results of the studies (n/mean/SD) were entered in RevMan and mean differences were presented without meta-analyses. If meta-analyses using standardised mean differences yielded materially similar results to those
using prevented fractions, we would also present these within MetaView. Deciduous and permanent teeth would be analysed separately throughout.

Investigation of heterogeneity

Heterogeneity was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95% confidence intervals and by formal tests of homogeneity undertaken prior to each meta-analysis (Thompson 1999).

In addition to aspects of study quality, four potential sources of heterogeneity were specified a priori as investigations of these formed part of the primary objectives of the review. We hypothesised that: (1) the effect of fluoride gels differs according to the baseline levels of caries severity, (2) the effect of fluoride gels differs according to exposure to other fluoride sources (in water, in toothpastes, etc), (3) the effect of fluoride gels differs according to mode/self-applied method of use, and (4) the effect of fluoride gels differs according to frequency of application and concentration. The association of these factors with estimated effects (D(M)FS PFs) were examined by performing random effects meta-regression analyses in Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998).

To allow such investigation, relevant data were dealt with as follows: data on 'baseline levels of caries' were calculated from the study sample analysed (final sample) unless otherwise stated, and were averaged among all relevant study groups. Data on 'background exposure to other fluoride sources' combined data on the use of fluoride toothpaste and the consumption of fluoridated water (or salt) and were grouped into two categories: one for studies which were based on samples provided with non-fluoride toothpaste and which were from non-fluoridated areas (non exposed), and another for studies based on samples using fluoride toothpaste or studies in fluoridated communities or both. When use or non-use of fluoride toothpaste was not clearly indicated in studies carried out in developed countries, it was assumed that fluoride toothpaste was widely used from the middle of the 1970s (Ripa 1989); this information was sought from authors (or obtained from other sources) when missing from studies carried out in other locations. When data on the year a study had begun was not provided this was calculated as a 'probable date' by subtracting the duration of the study (in years) plus one extra year, from the publication date of the study. The 'gel application modes/methods' were classified as either operator or self-applied under supervision and as self-applied supervised application by tray or by brush. Data on 'frequency of application' and 'concentration applied' have not been categorised, but a 'total intensity of application per year' covariate was produced by multiplying frequency of application (per year) by concentration of gel applied (in ppm F). Concentrations in multiple arm studies were averaged over fluoride gel groups prior to this calculation.

Further potential sources of heterogeneity were investigated by meta-regression, but these 'post hoc' analyses were to be reported as such and findings would be treated with caution. Again, sensitivity analysis would be performed if appropriate.

Investigation of publication bias

A funnel plot (plot of effect size versus standard error) was drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, though may also represent a true relationship between trial size and effect size. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger 1997.

Measures of effect and meta-analysis of other outcomes

For outcomes other than caries increment, continuous data would be analysed according to
differences in mean treatment effects and their standard deviations. Dichotomous outcome data were analysed by calculating risk ratios (RR) or, for adverse effects of fluoride treatment, risk differences (RD). The Cochrane Review Manager software (RevMan 4.1) was used for estimation of overall treatment effects. Again, random effects model was used to calculate a pooled estimate of effect. As a general rule only (relevant) outcomes with useable data would be shown in the analyses tables.

Description of studies

IDENTIFICATION OF REPORTS / STUDIES

Searching the core database in Reference Manager (using 'gel*' or 'fluoride gel*' or 'amine fluoride gel' or 'acidulated phosphate fluoride*' or 'acidulated fluorophosphate' or 'Elmex' as keywords combined with 'gel' or 'tray' in notes, and with 'gel' in titles and in all other fields) retrieved 694 records from MEDLINE, EMBASE, BIOSIS, SCISEARCH, SSCISEARCH, CINAHL, ERIC, ISTP and DISSERTATION ABSTRACTS. Searching LILACS (48 records), BBO (47 records), CCTR (86 records), SIGLE (6 records), and NIDR (24 records) databases produced a total of 211 records which were scanned outside Reference Manager. The last time LILACS and BBO were searched yielded 210 records (142 and 68 records respectively, also scanned outside Reference Manager). Searching OLD MEDLINE produced 545 records. Thus, 1670 records yielded by the original electronic searches for topical fluoride trials were scanned, but many of these were duplicates not merged in the core database. The specific MEDLINE search for fluoride gel trials performed without RCT filter produced 342 records, and the same specific search performed in the OHG specialised register produced 51 records. The search of non-electronic sources (reference lists of relevant studies, review articles or book chapters, and contacting authors) produced other 21 records for closer inspection. One of the six manufacturers of fluoride gel contacted, GABA, provided a list of 409 records from a search performed in GALIDENT (Database of GABA Library in Dentistry) using the keyword 'amine fluoride'. However, search results from these and, if provided, from other manufacturers will be reported in updates of this review.

From the search results above, a total of 88 reports were considered potentially eligible, sought and assessed further (including some only available as abstracts).

SELECTION OF STUDIES

From the 88 reports that were sought for detailed assessment, 31 were considered immediately irrelevant for this review, mainly as a result of the interventions compared with or used in addition to fluoride gel. Forty studies (57 reports) are considered in this review: these comprise 34 reports relating to 25 included studies (one of the reports relates to a study treated as two independent trials), 20 reports relating to 13 excluded studies, and three reports relating to two studies waiting assessment (in Polish) which require translation. There are no reports of ongoing studies. Twelve non-English reports (nine studies) listed either under included or excluded studies have been fully assessed: five in German (by a German translator, with the contact reviewer), four in Portuguese (by the contact reviewer), one in Russian (by a Czech translator, with the reviewer), one in Bulgarian (by a Bulgarian translator, with the reviewer), and one in Hungarian (by a Hungarian translator, with the reviewer).

EXCLUDED STUDIES

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See 'Characteristics of excluded studies' for the description of reasons for rejecting each study.

The 13 studies in this section were excluded for a variety of reasons. Two studies were clearly not randomized/quasi-randomized or did not imply randomization (not stated and not possible); one of these also had a very high dropout rate. One study did not mention or indicate blind outcome assessment (but described use of random or quasi-random allocation). Attempts were made to contact the author of this study, but no reply was received so it was assumed that blinding had not been done, and the study was excluded. Two studies did not mention or indicate random or quasi-random allocation or blind outcome assessment. The authors of these studies were contacted and due to a negative reply on blind outcome assessment, the studies were excluded. Three studies did not mention or indicate random or quasi-random allocation and blind outcome assessment. One of these also did not report main outcome data for control group. Attempts were made to contact the authors of these studies, but no replies were received so it was assumed that random allocation and blind assessment of outcome had not been done, and the studies were excluded.

Four studies had other fluoride-based interventions in addition to fluoride gel. One of these also did not state/indicate random or quasi-random allocation and blind outcome assessment; another was not randomized/quasi-randomized and the length of follow-up for the main outcome assessment was less than one year/school year; another had an 'inappropriate placebo' (not an inactive treatment), and another did not report any relevant outcome data. One study included institutionalised children with specific health problems.

INCLUDED STUDIES
See 'Characteristics of included studies' table for details of each study.

There are 25 trials included. The study conducted by Marthaler 1970 has been treated as two independent trials, since the results for the two age groups in the study have been reported separately as distinct studies. All 34 reports were published between 1967 and 1999. The 25 trials were conducted between 1964 and 1996: 12 during the 1960s, seven during the 1970s, five during the 1980s and one in the 1990s. Twelve trials were conducted in USA (eight of these during the 1960's), five in Europe, four in Brazil, one in each of the following countries: Canada, Israel, Hawaii, and Venezuela. Six studies had more than one publication, one of these studies had six published reports. While three of the included studies clearly stated no involvement with any manufacturer of fluoride gel, 10 acknowledged assistance (product provision, etc) and/or partial support from fluoride gel manufacturers.

Design and methods
All the included studies used parallel group designs. Eight of these had more than one fluoride gel treatment group compared to a control, and among these, one trial had two treatment groups and two placebo control groups. With regard to type of control group used, nine trials used a no treatment control group, and the remaining 16 used a placebo control group, four of which used an inactive treatment other than gel ('placebo' solution). The study duration (indicated by the total length of follow-up as well as the treatment duration) ranged from one to four years among included trials: one lasted four years, nine lasted three years, 11 lasted around two years, and the remaining four lasted 1.5 years or one year. Studies were large with only four allocating less than 200 children to relevant study groups. The total number of children participating in the trials (given by the sample analysed at the end of the trial periods) was 7747, and ranged from 41 in the smallest trial to 631 in the largest trial. All participants were recruited from school settings.

Participants
All included trials reported that the participants were aged 15 or less at the start, with similar numbers from both sexes (with the exception of Ran 1991, who included male participants only in the study). The ages of the children ranged from two to 15 years; 14 trials included participants who were 12 at start, and two trials included children younger than six years of age (in which deciduous teeth only were assessed for caries development). Decayed, missing and filled surfaces (DMFS) at baseline reported in all but three of the studies, ranged from 0.24 to 12.2, and was 3.7 defs in one of the two studies that reported data for deciduous teeth (where 'e' is teeth indicated for extraction). With regard to 'background exposure to other fluoride sources', all studies reported exposure or not to systemic sources, only five studies were conducted in fluoridated communities (water fluoridation in three and salt fluoridation in two studies); from the remaining 20 studies, no (or very low) exposure to fluoride dentifrices or to other fluoride sources was clearly reported in four studies, and substantial exposure to fluoride toothpaste (over 95%) was reported in three studies; exposure or not to fluoride toothpaste had to be assumed in the remaining 13 studies based on study location and year started, as described above. Information on dental treatment level could only be obtained from the most recently conducted study.

Interventions

Fourteen of the included trials reported gel application carried out by professionals and in the remaining 11 trials gel was self-applied under supervision (by dental personnel in four trials, by trained non-dental personnel in five trials and by mothers and dental personnel in another; data were not available for one of the studies). Gel was most usually administered using a tray (15 trials) or a brush (six trials), but the use of floss was reported in the most recent trial, and cotton application was reported in two trials carried out in Brazil and in one from USA. A variety of fluoride gel types were used, including Acidulated Phosphate Fluoride (APF), Sodium Fluoride (NaF), Amine Fluoride (AmF) and Stannous Fluoride (SnF2) (used in the most recent study only). The fluoride concentrations ranged from 24,25 ppm F (SnF2) to 12,500 ppm F (AmF and NaF). The common 12,300 ppm F APF gel concentration was used in at least 13 trials. The three studies which did not report the APF gel concentration are likely to have used the standard 12,300 ppm F, as all were carried out in the same country, started in consecutive years, and had APF gel applied by professionals once a year. The application frequency (times per year) ranged from once a year (the most common frequency of application, reported in seven studies) to 140 times a year (reported in the study of Englander 1967), but it varied greatly among the studies, with only five studies reporting 'twice a year' application frequency. With the exception of the study of Shern 1976 (with five consecutive - once a day or once a week applications in one year) all 14 studies where fluoride gel was professionally applied reported a frequency of application of four times a year or less; likewise, with one exception (Trubman 1973) where frequency of application was four times a year, the 11 studies of self-applied gel reported a frequency of application of five times a year or more. The amount of gel applied was reported in only a few studies (either in 'ml' or 'gr') and ranged from 1 to 4ml, and from 1 to 3mg. Where the application time was reported it ranged from two to 10 minutes, with 16 studies reporting three to five minutes gel application time. As regards the performance of some form of prior (professional or self-performed) tooth prophylaxis before administering the gel this was used in 16 studies; as long as performed with no paste or with a non-fluoride paste (if with a fluoride paste the trial would have been excluded), the prior toothcleaning was considered by the reviewers as a possible part of the technique of gel application and not as a separate intervention on its own.

Outcome measures

All 25 included trials reported caries increment data at the tooth surface level (DMFS reported in 23 trials, defs in the other two trials). Ten of the 23 trials reported caries increment data at the tooth level (D(M)FT) and both trials that reported caries increment data for deciduous teeth only
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(defs), also reported data at the tooth level (deft). With regard to the components of the DMFS index used (and types of teeth/surfaces assessed), 18 trials reported DMFS data (one trial for first molars only and 17 trials for all tooth surface types), and other five reported DFS data (one trial for all approximal surfaces only and four trials for all tooth surface types), one of these also reported DS and FS data separately. Two of the 10 trials which reported D(M)FS data on specific teeth or tooth surfaces - first molars, occlusal, mesio-distal (approximal) and/or buco-lingual - did not report data on all tooth surfaces. Fourteen trials presented D(M)FS data at more than one follow-up time: 12 trials at one year follow-up time, 13 trials at two years, and nine trials at three years. In four trials, assessments of D(M)FS increments were also made during a post-intervention follow-up period.

Clinical (all 25 trials) and radiographic examinations (five trials) provided the definition of different stages or grades of caries lesions. These have been grouped into two basic grades for each method of examination: NCA = non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor/walls) or showing frank cavitation; ER = any radiolucency in enamel/enamel-dentin junction; DR = radiolucency into dentin; 14 trials presented results using one caries grade only (CA/DR), the 11 remaining trials either did not report the grade (eight trials), in which case CA/DR was assumed, or reported both CA and NCA grades, in which case CA was chosen. Data on state of tooth eruption considered were specified in 11 trials: data for teeth erupted at baseline only were reported in 10 trials and combined data for erupting and erupted teeth were reported in only one trial. Only the two studies of Marthaler 1970 did not use full mouth recording.

Data on the proportion of children developing new caries were reported in one trial and on the proportion of children not remaining caries-free in two trials. Adverse symptoms (nausea/vomiting) were reported to have been assessed in three trials: two trials had useable data (one reported that there were no events, another reported that there were three participants from the treatment group who experienced one event each) but the remaining trial reported no clear data (the event was reported to have occurred "in many subjects"). Other outcome measures were reported, but without complete or useable data: 'no side effects' was reported in one trial, and 'no etching of enamel' was reported in another trial. Data for unacceptability of treatment (as measured by dropouts/exclusions) were fully reported in six of the nine no treatment control trials.

Methodological quality of included studies

Based on 28 studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, interrater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73). There was a considerable difference in the quality of the studies in this review (using the reported information and additional information obtained from investigators).

ALLOCATION CONCEALMENT
Eighteen included trials were described as randomized and assigned code B as no description was provided on how the 'random' allocation was done, and seven trials were considered to be quasi-randomized and assigned code C. None of the trials which described the randomization process or whose investigators provided further information in answer to our enquiry could be assigned code.
A (adequate concealment of allocation fully described).

BLINDING
Double-blinding was described in 14 trials (score A), single-blinding (blind outcome assessment but no placebo used) was described in six trials (score B) and blind outcome assessment likely/unclear was indicated in five trials (score C). Eleven of the 14 trials described as double-blinded were scored B for allocation concealment, and two of the five trials where blind outcome assessment was likely/unclear used a placebo control group.

FOLLOW-UP
All the participants included in the final analysis/present at the end of each study, as a proportion of all the participants present at start in all studies was 72% (6286 analysed out of 8739 randomized), excluding the six studies with no data on participants randomized to relevant groups. Dropout rates could be obtained from all but two of the 25 included studies. There was considerable variation in dropout rates ranging from 8% at one year to 55% at three years. Where this information was supplied, the most common reason for attrition was that participants were not available for follow-up examination at the end of the study; exclusions based on presence in all follow-up examinations were reported in nine trials, and exclusions based on compliance were reported in three trials. Other reasons for exclusions (when given) included characteristics of participants that should have been used as eligibility criteria before randomization (use of orthodontic bands, lifetime exposure to fluoridated water). Only one trial reported the numbers excluded according to reason for attrition.

OTHERS
Type of randomization: stratified randomization was used in 12 trials (but there was no mention of use of blocking).
Baseline comparisons and handling of any differences: two of the trials described as 'balanced' (for which randomization may have succeeded to produce nearly exact balance) did not report the actual values for the baseline characteristics (such as initial caries levels). Some degree of imbalance was reported in four trials (for characteristics considered most influential, usually initial caries levels) and either described as not significant or adjustment mentioned to have resulted in trivial differences in effect estimates.
Objectivity/reliability of primary outcome measurement: diagnostic methods used (clinical or radiographic) were described in all studies, but thresholds/definitions used for caries and monitoring of diagnostic errors were not always clearly described (see 'Notes' in the 'table of included studies' for methodological features assessed).

Results

EFFECT OF FLUORIDE GEL ON DENTAL CARIES INCREMENT
The effects of fluoride gels on dental caries increment were reported in a variety of different ways in the included studies. Where appropriate and possible these have been combined to produce pooled estimates as described in the methods section. The results are reported separately here for: (1) Decayed, Missing and Filled Surface Prevented Fraction (D(M)FS PF); (2) Decayed, Missing and Filled Teeth Prevented Fraction (D(M)FT PF); (3) D(M)FS and D(M)FT pooled using a standardised mean difference (SMD); (4) effects on deciduous dentition.
Standard deviations of mean caries increment data (new D(M)FS) were (partly) missing in four of the 23 studies which contributed data (Abadia 1978; Bijella 1981; Mestrinho 1983; Ran 1991). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries increment), (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses.

Similarly, this same regression equation was used to estimate missing standard deviation data for two of the 10 trials reporting D(M)FT data (Bijella 1981; Mestrinho 1983). No pooled estimate of the effects of fluoride gels on caries increment in deciduous teeth could be produced as neither of the two studies contributing data provided standard deviations of mean caries increment (new defs).

Effect on tooth surfaces: D(M)FS prevented fraction
For all 23 trials combined, the D(M)FS prevented fraction pooled estimate was 0.28 (95% CI, 0.19 to 0.37; p<0.0001), suggesting a substantial benefit from the use of fluoride gel. Substantial heterogeneity in results could be observed graphically and statistically (Q= 135 on 22 degrees of freedom, p<0.0001).

Meta-regression, subgroup and sensitivity analyses: D(M)FS prevented fraction
Univariate meta-regression suggested no significant association between estimates of D(M)FS prevented fractions and the pre-specified trial characteristics: baseline levels of caries, background exposure to other fluoride sources, background exposure to fluoridated water, background exposure to fluoride toothpaste, gel application mode (operator/self), gel application self-applied method (tray/brush), and fluoride concentration. There was an association of frequency of application as well as of 'total intensity of application per year' (frequency x concentration) with the prevented fraction, but both became non-significant when the trial of Englander 1967, a study with high influence, was excluded from the analysis.

Further univariate meta-regression analyses showed no significant association between estimates of D(M)FS prevented fractions and length of follow-up (duration of study), allocation concealment (random/quasi-random), blinding of outcome assessment (blind/blind likely or unclear) or drop-out rate. However, the pooled estimated treatment effect was 19% (95% CI, 5% to 33%; p=0.009) greater in trials with no treatment rather than placebo control groups. This association between type of control group and D(M)FS prevented fraction remained significant after excluding the trial of Englander 1967. The pooled estimate of treatment effect on D(M)FS PF from the nine trials with a no treatment control group was 0.38 (95% CI, 0.24 to 0.53; p<0.0001), while that from the 14 placebo-controlled trials was 0.21 (95% CI, 0.14 to 0.28; p<0.0001). There remained statistically significant heterogeneity in the analysis of the 14 trials with placebo control groups (Q= 22.52 on 13 degrees of freedom, p= 0.05) but this was substantially less than that observed when all trials were included in the meta-analysis. Although this was a post hoc analysis and thus should be viewed with caution, we have decided to present the results of the D(M)FS PF meta-analyses subgrouped by type of control group.

For each study, the D(M)FS prevented fraction and 95% CIs can be viewed in the Tables of other data; the results of the random effects meta-analyses of D(M)FS prevented fractions (performed in Stata) are given in Additional Table 01: Meta-analyses of prevented fractions. Forest plots showing the effects of fluoride gel (prevented fractions and 95% CI) on D(M)FS increments resulting from these meta-analyses, subgrouped by type of control group, are available on the Cochrane Oral Health Group web site (www.cochrane-oral.man.ac.uk). In addition, forest plots showing the effects of fluoride gel (PFs and 95% CIs) on D(M)FS increments resulting from a meta-analysis.
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stratified by type of control group are available in the 5th review in this series (whose results
invigorate the discussion of the influence of this factor on effect estimates): Topical fluoride
(toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and
adolescents (Comparison 01, Sub-categories 02 for placebo-controlled gel trials, and 05 for non-
placebo control gel trials).

The association between type of control group and D(M)FS prevented fraction also remained
significant when each one of the above investigated potential effect modifiers were included in
bivariate meta-regression analyses, with or without the trial of Englander 1967; the exceptions
occurred for adjustment by self-applied method of application, fluoride concentration and intensity
of application, when the association between prevented fraction and type of control group became
non-significant, irrespective of exclusion or not of the trial of Englander 1967, and for adjustment
by blinding of outcome assessment if the trial of Englander 1967 was excluded. While an
association between blind outcome assessment and prevented fraction not shown when adjusting
for type of control group appeared after excluding the trial of Englander 1967 from the analysis,
associations between (operator/self applied) mode of gel delivery and prevented fraction and
between application frequency and intensity and prevented fraction were shown when adjusting for
type of control group, but did not remain after excluding the trial of Englander 1967 from the
analysis.

Meta-regression results for all potential effect modifiers, including the Englander study and in each
case adjusting for type of control group are given in Additional Table 02: Random effects meta-
regression analyses of prevented fractions: D(M)FS. These results must be interpreted with caution
given the observational nature of the comparisons and the large number of comparisons made.
Note that differences between subgroups from meta-regression may differ from differences
between separate meta-analyses in separate subgroups (Additional Table 01) due to an assumption
of similar residual heterogeneity in the meta-regression.

In order to illustrate the magnitude of the effect, numbers of children needed to treat (NNT) to
prevent one D(M)FS were calculated based on the pooled D(M)FS prevented fraction and on the
caries increments in the control groups of the placebo-controlled trials, which ranged from 0.17 to
5.4 D(M)FS/year. The overall caries-inhibiting effect (%PF) derived from the pooled results of the
14 trials with placebo control groups was 21% (95% CI, 14% to 28%). In populations with a
caries increment of 0.2 D(M)FS per year (at the lowest end of the results seen in the included
studies), this implies an absolute caries reduction of 0.042 D(M)FS/year, equivalent to an NNT of
24 (95% CI, 18 to 36). In populations with a caries increment of 2.2 D(M)FS per year (at the mid
range of the results seen in the included studies), this implies an absolute caries reduction of 0.46
D(M)FS/year, equivalent to an NNT of 2 (95% CI, 1 to 3).

Funnel plot: D(M)FS prevented fraction
A funnel plot of the 23 included studies reporting D(M)FS PFS indicated a relationship between
prevented fraction and precision (related to sample size). The funnel plot is asymmetrical and the
Egger formal test for asymmetry (Egger 1997) suggests statistically significant asymmetry
(intercept (95% CI) = -2.7 (-5.08 to -0.31) (p= 0.03)). If this was a reflection of publication bias it
would imply that small studies with especially large beneficial effects of fluoride gel were missing.
The clinical significance of this result is unclear and appears to be related to the effects of two
outliers, a small study suggesting a large deleterious effect of fluoride gel and a large study
suggesting the largest positive effect.

The funnel plot is available on the Cochrane Oral Health Group web site (www.cochrane-
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oral.man.ac.uk). In addition, a funnel plot of the 23 trials comparing fluoride gel with placebo/no
treatment is available in 'Additional Figure 01', where D(M)FS standardized mean differences are
plotted against standard errors (see 'Alternative treatment effect measure' below).

Effect on whole teeth: D(M)FT prevented fraction
Ten trials reported data which allowed the calculation of the D(M)FT prevented fraction. All of
these trials are also included in the analysis of D(M)FS PF. The pooled estimate of D(M)FT
prevented fraction was 0.32 (95% CI, 0.19 to 0.46; p< 0.0001). There was substantial
heterogeneity between trials (Q= 102.50 on 9 degrees of freedom, p< 0.0001).

As with the estimates of the effects of gels on D(M)FS PF, a meta-regression suggested that the
estimates from trials using no treatment as opposed to placebo controls were substantially higher,
in this case by 26% (95% CI, 4% to 48%; p=0.02). The pooled estimate of the D(M)FT prevented
fraction from the six trials with a no treatment control group was 0.43 (95% CI, 0.29 to 0.5; p<
0.0001), while that from the four placebo-controlled trials was 0.18 (95% CI, 0.09 to 0.27; p<
0.0001). When the meta-analysis was confined to those trials with placebo controls, there remained
no statistically significant heterogeneity (Q= 3.18 on 3 degrees of freedom, p= 0.37).

For each study, the D(M)FT prevented fraction and 95% CI can be viewed in the Tables of other
data. The results of the random effects meta-analyses of D(M)FT prevented fractions performed in
Stata are also presented in Additional Table 01: Meta-analyses of prevented fractions.

Alternative treatment effect measure: Standardized mean difference (SMD)
Due to the character of D(M)FS data, mean caries increments are closely related to their standard
deviations (they are about the same). Thus, meta-analyses using standardised mean differences (the
difference between two means divided by an estimate of the within group standard deviation)
yielded materially similar results to those using prevented fractions (the difference in mean caries
increments between the treatment and control groups divided by the mean increment in the control
group). We therefore decided to present D(M)FS and D(M)FT SMDs in RevMan/Metaview,
grouped by type of control group (placebo/no treatment) since it was not possible to present the
main outcome analyses with prevented fractions. The results of these analyses are very similar to
and consistent with those reported above.

For the 14 placebo-controlled trials the pooled D(M)FS SMD estimate was 0.20 (95% CI, 0.10 to
0.29; p< 0.0005). There was heterogeneity between trials (chi-square = 29.55 on 13 degrees of
freedom, p< 0.0055). The pooled estimate in the nine trials with no treatment control groups was
0.46 (95% CI, 0.27 to 0.65; p< 0.0001) with substantial heterogeneity (chi-square = 44.42 on 8
degrees of freedom, p< 0.0001).

The pooled estimate of D(M)FT SMD based on the four placebo-controlled trials was 0.19 (95%
CI, 0.09 to 0.29; p< 0.0002). There was no statistical evidence of heterogeneity (p= 0.43). The
pooled estimate of D(M)FT SMD based on the six trials with no treatment controls was 0.73 (95%
CI, 0.32 to 1.13; p< 0.0004), and heterogeneity was substantial (chi-square = 76.81 on 5 degrees
of freedom, p< 0.0001).

Effect on deciduous dentition (defs increments)
Neither of the two trials reporting caries increment in deciduous tooth surfaces provided standard
deviations or data from which these could be derived and their results were therefore not pooled.
The trial of Englander 1978 reported equivocal results (no demonstrated effect of fluoride gel);
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while Treide 1988 reported an effect (def PF) of fluoride gel of 0.39 (CI not obtainable).

EFFECT OF FLUORIDE GEL ON OTHER OUTCOMES

Few trials report data for other relevant outcomes.

Proportion developing new caries and proportion not remaining caries-free
The only trial reporting on the proportion of children developing one or more new caries (Gisselsson 1999) reported a risk ratio (RR) of 0.82 (95% CI, 0.68 to 0.99). This is equivalent in the study population to an NNT to prevent one child from developing caries of 8 (95% CI, 4 to 100). Two trials reported results on the proportion of children not remaining caries-free (Gisselsson 1999; Englander 1978). The pooled estimate (random effects meta-analysis) of the risk ratio was 0.66 (95% CI, 0.45 to 0.97; chi-square for heterogeneity 0.55 on 1 degree of freedom, p= 0.46). This corresponds to an NNT to prevent one child ceasing to be caries-free of 7 (95% CI, 4 to 50) in a population with a caries risk the same as that found in the control groups in these trials.

Adverse symptoms (nausea/vomiting)
Only two trials reported usable data on adverse events (Mestrinho 1983; Hagan 1985), but one of these had no events in both arms. The pooled estimate of the risk difference between the gel and placebo arms was 0.01 (95% CI, -0.01 to 0.02; chi-square for heterogeneity 0.8 on 1 degree of freedom, p= 0.37), ie. marginally favouring the Placebo/No-treatment (PL/NT) arm, although the results were consistent with no difference.

Unacceptability of treatment (dropouts/exclusions)
The pooled estimate of the relative risk of dropping out from the gel as opposed to the non-treatment arm in the six non-placebo controlled trials that reported dropouts was 1.09 (95% CI, 0.70 to 1.72). There was substantial heterogeneity in these results (chi-square = 28.19 on 5 degrees of freedom, p< 0.0001).

Discussion

The main aim of this review was to estimate the effects on caries of using fluoride gel in children compared to placebo or no treatment. Over 4400 children were included in the trials comparing a fluoride gel with a placebo and over 2700 in those comparing fluoride gel with no treatment. For the great majority of children the fluoride gel they received was Acidulated Phosphate Fluoride (APF). There is clear evidence that fluoride gel has a caries-inhibiting effect. Basing the estimate on those trials with placebo rather than no-treatment controls, provides a more conservative estimate of treatment effect and suggests that use of this intervention is associated with a 21% (95% CI, 14% to 28%) reduction in decayed, missing and filled tooth surfaces. This would correspond to a number needed to treat (NNT) of 2 to avoid 1 D(M)FS per year in a child population with a caries increment of 2.2 D(M)FS per year (in the middle range of control group rates for included studies), or an NNT of 24 for children from a population with a caries increment of 0.2 D(M)FS/year (at the lowest end of the observed range).

This estimate is very similar to that reported in a previous meta-analysis on the caries preventive effect of fluoride gels (van Rijkom 1998), which found a pooled D(M)FS estimate of a 22% (95% CI, 18% to 25%) reduction in caries increment. There were substantial differences in selection
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criteria and methods between the reviews. Of the 19 studies included in the review by van Rijkom 1998, nine were also included in this review. Van Rijkom et al (van Rijkom 1998) included four trials where fluoride toothpaste in gel form was applied daily by toothbrush in standard concentrations (found in toothpastes) of less than 1500 ppm F, which did not meet the inclusion criteria for our review. The other six studies not included here were excluded for a variety of reasons. A further 10 studies were identified for this review including one (Gisselsson 1999) published after the van Rijkom review.

A secondary aim of this review was to examine whether there was any relationship between the caries-preventive effectiveness of fluoride gel and a number of factors including the initial level of caries severity, background exposure to fluoride and the mode and frequency of use. We were unable to detect a clear relationship between any of these factors and the magnitude of the treatment effect in spite of substantial variation between trials in these factors. This result should, however, be interpreted with caution. Even a meta-analysis including 23 trials has very limited power to detect such relationships and, like all analyses of observational data, is subject to the problem of potential confounding. For some factors such as 'background exposure to fluoride' there is, in addition, the problem of potential misclassification due to the poor quality of the reported data. We were forced to make a number of assumptions, for instance classifying 'use of fluoride toothpaste' for 13 of the studies on the basis of the year when the study was conducted. We were also forced to treat this as a dichotomous variable (before/after mid 1970s), although it is likely that use of fluoridated toothpaste gradually increased during the 1960s, 1970s, and 1980s. Similarly we grouped exposure to fluoride in toothpaste and fluoride in water into a single dichotomous variable which is likely to group studies whose participants had quite different levels of baseline exposure. These problems will bias any estimates of effect towards the null hypothesis.

We did observe significantly greater treatment effect with increased frequency and intensity (frequency x concentration) of gel application, before and after adjustment in the analysis for type of control group, and, after such adjustment, with self-applied compared with operator-applied gel treatment. Although plausible, these relationships were however dependent on the inclusion of one study with particularly powerful effects (Englander 1967). After exclusion of this study in a sensitivity analysis no significant association was seen with either of these factors. Attempts to disentangle these relationships are further complicated by the fact that those studies assessing the self-application of fluoride gels tended to employ higher frequencies of application. With the exception of one study (Trubman 1973) where frequency of application was four times a year, the nine studies of self-applied fluoride gel reported a frequency of application of five times a year or more. By contrast, the studies where fluoride gel was professionally applied, with the exception of one study (Sheni 1976) in which five consecutive daily or weekly applications in one year were performed, reported a frequency of application of four times a year or less. Nevertheless, considering that a 2.5% (95% CI, 0.8% to 4.2%, p<0.009) increase in effect is shown per 10 extra applications of fluoride gel/year (see Additional Table 02), little/no difference of treatment effects should be expected between the once and the twice a year lower frequency of application range with the traditional operator-applied mode of APF gel treatment. More robust investigations of these aspects of the intervention require direct, head-to-head comparisons of different frequencies and intensities, which were not within the scope of this review.

We made a thorough attempt to investigate sources of heterogeneity in this review, examining factors related to participants, interventions and study quality. None of the a priori specified factors was clearly related to heterogeneity. The only factor which was significantly related to heterogeneity of effect was whether the study employed a placebo or a no-treatment control group. The latter group of studies was associated with a 19% higher estimate of treatment effect on the
main outcome than those with a placebo control group. Blind assessment of outcome was an inclusion criterion for this review but clearly participants could not have been blinded in trials with no treatment controls. Although it is unclear why this should have been associated with differences in outcome in these particular circumstances, type of control group can be considered a useful 'proxy' for the use or not of double-blinding in included studies, a key methodological feature that probably represents the best indicator of study quality in this review. No association with treatment effect could be demonstrated for the key quality domain of allocation concealment, possibly due to the fact that this process was poorly described in the studies included.

We observed a degree of asymmetry in the funnel plot which suggested an association between smaller studies and a lower estimate of treatment effect. Publication bias is usually reported to result in a lower probability of publication of small studies with negative effects, the reverse of what is observed here. This asymmetry was strongly influenced by two outliers, a small study suggesting large negative effects out of line with all other results and a large study, which reported the largest positive effect. There may be other reasons for differences between the average effects in small and large studies and this result may well represent the effects of confounding by other study characteristics.

We found little useful information about the effects of fluoride gels on a number of other clinically important outcomes such as caries incidence in the deciduous dentition, use of dental services and acute side effects, nor on epidemiologically important outcomes such as the proportion of children remaining caries free. We also found no information on other adverse effects such as fluorosis, tooth staining, or oral allergic reactions. This lack of evidence about adverse effects makes it more difficult for clinicians and policy makers to weigh the benefits of fluoride gels in preventing caries against possible side effects.
Reviewers' conclusions

Implications for practice

This review suggests that the application of fluoride gels, either by professionals or self-applied, is associated with a substantial reduction in caries increment. We found no evidence that this relative effect was dependent on baseline caries level or exposure to other fluoride sources, although this result should be interpreted with caution. A higher D(M)FS prevented fraction was shown with increased frequency, intensity of application and with the self-applied gel treatment (where a higher frequency of application is apparent), although these relationships were dependent on the inclusion of one study with particularly powerful effect. Unfortunately the review does not provide useful information on the likelihood of significant side effects with this treatment.

Implications for research

The quality of the trials included in this review is relatively poor and many reports lacked important methodological details. This is likely in part to be due to the fact that most are relatively old. Many characteristics considered crucial for excluding bias, such as clearly stated randomization and allocation concealment, have only been more emphasised in later years, after most of the gel trials were reported. However, given the clarity of the results, further randomized comparisons of fluoride gel and placebo alone would be hard to justify. Head-to-head comparisons of fluoride gels and other preventive strategies may provide more useful information. It is important that future trials should include the assessment of potential adverse effects. The evaluation of possible differences in effect associated to fluoride gel application features, such as frequency of application, should be based on available/future trials that directly address the comparison of such features.
## Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
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<tr>
<td>Abadía 1978</td>
<td>Stratified quasi-random allocation; blind caries assessment stated but unclear (C); non-placebo-controlled; 13% drop-out after 1 year (study duration = 1 year). Natural losses only; no differential losses among groups.</td>
<td>254 children analysed at 1 year (available at final examination). Age range 11-12 years. Surfaces affected: 12.2 DMFS Exposure to other fluoride: none assumed Year study began: 1977 Location: Brazil</td>
<td>FG + ptc (2 groups)** versus NT (APF group 1 = 12,300 ppm F, APF group 2 = 12,300 ppm F). Operator-applied, with cotton-paint, once a year, applied for 4 minutes.</td>
<td>lyNetDMFS increment - (CA)(E). Reported at 1 year follow-up. O-DMFS MD-DMFS BL-DMFS Dropout</td>
<td>Participants randomized (N = C 291). Baseline characteristics (dental age, DMFS, gender) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = CA; state of tooth eruption included = E; diagnostic errors NR. **Prior prophylaxis with non-fluoride paste carried out in FG groups only.</td>
</tr>
</tbody>
</table>
| Bijella 1981 | Stratified quasi-random allocation; blind caries assessment stated but unclear (C); non-placebo-controlled; 20% drop-out after 1.5 years (study duration = 1.5 years). Exclusions based on 'statistical reasons' (made at random to keep groups of equal sizes, after 11% natural loss). | 320 children analysed at 1.5 years (after exclusions, available at final examination). Age range 7-10 years. Surfaces affected: 6.6 DMFS Exposure to other fluoride: none assumed Year study began: 1979 Location: Brazil | FG + ptc** versus NT (APF group = 12,300 ppm F). Operator-applied, with cotton-paint, once a year, 2ml applied for 4 minutes. | 1.5yDMFS increment - (CA)(E). Reported at 1.5 years follow-up. O-DMFS MD-DMFS BL-DMFS DMFT(CA)(E) Dropout (no data by group) | Participants randomized (N = C 401); numbers (natural dropout) by group NR. Baseline characteristics (dental age, DMFS, DMFT, gender) 'balanced'. Clinical (VT) caries assessment by four examiners; diagnostic threshold = CA; state of tooth eruption included = E; reversal rate = 2.2% and 0.7% of observed DMFS increment in FG and control groups respectively. **Prior prophylaxis with non-fluoride paste carried out
Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

**Bryan 1970**
- Random allocation; single-blind (B);
- non-placebo-controlled;
- 28% drop-out after 2 years (study duration = 2 years).
- Reasons for attrition NR; no differential group losses.
- 208 children analysed at 2 years (available at final examination).
- Age range 8-12 years (average = 9.5).
- Surfaces affected: 8.3 DMFS
- Exposure to other fluoride: none assumed
- Year study began: in/before 1966
- Location: USA
- FG+ptc versus NT+ptc (APF, concentration NR).
- Operator-applied, with tray, once a year, applied for 4 minutes.
- 2yNetDMFS increment - (CA).
- Reported at 1 and 2 years follow-ups.
- DMFT(CA)
- Dropout
- 2yNetDMFS increment - (CA).
- Reported at 0.5, 1, 1.5, and 2 years follow-ups.
- Dropout
- 3yNetDMFS increment - (E).
- Reported at 3 years follow-up.
- NetDMFT(E)

**Cobb 1980**
- Random allocation; single-blind (B);
- non-placebo-controlled;
- 19% drop-out after 2 years (study duration = 2 years).
- Reasons for attrition NR; differential group losses (but reported as NS difference).
- 193 children analysed at 2 years (available at final examination).
- Age range 11-14 years.
- Surfaces affected: 5.7 DMFS (data from original sample only)
- Exposure to other fluoride: toothpaste assumed
- Year study began: in/before 1977
- Location: USA
- FG+ptc versus NT+ptc (APF group = 12,300 ppm F).
- Operator-applied, with cotton-paint, twice a year, applied for 4 minutes.
- Participants randomized (N = B 237).
- Baseline characteristics (age, gender, ethnicity, regularity of dental care) described as 'balanced' (values NR); initial DMFS balanced.
- Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; diagnostic errors NR.

**Cons 1970**
- Random allocation; double-blind ('A');
- placebo-controlled ('PL');
- 26% drop-out after 3 years (study duration = 3 years).
- Natural losses; exclusions based on presence in all follow-up examinations; differential group losses.
- 589 children analysed at 3 years (present for all examinations).
- Age range 6-11 years (average = 8).
- Surfaces affected: 3 DMFS (first molar)
- Exposure to other fluoride: none assumed
- FG+ptc versus 'PL'+ptc (APF group = 12,300 ppm F).
- Operator-applied, with tray, once a year, applied for 4 minutes.
- Participants randomized (N = B 795).
- Baseline characteristics (DMFS, DMFT) with some imbalance, but "adjustment made little difference in the magnitude of caries increment".
- Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; diagnostic errors NR.
### Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

#### DePaola 1980
- **Random allocation; double-blind (A); placebo-controlled; drop-out rate NR nor obtainable (study duration = 2 years + 1 year post-study period).**
- **Exclusions based on compliance and presence in both follow-up examinations; any differential group losses not assessable.**
- **Year study began:** 1964
- **Location:** USA
- **270 children analysed at 1* year (after exclusions, present for both examinations).**
- **Age range 12-14 years (average = 13).**
- **Surfaces affected:** NR
- **Exposure to other fluoride:** toothpaste assumed
- **Year study began:** in/before 1977
- **Location:** USA
- **FG versus PL**
  - (APF group = 12,300 ppm F).
- **Self-applied under supervision, with tray, 10 consecutive applications (days) in 1st year, applied for 5 minutes.**
- **1y*NetDFS increment - (CA)cU+xr.**
- **Reported at 1 and 2 years follow-ups (and 1 year post-treatment).**

#### Englander 1967
- **Stratified random allocation; single-blind (B); non-placebo-controlled; 13% drop-out after 1.8 years (study duration = 1.8 years + 1.9 years post-intervention period).**
- **Natural losses and losses due to other reasons (NR); exclusions based on presence in all follow-up examinations; differential group losses.**
- **500 children analysed at 1.8 years (present for all examinations).**
- **Age range 11-14 years (average = 12).**
- **Surfaces affected:** 10.1 DMFS
- **Exposure to other fluoride:** no
- **Year study began:** 1964
- **Location:** USA
- **FG (2 groups) versus NT**
  - (APF group = 5000 ppm F, NaF group = 5000 ppm F).
- **Self-applied under supervision, with tray, 140 times a year (average), 1-2mg F (5-10 drops) applied for 6 minutes ***.**
- **1.8yDMFS increment - (CA).**
- **Reported at 1.8 years follow-up (and 1.9 years post-treatment).**
- **DMFT(CA)**
- **Dropout**
- **Etching of enamel (incomplete data)**

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<tr>
<th>Study</th>
<th>Allocation Method</th>
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<tr>
<td><strong>Englander 1971</strong></td>
<td>Stratified random allocation; single-blind (B); non-placebo-controlled; 38% drop-out after 2.5 years (study duration = 2.5 years). Reason(s) for high dropout rate NR; any differential group losses not assessable.</td>
<td>557 children analysed at 2.5 years (available at final examination). Age range 11-15 years (average = 12.2). Surfaces affected: 3.7 DMFS Exposure to other fluoride: water Year study began: 1967 Location: USA FG versus NT (APF group = 5000 ppm F). Self-applied under supervision, with tray, 85 times a year (average), 1-2 mg applied for 3 min. 2.5yNetDMFS increment - (CA)(E). Reported at 2.5 years follow-up. Dropout (no data by group)</td>
</tr>
<tr>
<td><strong>Englander 1978</strong></td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 37% drop-out after 1.5 years (study duration = 2.3 years). Main reason for high dropout rate described (large number of families transferred from study location); no differential group losses.</td>
<td>145 children analysed at 1.5* years (available at 2nd examination). Age range 2-6 years (average = 4.8). Surfaces affected: 3.7 defs Exposure to other fluoride: water Year study began: in/before 1974 Location: USA FG versus PL (APF group = 5000 ppm F). Self-applied under supervision, with tray, 76 times a year (average), 1 mg (5drops) applied for 3 minutes. 1.5y*defs increment - (CA)(E). Reported at 0.5, 1.5 and 2.3 years follow-ups. Proportion of children remaining caries-free</td>
</tr>
<tr>
<td><strong>Gisselsson 1999</strong></td>
<td>Stratified quasi-random allocation; double-blind (A), placebo-controlled; 12%</td>
<td>280 children analysed at 3 years (available at final examination). FG(2 groups) versus PL (NaF group = 4500 ppm F, SnF2 group = 2425 ppm F). 3yMD-DFS increment - (CA)cl+ (DR)xr. Reported at 3 years</td>
</tr>
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</table>

Participants randomized (N = B 896); numbers by group NR. Baseline characteristics (age, gender, ethnicity, DMFS, SAR) 'balanced'. Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; state of tooth eruption included = E; diagnostic errors NR. Results presented combined and separately by examiner; integrated results chosen.

Participants randomized (N = B 231). Baseline characteristics (age, def, defs, TAR, SAR, % caries-free) 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included = E; diagnostic errors NR. *Dramatic drop-out rate after 1.5 years of treatment (final 2.3 years results not considered).

Participants randomized (N = C 317). Baseline characteristics

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Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

Hagan 1985

Random allocation; double-blind (A); placebo-controlled; 26% drop-out after 2 years (study duration = 2 years). Natural losses; any differential group losses described as 'NS differences, ranging from 24% to 26%'.

316 children analysed at 2 years (available at final examination). Age range 11-15 years (average = 12.5). Surfaces affected: 4.6 DMFS Exposure to other fluoride: toothpaste Year study began: 1981 Location: USA

FG(2 groups)+ptc versus PL+ptc (APF group 1 = 12,300 ppm F, APF group 2 = 6000 ppm F). Operator-applied, with tray, twice a year, 2.5ml applied. 2yDMFS increment - (E). Reported at 2 years follow-up. PF-DMFS MD-BL-DMFS Nausea/vomiting within 15 min of gel application

Participants randomized (N = B 428); numbers by group NR. Baseline characteristics (age, gender, ethnicity, DMFS, regularity of dental care, previous exposure to other fluoride sources, etc) described as 'balanced' ("NS higher DMFS value for one group"). Clinical (VT) caries assessment by one examiner; diagnostic threshold NR; state of tooth eruption included = E; reversal rate less than 0.002% of observed caries increment in all groups.

Operator- applied, with floss+syringe, 4 times a year, 1ml applied for 10 minutes. follow-up. DS FS

Proportion of children remaining caries-free, proportion with one or more new DFS (at NCA/ER level)

Proportion of children remaining caries-free, proportion with one or more new DFS (at NCA/ER level)

Average age 13 years. Surfaces affected: 0.24 DFS*** - 39% caries free Exposure to other fluoride: toothpaste Year study began: 1993 Location: Sweden Dental treatment level (F/DF): 45%

Random allocation; double-blind (A); placebo-controlled; 26% drop-out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers (29 moved away, 8 refused participation); differential group losses.

Hagan 1985

316 children analysed at 2 years (available at final examination). Age range 11-15 years (average = 12.5). Surfaces affected: 4.6 DMFS Exposure to other fluoride: toothpaste Year study began: 1981 Location: USA

FG(2 groups)+ptc versus PL+ptc (APF group 1 = 12,300 ppm F, APF group 2 = 6000 ppm F). Operator-applied, with tray, twice a year, 2.5ml applied. 2yDMFS increment - (E). Reported at 2 years follow-up. PF-DMFS MD-BL-DMFS Nausea/vomiting within 15 min of gel application

Participants randomized (N = B 428); numbers by group NR. Baseline characteristics (age, gender, ethnicity, DMFS, regularity of dental care, previous exposure to other fluoride sources, etc) described as 'balanced' ("NS higher DMFS value for one group"). Clinical (VT) caries assessment by one examiner; diagnostic threshold NR; state of tooth eruption included = E; reversal rate less than 0.002% of observed caries increment in all groups.

Average age 13 years. Surfaces affected: 0.24 DFS*** - 39% caries free Exposure to other fluoride: toothpaste Year study began: 1993 Location: Sweden Dental treatment level (F/DF): 45%
### Heifetz 1970
- **Stratified quasi-random allocation; double-blind (A); placebo-controlled (PL);**
- **41% drop-out after 2 years (study duration = 2 years).**
- **Reason(s) for high dropout rate NR; exclusions based on compliance and presence in all follow-up examinations; no differential group losses.**
- **309 children analysed at 2 years (after exclusions, present for all examinations).**
- **Age range 12-13 years.**
- **Surfaces affected: 8.2 DMFS**
- **Exposure to other fluoride: none assumed**
- **Year study began: 1966**
- **Location: USA**
- **FG+ptc versus 'PL'+ptc**
  - **(APF group = 12,300 ppm F).**
  - **Self-applied under supervision, with toothbrush, 5 times a year, 4ml applied for 5 minutes.**

### Horowitz 1971
- **Stratified quasi-random allocation; single-blind (B); non-placebo-controlled;**
- **36% drop-out after 3 years (study duration = 3 years + 2 years post-intervention period).**
- **Natural losses; exclusions based on use of orthodontic bands; no differential group losses.**
- **352 children analysed at 3 years (available at final examination).**
- **Age range 10-12 years.**
- **Surfaces affected: 8.9 DMFS**
- **Exposure to other fluoride: none assumed**
- **Year study began: 1965**
- **Location: Hawaii**
- **FG+ptc versus NT+ptc**
  - **(APF group = 12,300 ppm F).**
  - **Operator-applied, with tray, once a year, applied for 4 minutes.**

### Horowitz 1974
- **Stratified quasi-random allocation; double-blind (A); placebo-controlled (PL);**
- **55% drop-out after 3 years (study duration = 3 years).**
- **Main reason for high dropout rate described (children leaving public school at an early age); exclusions based on presence in all follow-up examinations; no differential group losses.**
- **233 children analysed at 3 years (present for all examinations).**
- **Age range 11-14 years (average = 11.5).**
- **Surfaces affected: 11.4 DMFS**
- **Exposure to other fluoride: no**
- **Year study began: 1967**
- **FG+ptc versus 'PL'+ptc**
  - **(APF group = 12,300 ppm F).**
  - **Self-applied under supervision, with toothbrush, 5 times a year, 4ml applied for 2 minutes.**

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**Participants randomized (N = C 525).**
- Baseline characteristics (DMFS, DMFT) 'balanced'.
- Clinical (VT) caries assessment by two examiners; diagnostic threshold NR; state of tooth eruption included = E+U; reversal rate approximately 4% of observed DMFS increment for all groups combined.

**Participants randomized (N = C 552).**
- Baseline characteristics (DMFS, DMFT) 'balanced'.
- Clinical (VT) caries assessment by one examiner; diagnostic threshold NR; state of tooth eruption included = E; diagnostic errors NR.

**Participants randomized (N = C 512).**
- Baseline characteristics (age, dental age, DMFS) described as 'balanced'.
- Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; state of tooth eruption included NR.
### Fluoride gels for preventing dental caries in children and adolescents

#### THESIS CHAPTER 3

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<th>Study</th>
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<th>Clinical (VT) Caries Assessment</th>
<th>Diagnostic Errors</th>
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<tr>
<td>Ingraham 1970</td>
<td>Random allocation; single-blind (B); non-placebo-controlled; 23% drop-out after 2 years (study duration = 2 years). Reasons for attrition NR; no differential group losses.</td>
<td>1965-1967</td>
<td>23%</td>
<td>2.4 DMFS</td>
<td>None assumed</td>
<td>1965</td>
<td>Brazil</td>
<td>Balanced</td>
<td>Clinical assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; diagnostic errors NR.</td>
<td></td>
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<tr>
<td>Mainwaring 1978</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 18% drop-out (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable.</td>
<td>1974-1976</td>
<td>18%</td>
<td>7.9 DFS</td>
<td>None</td>
<td>1974</td>
<td>UK</td>
<td>Balanced</td>
<td>Clinical assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; diagnostic errors NR.</td>
<td></td>
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Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

Marthaler 1970

Random allocation; indication of blind caries assessment (C); placebo-controlled; 18% drop-out (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.

120 children analysed at 3 years (present for all examinations). Age range 6-7 years. Surfaces affected: 0.81 DMFS Exposure to other fluoride: salt Year study began: 1966 Location: Switzerland

FG versus PL (AmF/NaF group = 12,500 ppm F).

Self-applied under supervision, with toothbrush, 20 times a year, 1g applied for 6 minutes.

3yNetDFS increment - \( (CA)_{cl} + (DR)_{xr} \). Reported at 1 and 3 years follow-ups.

IstmPF-DFS (CA)_{cl} IstmMD-DFS (CA)_{xr}

less than 4% of observed DFS increment in all groups.

Participants randomized B (numbers for relevant groups NR). Baseline characteristics (age, DMFS, IstmDMFS) 'balanced'. Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. 'Sufficient agreement of the two examiners known from earlier work'.

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Marthaler 1970a

Random allocation; indication of blind caries assessment (C); placebo-controlled; 30% drop-out (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.

41 children analysed at 2&4* years (present for all examinations). Age range 7-9 years. Surfaces affected: 2.5 DMFS Exposure to other fluoride: salt Year study began: 1966 Location: Switzerland

FG versus PL (AmF/NaF group = 12,500 ppm F).

Self-applied under supervision, with toothbrush, 22 times a year, 1g applied for 6 minutes.

2yNetDFS increment - \( (CA)_{cl} + (DR)_{xr} \). Reported at 2 and 4 years follow-ups.

IstmPF-DFS (CA)_{cl} IstmMD-DFS (DR)_{xr}

Participants randomized B (numbers for relevant groups NR). Baseline characteristics (age, DMFS, IstmDMFS) 'balanced'. Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by
**Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)**

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<th>Outcomes</th>
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<td>Mestrinho 1983</td>
<td>Stratified quasi-random allocation; blind caries assessment stated but unclear (C); non-placebo-controlled; 20% drop-out after 1 year (study duration = 1 year). Exclusions based on 'statistical reasons' (made 'at random' to keep groups of equal sizes, after 8% natural loss).</td>
<td>174 children analysed at 1 year (after exclusions, available at final examination). Age range 7-10 years. Surfaces affected: NR Exposure to other fluoride: none assumed Year study began: 1981 Location: Brazil</td>
<td>FG+pte** versus NT (APF group = 9150 ppm F). Operator-applied, with tray, twice a year, 2.5ml applied.</td>
<td>1yDMFS increment. Reported at 1 year follow-up.</td>
<td>Participants randomized (N = 218); numbers by group NR. Baseline characteristics (dental age, DMFS) described as 'balanced' (values NR). Clinical (VT) caries assessment by three examiners; diagnostic threshold NR; state of tooth eruption included NR; diagnostic errors NR. **Prior toothbrushing with non-fluoride toothpaste and abrasive paste performed in FG group only.</td>
</tr>
</tbody>
</table>
| Olivier 1992 | Random allocation; double-blind (A); placebo-controlled; 12% drop-out after 2 years (study duration = 2 years). Natural losses; 'exclusions not based on compliance'; no differential group losses. | 431 children analysed at 2 years (available at final examination). Age range 6-7 years. Surfaces affected: 0.68 DMFS Exposure to other fluoride: toothpaste Year study began: 1985 Location: Canada | FG versus PL (APF group = 12,300 ppm F). Operator-applied, with tray, twice a year, applied for 4 minutes. | 2yDMFS increment - (CA). Reported at 2 years follow-up. | Participants randomized (N = 488). Baseline characteristics (age, DFMS, defs, daily sugar consumption, daily toothbrushing, exposure to other fluoride, etc) 'balanced'. Clinical (VT) caries assessment by five...
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<td>Ran 1991</td>
<td>Random allocation; double-blind (A); placebo-controlled; 20% drop-out (for all study groups combined) after 1.5 years (study duration = 1.5 years + 0.5 year post-intervention period). Reasons for attrition/ handling of exclusions NR; any differential group losses not assessable.</td>
<td>83 children analysed at 1.5 years; all male. Average age 13 years. Surfaces affected: 6.5 DMFS Exposure to other fluoride: data not obtained for dentifrice. Year study began: in/before 1989 Location: Israel</td>
<td>Baseline characteristics (DMFS) with some imbalance (reported as NS difference). Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; intra-examiner reproducibility checks for DMFS (icc reaching 0.97).</td>
<td>FG (2 groups) versus PL. (AmF group 1 = 4000 ppm F, AmF group 2 = 12,500 ppm F). Self-applied under supervision, with toothbrush, 25 times a year, 1g applied for 4 minutes.</td>
<td>1.5yNetDMFS increment - (CA). Reported at 0.5 and 1.5 years follow-ups (and 0.5 year post-treatment).</td>
</tr>
<tr>
<td>Shern 1976</td>
<td>Random allocation; double-blind (A); placebo-controlled; 8% drop-out after 1 year (study duration = 2 years). Natural losses only; 'losses distributed evenly among groups'.</td>
<td>562 children analysed at 1* year (available at 1st examination). Age range 6-13 years. Surfaces affected: 2.7 DMFS (data from original sample only) Exposure to other fluoride: none assumed. Year study began: in/before 1973 Location: Venezuela</td>
<td>Baseline characteristics (DFMS) with some imbalance (reported as NS difference). Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; intra-examiner reproducibility checks for DMFS (icc over 0.96).</td>
<td>FG (3groups)+ptc versus PL(2 groups)+ptc (APF group 1 = 12,300 ppm F, AmF group 1 = 12,500 ppm F, AmF group 2 = 12,500 ppm F). Operator-applied, with tray 5 consecutive applications (every day/week) in 1st year, 3 mg (about 14 drops) applied for 5 min.</td>
<td>1y*NetDMFS increment. Reported at 1 and 2 years follow-ups.</td>
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</table>

Participants randomized (N = 614). Baseline characteristics (DFMS) 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold NR; state of tooth eruption included NR; diagnostic errors NR. *Intervention applied during 1st year of study only (final 2 years results not considered).
Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

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<th>Year Study Began</th>
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<td>Szwejda 1972</td>
<td>Random allocation; double-blind ('A'); placebo-controlled ('PL'); drop-out rate NR not obtainable (study duration = 3 years). Exclusions based on lifetime exposure to fluoridated water, compliance to treatment, and presence in all follow-up examinations; any differential group losses not assessable.</td>
<td>316 children analysed at 3 years (after exclusions, present for all examinations). Age range 7-9 years. Surfaces affected: 0.86 DMFS Exposure to other fluoride: water Year study began: in/before 1968 Location: USA</td>
<td>0.86</td>
<td>3yNetDMFS increment - (E). Operator-applied, with tray once a year.</td>
<td>FG+ptc versus 'PL'+ptc (APF, concentration NR). Reported at 3 years follow-up.</td>
<td>3yNetDMFS increment - (E).</td>
<td>Participants randomized (numbers NR). Baseline characteristics (age, DMFT, DMFS, TAR, SAR) 'balanced'. Clinical (VT) caries assessment by two examiners; diagnostic threshold NR; state of tooth eruption included = E.</td>
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<tr>
<td>Treide 1988</td>
<td>Random allocation; double-blind (A); placebo-controlled; 33% drop-out after 3 years (study duration = 3 years). No differential group losses.</td>
<td>433 children analysed at 3 years. Average age 3.5 years. Surfaces affected: NR (but dmft data reported from original sample only = 0.8) Exposure to other fluoride: no Year study began: 1983 Location: GDR</td>
<td>0.8</td>
<td>3ydmfs increment - (E). Self-applied under supervision, with toothbrush, approximately 130 times a year.</td>
<td>FG (3 groups) +ptc versus PL+ptc (NaF+hexaf group = 12,500 ppm F, NaF group = 12,500 ppm F, AmF group = NR).</td>
<td>3ydmfs increment - (E).</td>
<td>Participants randomized (N = 643). Baseline characteristic (dmft) 'balanced'. Clinical (VT) caries assessment by two examiners; diagnostic threshold NR; state of tooth eruption included = E.</td>
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<tr>
<td>Trubman 1973</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 46% drop-out after 3 years (study duration = 3 years). Main reason(s) for high dropout rate NR; exclusions based on</td>
<td>311 children analysed at 3 years (present for all examinations). Average age 8.1 years. Surfaces affected: 2.1 DMFS Exposure to other fluoride: none assumed</td>
<td>0.8</td>
<td>3yNetDMFS increment - (E).</td>
<td>FG+ptc versus PL+ptc (APF group = 12,300 ppm F).</td>
<td>3yNetDMFS increment - (CA).</td>
<td>Participants randomized (N = 575). Baseline characteristics (age, DMFT, DMFS) with some imbalance (DMFS) &quot;but adjustment results in trivial changes in crude means&quot;.</td>
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<td></td>
</tr>
</tbody>
</table>
Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

Year study began: 1969
Location: USA

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

N = numbers; NR = not reported; NS = not significant; PL = placebo gel; 'PL' = not a true placebo (inactive treatment other than gel used); 'A' = classified as double-blind but participants may not be blind ('PL' used); NT = no treatment; FG = fluoride gel treatment; ptc = prior tooth cleaning performed with or without a non-fluoride paste; APF = acidulated phosphate fluoride; NaF = sodium fluoride; AmF = amine fluoride; SnF2 = stannous fluoride; ppm F = parts per million of fluoride; D(M)FS/T = decayed, (missing) and filled permanent surfaces or teeth; deft/s = decayed, missing and filled deciduous teeth or surface; dmft/s = decayed, missing and filled deciduous teeth or surface; O = occlusal surfaces; PF = pit and fissure surfaces; MD = mesial and distal surfaces; BL = buccal and lingual surfaces; 1stm = first permanent molar; SAR = surfaces at risk; TAR = teeth at risk; CIR = caries incidence rate; CL = clinical examination; VT = visual-tactile assessment; XR = radiographic examination; postBW = posterior bite-wing x-ray assessment; E = teeth erupted at baseline; U = teeth unerupted at baseline; NCA = non-cavitated enamel lesions visible as white spots or discolored fissures; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, with rough softened floor/walls when probed) or showing frank cavitation; ER = any radiolucency in enamel/ enamel-dentin junction; DR = radiolucency into dentin; icc = intra-class correlation

Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; state of tooth eruption included NR; reversal rate 18.4% and 9.2% of observed DMFT increment in FG and PL groups respectively.
coefficient.
## Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellini 1981</td>
<td>Additional fluoride based intervention associated to fluoride gel. Blind outcome assessment not stated and unlikely. Note - No relevant outcome reported.</td>
</tr>
<tr>
<td>Boyd 1985</td>
<td>Additional fluoride based intervention associated to fluoride gel. Clearly not randomized or quasi-randomized. Blind outcome assessment not stated. Length of follow-up of less than one year/school year.</td>
</tr>
<tr>
<td>Heifetz 1979</td>
<td>Additional fluoride based intervention associated to fluoride gel. Note - Inappropriate 'placebo' used.</td>
</tr>
<tr>
<td>Ivanova 1990</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Kukleva 1983</td>
<td>Random or quasi-random allocation not stated or indicated. Open outcome assessment reported after contacting author.</td>
</tr>
<tr>
<td>Kukleva 1998</td>
<td>Random or quasi-random allocation not stated or indicated. Open outcome assessment reported after contacting author.</td>
</tr>
<tr>
<td>Mellberg 1978</td>
<td>Blind outcome assessment not stated and unlikely in any element/phase of assessment.</td>
</tr>
<tr>
<td>Pinto 1993</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Shobha 1987</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. Note - Main outcome data not reported in control group (and not obtainable).</td>
</tr>
<tr>
<td>Spears 1978</td>
<td>No random or quasi-random allocation used (non-random concurrent control). Blind outcome assessment not stated and unlikely. Note - Dramatic drop-out rate during the study period.</td>
</tr>
<tr>
<td>Stadtler 1982</td>
<td>Medically compromised group of institutionalised children selected.</td>
</tr>
<tr>
<td>Szoke 1989</td>
<td>Additional fluoride or non-fluoride based intervention associated to fluoride gel. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Szwejda 1971</td>
<td>No random or quasi-random allocation used (concurrent control taken from another study).</td>
</tr>
</tbody>
</table>
References to studies

Included studies

Abadia 1978 {published data only}

Bijella 1981 {published data only}


Bryan 1970 {published data only}


Cobb 1980 {unpublished data sought but not used}

Cons 1970 {published data only}

DePaola 1980 {unpublished data sought but not used}


Englander 1967 {published data only}
Englander HR, Carlos JP, Senning RS, Mellberg JR. Residual anticaries effect of repeated topical sodium fluoride applications by mouthpieces. Journal of the American Dental Association
Fluoride gels for preventing dental caries in children and adolescents

1969;78:783-87.


**Englehard 1971**


**Englehard 1978**


**Gisselsson 1999**


**Hagan 1985**


**Heifetz 1970**


**Horowitz 1971**


Horowitz HS. Effect of topically applied acidulated phosphate-fluoride on dental caries in Hawaiian
Fluoride gels for preventing dental caries in children and adolescents


Horowitz 1974 {published and unpublished data}


Ingraham 1970 {published data only}


Mainwaring 1978 {published data only}


Marthaler 1970 {published data only}


Marthaler 1970a {published data only}


Mestrinho 1983 {published and unpublished data}


Olivier 1992 {published and unpublished data}


Ran 1991 {unpublished data sought but not used}

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Fluoride gels for preventing dental caries in children and adolescents


Shern 1976


Szwejda 1972


Treide 1988


Trubman 1973


Excluded studies

Bellini 1981


Boyd 1985


Heifetz 1979


Ivanova 1990

Ivanova EN. Sravnitel'naia effektivnost' mestnykh protivokarioznykh sredstv [The comparative
Fluoride gels for preventing dental caries in children and adolescents


Kukleva 1983


Kukleva 1998

Kukleva M, Kondeva V, Kotsikas M. Group caries prophylactic with fluoride gel. 3rd Balkan Congress of Medicine and Dentistry for Students and Young Doctors; 1999 Nov 5-7; Bursa (Turkey).


Mellberg 1978


Pinto 1993

Pinto IL. Prevenção da carie dental com aplicação tópicas semestrais de fluor fosfato [Dental caries prevention through APF Gel-Tray applications each six months]. Revista de Saude Publica 1993;27:277-90.

Shobha 1987


Spears 1978


Stadtler 1982


Stadtler P. Ergebnisse einer dreijährigen klinisch-experimentellen Doppelblindstudie mit
Fluoride gels for preventing dental caries in children and adolescents


Szoke 1989


Szwejda 1971

{published data only}


Studies awaiting assessment

Cichocka 1981

{published data only}


Mitrega 1981

{published data only}


* indicates the primary reference for the study
Fluoride gels for preventing dental caries in children and adolescents

Other references

Additional references

Bratthall 1996

Burt 1998

Clark 1985

Clarke 2000

de Liefde 1998

Dubey 1965

Egger 1997

Featherstone 1988

Featherstone 1999
Featherstone JD. Prevention and reversal of dental caries: role of low level fluoride. Community
Fluoride gels for preventing dental caries in children and adolescents


Glass 1982


Helfenstein 1994


Johnson 1993


Krasse 1996


Marinho 1997


Marthaler 1994


Marthaler 1996


Murray 1991


Murray 1991a


Nadanovsky 1995

Nadanovsky P, Sheiham A. Relative contribution of dental services to the changes in caries levels of 12-year-old children in 18 industrialized countries in the 1970s and early 1980s. Community
Fluoride gels for preventing dental caries in children and adolescents


O'Mullane 1994


Ripa 1989


Ripa 1990


Ripa 1991


Rolla 1991


Sharp 1998


Stamm 1995


Thompson 1999


van Rijkom 1998


Whitford 1992

### Table of comparisons

01 Fluoride Gel versus Placebo/No-treatment
  01 D(M)FS increment (prevented fraction) - nearest to 3 years (23 trials)
    01 Placebo control
    02 No-treatment control
  02 D(M)FT increment (prevented fraction) - nearest to 3 years (10 trials)
    01 Placebo control
    02 No-treatment control
  03 D(M)FS increment (SMD) - nearest to 3 years (23 trials)
    01 Placebo control
    02 No-treatment control
  04 D(M)FT increment (SMD) - nearest to 3 years (10 trials)
    01 Placebo control
    02 No-treatment control
  05 Signs of acute toxicity - nausea, vomiting (2 trials)
  06 Unacceptability of treatment as measured by leaving study early (6 trials)
Other data tables

01 Fluoride Gel versus Placebo/No-treatment

01 D(M)FS increment (prevented fraction) - nearest to 3 years (23 trials)

01 Placebo control

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cons 1970</td>
<td>18%</td>
<td>(1% to 35%)</td>
</tr>
<tr>
<td>DePaola 1980</td>
<td>6%</td>
<td>(-14% to 26%)</td>
</tr>
<tr>
<td>Gisselsson 1999</td>
<td>12%</td>
<td>(-32% to 56%)</td>
</tr>
<tr>
<td>Hagan 1985</td>
<td>27%</td>
<td>(10% to 44%)</td>
</tr>
<tr>
<td>Heifetz 1970</td>
<td>8%</td>
<td>(-15% to 30%)</td>
</tr>
<tr>
<td>Horowitz 1974</td>
<td>33%</td>
<td>(22% to 44%)</td>
</tr>
<tr>
<td>Mainwaring 1978</td>
<td>14%</td>
<td>(3% to 25%)</td>
</tr>
<tr>
<td>Marthaler 1970</td>
<td>40%</td>
<td>(22% to 58%)</td>
</tr>
<tr>
<td>Marthaler 1970a</td>
<td>16%</td>
<td>(-27% to 59%)</td>
</tr>
<tr>
<td>Olivier 1992</td>
<td>9%</td>
<td>(-8% to 27%)</td>
</tr>
<tr>
<td>Ran 1991</td>
<td>-85%</td>
<td>(-398% to 228%)</td>
</tr>
<tr>
<td>Shern 1976</td>
<td>28%</td>
<td>(-6% to 61%)</td>
</tr>
<tr>
<td>Szwejda 1972</td>
<td>4%</td>
<td>(-21% to 28%)</td>
</tr>
<tr>
<td>Trubman 1973</td>
<td>35%</td>
<td>(19% to 50%)</td>
</tr>
</tbody>
</table>

02 No-treatment control

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abadia 1978</td>
<td>14%</td>
<td>(-6% to 34%)</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bijella 1981</td>
<td>51%</td>
<td>(42% to 60%)</td>
</tr>
<tr>
<td>Bryan 1970</td>
<td>37%</td>
<td>(23% to 52%)</td>
</tr>
<tr>
<td>Cobb 1980</td>
<td>35%</td>
<td>(14% to 56%)</td>
</tr>
<tr>
<td>Englander 1967</td>
<td>77%</td>
<td>(67% to 88%)</td>
</tr>
<tr>
<td>Englander 1971</td>
<td>29%</td>
<td>(10% to 48%)</td>
</tr>
<tr>
<td>Horowitz 1971</td>
<td>24%</td>
<td>(9% to 40%)</td>
</tr>
<tr>
<td>Ingraham 1970</td>
<td>41%</td>
<td>(19% to 64%)</td>
</tr>
<tr>
<td>Mestrinho 1983</td>
<td>27%</td>
<td>(4% to 51%)</td>
</tr>
</tbody>
</table>
Other data tables

01 Fluoride Gel versus Placebo/No-treatment

02 D(M)FT increment (prevented fraction) - nearest to 3 years (10 trials)

01 Placebo control

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cons 1970</td>
<td>25%</td>
<td>(12% to 37%)</td>
</tr>
<tr>
<td>Heifetz 1970</td>
<td>12%</td>
<td>(-7% to 31%)</td>
</tr>
<tr>
<td>Szwejda 1972</td>
<td>5%</td>
<td>(-15% to 25%)</td>
</tr>
<tr>
<td>Trubman 1973</td>
<td>23%</td>
<td>(3% to 42%)</td>
</tr>
</tbody>
</table>

02 No-treatment control

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bijella 1981</td>
<td>52%</td>
<td>(46% to 58%)</td>
</tr>
<tr>
<td>Bryan 1970</td>
<td>45%</td>
<td>(28% to 61%)</td>
</tr>
<tr>
<td>Englander 1967</td>
<td>65%</td>
<td>(59% to 72%)</td>
</tr>
<tr>
<td>Horowitz 1971</td>
<td>15%</td>
<td>(0% to 31%)</td>
</tr>
<tr>
<td>Ingraham 1970</td>
<td>52%</td>
<td>(36% to 69%)</td>
</tr>
<tr>
<td>Mestrinho 1983</td>
<td>18%</td>
<td>(-2% to 37%)</td>
</tr>
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</table>
## Additional tables

### 01 Meta-analyses of prevented fractions

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. studies</th>
<th>r.e. estimate</th>
<th>95% c.i.</th>
<th>Meta-analysis p-val</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(M)FS - all studies</td>
<td>23</td>
<td>28%</td>
<td>(19% to 37%)</td>
<td>p&lt;0.0001</td>
<td>Q=135 (22 d.f.); p&lt;0.0001</td>
</tr>
<tr>
<td>D(M)FS - placebo controlled</td>
<td>14</td>
<td>21%</td>
<td>(14% to 28%)</td>
<td>p&lt;0.0001</td>
<td>Q=22.5 (13 d.f.); p=0.05</td>
</tr>
<tr>
<td>D(M)FS - no-treatment control</td>
<td>9</td>
<td>38%</td>
<td>(24% to 53%)</td>
<td>p&lt;0.0001</td>
<td>Q=62 (8 d.f.); p&lt;0.0001</td>
</tr>
<tr>
<td>D(M)FT - all studies</td>
<td>10</td>
<td>32%</td>
<td>(19% to 46%)</td>
<td>p&lt;0.0001</td>
<td>Q=103 (9 d.f.); p&lt;0.0001</td>
</tr>
<tr>
<td>D(M)FT - placebo controlled</td>
<td>4</td>
<td>18%</td>
<td>(9% to 27%)</td>
<td>p&lt;0.0001</td>
<td>Q=3.2 (3 d.f.); p=0.37</td>
</tr>
<tr>
<td>D(M)FT - no-treatment control</td>
<td>6</td>
<td>43%</td>
<td>(29% to 57%)</td>
<td>p&lt;0.0001</td>
<td>Q=48 (5 d.f.); p&lt;0.0001</td>
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</tbody>
</table>
### Additional tables

**02 Random effects meta-regression analyses of prevented fractions: D(M)FS.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. studies</th>
<th>Slope estimate</th>
<th>95% c.i.</th>
<th>Slope interpretation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>23</td>
<td>19%</td>
<td>(5% to 33%)</td>
<td>Higher PF for no-treatment compared with placebo</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean baseline caries</td>
<td>21</td>
<td>0.2%</td>
<td>(-2.0% to 2.5%)</td>
<td>Increase per unit increase in mean baseline caries</td>
<td>0.8</td>
</tr>
<tr>
<td>Background fluorides</td>
<td>22</td>
<td>-6.6%</td>
<td>(-22% to 9%)</td>
<td>Lower PF in presence of background fluorides</td>
<td>0.4</td>
</tr>
<tr>
<td>Fluoride dentrifice use</td>
<td>22</td>
<td>-7.4%</td>
<td>(-26% to 11%)</td>
<td>Lower PF in presence of fluoride dentrifice use</td>
<td>0.1</td>
</tr>
<tr>
<td>Fluoridated water</td>
<td>23</td>
<td>-1.9%</td>
<td>(-22% to 18%)</td>
<td>Lower PF in presence of water fluoridation</td>
<td>0.9</td>
</tr>
<tr>
<td>Mode of application</td>
<td>23</td>
<td>14%</td>
<td>(1% to 28%)</td>
<td>Higher PF when self-applied compared with operator-applied</td>
<td>0.04</td>
</tr>
<tr>
<td>Method of self-application</td>
<td>9</td>
<td>-4.3%</td>
<td>(-41% to 32%)</td>
<td>Among self-applied, lower PF for tray compared with brush</td>
<td>0.8</td>
</tr>
<tr>
<td>Frequency of application</td>
<td>23</td>
<td>2.5%</td>
<td>(0.8% to 4.2%)</td>
<td>Increase per 10 extra applications/year</td>
<td>0.003</td>
</tr>
<tr>
<td>Fluoride concentration in gel</td>
<td>20</td>
<td>-2.1%</td>
<td>(-5% to 0%)</td>
<td>Decrease per 1000 ppm F</td>
<td>0.2</td>
</tr>
<tr>
<td>Intensity (freq times conc)</td>
<td>20</td>
<td>0.5%</td>
<td>(0.2% to 0.9%)</td>
<td>Increase per extra equivalent to 10 more applications 1000 ppmF higher</td>
<td>0.003</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>23</td>
<td>2.8%</td>
<td>(-8% to 14%)</td>
<td>Increase per extra year of follow-up</td>
<td>0.6</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>23</td>
<td>-7.4%</td>
<td>(-23% to 8%)</td>
<td>Lower PF with poorly concealed allocation</td>
<td>0.4</td>
</tr>
<tr>
<td>Blind outcome assessment</td>
<td>23</td>
<td>0.2%</td>
<td>(-18% to 18%)</td>
<td>Higher PF with blind outcome assessment indicated (not clearly stated)</td>
<td>0.98</td>
</tr>
<tr>
<td>Double blinding</td>
<td>23</td>
<td>15%</td>
<td>(-14% to 44%)</td>
<td>Higher PF with lack of double-blinding</td>
<td>0.3</td>
</tr>
<tr>
<td>Drop-out</td>
<td>21</td>
<td>0.1%</td>
<td>(-6% to 6%)</td>
<td>Increase per 10 drop-outs</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Review Manager 4.2.2  25/09/2003*
Additional figures

Figure 01

Funnel Plot of D(M)FS SMDs according to standard errors of the studies included in the meta-analysis

Review: Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)
Comparison: 01 Fluoride Gel versus Placebo/No-treatment
Outcome: 03 D(M)FS increment (SMD) - nearest to 3 years (23 trials)
### Comparison or outcome

<table>
<thead>
<tr>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride Gel versus Placebo/No-treatment</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
</tr>
<tr>
<td>01 D(M)FS increment (prevented fraction) - nearest to 3 years (23 trials)</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
</tr>
<tr>
<td>02 D(M)FT increment (prevented fraction) - nearest to 3 years (10 trials)</td>
<td>SMD (random), 95% CI</td>
<td>Subtotals only</td>
<td></td>
</tr>
<tr>
<td>03 D(M)FS increment (SMD) - nearest to 3 years (23 trials)</td>
<td>SMD (random), 95% CI</td>
<td>Subtotals only</td>
<td></td>
</tr>
<tr>
<td>04 D(M)FT increment (SMD) - nearest to 3 years (10 trials)</td>
<td>RD (random), 95% CI</td>
<td>0.01 [-0.01, 0.02]</td>
<td></td>
</tr>
<tr>
<td>05 Signs of acute toxicity - nausea, vomiting (2 trials)</td>
<td>2 490</td>
<td>RR (random), 95% CI</td>
<td>1.09 [0.70, 1.72]</td>
</tr>
<tr>
<td>06 Unacceptability of treatment as measured by leaving study early (6 trials)</td>
<td>6 2096</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total number of included studies:** 25
Comparison: Fluoride Gel versus Placebo/No-treatment

Outcome: (A) UFxP (SMD) - nearest to 3 years (23 trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sub-category</th>
<th>Fluoride Gel (n=SD)</th>
<th>Placebo/NT (n=SD)</th>
<th>SMD (random)</th>
<th>Weight</th>
<th>SMD (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
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</thead>
<tbody>
<tr>
<td>Placebo control</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1970</td>
<td></td>
<td>278 1.10 (1.07)</td>
<td>311 1.09 (1.04)</td>
<td>0.59</td>
<td>0.02</td>
<td>-0.07 - 0.16</td>
<td>1970</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Delapa 1971</td>
<td></td>
<td>140 0.45 (0.24)</td>
<td>160 0.45 (0.24)</td>
<td>1.00</td>
<td>0.04</td>
<td>1.37</td>
<td>1971</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Horowitz 1973</td>
<td></td>
<td>145 1.29 (1.31)</td>
<td>150 1.30 (1.29)</td>
<td>0.58</td>
<td>0.02</td>
<td>-0.07</td>
<td>1973</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gisselsson 1999</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Test for heterogeneity: ChI² = 2.96, df = 1 (P = 0.087), 1 = 0%

Review: Fluoride gels for preventing dental caries in children and adolescents (THESIS CHAPTER 3)

Comparison: Fluoride Gel versus Placebo/No-treatment

Outcome: (A) UFxP (SMD) - nearest to 3 years (23 trials)

<table>
<thead>
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<th>Study</th>
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CHAPTER 4

FLUORIDE VARNISHES FOR PREVENTING DENTAL CARIES IN CHILDREN AND ADOLESCENTS
Fluoride varnishes for preventing dental caries in children and adolescents

Cover sheet

Title
Fluoride varnishes for preventing dental caries in children and adolescents (THESIS CHAPTER 4)

Reviewers
Marinho VCC, Higgins JPT, Logan S, Sheiham A

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Contribution of reviewers
All authors contributed to the development of the protocol. VM wrote the protocol, conducted searches, selected studies and extracted data. JH duplicated study selection and data extraction in a sample of studies, and SL or AS were consulted where necessary. VM entered and analysed the data in consultation with JH. VM prepared the full review and all authors were active in its revision and approval.

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Potential conflict of interest
None known.
Abstract

Background
Topically applied fluoride varnishes have been used as an operator-applied caries-preventive intervention for over three decades.

Objectives
To determine the effectiveness and safety of fluoride varnishes in the prevention of dental caries in children and to examine factors potentially modifying their effect.

Search strategy
We searched the Cochrane Oral Health Group's Trials Register (May 2000), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2000), MEDLINE (1966 to January 2000), plus several other databases. We handsearched journals, reference lists of articles and contacted selected authors and manufacturers.

Selection criteria
Randomized or quasi-randomized controlled trials with blind outcome assessment, comparing fluoride varnish with placebo or no treatment in children up to 16 years during at least one year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS).

Data collection & analysis
Inclusion decisions, quality assessment and data extraction were duplicated in a random sample of one third of studies, and consensus achieved by discussion or a third party. Study authors were contacted for missing data. The primary measure of effect was the prevented fraction (PF), that is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed where data could be pooled. Potential sources of heterogeneity were examined in random effects meta-regression analyses.

Main results
Nine studies were included, involving 2709 children. For the seven that contributed data for the main meta-analysis, the D(M)FS pooled prevented fraction estimate was 46% (95% CI, 30% to 63%; p<0.0001). There was substantial heterogeneity, confirmed statistically (p<0.0001). The pooled d(e/m)fs prevented fraction estimate was 33% (95% CI, 19% to 48%; p<0.0001). No significant association between estimates of D(M)FS prevented fractions and baseline caries severity or background exposure to fluorides was found in meta-regression, and a funnel plot of the seven studies indicated no relationship between prevented fraction and study precision. In both methods, power is limited when only a few trials are included. There is little information concerning possible side effects or acceptability of treatment in the included trials.

Reviewers' conclusions
The review suggests a substantial caries-inhibiting effect of fluoride varnish in both the permanent and the deciduous dentitions based largely on trials with no treatment controls. Given the relatively poor quality of most of the included studies and the wide confidence intervals around the estimates of effect, there remains a need for further trials. It is important that these trials should be of high quality and include assessment of potential adverse effects.
Background

The prevention of dental caries in children and adolescents is generally regarded as a priority for dental services and considered more cost-effective than its treatment (Burt 1998). Fluoride therapy has been the centrepiece of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray 1991). These were introduced when caries was highly prevalent and severe, and when even modest prevention activities led to considerable reductions in disease levels. In the last twenty years, with the substantial decline in dental caries rates in many western countries, an increase in dental fluorosis levels in some countries, and intensive research on the mechanism of action of fluoride highlighting the primary importance of its topical effect, greater attention has been paid to the appropriate use of other fluoride-based interventions (Glass 1982; Featherstone 1988; Ripa 1991; O'Mullane 1994; Marthaler 1996; Featherstone 1999).

The use of topically applied fluoride products in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades. By definition, the term 'topically applied fluoride' is used to describe those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect, and are therefore not intended for ingestion. The most important anti-caries effect of fluoride is considered to result from its action on the tooth/plaque interface, through promotion of remineralization of early caries lesions and by reducing tooth enamel solubility (Featherstone 1988). Fluoride containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most commonly used at present, either alone or in combination. Various products are marketed in different countries and a variety of caries preventive programs based on these have been implemented. Toothpastes are by far the most widespread form of fluoride usage (Murray 1991a; Ripa 1991) and although the reasons for the decline in the prevalence of dental caries in children from different countries continues to be debated (Nadanovsky 1995; Krasse 1996; Marthaler 1996; de Liefde 1998), it has been mainly attributed to the gradual increase in, and regular home use of fluoride in toothpaste (Glass 1982; Ripa 1991; Rolla 1991; Marthaler 1994; O'Mullane 1994; Bratthall 1996).

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

The evidence on the effect of topical fluorides on the prevention of dental caries in children has been extensively reviewed in a number of traditional narrative reviews. A small number of reviews focusing on the evaluation of specific fluoride active agents within specific delivery systems have used a quantitative meta-analytical approach to synthesise studies results (Clark 1985; Johnson 1993; Helfenstein 1994; Stamm 1995; van Rijkom 1998). However, a systematic quantitative evaluation of the available evidence on the effect of the main modalities of topically applied fluoride has never been undertaken.

This review is one in a series of systematic reviews of topical fluoride interventions and assesses the effectiveness of fluoride varnishes in the prevention of dental caries in children.

FLUORIDE VARNISHES
Professionally-applied fluoride varnishes, developed in the 1960s as a preventive intervention for dental caries, have been extensively used in Europe, Scandinavia and Canada and their use in other countries seems to be increasing in recent years (WHO 1994; Bawden 1998; Kallestal 1999). The use of fluoride varnishes is considered appropriate for at-risk tooth-surfaces in caries susceptible individuals and for moderate and high caries prevalence child populations in community-based preventive programs (Petersson 1997). Varnishes were originally developed to prolong the contact time between fluoride and dental enamel, as they adhere to the tooth surface for longer periods (12 hours or more) in a thin layer, and prevent the immediate loss of fluoride after application, thus acting as slow-releasing reservoirs of fluoride (Ogaard 1994). Although different formulations of fluoride varnishes are available, there are two main preparations commercially known as Duraphat and Fluor Protector, which contain sodium fluoride in concentration of 22600 parts per million of fluoride (ppm F) and difluorsilane in concentration of 7000 ppm F respectively. Varnishes are usually applied with small brushes, syringes, or cotton pellets, with or without prior dental prophylaxis, at the frequency of two to four times a year. They are considered safe, despite their high fluoride concentration, because the amount of varnish usually applied to treat one child is only 0.5 ml on average (Ripa 1990; Petersson 1993), which delivers 3-11 mg of fluoride ion. This is far below the probable toxic dose (PTD) of 5 mg/kg body weight (Whitford 1992), even with the potential exposure (ingestion) varying from 3.5-11.3 mg of fluoride ion (Johnston 1994).

Numerous clinical trials evaluating the caries preventive effect of fluoride varnishes in both the permanent and deciduous dentitions have been reported, and these have been the subject of several narrative reviews (Clark 1982; Vanover 1982; Primosch 1985; De Bruyn 1987; Seppa 1991; Petersson 1993; Petersson 1997; Beltran-Aguilar 2000) and of two meta-analyses (Clark 1985; Helfenstein 1994). Although it is evident from these reviews and meta-analyses that fluoride varnishes are caries-inhibitory agents, they did not include a comprehensive search for individual studies nor a formal evaluation of the internal validity of included studies, despite obvious drawbacks in study design and methods. Some reviews included trials, mainly carried out in the 1970s, that had adopted the 'split-mouth' design for example, i.e. used half-mouth controls. There is a general agreement against the use of the within-subject paired design for fluoride varnish trials in the literature; a major drawback is that the possibility of significant contamination of control sites cannot be excluded, regardless of the adhesiveness of the material to the tooth surface in the first hours after application (Clark 1982; De Bruyn 1987; Petersson 1993).

**Objectives**

1. To determine the effectiveness and safety of fluoride varnishes in preventing dental caries in the child/adolescent population.
2. To examine whether the effect of fluoride varnishes is influenced by the initial level of caries severity.
3. To examine whether the effect of fluoride varnishes is influenced by the background exposure to fluoride in water (or salt), toothpastes, or reported fluoride sources other than the study option(s).

**Criteria for considering studies for this review**

**Types of studies**
Randomized or quasi-randomized controlled trials using or indicating blind outcome assessment, in which fluoride varnish is compared concurrently to a placebo or no treatment group during at least one year/school year.

Randomized or quasi-randomized controlled trials using within-group paired comparison designs (e.g. split-mouth trials), or with open outcome assessment or no indication of blind assessment, or lasting less than one year/one school year, or controlled trials where random or quasi-random allocation was not used or indicated were excluded.

Types of participants

Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started). Studies where participants were selected on the basis of special (general or oral) health conditions were excluded.

Types of interventions

Topical fluoride in the form of varnishes only, using any fluoride agent, at any concentration (ppm F), amount or duration of application, and with any technique of application, prior- or post-application. However, frequency of application should be at least once a year. The control group is placebo or no treatment resulting in the following comparison: Fluoride varnish compared with a placebo or no treatment.

Studies where the intervention consisted of any other caries preventive agent or procedure (e.g. other fluoride-based measures, chlorhexidine, sealants, oral hygiene interventions, xylitol chewing gums, glass ionomers) used in addition to fluoride varnish were excluded.

Types of outcome measures

The primary outcome measure in this review is caries increment, as measured by change from baseline in the decayed, (missing) and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. Caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis. (See 'Methods of the review' for the different ways of reporting the D(M)FT/S scores in clinical trials of caries preventives.)

The following outcomes were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions, tooth loss, dental pain/discomfort, specific side effects (fluorosis, tooth staining/discoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting), unacceptability of preventive treatment as measured by dropouts during the trial/post randomization exclusions (in non-placebo controlled studies), use of health service resources (such as visits to dental care units, length of dental treatment time).

Studies reporting only on plaque/gingivitis, calculus, dentin hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc) were excluded.

Search strategy for identification of studies

With a comprehensive search, we attempted to identify all relevant studies irrespective of language,
Fluoride varnishes for preventing dental caries in children and adolescents (THE)

from 1965 onwards.

ELECTRONIC SEARCHING (databases and registers)

Up to 1998

Relevant studies were identified (for the series of topical fluoride reviews) by searching several databases from date of inception: MEDLINE (1966-1997), EMBASE (1980-1997), SCISEARCH (1981-1997), SSCISEARCH (1981-1997), ISTP (1982-1997), BIOSIS (1982-1997), CINAHL (1982-1997), ERIC (1966-1996), DISSERTATION ABSTRACTS (1981-1997) and LILACS/BBO (1982-1997). Two overlapping but complementary subject search phrases (below) with very low specificity (but high sensitivity), using 'free-text' and 'controlled vocabulary' terms, were formulated within Silverplatter MEDLINE around two main concepts - fluoride and caries - and combined with all three levels of the Cochrane Optimal Search Strategy for Randomized Controlled Trials (RCTs). These subject search phrases were customised for searching EMBASE and other databases:

(a) 
[("DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS" all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or DMF*) and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR SMFP OR MFP OR MONOFUOR*) or ("CARIOSTATIC-AGENTS" explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or "DENTIFRICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or CARIOTA* or PROPHYLA* or ANTICARI* or ANTI CARI* or VARNISH* or LACQUER* or DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRIC* or MOUTHRINS* or MOUTH RINS* or RINS* or MOUTHWASH* or MOUTH WASH*)].

(b) 
[((FLUORIDES/ all subheadings) or (FLUORIDES-TOPICAL/ ALL SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFUOR* OR DURAPHAT) and (CARI* or (DMF*) or (TOOTH* or (TEETH* or (DENT* in TI, in AB, in MESH)) or (CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or (MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or (MOUTHRINS* or MOUTH RINS*) or (VARNISH* or LACQUER*)].

RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISSERTATION ABSTRACTS, and LILACS/BBO. All the strategies (subject search and methodological filters) developed to search each database are fully described in a report produced for the Systematic Reviews Training Unit (Marinho 1997), and are available on request. These were used for the development of a register of topical fluoride clinical trials for the systematic reviews, as the Cochrane Oral Health Group's Trials Register was not yet developed in 1997/98.

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1,1997), the Community of Science database (1998), which included ongoing trials funded by the National Institute of Dental Research (NIDR), the System for Information on Grey Literature in Europe (SIGLE) database (1980-1997), and OLD MEDLINE (1963-1965) were searched using the terms 'fluor' and 'carie' truncated. (Grey literature search had also been carried out by searching the Index to Scientific and Technical Proceedings (ISTP) and DISSERTATION ABSTRACTS).

From 1999 to 2001

The following strategy was used to search LILACS/BBO in 1999 (1982-98), where free-text subject search terms were combined with a methodological filter for RCTs:
Fluoride varnishes for preventing dental caries in children and adolescents (THE)

A supplementary and more specific subject search phrase (including 'free-text' and 'controlled vocabulary' terms), refined exclusively for this review, formulated around three concepts - varnish, fluoride and caries - was used to search Silverplatter MEDLINE (up to January 2000) without methodological filters:

((CARIE* or (DENT* near CAVIT*) or TOOTH* DECAY* or DMF* or (explode "DENTAL-CARIES"/ ALL SUBHEADINGS))
and ((FLUOR* or explode "FLUORIDES"/ ALL SUBHEADINGS) and ((VARNISH*) or (LACQUER* or LAQUER*) or (VERNIZ*) or (LACKER*) or (LAKK*) or (SILANE* or POLYURETHANE*)) or (DURAPHAT* or FLUOR PROTECTOR*).

This strategy was adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and has also been run on CENTRAL (The Cochrane Library Issue 2, 2000) to double-check.

The metaRegister of Controlled Trials was searched in October 2001 for ongoing randomized controlled trials using the terms 'fluoride' and 'caries'.

REFERENCE SEARCHING

All eligible trials retrieved from the searches, meta-analyses and review articles were scanned for relevant references. Reviews had been identified mainly by a MEDLINE search strategy specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic, when the Cochrane Library database - Cochrane Database of Systematic Reviews (CDSR), and the CRD databases - Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED), were also searched. Reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions were also consulted.

FULL-TEXT SEARCHING

Prospective handsearching of those journals (seven) identified as having the highest yield of eligible RCTs/CCTs were carried out, from January 1999 until January 2000: British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (1990-December 1999), as this was the journal with the highest yield of eligible reports.

PERSONAL CONTACT

Searching for unpublished studies (including 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published during the last two decades, in

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order to obtain information on possible unpublished studies eligible for inclusion. All the authors of studies who had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies.

Based on information extracted mainly from included studies, a list of manufacturers of fluoride varnishes was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group (COHG), in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Three fluoride varnish manufacturers were contacted (October 2000) and information on any unpublished trials requested: Colgate Oral Pharmaceuticals, Ivoclar North America, Pharmascience.

Methods of the review

IDENTIFICATION OF RELEVANT REPORTS

Because multiple databases were searched, the downloaded set of records from each database, starting with MEDLINE, was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS, BBO, CCTR, SIGLE and NIDR databases were not imported to Reference Manager and were scanned without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filter were imported to Reference Manager for inspection but in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register and the metaRegister of Controlled Trials were also checked outside Reference Manager.

All records electronically identified by the searches were printed off and scanned on the basis of title first, then by abstract (when this was available in English or in languages known by the reviewer) and/or keywords by one reviewer (VM). Obviously irrelevant reports (according to study design/duration, participants, or interventions/comparisons) were discarded and the full-text of all remaining were obtained.

All potentially relevant articles identified when searching other sources (reference lists of relevant studies, review articles and book chapters; journal handsearch; personal contact) were also obtained. (Reports that might be identified by contacting manufacturers will be obtained to feature in updates of this review.)

It was considered essential to identify and check all reports related to the same study; and in case of any discrepancy authors were contacted.

STUDY SELECTION

With the inclusion criteria form previously prepared and pilot tested, one reviewer (VM) assessed all studies for inclusion in the review, and a second reviewer (JH) independently duplicated the process for a sample of those (approximately 30%). In addition, any study that could not be classified by the first reviewer was independently assessed by the second. A third reviewer was consulted (SL or AS) to resolve any disagreement. It was decided in advance to exclude any trial where agreement could not be reached but this did not occur. Trial reports thought to be
potentially relevant in languages not known by the reviewers were translated and the reviewer (VM) completed the inclusion form with reference to the translator. Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met.

QUALITY ASSESSMENT

The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Collaboration Reviewers' Handbook (Clarke 2000) used in RevMan. Allocation concealment for each trial was rated as belonging to one of three categories:

A. Adequately concealed (an adequate method to conceal allocation is described).
B. Concealment unclear ("random" allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
C. Inadequately concealed (an inadequate method of allocation concealment is described).

Excluded: random (or quasi-random) allocation clearly not used in the trial, or "random" allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:

A. Double-blind (blind outcome assessment and use of placebo described).
B. Single-blind (blind outcome assessment stated and no placebo used).
C. Blinding indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment - e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).

Excluded: clearly open outcome assessment or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, of x-rays registered independently of clinical examination, of use of a placebo, and of examiners clearly not involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated the process for a random sample of approximately one third of those. Any disagreement was discussed and where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not be resolved an effort was made to contact authors directly to clarify the method used to conceal allocation or whether assessment of the main outcome had been carried out blind.

Other methodological characteristics of the trials such as blinding of participants (placebo or no treatment control), completeness of follow-up (proportion excluded) and handling of exclusions (extent to which reasons for attrition are explicitly reported, or losses are independent of treatment allocated) were not used as thresholds for inclusion. However, all assessments of study quality are described in the table of included studies, and were coded for possible use in meta-regression/sensitivity analyses.

DATA EXTRACTION
Data from all included studies were extracted by one reviewer (VM) using a pilot tested data extraction form. A second reviewer (JH) extracted data from a random sample of approximately one third of included studies. However, in future updates all reports will be data extracted and quality assessed in duplicate. Checking of interobserver reliability was limited to validity assessments. Again, data that could not be coded by the first reviewer were independently coded by the second, any disagreement was discussed and a third reviewer consulted to achieve consensus where necessary. Provision was made to exclude data where agreement could not be reached but this situation did not occur. Data presented only in graphs and figures were extracted whenever possible, but were included only if two reviewers independently had the same result. Attempts were made to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary.

Additional information related to study methodology or quality that was extracted included: study duration (years of follow-up), comparability of baseline characteristics - methods used pre-randomization in sizing/balancing (stratification based on relevant variables) or used post-randomization in analysing/adjusting for possible differences in prognostic factors between groups, objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors), any co-intervention and/or contamination. Information on sponsoring institutions and manufacturers involved was also recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries severity at start (average DMFS, DFS, or other measure), background exposure to other fluoride sources (toothpaste, water, etc), year study began, location where study was conducted (country), setting where participants were recruited, and dental treatment level (F/DMF). Characteristics of the intervention that were extracted included: methods (technique/device) of application, prior- and post-application, fluoride active agents and concentrations used, frequency and duration of application, and amount applied.

Different ways of assessing/reporting caries increment in the trials (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units measured (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (deciduous teeth/surfaces, first molar teeth, approximal surfaces, etc), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiolographical), and approaches to account or not for reversals in caries increment adopted (in a net or observed increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow-ups).

As we were aware that caries increment could be reported differently in different trials we developed a set of a priori rules to choose the primary outcome data for analysis from each study: data on permanent teeth would be chosen over data on deciduous teeth, data on surface level would be chosen over data on tooth level, DFS data would be chosen over DMFS data, and this would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted' only, and this over data for 'erupting' only; data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological' only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated esions; net caries increment data would be chosen over crude (observed) increment data; and follow-up nearest to three years (often the one at the end of the treatment period) would be chosen.
over all other lengths of follow-up, unless otherwise stated. When no specification was provided with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices described above were assumed.

The table of included studies provides a description of all the main outcome data reported from each study with the primary measure chosen featuring at the top. All other relevant outcomes identified as being assessed in the trials are also listed in this table.

ANALYSES

Handling of missing main outcome data
It was decided that missing standard deviations for caries increments that were not revealed by contacting the original researchers would be imputed through linear regression of log standard deviations on log mean caries increments. This is a suitable approach for caries prevention studies since, as they follow an approximate Poisson distribution, caries increments are closely related (similar) to their standard deviations (van Rijkom 1998).

Handling of results of studies (main outcome) with more than one treatment arm
In the studies with more than one relevant intervention group and a common control group, such as those comparing different active fluoride agents or concentrations of fluoride ions to a placebo group, raw results (the numbers, mean caries increments and standard deviations) from all relevant experimental groups were combined in order to obtain a measure of treatment effect. This enables the inclusion of all relevant data in the primary meta-analysis, although may slightly compromise any secondary investigations of dose response.

Choice of measure of effect and meta-analyses of main outcome
The chosen measure of treatment effect was the prevented fraction (PF), that is (mean increment in the controls minus mean increment in the treated group) divided by mean increment in the controls. For an outcome such as caries increment (where discrete counts are considered to approximate to a continuous scale and are treated as continuous outcome), this measure was considered more appropriate than the mean difference or standardised mean difference since it allows combination of different ways of measuring caries increment and a meaningful investigation of heterogeneity between trials. It is also simple to interpret. The meta-analyses were conducted as inverse variance weighted averages. Variances were estimated using the formula presented in Dubey 1965 which was more suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable. Random effects meta-analyses were performed throughout.

With the use of prevented fraction, it was not possible to perform the main outcome analyses in RevMan/MetaView (when the review was first published). However, the raw results of the studies (mean/SD/n) were entered in RevMan and mean differences were presented without meta-analyses. If meta-analyses using standardised mean differences yielded materially similar results to those using prevented fractions, we would also present these within MetaView. Deciduous and permanent teeth would be analysed separately throughout.

For illustrative purposes the results were also presented as the number of children needed to treat (NNT) to prevent one carious teeth/surface. These were calculated by combining the overall prevented fraction with an estimate of the caries increment in the control groups of the individual studies.
Assessment of heterogeneity and investigation of reasons for heterogeneity

Heterogeneity was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95% confidence intervals and by formal tests of homogeneity undertaken prior to each meta-analysis (Thompson 1999).

In addition to aspects of study quality, two potential sources of heterogeneity were specified a priori as investigations of these formed part of the primary objectives of the review. We hypothesised that: (1) the effect of fluoride varnishes differs according to the baseline levels of caries severity and (2) the effect of fluoride varnishes differs according to exposure to other fluoride sources (in water, in toothpastes, etc). If sufficient number of studies were included, the association of these factors with estimated effects (D(M)FS PFs) would be examined by performing random effects meta-regression analyses in Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998).

To allow such investigation, relevant data were dealt with as follows: data on 'baseline levels of caries' were calculated from the study sample analysed (final sample) unless otherwise stated, and were averaged among all relevant study groups. Data on 'background exposure to other fluoride sources' combined data on the use of fluoride toothpaste and the consumption of fluoridated water (or salt) and were grouped into two categories: one for studies which were based on samples provided with non-fluoride toothpaste and which were from non-fluoridated areas (non exposed), and another for studies based on samples using fluoride toothpaste or studies in fluoridated communities or both. When use or non-use of fluoride toothpaste was not clearly indicated in studies carried out in developed countries, it was assumed that fluoride toothpaste was widely used from the middle of the 1970s (Ripa 1989); this information was sought from authors (or obtained from other sources) when missing from studies carried out in other locations. When data on the year a study had begun was not provided this was calculated as a 'probable date' by subtracting the duration of the study (in years) plus one extra year, from the publication date of the study.

Investigation of publication and other biases

A funnel plot (plots of effect estimates versus the inverse of their standard errors) was drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, though may also represent a true relationship between trial size and effect size. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger et al (1997).

Measures of effect and meta-analysis of other outcomes

For outcomes other than caries increment, continuous data were to be analysed according to differences in mean treatment effects and their standard deviations. Dichotomous outcome data were analysed by calculating risk ratios (RR). The Cochrane Review Manager software (RevMan 4.1) was used for estimation of overall treatment effects. Again random effects model was used to calculate a pooled estimate of effect. As a general rule only (relevant) outcomes with useable data would be shown in the analyses tables.

Description of studies

IDENTIFICATION OF REPORTS / STUDIES

Searching the core database in Reference Manager (using 'varnish' or 'fluoride varnish' or 'lacquer'
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or 'duraphat' or 'fluor protector' or 'carex' or 'polyurethan*' or 'silanes*' or 'sodium fluoride*' as keywords combined with 'varnish' or 'lacquer' or 'duraphat' or 'fluor protector' in titles, and with 'varnish' in notes and all other fields) retrieved 1381 records from MEDLINE, EMBASE, BIOSIS, SCISEARCH, SSCISEARCH, CINAHL, ERIC, ISTP and DISSERTATION ABSTRACTS.

There were 211 records scanned outside Reference Manager produced by searching LILACS (48 records), BBO (47 records), CCTR (86 records), SIGLE (6 records), and NIDR/Community of Science Database (24 records). When LILACS and BBO were searched for the second time with a modified search strategy the yield was 210 records (142 and 68 records respectively) also scanned outside Reference Manager. Searching OLD MEDLINE produced 545 records. Thus, 2347 records yielded by the original electronic searches for topical fluoride trials were scanned, but many of these were duplicates not merged in the core database. The specific MEDLINE search for fluoride varnish trials performed without RCT filter produced 331 records, and the search performed in the OHG specialised register produced 65 records. The search for ongoing studies in the metaRegister of Controlled Trials database produced 5 records. Searching other non-electronic sources (reference lists of relevant studies, review articles or book chapters; journals; contacting authors) produced 24 additional records for inspection. (Any search results that might be produced by contacting manufacturers will feature in updates of this review.)

From the search results above a total of 116 records were considered potentially eligible, sought and assessed further.

SELECTION OF STUDIES

One hundred and sixteen reports were sought for detailed assessment, of which 47 were considered immediately irrelevant for this review, mainly as a result of the type of interventions compared with fluoride varnish, or study design. Fifty studies (69 reports) are considered in this review. These comprise 17 reports relating to nine included studies, 44 reports relating to 33 excluded studies, two reports relating to two ongoing studies, and six reports relating to six studies waiting assessment either because they require translation (two in Polish, one in Hungarian, and one in Norwegian) or because translation and contact with the authors have not ascertained whether all inclusion criteria have been met (one in German).

There were 26 non-English reports (22 studies) listed either under excluded or included studies. Seven of these reports (five studies) were excluded either on the basis of the English abstract alone, or due to the availability of a full-text English report, or because sufficient information was available from other sources such as previous reviews. There remained 19 non-English reports that were fully assessed (16 studies): 11 in German (by a German translator, with the contact reviewer), five in Russian (by a Czech translator, with the reviewer), two in Hungarian (by a Hungarian translator, with the reviewer), and one in Portuguese (by the contact reviewer).

EXCLUDED STUDIES

See 'Characteristics of excluded studies' for the description of reasons for rejecting each study.

The 33 studies in this section were excluded for a variety of reasons. Ten studies used the within-subject paired design, or 'split-mouth' design. Although three of these were described as double-blind trials they did not indicate random allocation of right/left sides of the mouth to treatment (one of which reported a systematic allocation process); among the other seven non-placebo controlled trials, one was a quasi-randomized trial reporting blind outcome assessment, one reported blind outcome assessment but nothing about the allocation process, and the remaining split-mouth trials did not indicate random/quasi-random allocation or blind outcome assessment.
Five studies were clearly not randomized/quasi-randomized and did not mention or indicate blind outcome assessment. One of these also applied the varnish only once in a 15-month period. One study clearly used open outcome assessment (but described the use of quasi-random allocation). Another was not randomized/quasi-randomized (but used blind outcome assessment). Seven studies did not mention or indicate random/quasi-random allocation nor blind outcome assessment. One of these also did not report main outcome data for control group and another reported post-treatment outcome data only. Attempts were made to contact the authors of three of these studies, but no replies were received. One study did not mention or indicate random or quasi-random allocation and blind was not stated (but not unlikely), an attempt to contact the author was unsuccessful. Two studies did not mention or indicate random or quasi-random allocation (but reported blind outcome assessment), one of these had each of two clusters assigned to the varnish and control groups; an attempt to contact the authors of the other study was unsuccessful.

Three studies had other fluoride or non-fluoride based interventions in addition to fluoride varnish. Two of these also did not state/indicate random or quasi-random allocation and blind outcome assessment. One study used a fluoride-based intervention in the control group. Two studies included participants who were medically compromised; none stated/indicated random or quasi-random allocation, one did not indicate blind assessment and the other used open outcome assessment.

INCLUDED STUDIES
See 'Characteristics of included studies' table for details of each study.

There are nine trials included. All 17 reports were published between 1975 and 1997. The nine trials were conducted between 1973 and 1992: five during the 1970s, three during the 1980s and one in the 1990s. Five trials were conducted in Sweden and four in each of the following countries: Canada, Spain, GDR and India. Five studies had multiple publications. Eight of the included studies did not mention involvement with a fluoride varnish manufacturer. The only one which acknowledged partial financial support from a fluoride varnish manufacturer (Frostell 1991) also acknowledge support from a sugar company.

Design and methods
All the included studies used parallel group designs (the split-mouth trials were excluded). Two studies had more than one fluoride varnish treatment group compared to a placebo. With regard to type of control group used, six trials used a no treatment control group, and the remaining three used a placebo control group, two of which used an inactive treatment other than varnish ('placebo' solution/distilled water). The study duration (indicated by the total length of follow-up as well as the treatment duration) ranged from 1 to 4.5 years among included trials (four of these lasted two years). Studies were relatively large with only two allocating less than 100 children (but more than 60) to relevant study groups. The total number of children participating in the nine included trials (given by the sample analysed at the end of the trial period) was 2709, and ranged from 95 in the smallest trial to 676 in the largest trial. Participants of five trials were recruited from school settings (centre for recruitment was not clearly reported in the remaining four studies).

Participants
The ages of the children at the start of the trials ranged from three to 15 years, with similar numbers from both sexes (where these data were reported); seven trials included participants who were over six years at start, and two trials included three and four year-olds (in which deciduous teeth only could have been assessed for caries development). Decayed, (missing) and filled surfaces
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(D(M)FS) at baseline, reported in six of the studies, ranged from 0.39 to 29.2, and from 0.88 (ds) to 9.66 (dmfs) in the three studies that reported data for deciduous teeth. With regard to 'background exposure to other fluoride sources', only one study was conducted in a fluoridated community and only one (another) clearly reported no exposure to fluoride toothpastes; the four studies clearly reporting a moderate to high exposure to fluoride toothpaste (over 70% of children) also reported exposure to fluoride rinses and/or tablets, and two studies which did not report exposure to toothpaste clearly reported exposure to rinses. Information on dental treatment level could be obtained from the studies conducted in Spain and Canada, and from one of the studies conducted in Sweden.

Interventions

Teeth were usually painted with a fluoride varnish using a small brush (four trials), but the use of probe and cotton swab was also reported. The use of NaF based varnishes (Duraphat or Lawefluor, or Bifluorid 12) was reported in all trials. Difluorosilane (Fluor Protector) was used in only one of the studies included. The fluoride concentrations ranged from 7000 ppm F (difluorosilane) to 56,300 ppm F (6%NaF+6%CaF *data obtained from Beltran-Aguilar 2000). The application frequency of twice a year was tested in eight studies and that of four times a year in only two studies. The amount of varnish applied was usually of around 0.5ml per child (reported in five studies). Where the actual application time was reported it ranged from one to four minutes. The performance of some form of prior tooth prophylaxis before administering the varnish was used in seven studies; as long as performed with no paste or with a non-fluoride paste (if with a fluoride paste the trial would have been excluded), the prior toothcleaning was considered by the reviewers as a possible part of the technique of varnish application and not as a separate intervention on its own.

Outcome measures

All nine included trials reported caries increment data at the tooth surface level (D(M)FS reported in seven trials, one of these also reported dfs data; dfs/dmfs data were reported in the other two trials). Three of the nine trials reported caries increment data at the tooth level (D(M)FT) and only one of the three trials that reported caries increment data for deciduous teeth (dmfs) reported these data at the tooth level (dmft). With regard to the components of the DMFS index used (and types of teeth/surface assessed), five trials reported DMFS data (one trial for first molars only and four trials for all tooth surface types) and the other two reported DFS data (one trial for posterior approximal surfaces only and another for first molar fissures only), one also reported DS and FS data separately. (No choice had to be made between DMFS or DFS data in any one trial, but DFS data were chosen over DS/FS data in one of the trials.) All trials reported D(M)FS data on specific teeth or tooth surfaces - first molars, occlusal, mesio-distal (approximal) and/or buco-lingual - but three of these did not report data on all tooth surfaces (whole mouth). D(M)FS data were reported at more than one follow-up time in two trials only; follow-up of two years was the most common among all trials.

Clinical (eight of the nine included trials) and radiographic examinations (four trials) provided the definition of different stages or grades of caries lesions. These have been grouped into two basic grades for each method: NCA = non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor/walls) or showing frank cavitation; ER = any radiolucency in enamel/enamel-dentin junction; DR = radiolucency into dentin. Five trials presented results using one caries grade only (CA/DR); the remaining four reported both CA/DR and NCA/ER grades, in which case CA/DR was chosen. Data on state of tooth eruption considered was clearly presented in eight trials: data for teeth erupted at baseline only were reported in four.
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trials, data for erupting teeth only were reported in one trial, combined data for erupting and erupted teeth were reported in two trials, and separately reported in one trial.

Other dental caries data reported: caries incidence rate (one trial), caries progression rate (one trial), proportion of children developing new caries (two trials), proportion of teeth developing new caries and failures - carious teeth - over time (one trial).

No data were reported on adverse effects. Data for unacceptability of treatment (as measured by dropouts/exclusions) were reported in two of the no treatment control trials.

ONGOING STUDIES
See 'Characteristics of Ongoing Studies' table for details of each study.

We have identified two ongoing randomized trials, one from UK and the other from USA, which are described in the table of ongoing studies.

Methodological quality of included studies

Based on 28 studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, interrater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73). There were clear differences in the quality of the studies in this review (using the reported information and additional information obtained from investigators).

ALLOCATION CONCEALMENT

Six included trials were described as randomized and assigned code B (no information was reported on allocation concealment), and three trials were clearly quasi-randomized and assigned code C. None of the trials whose investigators provided further information in answer to our enquiry could be assigned code A (adequate concealment of allocation fully described).

BLINDING

Three trials were classified as double-blind (score A), although two of these did not use a true placebo, but an inactive treatment other than varnish. Single-blinding (blind dental caries assessment but no placebo used) was described in five trials (score B). Blind outcome assessment was unclear/indicated in one trial (score C), which was a non-placebo controlled trial.

FOLLOW-UP

All the participants considered at the end of each study as a proportion of all the participants present at start in all studies was 89% (2289 analysed out of 2578 randomized); this excludes two studies with no data on participants randomized. The drop-out rate could not be obtained from one of the nine included studies. Where dropout was reported it varied from 6% at 2.5 years to 18% at 3 years.

Reasons for exclusions (when given) included moving away, refusal to participate/poor compliance, and characteristics of participants that should have been used as eligibility criteria before randomization (e.g. use of orthodontic bands). Only one trial reported the numbers excluded...
in each study arm according to reason for attrition.

OTHERS

Units of randomization: cluster randomization was used in one trial (Bravo 1997) where school classes were used as units of randomization and children used as units of analysis. Baseline comparisons and handling of any differences: one of the trials described as 'balanced' (for which randomization may have succeeded to produce nearly exact balance) did not report any of the actual values for the baseline characteristics (such as initial caries levels); another trial with incomplete reporting of baseline factors showed some degree of imbalance of initial DFS (where 8% - 20 children - had been excluded from the varnish group on the basis of compliance). Objectivity/reliability of primary outcome measurement: diagnostic methods used (clinical or radiographic) and thresholds/definitions used for caries were described in all studies, but monitoring of diagnostic errors were not always clearly described (see 'Notes' in the 'table of included studies' for methodological features assessed).

Results

EFFECT OF FLUORIDE VARNISH ON DENTAL CARIES INCREMENT

The effects of fluoride varnishes on dental caries increment were reported in a variety of different ways in the included studies. Where appropriate and possible these have been combined to produce pooled estimates as described in the methods section. The results are reported separately here for: (1) Decayed, (Missing) and Filled Surface Prevented Fraction (D(M)FS PF), (2) Decayed, Missing and Filled Teeth Prevented Fraction (D(M)FT PF), (3) D(M)FS and D(M)FT pooled using a standardised mean difference (SMD), (4) decayed, (missing/extraction indicated), and filled deciduous surfaces pooled using prevented fraction (d(m/e)fs PF) and standardised mean difference (d(m/e)fs SMD).

Standard deviations of mean caries increment data (new D(M)FS) were (partly) missing in two of the seven studies which contributed data (Modeer 1984; Clark 1985). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries increment), (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses. Similarly, this same regression equation was used to estimate missing standard deviation for one of the three trials reporting D(M)FT data (Holm 1984) and for two of the three trials (Clark 1985; Frostell 1991) reporting mean caries increment data in the deciduous dentition (new defs).

Effect on tooth surfaces: D(M)FS prevented fraction
For all seven trials combined, the D(M)FS prevented fraction pooled estimate was 0.46 (95% CI, 0.30 to 0.63; p<0.0001), suggesting a substantial benefit from the use of fluoride varnish. The confidence intervals are relatively wide, however, and substantial heterogeneity in results could be observed graphically and statistically (Q= 28.17 on 6 degrees of freedom, p<0.0001).

For each study, the D(M)FS prevented fraction and 95% CIs can be viewed in the 'Tables of other data'; the results of the random effects meta-analysis of D(M)FS prevented fractions (performed in Stata) are presented in Additional Table 01: Meta-analyses of prevented fractions.
We have decided not to present the meta-analysis results stratified by type of control group (placebo/no treatment) in this review which included so few studies, even though this might represent a strong indicator of study quality and source of heterogeneity in the topical fluoride reviews, as suggested in the first review in this series (Marinho 2002). However, forest plots showing the effects of fluoride varnishes (PFs and 95% CIs) on D(M)FS increments resulting from a meta-analysis stratified by type of control group are available in the 5th review in this series (whose results invigorate the discussion of the influence of this factor on effect estimates): Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents (Comparison 01, Sub-categories 03 for placebo-controlled varnish trials, and 06 for fluoride varnish trials using no treatment controls).

Meta-regression and sensitivity analyses: D(M)FS prevented fraction
Univariate meta-regression suggested no significant association between estimates of D(M)FS prevented fractions and the pre-specified factors: baseline caries severity, background exposure to fluoridated water, background exposure to fluoride toothpaste, or background exposure to any reported fluoride source. Further univariate meta-regression analyses showed no significant association between estimates of D(M)FS prevented fractions and length of follow-up (duration of study), allocation concealment (random/quasi-random), blinding of outcome assessment (blind/blind likely or unclear), drop-out rate, or type of control group (placebo/no treatment).

In spite of the considerable variation in treatment effects between studies, because the meta-analysis included only seven trials, no further exploration of competing explanations for heterogeneity in treatment effects was considered. Meta-regression would have very limited power to detect any true relationship between the caries-preventive effectiveness of fluoride varnish and factors specified (or not) a priori in these circumstances. Meta-regression results for potential effect modifiers specified a priori are given in Additional Table 02: Random effects meta-regression analyses of prevented fractions: D(M)FS.

We performed a sensitivity analysis for the main meta-analysis of D(M)FS prevented fraction, to take account of the additional uncertainty we should have about the cluster randomized trial by Bravo 1997. We inflated the variance of the prevented fraction estimate by an amount equal to \((1 + (m-1) * \text{ICC})\), where \(m\) is the average cluster size and ICC the intraclass correlation coefficient. A conservative value of 0.1 for the ICC was used since we could not find an ICC from this or any similar trial. The D(M)FS PF pooled estimate was 0.46 (95% CI, 0.29 to 0.64; \(p<0.0001\)). These results are almost identical to the analysis ignoring the cluster randomized design, since the estimate for this trial is similar to the meta-analysis result and altering its weight has minimal effect.

In order to illustrate the magnitude of the effect, numbers of children needed to treat (NNT) to prevent one D(M)FS were calculated based on the pooled D(M)FS prevented fraction and on the caries increments in the control groups of the trials that contributed data to the meta-analysis. The overall caries-inhibiting effect (%PF) derived from the pooled results of the seven trials was 46% (95% CI, 30% to 63%); the caries increments ranged from 0.67 to 4 D(M)FS/year. In populations with a caries increment of 0.67 DMFS per year (at the lowest end of the results seen in the included studies), this implies an absolute caries reduction of 0.31 DMFS/year, equivalent to an NNT of 3.2 (95% CI, 2.4 to 5); i.e. 3.2 children need to have fluoride varnish applications two to four times a year to avoid one D(M)FS. In populations with a caries increment of 1.6 DMFS per year (at the mid range of the results seen in the included studies), this implies an absolute caries reduction of 0.74 DMFS/year, equivalent to an NNT of 1.4 (95% CI, 1 to 2); i.e. 1.4 children need...
Fluoride varnishes for preventing dental caries in children and adolescents (THE 2002 to have fluoride varnishes applied to avoid one DMFS.

Funnel plot and test for funnel plot asymmetry: DMFS prevented fraction
A funnel plot of the seven studies reporting DMFS PFs indicated no clear relationship between prevented fraction and precision (it appears asymmetric). The formal test for asymmetry (Egger 1997) was not statistically significant (asymmetry intercept (95% Cl) = 3.18 (-6.12 to 12.5) (p=0.42)), but, similarly to meta-regression methods, power is limited when only a few trials are included.

The funnel plot of the seven trials comparing fluoride varnish with placebo/no treatment is available in 'Additional Figure 01', where DMFS standardized mean differences are plotted against standard errors (see 'Alternative treatment effect measure' below).

Effect on whole teeth: DMFT prevented fraction
Three trials reported data which allowed the calculation of the DMFT prevented fraction. All three are also included in the analysis of DMFS PF. The pooled estimate of DMFT prevented fraction was 0.53 (95% CI, 0.23 to 0.82; p<0.0001), suggesting a considerable benefit of fluoride varnish; the confidence intervals are wide, however. There was, again, substantial heterogeneity between trials (Q= 11.06 on 2 degrees of freedom, p=0.004).

For each study, the DMFT prevented fraction and 95% CI can be viewed in the Tables of other data. The results of the random effects meta-analyses of DMFT prevented fractions performed in Stata are also presented in Additional Table 01: Meta-analyses of prevented fractions.

Alternative treatment effect measure: Standardized mean difference (SMD)
Due to the character of DMFS data, mean caries increments are closely related to their standard deviations (they are about the same). Thus, meta-analyses using standardised mean differences (the difference between two means divided by an estimate of the within group standard deviation) yielded materially similar results to those using prevented fractions (the difference in mean caries increments between the treatment and control groups divided by the mean increment in the control group). We therefore decided to present DMFS SMDs in RevMan, since it was not possible to present the main outcome analyses with prevented fractions in MetaView/RevMan 4.1. The results of this analysis are very similar to and consistent with those reported above. For the seven trials the pooled DMFS SMD estimate was 0.46 (95% CI, 0.26 to 0.65; p<0.0001) and confidence intervals were wide. There was substantial heterogeneity between trials (chi-square = 26.90 on 6 degrees of freedom, p=0.004).

The pooled estimate of DMFT SMD based on the three trials that contributed data was 0.40 (95% CI, 0.25 to 0.54; p<0.0001). There was no statistically significant heterogeneity (p=0.30). These results are not totally consistent with those observed for the random effects meta-analysis of DMFT PF, because of a particularly low caries increment rate (relative to its standard deviation) in the fluoride varnish group in the Tewari study (1990). Due to this discrepancy, the meta-analysis of SMDs is not presented.

Effect on deciduous dentition: defS PF and defS SMD
Three trials reported data which allowed the calculation of the 'd(e/m)fs' prevented fraction. Only one of these (Clark 1985) is also included in the analysis of DMFS PF. The pooled estimate of (m/e)fs prevented fraction was 0.33 (95% CI, 0.19 to 0.48; p<0.0001), suggesting a substantial benefit of fluoride varnish in the deciduous dentition. There was no statistically significant
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heterogeneity between trials (Q = 3.48 on 2 degrees of freedom, p = 0.18).

The results of the def SMD analysis are consistent with those reported above. We therefore decided to present these. For the three trials, the pooled d(m/e)fs SMD estimate was 0.30 (95% CI, 0.11 to 0.48; p = 0.002). There was no statistically significant heterogeneity between trials (chi-square = 4.02 on 2 degrees of freedom, p = 0.13).

Numbers of children needed to treat (NNT) to prevent one d(em)fs were calculated based on the pooled d(e/m)fs prevented fraction and on the caries increments in the control groups of the three trials in the meta-analysis. In populations with a caries increment of 0.82 dfs per year (at the lowest end of the results seen in the included studies), this implies an absolute caries reduction of 0.27 dfs/year, equivalent to an NNT of 3.7 (95% CI, 2.5 to 6.4). In populations with a caries increment of 1.9 dfs per year (at the highest range of the results seen in the included studies), this implies an absolute caries reduction of 0.63 dfs/year, equivalent to an NNT of 1.6 (95% CI, 1.1 to 2.8).

EFFECT OF FLUORIDE VARNISH ON OTHER OUTCOMES

Few trials report data for other relevant outcomes.

Proportion developing new caries
Two trials reported results on the proportion of children developing one or more new caries (Holm 1979; Holm 1984). The pooled estimate (random effects meta-analysis) of the risk ratio was 0.80 (95% CI, 0.70 to 0.92; chi-square for heterogeneity 0.38 on 1 degree of freedom, p = 0.54). This corresponds to an NNT to prevent one child from developing caries of 6 (95% CI, 3 to 20) in a population with a caries risk the same as that found in the control groups in these trials (six children receiving varnish applications will prevent new caries development in one child).

Unacceptability of treatment (dropouts/exclusions)
The pooled estimate of the relative risk of dropping out from the varnish as opposed to the non-treatment arm in the two non-placebo controlled trials that reported dropouts was 1.78 (95% CI, 0.70 to 4.55; chi-square for heterogeneity 3.65 on 1 degree of freedom, p = 0.06).

Discussion

Selection of a professionally applied topical fluoride procedure should be based on three general considerations. First, the procedure should be effective in preventing dental caries. Second, it should be safe and, lastly, it should be easy to use and acceptable to the patient. The main question addressed by this review is how effective the use of fluoride varnish for the prevention of caries in children is compared to placebo or no treatment. Over 2700 children were included in the trials comparing a fluoride varnish with a placebo or no treatment, and for almost all children the fluoride varnish they received was the 22,600 ppm F NaF formulation. There is evidence of a considerable caries inhibiting effect with the use of this intervention in both the permanent and the deciduous dentition. However, the confidence intervals are relatively wide and the variation among the results of the studies is substantial. Further, relatively few trials were included in both meta-analyses, and very few among these were placebo-controlled trials, making it difficult to rule out the possibility of an overestimation of treatment effects, due to the preponderance of no treatment control studies of lower methodological quality in this review (Marinho 2002). This calls for a cautious interpretation of the data.
The meta-analysis of the seven studies assessing the effect of fluoride varnish on the permanent dentition suggests that the use of this intervention is associated on average with a 46% (95% CI, 30% to 63%) reduction in decayed, missing and filled tooth surfaces. This would correspond to a number needed to treat (NNT) of 1.4 to avoid one D(M)FS per year in a child population with a caries increment of 1.6 D(M)FS per year (in the middle range of control group rates for included studies), or an NNT of 3.2 for children from a population with a caries increment of 0.7 D(M)FS/year (at the lowest end of the observed range). The meta-analysis of the three studies assessing the effect of varnishes on the deciduous dentition suggests a 33% (95% CI, 19% to 48%) reduction in decayed, missing and filled tooth surfaces, and the NNTs are similar for similar caries increment rates observed.

We performed a sensitivity analysis for the main meta-analysis to take account of the additional uncertainty we should have about the cluster randomized trial by Bravo (Bravo 1997). This showed results almost identical to the analysis ignoring the cluster randomized design since the estimate for this trial is similar to the meta-analysis result and altering its weight would have minimal effect.

The caries reduction suggested for the permanent dentition in our review is somewhat similar to that reported in a previous meta-analysis (Helfenstein 1994) on the caries preventive effect of fluoride varnishes in permanent tooth surfaces, which found a 38% (95% CI, 19% to 57%) reduction in caries increment. There were substantial differences in selection criteria and methods between the reviews. Of the 12 studies included in the review by Helfenstein and Steiner (1994), four were also included in this review. Helfenstein and Steiner (Helfenstein 1994) included three trials that did not meet the inclusion criteria for our review, where fluoride varnishes were compared to fluoride rinses (instead of placebo or no treatment). The other five studies not included here were excluded for a variety of reasons. A further five studies were included in this review, and one of these (Bravo 1997) was published after the review by Helfenstein and Steiner.

A secondary aim of this review was to examine whether there was any relationship between the caries-preventive effectiveness of fluoride varnish and the initial level of caries severity and background exposure to fluoride. We were unable to detect a clear relationship between these (and other) factors and the magnitude of the treatment effect in spite of substantial variation between trials in these factors. This result is, however, to be expected. A meta-analysis including only a few trials has very limited power to detect such relationships.

No clear relationship between prevented fraction and precision could be observed in the funnel plot of the seven studies (it appeared asymmetric), and the formal test for asymmetry (Egger 1997) was not statistically significant, but, as for meta-regression methods, power is limited when only a few trials are included.

We found scarce information about the effects of fluoride varnishes on other outcomes such as the proportion of children developing caries or on acceptance of fluoride varnish treatment. We found no information on possible adverse effects. Even though fluoride varnishes are generally considered safe and well accepted, this lack of evidence makes it more difficult for clinicians and policy makers to weigh the benefits of fluoride varnishes in preventing caries against possible shortcomings of the procedure.
Reviewers' conclusions

Implications for practice

This review suggests that the application of fluoride varnishes two to four times a year, either in the permanent or deciduous dentition, is associated with a substantial reduction in caries increment. We found no evidence that this relative effect was dependent on baseline caries level or exposure to other fluoride sources. Both results should be interpreted with caution due to the reasons discussed above. The review does not provide any information on the likelihood of side effects with this treatment and inconclusive information on acceptability.

Implications for research

Despite the considerable number of clinical trials identified, there is a paucity of evidence from placebo controlled studies assessing the effectiveness of fluoride varnishes for the prevention of caries in children. Hopefully, the currently ongoing randomized trials will gather sufficient high quality evidence to increase the precision of estimates of the effect of this treatment. It is important that future trials should include the assessment of other relevant outcomes such as potential side effects (e.g. tooth discoloration, oral allergic reactions) and those related to acceptability of treatment.
### Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borutta 1991</td>
<td>Random allocation; double-blind (A); placebo-controlled; 10% drop-out after 2 years (study duration = 2 years); 'Groups (arms in the trial) kept at equal sizes for statistical reasons'</td>
<td>360 children analysed at 2 years (available at final examination). Age range 12-14 years. Surfaces affected: 5.25 DMFS. Exposure to other fluoride: no. Year study began: in/before 1988. Location: GDR.</td>
<td>FV(3 groups)+ptc versus PL+ptc. Group 1 (Bifluorid 12®): NaF+CaF (27,100+29,200 ppm F) applied twice a year. Group 2 (Bifluorid 12®): NaF+CaF (27,100+29,200 ppm F) applied 4 times a year. Group 3 (Lamefluor®): NaF (22,600 ppm F) applied 4 times a year. Placebo group: applied 4 times a year.</td>
<td>2yDMFS increment - (CA)cl. Reported at 2 years follow-up. O-DMFS. MD-DMFS. BL-DMFS. DMFT(CA).</td>
<td>Participants randomized (N=400). Baseline characteristics (DMFS, DMFT) 'balanced'. Clinical caries assessment by two examiners; diagnostic threshold = CA (FOTI assessment - loss of translucency on transillumination for approximal surfaces). State of tooth eruption included NR; inter-examiner reproducibility checked for DMFS. Results presented separately by examiner (one chosen by coin flip).</td>
</tr>
<tr>
<td>Bravo 1997</td>
<td>Cluster quasi-random allocation; single-blind (B); non-placebo-controlled; 13% drop-out (for all study groups combined) after 2 years (study duration = 4 years). Natural losses (moved to other schools); any differential group losses not assessable.</td>
<td>214 children analysed at 2* years (present for all examinations). Age range 6-8 years (average = 7). Surfaces affected: 0.61 DMFS. Exposure to other fluoride: data not obtained for dentifrice. Year study began: 1990. Location: Spain. Dental treatment level (F/DMF): 4.3%</td>
<td>FV versus NT (NaF Group (Duraphat®) = 22,600 ppm F). Applied twice a year, with Q-tip, about 0.1 ml applied per tooth (1stm) or 0.4 ml per child, left to dry for 15 seconds.</td>
<td>2y*Net1stmDMFS increment - (CA)(E+U). Reported at 2 years follow-up. IstmPF-DMFS. IstmMD-BL-DMFS. Istm-DMFS.</td>
<td>School-classes randomized (15) and children taken as units for caries increment analyses, molars as units for caries incidence and survival analyses; number of children by group NR. Baseline characteristics (age, gender, SES, dft, IstmF/DM, IstmM; IstmDMFS) described as 'balanced' (results NR). Clinical (VT) caries assessment by one examiner;</td>
</tr>
</tbody>
</table>
Fluoride varnishes for preventing dental caries in children and adolescents (THESIS CHAPTER 4)

Clark 1985

Stratified random allocation; double-blind ('A'); placebo-controlled ('PL'); 14% drop-out after 2.5 years (study duration = 4.5 years).

Reasons for attrition NR; no differential group losses.

676 children analysed at 2.5* years (available at 2nd examination, present in at least 5 of 6 treatments). Age range 6-7 years. Surfaces affected: 0.39 DMFS

Exposure to other fluoride: toothpaste + others

Year study began: 1981

Location: Canada

Dental treatment level (F/DMF): 83%

FV(2 groups)+ptc versus 'PL'+ptc

Group 1 (Fluor Protector®): Difluorsilane (7000 ppm F)

Group 2 (Duraphat®): NaF (22,600 ppm F)

Applied twice a year, about 0.5 ml applied per child.

2.5y*DMFS increment - (CA)(E+U)

1st&2ndmolars dfs (CA)(E)

Reported at 1.5, 2.5 and 4.5 years follow-ups**.

O-DMFS

MD-DMFS

BL-DMFS

Diagnostic threshold = CA; state of tooth eruption included = E+U; examiner reproducibility checks (Kappa coefficient) in 10% sample greater than 0.71 in all 1stmDFT measurements.

*Only survival analysis (molar failures over time) reported at 4 years, when results were not available for DMFS increment.

Participants randomized (N = 787).

Baseline characteristics (dental age, DMFS) 'balanced'.

Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; state of tooth eruption included = E+U/E; duplicate examination of 10%sample between examiners done (mean difference of 0.86 DMFS), "results of integrated analysis of treatment and examiner effects remained the same (significant)". Results presented separately by examiner and combined (integrated results chosen).

* Results closest to 3 years
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Design</th>
<th>Allocation</th>
<th>Sample Size</th>
<th>Description</th>
<th>Fluoride Application</th>
<th>Outcome Measures</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frostell 1991</td>
<td>Quasi-random allocation; single-blind (B); non-placebo-controlled; drop-out rate NR (study duration = 2 years). Exclusions based on compliance, any differential group losses not assessable.</td>
<td>206 children analysed at 2 years (after exclusions, available at final examination). Average age 3 years. Surfaces affected: 4.79 dmfs. Exposure to other fluoride: toothpaste + others. Year study began: 1977. Location: Sweden.</td>
<td>FV+ptc** versus NT (NaF Group (Duraphat®) = 22,600 ppm F). Applied twice a year, with small brush, left to dry for 2 min.</td>
<td>dmft</td>
<td>2ydmfs increment - (E) (CA)cl+(DR)xr. Reported at 2 years follow-up.</td>
<td>Participants randomized (N = C 250). Baseline characteristics (dmft/s) 'balanced'. Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included = E. Radiographic assessment (4postBW) by one examiner; diagnostic threshold = DR and ER. Diagnostic errors NR. **Prior prophylaxis with non-fluoride paste carried out in FV group only.</td>
<td></td>
</tr>
<tr>
<td>Holm 1979</td>
<td>Quasi-random allocation; single-blind (B); non-placebo-controlled; 10% drop-out after 2 years (study duration = 2 years). Natural losses; no differential group losses.</td>
<td>225 children analysed at 2 years (available at final examination). Average age 3 years. Surfaces affected: 0.88 defs (but no teeth filled or extracted) - 70% caries-free Exposure to other fluoride: toothpaste + others. Year study began: in/before 1976. Location: Sweden.</td>
<td>FV versus NT (NaF Group (Duraphat®) = 22,600 ppm F). Applied twice a year, with small brush, left to dry (duration NR).</td>
<td>dmft</td>
<td>2ydefs increment - (E) (CA)c1+(DR)xr. Reported at 1 and 2 years follow-ups. O- defs MD- defs BL- defs ds Proportion of children with one or more new defs (at CA level).</td>
<td>Participants randomized (N = C 250). Baseline characteristics (defs) 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA and NCA; state of tooth eruption included = E. Radiographic assessment (if required) by one examiner; diagnostic threshold = DR. Diagnostic errors NR.</td>
<td></td>
</tr>
<tr>
<td>Holm 1984</td>
<td>Random allocation;</td>
<td>95 children analysed at 2 years. Surfaces affected: 0.88 dmfs. Exposure to other fluoride: toothpaste + others. Year study began: 1984. Location: Sweden.</td>
<td>FV+ptc** versus NT</td>
<td>dmft</td>
<td>2y1stmDFS (fissures only). Dropout</td>
<td>Participants randomized (N = B 250). Baseline characteristics (dmft/s) 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA and NCA; state of tooth eruption included = E. Radiographic assessment (if required) by one examiner; diagnostic threshold = DR. Diagnostic errors NR.</td>
<td></td>
</tr>
</tbody>
</table>
Koch 1975

**Fluoride varnishes for preventing dental caries in children and adolescents (THESIS CHAPTER 4)**

**Random allocation; single-blind (B); non-placebo-controlled; 10% drop-out after 1 year (study duration = 1 year).**

121 children analysed at 1 year (available at final examination).

- Average age 15 years.
- Surfaces affected: 29.2 DMFS.
- Exposure to other fluoride: rinse.
- Location: Sweden.

**Participants randomized B.**

1) DFS increment (F)

- Baseline characteristics (DMFS) balanced.
- Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included = E; intra-examiner reproducibility checks for DMFS examinations in 20% sample (mean difference of 0.2 DFS).
- Prior prophylaxis with non-fluoride paste in FV group only.

**FV+ptc** versus NT (NaF Group (Duraphat®) = 22,600 ppm F).

- Applied twice a year, with a cotton swab, about 0.7 ml applied per child (full mouth treatment), left to dry for 2 min.
- Proportion of children with one or more new IstimDFS (at CA level), proportion of carious 1st molars.

**IstmDFT increment**

- Reported at 2 years follow-up.
- Proportion of children with one or more new IstimDFS included = U; intra-examiner reproducibility checks for 1st molars.

**Baseline characteristics (dmfs) balanced.**

- Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA and NCA; state of tooth eruption included = E.
- Radiographic assessment (full-mouth BW) by one examiner; diagnostic threshold = DR and ER.
- Intra-examiner reproducibility checked for DFS and DMFS examinations in 20% sample (mean difference of 0.2 DFS).
**Fluoride varnishes for preventing dental caries in children and adolescents (THESIS CHAPTER 4)**

### Modeer 1984

- **Random allocation; single-blind (B); non-placebo-controlled; 18% drop-out after 3 years (study duration = 3 years).** Reasons for attrition described with respective numbers in each group (8 moved away, 14 ortho treated, 20 - all in varnish group, refused participation); differential group losses.
  - 194 children analysed at 3 years (available at final examination).
  - Average age 14 years.
  - Surfaces affected: 1.43 DFS
  - Exposure to other fluoride: toothpaste + rinse
  - Year study began: 1979
  - Location: Sweden
  - Dental treatment level (F/DF): 86%
  - FV+ptc** versus NT (NaF Group (Duraphat®) = 22,600 ppm F).
  - Applied four times a year, with small brush, 0.3-0.5 ml applied per child.

### Tewari 1990

- **Stratified random allocation; double-blind (‘A’); placebo-controlled (‘PL’); 6% drop-out after 2.5 years (study duration = 4.5 years).** Natural losses; no differential group losses.
  - 618 children analysed at 2.5* years (available at 2nd examination).
  - Age range 6-12 years (average = 8.5).
  - Surfaces affected: 2.53 DMFS
  - Exposure to other fluoride: data not obtained for dentifrice
  - Year study began: in/before 1982
  - FV+ptc versus ‘PL’+ptc (NaF group (Duraphat®) = 22,600 ppm F).
  - Applied twice a year, with single tufted brush, about 0.5 ml applied per child, left to dry for 4 min.

### Additional Information
- **3yMD-DFS increment - (E)**
  - (DR)xr
  - Reported at 3 years follow-up.
  - Caries progression rate
  - Dropout

- **Non-fluoride paste carried out in FV group only.**
  - Participants randomized (N = B 236).
  - Baseline characteristics (toothbrushing frequency, toothpaste use, participation in rinsing program, SES) described as 'balanced' (values NR); initial DFS unbalanced.
  - No clinical assessment of caries.
  - Radiographic assessment (4postBW) by one examiner; diagnostic threshold = ER/DR; intra-examiner reproducibility checks (icc= 0.89).
  - **Prior prophylaxis with non-fluoride paste carried out in FV group only.**

- **Participants randomized (N = B 657).**
  - Baseline characteristics (age, DMFS, DMFT) balanced.
  - Clinical (VT) caries assessment by two examiners; diagnostic threshold = NCA/CA; state of tooth eruption included = E/U; constant duplicate examination of 10% sample between same and both

**Review Manager 4.2.2**

25/09/2003
Dropout rate based only on groups relevant to review, on relevant follow-ups, unless otherwise stated. Baseline caries experience averaged among relevant study arms, and based on the study sample analysed at the end of treatment period (final sample), unless otherwise stated. Age range (average age when reported) at the time the study started based on all study participants (or on groups relevant to the review when data were available).

Istm = first permanent molar; 'A' = classified as double-blind but participants may not be blind (as a PL' was used); CaF = calcium fluoride; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, rough/softened floor walls when probed) or showing frank cavitation; CIR = caries incidence rate; cl = clinical examination; deft/s = decayed, extracted and filled deciduous teeth or surface; dmft/s = decayed, missing (or extracted) and filled deciduous teeth or surface; D(M)FS/T = decayed, (missing) and filled permanent surfaces or teeth; DR = radiolucency into dentin; E = teeth erupted at baseline; ER = any radiolucency in enamel/enamel-dentin junction; FV = fluoride varnish treatment; icc = intra-class correlation coefficient (for inter-rater reliability); M = missing permanent teeth; MD = mesio and distal surfaces; N = numbers; NaF = sodium fluoride; NCA = non-cavitated enamel lesions visible as white spots or discoloured fissures; NR = not reported; NS = not significant; NT = no treatment; O = occlusal surfaces; PF = pit and fissure surfaces; PL = placebo varnish; 'PL' = not a true placebo (inactive treatment other than varnish used); post BW = posterior bite-wing x-ray assessment; ppm F = parts per million of fluoride; ptc = prior tooth-cleaning performed with or without a non-fluoride paste; U = teeth unerupted at baseline; VT = visual-tactile assessment; xr = radiographic examination.

Location: India

♦Final 4.5 years results not available (results closest to 3 years chosen).
## Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bily-Pryga 1983</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
</tr>
<tr>
<td>Grodzka 1982</td>
<td>No random or quasi-random allocation used. Open outcome assessment reported after contacting author.</td>
</tr>
<tr>
<td>Hetzer 1973</td>
<td>Additional non-fluoride based intervention associated to fluoride varnish. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Heuser 1968</td>
<td>No random or quasi-random allocation used (non-random concurrent control). Blind outcome assessment not stated and unlikely. Varnish applied once in 15 months.</td>
</tr>
<tr>
<td>Hochstein 1975</td>
<td>Medically compromised group of children selected. No random or quasi-random allocation used (non-random concurrent control). Open outcome assessment.</td>
</tr>
<tr>
<td>Ivanova 1990</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Kolehmainen 1979</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and placebo groups.</td>
</tr>
<tr>
<td>Kolehmainen 1981</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and placebo groups.</td>
</tr>
<tr>
<td>Kunin 1991</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Lagutina 1978</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Lieser 1978</td>
<td>No random or quasi-random allocation used (non-random concurrent control - by matching procedure). Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Lindquist 1989</td>
<td>Fluoride based intervention associated to control group.</td>
</tr>
<tr>
<td>Maiwald 1973</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
</tr>
<tr>
<td>Maiwald 1978</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Mari 1988</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Reference</td>
<td>Design and Allocation</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Mari 1988a</td>
<td>Random or quasi-random allocation not stated or indicated. Note - Two clusters, each assigned to one of the two groups.</td>
</tr>
<tr>
<td>Murray 1977</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and placebo groups.</td>
</tr>
<tr>
<td>Pashaev 1977</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups. Random or quasi-random allocation not stated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Petersson 1998</td>
<td>No random or quasi-random allocation used (non-random concurrent controls - by matching procedure). Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Ramos 1995</td>
<td>Open outcome assessment.</td>
</tr>
<tr>
<td>Riethe 1977</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
</tr>
<tr>
<td>Rodriguez Miro 1988</td>
<td>Additional non-fluoride based intervention associated to fluoride varnish.</td>
</tr>
<tr>
<td>Ruszynska 1978</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
</tr>
<tr>
<td>Salem 1979</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
</tr>
<tr>
<td>Schmidt 1970</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
</tr>
<tr>
<td>Seppa 1982</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
</tr>
<tr>
<td>Shobha 1987</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. Note - Main outcome data not reported in control group (and not obtainable).</td>
</tr>
<tr>
<td>Suntsov 1991</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. Note - Only post-treatment effects reported.</td>
</tr>
<tr>
<td>Todorashko 1983</td>
<td>Additional fluoride based intervention associated to fluoride varnish. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>van Eck 1984</td>
<td>No random or quasi-random allocation used (non-random concurrent control - by matching procedure).</td>
</tr>
<tr>
<td>Wegner 1976</td>
<td>Medically compromised group of children selected. No random or</td>
</tr>
</tbody>
</table>
Fluoride varnishes for preventing dental caries in children and adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation Method</th>
<th>Blind Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter 1975</td>
<td>No random or quasi-random allocation used (non-random concurrent control). Blind outcome assessment not stated and unlikely.</td>
<td></td>
</tr>
<tr>
<td>Zimmer 1999</td>
<td>No random or quasi-random allocation used (non-random concurrent control). Blind outcome assessment not used.</td>
<td></td>
</tr>
</tbody>
</table>
## Characteristics of ongoing studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Trial name</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Starting date</th>
<th>Contact info</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mancunian</td>
<td>The Mancunian Fluoride Varnish Project</td>
<td>Inclusion criteria: Years 2 and 3 children (aged 6 to 8 years at start) Setting: 24 schools in South Manchester, UK</td>
<td>FV - Duraphat vs NT (NaF group = 22600 ppm F twice a year)</td>
<td>Primary measure: Two-year caries incidence in primary and permanent dentitions</td>
<td>Starting date: 2000</td>
<td>Dr Gill Davies, Mancunian Community Health NHS Trust Mauldeth House Mauldeth Road West Chorlton Manchester M21 7RL England 0161 958 4049 0161 958 4045 <a href="mailto:gill@daviesg28.fsnet.co.uk">gill@daviesg28.fsnet.co.uk</a></td>
<td>Cluster randomised controlled trial with a single blindness</td>
</tr>
<tr>
<td>PECC</td>
<td>Prevention of Early Childhood Caries</td>
<td>Inclusion criteria: Children aged 6 to 36 months at enrollment, no gender or ethnicity restriction (most are Chinese or Hispanic), with 4 erupted maxillary anterior teeth, without white spots, caries-free on all teeth Setting: General Hospital and Family Dental Center in California, USA</td>
<td>FV - Duraphat (2 groups) vs PL (NaF group 1 = 22600 ppm F once a year, NaF group 2 = 22600 ppm F twice a year)</td>
<td>Primary measure: Two-year caries incidence in primary dentition</td>
<td>Recruitment phase: 2001</td>
<td>Prof Jane A. Weintraub, Division of Oral Epidemiology and Dental Public Health Department of Preventive and Restorative Dental Sciences San Francisco School of Dentistry University of California 3333 California Street, Suite 495 San Francisco</td>
<td>Double-blind, parallel design, randomised controlled trial</td>
</tr>
</tbody>
</table>

**Notes:**
- Inequalities in Health Research Initiative - DOH
- Participating organisations: University of Manchester
- Funding organisation: Inequalities in Health Research Initiative - DOH
- Double-blind, parallel design, randomised controlled trial
- Expected or actual study completion date: Spring 2004
- Participating organisations: University of California, San Francisco
- Funding organisation: NIH/NIDCR

---

*Review Manager 4.2.2* 25/09/2003
FV = fluoride varnish treatment; NT = no treatment; NaF = sodium fluoride;
References to studies

Included studies

Borutta 1991  

Bravo 1997  

Bravo 1996  


Clark 1985  


Frostell 1991  

Peyron M, Matsson L, Birkhed D. Progression of approximal caries in primary molars and the effect...
Fluoride varnishes for preventing dental caries in children and adolescents


Holm 1979


Holm 1984


Koch 1975


Modeer 1984


Tewari 1990


Excluded studies

Bily-Pryga 1983


Grodzka 1982


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25/09/2003
Fluoride varnishes for preventing dental caries in children and adolescents


Hetzer 1973

Heuser 1968


Hochstein 1975

Ivanova 1990

Kolehmainen 1979

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Fluoride varnishes for preventing dental caries in children and adolescents

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Maiwald 1978

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Mari 1988a

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Fluoride varnishes for preventing dental caries in children and adolescents

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Ramos 1995


Riethe 1977


Rodriguez Miro 1988


Ruszynska 1978


Salem 1979


Schmidt 1970


Seppa 1982

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Fluoride varnishes for preventing dental caries in children and adolescents


Shobha 1987  {unpublished data sought but not used}


Suntsov 1991  {published data only}


Todorashko 1983  {published data only}


van Eck 1984  {unpublished data sought but not used}


Wegner 1976  {published data only}

Review Manager 4.2.2  25/09/2003
Fluoride varnishes for preventing dental caries in children and adolescents


Winter 1975


Zimmer 1999


Studies awaiting assessment

Bodnar 1984


Schioth 1981


Treide 1980


Ulvestad 1978


Wacinska 1987


Wojtowicz 1986

Wojtowicz D, Banach J. Ocena kliniczna laku Duraphat w profilaktyce prochnicy zebow u dzieci oraz w zwalczaniu wrazlivości szyjek zebow u dorosłych [Clinical evaluation of Duraphat varnish in the prevention of dental caries in children and in the control of cervical hypersensitivity in adults].

Review Manager 4.2.2 25/09/2003
Ongoing studies

Mancunian

Davies G. The Mancunian Fluoride Varnish Project. Ongoing trial.

PECC


*indicates the primary reference for the study
Other references

Additional references

Bawden 1998


Beltran-Aguilar 2000


Bratthall 1996


Burt 1998


Clark 1982


Clark 1985


Clarke 2000


De Bruyn 1987


de Liefde 1998

Fluoride varnishes for preventing dental caries in children and adolescents

Dubey 1965


Egger 1997


Featherstone 1988


Featherstone 1999


Glass 1982


Helfenstein 1994


Johnson 1993


Johnson 1994


Kallestal 1999


Krasse 1996

Krasse B. The caries decline: is the effect of fluoride toothpaste overrated? European Journal of Oral...
Marinho 1997


Marinho 2002


Marthaler 1994


Marthaler 1996


Murray 1991


Murray 1991a


Nadanovsky 1995


O'Mullane 1994


Ogaard 1994


Petersson 1993

Fluoride varnishes for preventing dental caries in children and adolescents

Petersson 1997

Primosch 1985

Ripa 1989

Ripa 1990

Ripa 1991

Rolla 1991

Seppa 1991

Sharp 1998

Stamm 1995

Thompson 1999

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van Rijkom 1998

Whitford 1992

WHO 1994

Yanover 1982

Classification pending

Treide 1980
Table of comparisons

01 Fluoride Varnish versus Placebo/No-treatment
   01 D(M)FS increment (prevented fraction) - nearest to 3 years (7 trials)
   02 D(M)FT increment (prevented fraction) - nearest to 3 years (3 trials)
   03 D(M)FS increment (SMD) - nearest to 3 years (7 trials)
   04 D(M)FT increment (SMD) - nearest to 3 years (3 trials)
   05 d(e/m)fs increment (SMD) - nearest to 3 years (3 trials)
   06 Developing one or more new caries (2 trials)
   07 Unacceptability of treatment as measured by leaving study early (2 trials)
Other data tables

01 Fluoride Varnish versus Placebo/No-treatment

01 D(M)FS increment (prevented fraction) - nearest to 3 years (7 trials)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borutta 1991</td>
<td>29%</td>
<td>(8% to 49%)</td>
</tr>
<tr>
<td>Bravo 1997</td>
<td>43%</td>
<td>(23% to 63%)</td>
</tr>
<tr>
<td>Clark 1985</td>
<td>20%</td>
<td>(5% to 35%)</td>
</tr>
<tr>
<td>Holm 1984</td>
<td>55%</td>
<td>(39% to 70%)</td>
</tr>
<tr>
<td>Koch 1975</td>
<td>77%</td>
<td>(53% to 102%)</td>
</tr>
<tr>
<td>Modeer 1984</td>
<td>30%</td>
<td>(0% to 60%)</td>
</tr>
<tr>
<td>Tewari 1990</td>
<td>75%</td>
<td>(50% to 99%)</td>
</tr>
</tbody>
</table>
Other data tables

01 Fluoride Varnish versus Placebo/No-treatment

02 D(M)FT increment (prevented fraction) - nearest to 3 years (3 trials)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borutta 1991</td>
<td>25%</td>
<td>(5% to 45%)</td>
</tr>
<tr>
<td>Holm 1984</td>
<td>60%</td>
<td>(37% to 83%)</td>
</tr>
<tr>
<td>Tewari 1990</td>
<td>73%</td>
<td>(52% to 95%)</td>
</tr>
</tbody>
</table>
## Additional tables

### 01 Meta-analyses of prevented fractions

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. studies</th>
<th>r.e. estimate</th>
<th>95% c. i.</th>
<th>Meta-analysis p-val</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(M)FS - all studies</td>
<td>7</td>
<td>46%</td>
<td>30% to 63%</td>
<td>p&lt;0.0001</td>
<td>Q= 28.17 (6 d.f.); p&lt;0.0001</td>
</tr>
<tr>
<td>D(M)FT - all studies</td>
<td>3</td>
<td>53%</td>
<td>23% to 82%</td>
<td>p&lt;0.0001</td>
<td>Q= 11.06 (2 d.f.); p= 0.004</td>
</tr>
</tbody>
</table>

*Review Manager 4.2.2 25/09/2003*
### Additional tables

#### 02 Random effects meta-regression analyses of prevented fractions: D(M)FS.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. studies</th>
<th>Slope estimate</th>
<th>95% c.i.</th>
<th>Slope interpretation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline caries</td>
<td>6</td>
<td>1.4%</td>
<td>(-0.3% to 3.1%)</td>
<td>Increase per unit increase in mean baseline caries</td>
<td>0.1</td>
</tr>
<tr>
<td>Background fluorides</td>
<td>5</td>
<td>17%</td>
<td>(-40% to 73%)</td>
<td>Higher PF in presence of background fluorides</td>
<td>0.6</td>
</tr>
<tr>
<td>Fluoride dentrifice use</td>
<td>5</td>
<td>-17%</td>
<td>(-62% to 28%)</td>
<td>Lower PF in presence of fluoride dentrifice use</td>
<td>0.5</td>
</tr>
<tr>
<td>Fluoridated water</td>
<td>6</td>
<td>16%</td>
<td>(-26% to 59%)</td>
<td>Higher PF in presence of water fluoridation</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Additional figures

Figure 01

Funnel Plot of D(M)FS SMDs according to standard errors of the studies included in the meta-analysis

Review: Fluoride varnishes for preventing dental caries in children and adolescents (THESIS CHAPTER 4)
Comparison: 01 Fluoride Varnish versus Placebo/No-treatment
Outcome: 03 D(M)FS increment (SMD) - nearest to 3 years (7 trials)

Review Manager 4.2.2
25/09/2003
Review: Fluoride varnishes for preventing dental caries in children and adolescents (THESIS CHAPTER 4)

Total number of included studies: 9

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>01 Fluoride Varnish versus Placebo/No-treatment</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 D(M)FS increment (prevented fraction) - nearest to 3 years (7 trials)</td>
<td>7</td>
<td>2278</td>
<td>SMD (random), 95% CI</td>
<td>-0.46 [-0.65, -0.26]</td>
</tr>
<tr>
<td>02 D(M)FT increment (prevented fraction) - nearest to 3 years (3 trials)</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 D(M)FS increment (SMD) - nearest to 3 years (7 trials)</td>
<td>3</td>
<td>1107</td>
<td>SMD (random), 95% CI</td>
<td>-0.30 [-0.48, -0.11]</td>
</tr>
<tr>
<td>04 D(M)FT increment (SMD) - nearest to 3 years (3 trials)</td>
<td>2</td>
<td>334</td>
<td>RR (random), 95% CI</td>
<td>0.80 [0.70, 0.92]</td>
</tr>
<tr>
<td>05 d(e/m)fs increment (SMD) - nearest to 3 years (3 trials)</td>
<td>2</td>
<td>486</td>
<td>RR (random), 95% CI</td>
<td>1.78 [0.70, 4.55]</td>
</tr>
<tr>
<td>06 Developing one or more new caries (2 trials)</td>
<td>No total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>07 Unacceptability of treatment as measured by leaving study early (2 trials)</td>
<td>No total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comparison 01 Fluoride Varnish versus Placebo/No-treatment
Outcome 04 DMFS increment (SMD) - nearest to 3 years (3 trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride Varnish</th>
<th>Placebo/NT</th>
<th>SMD (random)</th>
<th>Weight</th>
<th>SMD (random)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>95% CI</td>
<td>%</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Bravo 1997</td>
<td>58</td>
<td>4.12 (2.80)</td>
<td>1.16</td>
<td>0.00 (0.30)</td>
<td>1.00 (0.50)</td>
<td>0.00 (0.90)</td>
</tr>
<tr>
<td>Borutta 1991</td>
<td>167</td>
<td>2.07 (0.28)</td>
<td>1.24</td>
<td>2.05 (0.36)</td>
<td>1.02 (0.39)</td>
<td></td>
</tr>
<tr>
<td>Tewan 1990</td>
<td>270</td>
<td>2.16 (0.20)</td>
<td>1.16</td>
<td>2.05 (0.36)</td>
<td>1.02 (0.39)</td>
<td></td>
</tr>
<tr>
<td>Clark 1985</td>
<td>234</td>
<td>2.04 (0.20)</td>
<td>1.15</td>
<td>2.05 (0.36)</td>
<td>1.02 (0.39)</td>
<td></td>
</tr>
<tr>
<td>Holm 1979</td>
<td>36</td>
<td>0.90 (0.30)</td>
<td>0.00</td>
<td>4.00 (0.70)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 2.05 (0.36) - 2.05 (0.36)

Test for heterogeneity: Chi² = 26.41, df = 6 (P = 0.0002), I² = 72.6%
Test for overall effect: Z = 4.57 (P < 0.00001)

Comparison 01 Fluoride Varnish versus Placebo/No-treatment
Outcome 05 Developing one or more new cavities (2 trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride Varnish</th>
<th>Placebo/NT</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>95% CI</td>
<td>%</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Holm 1979</td>
<td>44/112</td>
<td>77/113</td>
<td>0.54 (0.36, 0.78)</td>
<td>0.00 (0.15, 0.85)</td>
<td>1979 C 0</td>
<td></td>
</tr>
<tr>
<td>Holm 1984</td>
<td>36/50</td>
<td>59/59</td>
<td>0.77 (0.46, 1.33)</td>
<td>1984 B 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 0.54 (0.36, 0.78) - 0.54 (0.36, 0.78)

Test for heterogeneity: Chi² = 3.65, df = 1 (P = 0.06), I² = 72.6%
Test for overall effect: Z = 1.21 (P = 0.23)
CHAPTER 5

FLUORIDE TOOTHPASTES FOR PREVENTING DENTAL CARIES IN CHILDREN AND ADOLESCENTS
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

Reviewers
Marinho VCC, Higgins JPT, Sheiham A, Logan S

Dates
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Date of last substantive update: 13/09/2002
Date of last minor update: / /
Date next stage expected: 15/01/2005
Review first published: Issue 1, 2003

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Medical Research Council, UK

External sources of support
CAPES - Ministry of Education, BRAZIL

Contribution of reviewers
All authors contributed to the development of the protocol. Valeria Marinho (VM) wrote the protocol, conducted searches, selected studies and extracted data. Julian Higgins (JH) duplicated the study selection and data extraction in a sample of studies, and Stuart Logan (SL) or Aubrey Sheiham (AS) were consulted where necessary. VM entered and analysed the data in consultation with JH. VM prepared the full review and all authors were active in its revision and approval.

Acknowledgements
We would like to thank the following investigators who provided additional information about their trials: A Blinkhorn (University of Manchester), P Gjermo (University of Oslo), H Messer (University of Melbourne), J Murray (University of Newcastle upon Tyne). We would also like to thank the help and expertise of the following: A Schreiber (German translations), O Duperrex (French translations), H Pikhart (Czech translation), K Turai (Russian translation), I Masao (Japanese translation); B Anagnostelys and L Jones (Systematic Reviews Training Unit, London), E Tavender, L Fernandez and S Bickley (Cochrane Oral Health Group, Manchester). Finally, we would like to thank those who have provided comments or editorial input to this review: R Davies (University of Manchester), M Esposito (Goteborg University), A-M Glenny (Cochrane Oral Health Group), L Hooper (Cochrane Oral Health Group), M Lennon (University of Liverpool), I Needleman (Eastman Dental Institute), S Poulsen (University of Aarhus), and K Stephen (University of Glasgow).

Potential conflict of interest
None known.
Abstract

Background
Fluoride toothpastes have been widely used for over three decades and remain a benchmark intervention for the prevention of dental caries.

Objectives
To determine the effectiveness and safety of fluoride toothpastes in the prevention of caries in children and to examine factors potentially modifying their effect.

Search strategy
We searched the Cochrane Oral Health Group's Trials Register (May 2000), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2000), MEDLINE (1966 to January 2000), plus several other databases. We handsearched journals, reference lists of articles and contacted selected authors and manufacturers.

Selection criteria
Randomized or quasi-randomized controlled trials with blind outcome assessment, comparing fluoride toothpaste with placebo in children up to 16 years during at least one year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS).

Data collection & analysis
Inclusion decisions, quality assessment and data extraction were duplicated in a random sample of one third of studies, and consensus achieved by discussion or a third party. Authors were contacted for missing data. The primary measure of effect was the prevented fraction (PF) that is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed where data could be pooled. Potential sources of heterogeneity were examined in random effects meta-regression analyses.

Main results
Seventy-four studies were included. For the 70 that contributed data for meta-analysis (involving 42,300 children) the D(M)FS pooled PF was 24% (95% confidence interval (CI), 21 to 28%; p<0.0001). This means that 1.6 children need to brush with a fluoride toothpaste (rather than a non-fluoride toothpaste) to prevent one D(M)FS in populations with caries increment of 2.6 D(M)FS per year. In populations with caries increment of 1.1 D(M)FS per year, 3.7 children will need to use a fluoride toothpaste to avoid one D(M)FS. There was clear heterogeneity, confirmed statistically (p<0.0001). The effect of fluoride toothpaste increased with higher baseline levels of D(M)FS, higher fluoride concentration, higher frequency of use, and supervised brushing, but was not influenced by exposure to water fluoridation. There is little information concerning the deciduous dentition or adverse effects (fluorosis).

Reviewers' conclusions
Supported by more than half a century of research, the benefits of fluoride toothpastes are firmly established. Taken together, the trials are of relatively high quality, and provide clear evidence that fluoride toothpastes are efficacious in preventing caries. Based on the direct evidence from the trials, no conclusion could be reached about any effects that fluoride toothpastes might have on
Fluoride toothpastes for preventing dental caries in children and adolescents (TH fluorosis.

Review Manager 4.2.2 25/09/2003
Background

The prevention of dental caries in children and adolescents is generally regarded as a priority for dental services and considered more cost-effective than its treatment (Burt 1998). Fluoride therapy has been the centerpiece of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray 1991). These were introduced when caries was highly prevalent and severe, and when even modest prevention activities led to considerable reductions in disease levels. In the last twenty years, with the substantial decline in dental caries rates in many western countries, an increase in dental fluorosis levels in some countries, and intensive research on the mechanism of action of fluoride highlighting the primary importance of its topical effect, greater attention has been paid to the appropriate use of other fluoride-based interventions (Glass 1982; Featherstone 1988; Ripa 1991; O'Mullane 1994; Marthaler 1996; Featherstone 1999).

The use of topically applied fluoride products in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades. By definition, the term 'topically applied fluoride' is used to describe those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect, and are therefore not intended for ingestion. The most important anti-caries effect of fluoride is considered to result from its action on the tooth/plaque interface, through promotion of remineralization of early caries lesions and by reducing tooth enamel solubility (Featherstone 1988). Fluoride-containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most commonly used at present, either alone or in combination. Various products are marketed in different countries and a variety of caries preventive programs based on these have been implemented. Toothpastes are by far the most widespread form of fluoride usage (Murray 1991a; Ripa 1991) and although the reasons for the decline in the prevalence of dental caries in children from different countries continues to be debated (Nadanovsky 1995; Krasse 1996; Marthaler 1996; de Liefde 1998), it has been mainly attributed to the gradual increase in, and regular home use of fluoride in toothpaste (Glass 1982; Ripa 1991; Rolla 1991; Marthaler 1994; O'Mullane 1994; Bratthall 1996).

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

The evidence on the effect of topical fluorides on the prevention of dental caries in children has been extensively reviewed in a number of traditional narrative reviews. A small number of reviews focusing on the evaluation of specific topical fluoride active agents within specific delivery systems have used a quantitative meta-analytical approach to synthesise studies results (Clark 1985; Johnson 1993; Helfenstein 1994; Stamm 1995; van Rijkom 1998). However, a systematic quantitative evaluation of the available evidence on the effect of the main modalities of topical fluorides has never been undertaken.

This review is one in a series of systematic reviews of topical fluoride interventions and assesses the effectiveness of fluoride toothpastes in the prevention of dental caries in children.

FLUORIDE TOOTHPASTES (DENTIFRICES)
Toothbrushing with fluoride toothpaste is by far the most common form of caries control in use today. The intensive promotion of fluoride toothpastes by the oral health care industry has been a major factor in their increased use, and, in the developed world, since the 1980s, nearly all commercially available toothpaste formulations contain fluoride. Various fluoride compounds have been used alone or combined in the formulations, 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 toothpastes 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 toothpastes are available in the translucent form of gel, they are different from fluoride gels, which have higher fluoride levels, no abrasives and are applied much less frequently, usually by a professional.

Consensus among researchers and public health authorities places fluoride toothpaste as the method of choice for preventing caries, as it is convenient and culturally approved, widespread, and it is commonly linked to the decline in caries prevalence in many countries. There is an argument that the effect of fluoride toothpastes are underestimated in 'short term' clinical trials of two to three years duration, as these are used throughout life. In addition, it is argued that the use of fluoride toothpaste in fluoridated areas 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 six years), is increasing in both fluoridated and non-fluoridated communities, and the early use of fluoride toothpastes by young children may be an important risk factor (Horowitz 1992; Stookey 1994; Ellwood 1995).

The usual concentration of fluoride in toothpastes is 1000/1100 parts per million (ppm F); toothpastes with higher (1500 ppm F) and lower than conventional fluoride levels (around 500 ppm F) are available in many countries. While the evidence of the effectiveness of low fluoride-containing toothpastes in reducing dental caries appears to be conflicting, toothpastes containing higher concentrations of fluoride confer greater protection against caries (Stephen 1988; O'Mullane 1997), but increase the risk of fluorosis, which is related to both, the amount ingested and the fluoride concentration. Chronic ingestion of fluoride from toothpaste in 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 amount of fluoride ingested beyond which fluorosis may occur is not known accurately, a threshold of 0.05 to 0.07 mgF/kg body weight has been suggested (Burt 1992). A child-sized toothbrush covered with a full strip of toothpaste holds approximately 0.75 to 1.0 g of toothpaste, and each gram of fluoride toothpaste, contains approximately 1.0 mg of fluoride; children aged less than six 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 under 6 years of age should be supervised when brushing their teeth, and that no more than a pea-sized amount, approximately 5 mm, should be used. The frequency of toothpaste use and the rinsing method after toothbrushing would be other factors influencing the effectiveness of fluoride toothpastes (and also their safety). 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 (Chesters 1992; O'Mullane 1997; Chestnutt 1998; Ashley 1999). A formal investigation of these
aspects should help to clarify the optimal level of fluoride toothpaste needed to achieve caries prevention while limiting objectionable enamel fluorosis.

Although acute toxicity is extremely rare, young children are particularly at risk of ingesting toxic doses of fluoride from a standard toothpaste tube of 125 g, generally containing 1100 ppm F (1.1 mgF/g paste). As the probable toxic dose (PTD) is around 5 mgF/kg body weight (Whitford 1992), the accidental swallowing of one-third of a toothpaste tube (45 g) or two-thirds of it (90 g) is potentially life-threatening for a one-year-old (10 kg) or for a five to six-year-old (20 kg) respectively (Ellwood 1998). For this reason it is recommended that a fluoride toothpaste tube should be kept out of the reach of young children.

More than 100 clinical trials conducted in many areas of the world since the 1940s, and summarised in several narrative reviews since the 1950s, have investigated the caries-reducing effect of fluoride toothpastes in children. In the late 1970s, the acceptance of fluoride toothpastes as effective caries inhibiting agents had become so well established that clinical trials in many developed countries had to be benchmarked against standard fluoride toothpastes, as it was considered unethical to withdraw their benefit from a study group. Thus, the effectiveness of new forms and concentrations of fluoride toothpastes has not been so extensively investigated in placebo-controlled trials in children with the lower levels of dental caries prevalence prevailing in many countries.

In the last twenty years, guidelines for caries clinical trials have changed (FDI 1982; CDT-ADA 1988; ICW-CCT 2002) in recognition of the fact that with the decline in caries prevalence and the need, for ethical reasons, to use a positive control instead of a placebo in fluoride toothpaste trials, differences between treatments had become smaller in both absolute and percentage terms. In order to overcome this problem of small group differences, study design approaches have been modified. The most important general strategies have focused on increasing sample size and power, reducing measurement error and conducting studies with high risk subjects, mainly defined on the basis of initial caries scores.

To date, there are two published meta-analyses investigating the comparative efficacy of the two commercially available fluoride toothpaste compounds used most commonly nowadays: sodium fluoride (NaF) and sodium monofluorophosphate (SMFP) (Johnson 1993; Stamm 1995), a question that is not addressed in the present review. There is, however, no systematic quantitative investigation assessing the overall effectiveness and safety of fluoride toothpastes in comparison to placebo and examining formally the main factors that may influence their effectiveness.

Objectives

(1) To determine the effectiveness and safety of fluoride toothpaste in preventing dental caries in the child/adolescent population.
(2) To examine whether the effect of fluoride toothpaste is influenced by the initial level of caries severity.
(3) To examine whether the effect of fluoride toothpaste is influenced by the background exposure to fluoride in water (or salt), or reported fluoride sources other than the study option.
(4) To examine whether the effect of fluoride toothpaste is influenced by fluoride concentration or application features, such as frequency of use.

Criteria for considering studies for this review
Fluoride toothpastes for preventing dental caries in children and adolescents (TH)

Types of studies
Randomized or quasi-randomized controlled trials (RCTs) using or indicating blind outcome assessment, in which fluoride toothpaste is compared concurrently to placebo toothpaste during at least one year/school year.
RCTs with open outcome assessment or no indication of blind assessment, or lasting less than one year/school year, or controlled trials where random or quasi-random allocation is not used or indicated were excluded.

Types of participants
Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started).
Studies where participants were selected on the basis of special (general or oral) health conditions were excluded.

Types of interventions
Topical fluoride in the form of toothpastes only, using any of the following fluoride agents combined or not in the formulation: sodium fluoride (NaF), sodium monofluorophosphate (SMFP), stannous fluoride (SnF2), acidulated phosphate fluoride (APF), amine fluoride (AmF). These may be formulated with any compatible abrasive system and are considered at any fluoride concentration (ppm F), frequency of use, amount or duration of application, and with any technique of toothbrushing or post-brushing procedure. The control group is placebo (non-fluoride toothpaste) which makes the following as the relevant comparison: Fluoride toothpaste compared with placebo toothpaste.
Studies where the intervention consisted of any other active agent(s) or caries preventive measure(s) (e.g. chlorhexidine agent, other fluoride-based procedures, oral hygiene procedures, sealants, xylitol chewing gums, glass ionomers) used in addition to fluoride toothpaste were excluded.

Types of outcome measures
The primary outcome measure in this review is caries increment, as measured by change from baseline in the decayed, (missing) and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. Dental caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis. (See ‘Methods of the review’ for the different ways of reporting the decayed, (missing) and filled teeth or surfaces (D(M)FT/S) scores in clinical trials of caries preventives).
The following outcomes were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions; tooth loss; dental pain/discomfort; specific side effects (fluorosis, tooth staining/discoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting); use of health service resources (such as visits to dental care units, length of dental treatment time).
Studies reporting only on plaque/gingivitis, calculus, dentin hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc) were excluded.

Search strategy for identification of studies
With a comprehensive search, we attempted to identify all relevant studies irrespective of language,
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from 1965 onwards.

ELECTRONIC SEARCHING
Up to 1998

Relevant studies were identified (for the series of topical fluoride reviews) by searching several
databases from date of inception: MEDLINE (1966-1997), EMBASE (1980-1997), SCISEARCH
(1982-1997), ERIC (1966-1996), DISSERTATION ABSTRACTS (1981-1997) and
LILACS/BBO (1982-1997). Two overlapping but complementary subject search phrases (below)
with very low specificity (but high sensitivity), using 'free-text 'and 'controlled vocabulary', were
formulated within Silverplatter MEDLINE around two main concepts, fluoride and caries, and
combined with all three levels of the Cochrane Optimal Search Strategy for Randomized
Controlled Trials (RCTs). These subject search phrases were customised for searching EMBASE
and the other databases:

(a) \["DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS"
all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or
DMF*) and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all
subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR
SODIUM F OR APF OR SMFP OR MFP OR MONOFLUOR*) or ("CARIOSTATIC-AGENTS"
explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or
"DENTIFRICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or
CARIOSTA* or PROPHYLA* or ANTICARI* or ANTI CARI* or VARNISH* or LACQUER* or
DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRIC*
or MOUTH RINS* or RINS* or MOUTHWASH* or MOUTH WASH*)].

(b) \[(explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPICAL/ ALL
SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR
SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT) and
(CARI*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT* in TI, in AB, in MESH)) or
(explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or
(explode MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or
(MOUTH RINS* or RINS*) or (VARNISH* or LACQUER*)].

RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISSERTATION
ABSTRACTS, and LILACS/BBO. All the strategies (subject search and methodological filters)
developed to search each database are fully described in a report produced for the Systematic
Reviews Training Unit (Marinho 1997), and are available on request. These were used for the
development of a register of topical fluoride clinical trials for the systematic reviews, as the
Cochrane Oral Health Group's Trials Register was not yet developed in 1997/98.

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue
1,1997), the Community of Science database (1998), which included ongoing trials funded by the
National Institute of Dental Research (NIDR), the System for Information on Grey Literature in
Europe (SIGLE) database (1980-1997), and OLD MEDLINE (1963-1965) were searched using
the terms 'fluor' and 'carie' truncated. (Grey literature search had also been carried out by searching
the Index to Scientific and Technical Proceedings (ISTP) and DISSERTATION ABSTRACTS).

From 1999 to 2001
The following strategy was used to search LILACS/BBO in 1999 (1982-98), where free-text
subject search terms were combined with a methodological filter for RCTs:

((fluor$ or ppmf or ppm f or amf or snf or naf or apf or mfp or smfp or monofluor$ or duraphat$)
A supplementary and more specific subject search phrase (including 'free-text' and 'controlled vocabulary' terms), refined exclusively for this review, formulated around three concepts: toothpaste, fluoride and caries, was used to search Silverplatter MEDLINE (up to January 2000) without methodological filters: 

\[ (\text{CARIE}^* \text{ or (DENT}^* \text{ near CAVIT})^* \text{ or TOOTH}^* \text{ DECAY}^* \text{ or DMF}^* \text{ or (explode "DENTAL-CARIES"/ ALL SUBHEADINGS]]) \text{ and (FLUOR}^* \text{ or APF}^* \text{ or NAF}^* \text{ or AMINE FOR SNF}^* \text{ or ACIDULATED* PHOSPHATE* FLUORID* or ACIDULATED* FLORID* or PHOSPHATE* FLUORID* or SODIUM* FLUORID* or AMINE* FLUORID* or STANNOUS* FLUORID* or (explode "FLUORIDES"/ ALL SUBHEADINGS)] and (TOOTHPASTE* or TOOTH* PASTE* or DENTIFRICE* or PASTE*) or (explode "DENTIFRICES"/ all subheadings])].

This strategy was adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and has also been run on CENTRAL (The Cochrane Library Issue 2, 2000) to double-check.

The metaRegister of Controlled Trials was searched in October 2001 for ongoing RCTs using the terms 'fluoride' and 'caries'.

REFERENCE SEARCHING
All eligible trials retrieved from the searches, meta-analyses and review articles were scanned for relevant references. Reviews had been identified mainly by a MEDLINE search strategy specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic, when The Cochrane Library database: Cochrane Database of Systematic Reviews (CDSR), and the CRD databases: Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED), were also searched. Reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions were also consulted.

FULL-TEXT SEARCHING
Prospective handsearching of those journals (seven) identified as having the highest yield of eligible RCTs/controlled clinical trials (CCTs) were carried out, from January 1999 until January 2000: British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (1990 to December 1999), as this was the journal with the highest yield of eligible reports.

PERSONAL CONTACT
Searching for unpublished studies (or 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published during the last two decades in order to obtain information on possible unpublished studies eligible for inclusion. All the authors of studies who
had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies.

Based on information extracted mainly from included studies, a list of manufacturers of fluoride toothpastes was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group, in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Nine fluoride toothpaste manufacturers were contacted (October 2000) and information on any unpublished trials requested: Colgate-Palmolive, Unilever/Gibbs, Gaba AG, Smithkline Beecham, Procter and Gamble, Oral-B, Bristol-Myers Co, Warner-Lambert, Synthelabo.

**Methods of the review**

**IDENTIFICATION OF REPORTS PRODUCED BY THE SEARCHES**

Because multiple databases were searched, the downloaded set of records from each database, starting with MEDLINE, was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS, BBO, CENTRAL, SIGLE and NIDR databases were not imported to Reference Manager and were scanned without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filter were imported to Reference Manager for inspection, in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register and the metaRegister of Controlled Trials were also checked outside Reference Manager.

All records electronically identified by the searches were printed off and scanned on the basis of title first, then by abstract (when this was available in English or in languages known by the reviewer) and/or keywords by one reviewer, Valeria Marinho (VM). Obviously irrelevant records were discarded and the full text of all remaining were obtained. Records were considered irrelevant according to study design/duration, participants, or interventions/comparisons (if it could be determined that the article was not a report of a randomized/quasi-randomized controlled trial; or the trial was of less than six to eight months duration; or the trial was exclusively in adults; or the trial did not address a fluoride toothpaste intervention; or the trial compared fluoride toothpaste exclusively to no treatment, instead of fluoride-free toothpaste).

All potentially relevant reports identified when searching other sources (reference lists of relevant studies, review articles and book chapters, journal handsearch, personal contact) were also obtained. (Reports that might be identified by contacting manufacturers will be obtained to feature in updates of this review).

It was considered essential to identify and check all reports related to the same study; in case of any discrepancy, authors were contacted.

**SELECTION OF STUDIES**

With the inclusion criteria form previously prepared and pilot tested, one reviewer (VM) assessed all studies for inclusion in the review, and a second reviewer, Julian Higgins (JH), independently duplicated the process for a sample of those (approximately 30 per cent). In addition, any study that could not be classified by the first reviewer was independently assessed by the second. A third reviewer was consulted, Stuart Logan (SL) or Aubrey Sheiham (AS), to resolve any disagreement.
It was decided in advance to exclude any trial where agreement could not be reached (but this did not occur). Trial reports thought to be potentially relevant in languages not known by the reviewers were translated and the reviewer (VM) completed the inclusion form with reference to the translator. Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met.

QUALITY ASSESSMENT
The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Collaboration Reviewers' Handbook (Clarke 2000) used in the Cochrane Review Manager software (RevMan). Allocation concealment for each trial was rated as belonging to one of three categories:
A. Adequately concealed (an adequate method to conceal allocation is described).
B. Concealment unclear ('random' allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
C. Inadequately concealed (an inadequate method of allocation concealment is described).
Excluded: random (or quasi-random) allocation clearly not used in the trial, or 'random' allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:
A. Double-blind (blind outcome assessment and use of placebo described).
B. Single-blind (blind outcome assessment stated and no placebo used).
C. Blending indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment, e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind outcome assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).
Excluded: clearly open outcome assessment used or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, of x-rays registered independently of clinical examination, of use of a placebo, and of examiners clearly not involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated the process for a random sample of approximately one third of those. Any disagreement was discussed and where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not be resolved an effort was made to contact authors directly to clarify the method used to conceal allocation or whether assessment of the main outcome had been carried out blind.

Other methodological characteristics of the trials such as completeness of follow up (proportion excluded) and handling of exclusions (extent to which reasons for attrition are explicitly reported, or losses are independent of treatment allocated) were not used as thresholds for inclusion. However, all assessments of study quality are described in the table of included studies, and were coded for possible use in metaregression/sensitivity analyses.

DATA EXTRACTION
Data from all included studies were extracted by one reviewer (VM) using a pilot tested data extraction form. A second reviewer (JH) extracted data from a random sample of approximately
one third of included studies. However, in future updates all reports will be data extracted and quality assessed in duplicate. Checking of interobserver reliability was limited to validity assessments. Again, data that could not be coded by the first reviewer were independently coded by the second, any disagreement was discussed and a third reviewer consulted to achieve consensus where necessary. Provision was made to exclude data where agreement could not be reached but this situation did not occur. Data presented only in graphs and figures were extracted whenever possible, but were included only if two reviewers independently had the same result. Attempts were made to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary.

Additional information related to study methodology or quality that was extracted included: study duration (years of follow up); comparability of baseline characteristics: methods used pre-randomization in sizing/balancing (stratification based on relevant variables) or used post-randomization in analysing/adjusting for possible differences in prognostic factors between groups; objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors); any co-intervention and/or contamination. Information on sponsoring institutions and manufacturers involved was also recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries severity at start (average DMFS, DFS, or other measure), background exposure to other fluoride sources (in water, topical applications, etc), year study began, location where study was conducted (country), setting where participants were recruited, and dental treatment level (F/DMF).

Characteristics of the intervention that were extracted included: mode of application (how the intervention was delivered), methods (technique/device) of application, prior- and post-application (rinsing with water), fluoride active agents and concentrations used, frequency and duration of application, and amount applied.

Different ways of assessing/reporting caries increment in the trials (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units of measurement (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (permanent/deciduous teeth/surfaces, first molar teeth, approximal surfaces, etc), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiolographical), and approaches to account or not for reversals in caries increment adopted (in a net or observed/crude caries increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow ups).

As we were aware that caries increment could be reported differently in different trials we developed a set of a priori rules to choose the primary outcome data for analysis from each study: data on permanent teeth would be chosen over data on deciduous teeth; data on surface level would be chosen over data on tooth level; DFS data would be chosen over DMFS data, and this would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted only', and this over data for 'erupting only'; data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological' only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated lesions; net caries increment data would be chosen over crude (observed) increment data; and follow up nearest to three years (often the one at the end of the treatment period) would be chosen.
over all other lengths of follow up, unless otherwise stated. When no specification was provided with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices described above were assumed.

The 'Table of included studies' provides a description of all the main outcome data reported from each study with the primary measure chosen featuring at the top. All other relevant outcomes assessed/reported in the trials are also listed in this table.

ANALYSES
Handling of missing main outcome data
It was decided that missing standard deviations for caries increments that were not revealed by contacting the original researchers would be imputed through linear regression of log standard deviations on log mean caries increments. This is a suitable approach for caries prevention studies since, as they follow an approximate Poisson distribution, caries increments are closely related (similar) to their standard deviations (van Rijkom 1998).

Handling of results of studies (main outcome) with more than one treatment arm
In the studies with more than one relevant intervention group and a common control group, such as those comparing different active fluoride agents or concentrations of fluoride ions to a placebo group, raw results (the numbers, mean caries increments and standard deviations) from all relevant experimental groups were combined in order to obtain a measure of treatment effect. This enables the inclusion of all relevant data in the primary meta-analysis, although may slightly compromise the secondary investigations of dose response.

Choice of measure of effect and meta-analyses of main outcome
The chosen measure of treatment effect was the prevented fraction (PF), that is (mean increment in the controls minus mean increment in the treated group) divided by mean increment in the controls. For an outcome such as caries increment (where discrete counts are considered to approximate to a continuous scale and are treated as continuous outcome) this measure was considered more appropriate than the mean difference or standardised mean difference, since it allows combination of different ways of measuring caries increment and a meaningful investigation of heterogeneity between trials. It is also simple to interpret. The meta-analyses were conducted as inverse variance weighted averages. Variances were estimated using the formula presented in Dubey 1965 which was more suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable. Random effects meta-analyses were performed throughout.

With the use of prevented fraction, it was not possible to perform the main outcome analyses in RevMan/MetaView (when the review was first published). The raw results of the studies (mean/SD/n) were entered in RevMan and mean differences were presented without meta-analyses. If meta-analyses using standardised mean differences yielded materially similar results to those using prevented fractions, we would also present these within MetaView. Deciduous and permanent teeth would be analysed separately throughout.

For illustrative purposes the results were also presented as the number of children needed to treat (NNT) to prevent one carious teeth/surface. These were calculated by combining the overall prevented fraction with an estimate of the caries increment in the control groups of the individual studies.

Assessment of heterogeneity and investigation of reasons for heterogeneity
Heterogeneity was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95 per cent confidence intervals and by formal tests of homogeneity undertaken prior to each meta-analysis (Thompson 1999).

In addition to aspects of study quality, three potential sources of heterogeneity were specified a priori as investigations of these formed part of the primary objectives of the review. We hypothesised that: (1) the effect of fluoride toothpastes differs according to the baseline levels of caries severity; (2) the effect of fluoride toothpastes differs according to exposure to other fluoride sources (in water, etc); and (3) the effect of fluoride toothpastes differs according to concentration of fluoride. The association of these factors with estimated effects (D(M)FS PFs) were examined by performing random effects meta-regression analyses in Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998).

To allow such investigation, relevant data were dealt with as follows: data on 'baseline levels of caries' were calculated from the study sample analysed (final sample) and in connection with the caries increment index chosen unless otherwise stated, and were averaged among all relevant study groups. Data on 'background exposure to other fluoride sources' combined reported 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, and were grouped into two categories: one for studies which were based on samples not using/not reporting background use of fluorides and which were from non-fluoridated areas (clearly non-exposed), and another for studies based on samples using fluorides or studies in fluoridated communities, or both. 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, and exposure to water/salt fluoridation should be above 0.3 ppm F. When background use or not of fluoride toothpaste (again, only for studies where the intervention was tested under supervision at school and no supply of any toothpaste had been provided for home use) was not clearly indicated in studies carried out in developed countries, it was assumed that fluoride toothpaste was widely used from the middle of the 1970s (Ripa 1989). This information was sought from authors (or obtained from other sources) when missing from studies carried out in other locations. When data on the year a study had begun was not provided this was calculated as a 'probable date' by subtracting the duration of the study (in years) plus one extra year, from the publication date of the study. Data on 'concentration applied' and 'frequency of use' have not been categorised, but a 'total intensity of application per year' covariate was produced by multiplying frequency of application (per year) by concentration of toothpaste applied (in ppm F). Concentrations in multiple arm studies were averaged over fluoride toothpaste groups prior to this calculation. Frequency of use of once a day (365 times a year) was assumed when it was not precisely reported in studies of supervised use of fluoride toothpaste at school (where participants were provided with appropriate toothpastes for home use) or in studies of 'unsupervised' home use of fluoride toothpaste (even if it was reported that instructions to brush more than once a day were given); frequency of 200 times (days) a year was assumed when it was not precisely reported in studies of supervised use of fluoride toothpaste at school (where children were provided with non-fluoride toothpastes for home use or not provided with any toothpaste for home use).

Further potential sources of heterogeneity were investigated by metaregression. These 'post hoc' analyses are clearly identified and the results should be treated with caution. These include assessment of the effect of toothpaste application mode, classified as either self-applied under supervision (at school/institution) or as unsupervised use (at home).
Investigation of publication and other biases
A funnel plot (plots of effect estimates versus the inverse of their standard errors) was drawn.
Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size,
though may also represent a true relationship between trial size and effect size. A formal
investigation of the degree of asymmetry was performed using the method proposed by Egger
1997.

Measures of effect and meta-analysis of other outcomes
For outcomes other than caries increment, continuous data were to be analysed according to
differences in mean treatment effects and their standard deviations. Dichotomous outcome data
were analysed by calculating risk ratios (RR) or, for adverse effects of fluoride treatment, risk
differences (RD). RevMan 4.1 was used for estimation of overall treatment effects. Again, a
random effects model was used to calculate a pooled estimate of effect. As a general rule only
(relevant) outcomes with useable data would be shown in the analyses tables.

Description of studies

SEARCH RESULTS
Searching the core database in Reference Manager retrieved 2600 records from MEDLINE,
EMBASE, BIOSIS, SCISEARCH, SCISEARCH, CINAHL, ERIC, ISTP and DISSERTATION
ABSTRACTS. The specific search used was: 'dentifrice*' or 'fluoride dentifrice*' or 'toothpaste*' or
'toothbrush*' or 'tooth brush*' or 'acidulated fluorophosphate*' or 'acidulated phosphate
fluoride*' or 'fluorophosphate*' or 'amine fluoride*' or 'sodium fluoride*' or 'stannous fluoride*' as
keywords, combined with 'dentifrice' or 'toothpaste' or 'tooth paste' or 'paste' or 'toothbrush' or
'tooth brush' or 'brush' in titles, notes and all other fields. There were 211 records scanned outside
Reference Manager produced by searching LILACS (48 records), BBO (47 records), CENTRAL
(86 records), SIGLE (6 records), and NIDR/Community of Science Database (24 records). When
LILACS and BBO were searched for the second time with a modified search strategy the yield was
210 records (142 and 68 records respectively) also scanned outside Reference Manager. Searching
OLD MEDLINE produced 545 records. Thus, 3566 records yielded by the original electronic
searches for topical fluoride trials were scanned, but many of these were duplicates not merged in
the core database. The specific MEDLINE search for fluoride toothpaste trials performed without
a randomized controlled trial (RCT) filter produced 1005 records, and the search performed in the
Cochrane Oral Health Group Trials Register produced 244 records. The search for ongoing studies
in the metaRegister of Controlled Trials produced five records.

Searching other non-electronic sources (reference lists of potentially relevant reports, review
articles or book chapters, journals, and contacting authors) produced 99 additional records for
inspection. One of the nine manufacturers of fluoride toothpastes contacted, GABA, provided a list
of 409 records from a search performed in GALIDENT (Database of GABA Library in Dentistry)
using the keyword 'amine fluoride'. However, search results from these and, if provided, from other
manufacturers will be taken into account in updates of this review.

From the search results above a total of 299 records were considered potentially eligible, and
sought for further assessment.

SELECTION OF STUDIES
Two hundred and ninety nine reports were sought for detailed assessment for inclusion, of which
10 full-text reports could not be obtained (most of these were incomplete references to unpublished
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studies conducted decades ago by toothpaste manufacturers). One hundred and ten (110) reports were considered immediately irrelevant for this review (largely as a result of the type of interventions compared with, or used in addition to fluoride toothpaste, including head to head studies without a placebo group). Thus, 118 studies (179 reports) are considered cited in this review. These comprise 120 reports relating to 74 included studies, 49 reports relating to 36 excluded studies, and 10 reports relating to eight studies waiting assessment: either because they require translation (three reports in Polish of two studies, two reports/studies in Japanese, one report/study in German), or because translations and/or attempted contact with the authors have not ascertained whether all inclusion criteria have been met (two reports, one in French and another in Dutch, of one study), or because additional information could not be obtained yet for two studies in abstract form. There were no reports of ongoing studies.

Thirty non-English reports (19 studies) are listed either under excluded or included studies. Three of these (three studies) were excluded either on the basis of the English abstract alone, or due to the availability of a full-text English report of the same study; four reports/studies were included based on an English publication related to the same study; and one report of an excluded study had other publications that did not require translation. There remained 22 non-English reports that have been fully assessed (12 studies): 14 in German (by a German translator, with the contact reviewer), three in French (by a French translator, with the reviewer), one in Russian (by a Russian translator, with the reviewer), one in Czech (by a Czech translator, with the reviewer), one in Japanese (by a Japanese translator, with the reviewer), and two in Italian (by the contact reviewer).

EXCLUDED STUDIES
See 'Characteristics of excluded studies' for the description of reasons for rejecting each study.

The thirty-six studies in this section were excluded for a variety of reasons. One study was clearly not randomized/quasi-randomized. One study randomized two clusters, each to one of the two groups compared. Six studies did not mention or indicate random/quasi-random allocation nor blind outcome assessment. Six studies did not mention random or quasi-random allocation (but used/indicated blind outcome assessment), and two other studies did not state/indicate blind outcome assessment (but indicated random allocation); the attempt to contact the author(s) of these studies was unsuccessful and they were excluded.

Ten studies had other active agents or other fluoride-based interventions in addition to fluoride toothpaste. Three of these also did not state/indicate blind outcome assessment; another had only two clusters (one as each group); and another included participants older than those considered in this review.

Two studies included institutionalised children with specific health problems. One of these also included young adults. Eight studies included participants older than 16 years old. One of these did not mention blind outcome assessment; three others did not mention or indicate random/quasi-random allocation; and another did not mention or indicate random/quasi-random allocation nor blind outcome assessment.

INCLUDED STUDIES
See 'Characteristics of included studies' table for details of each study.

There are 74 trials included. The studies by Forsman 1974; Hargreaves 1973; Marthaler 1970; Zacherl 1970; Held 1968; Marthaler 1965; Torell 1965 and one of the three studies by Koch 1967 have been treated as two (or more) independent trials each, since the results for two (or more) age
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groups and/or study sites in these studies have been reported separately as distinct studies. There were also completely distinct studies published as such in the same year by the same author: Zacherl 1972/Zacherl 1972a; Koch 1967a/Koch 1967b/Koch 1967c; and Slack 1967/Slack 1967a. All 120 reports were published between 1955 and 1996. The seventy-four trials were conducted between 1954 and 1994: three in the 1950s, 41 in the 1960s, 28 in the 1970s, one in the 1980s, and one in the 1990s. Twenty-four trials were conducted in USA, 20 in UK, nine in Sweden, six in Switzerland, five in France, three in Australia, two in Canada, and one in each of the following countries: Denmark, Norway, FRG, Italy, and Israel. Thirty-five studies had more than one publication, 12 of these had four or more published reports each. Fifty-five studies acknowledged assistance (product provision, etc) and/or financial support from fluoride toothpaste manufacturers. Of a total of twenty-two studies whose authors were sent request letters for unpublished information, replies related to four studies were obtained.

Design and methods
Twenty-two studies had more than one fluoride toothpaste treatment group compared to a control (multi-treatment studies) and among these, two trials had two treatment groups and two placebo control groups. Ten trials used a factorial design to investigate the effects of multiple topical fluoride interventions. All trials used a placebo or non-fluoride toothpaste control group. The study duration (indicated by the total length of follow up as well as the treatment duration) ranged from one to seven years among included trials: seven lasted four years or more, 36 lasted three years, 27 lasted around two years, and the remaining four lasted one and a half years. Studies were generally large with only nine allocating less than 100 children to relevant study groups. The total number of children participating in the 74 trials (given by the sample analysed at the end of the trial period) was 45,073, and ranged from 32 in the smallest trial to 2008 in the largest trial (average of 609 participants per trial). With the exception of five trials, where participants were in orphanages/institutions, participants were recruited from school settings.

Participants
All included trials reported that the participants were aged 16 or less at the start, with similar numbers from both sexes (where these data were reported); the exceptions were Ran 1991, who included male participants only in the study, and the two trials of Slack 1967; Slack 1967a that included only females. The ages of the children at the start of the trials ranged from five to 16 years; at least 49 trials included children who were 12, at least four trials included children younger than six years of age (five year-olds) and 18 trials included children who were five or six (in which deciduous teeth caries increment data could have been reported). Decayed, (missing) and filled surfaces (D(M)FS) data at baseline were reported in all but five studies, and ranged from 0.97 to 17.4 (this includes the study by Cahen 1982, where data for the control group only were available); only baseline data for deciduous tooth surface (dfs) were reported in one of the studies by Hargreaves 1973 (although it did not report caries increment data for the deciduous dentition). Where information on 'background exposure to other fluoride sources' was available/obtained, 11 studies were conducted in fluoridated communities (water fluoridation in six, low salt fluoridation in five), and 49 in low/non-fluoridated areas; generalised use of other fluoride programmes (rinsing) was reported in only two of these. For the two trials where the intervention was tested under supervision at school and no supply of any toothpaste had been provided for home use, data on general use of fluoride toothpaste at home could not be obtained for one trial (Ran 1991) and was assumed based on study location and year started for the other (Koch 1967c). Thus, some form of fluoride exposure could be considered for 13 trials, and no exposure for 46; this information was not available for 15 trials.

Interventions
Fifty-six of the included trials reported unsupervised (ad libitum) use of toothpaste at home, and in the remaining trials toothpaste was used under supervision either at school (13 trials, 11 of which reported provision of enough toothpaste for ad libitum home use) or institution (five trials). Toothpaste was administered using a toothbrush in all trials. A variety of fluoride agents were tested, including Stannous Fluoride (SnF2) in 29 trials, Sodium Monofluorophosphate (SMFP) in 27 trials, Sodium Fluoride (NaF) in 14 trials, Amine Fluoride (AmF) in eight trials, Acidulated Phosphate Fluoride (APF) in five trials, and mixed agents in five trials (SMFP-NaF in three, NaF-SnF2 in two); these were formulated with various abrasive systems (see table). The fluoride concentrations used in a toothpaste ranged from 250 ppm F to 2500 ppm F (SMFP-NaF), but the 1000/1100 ppm F toothpaste concentration was tested in at least 56 trials (the two studies which did not report these data are likely to have used this fluoride concentration). Ten studies investigated toothpaste with fluoride levels of 1250/1500 ppm F, and five studies investigated toothpaste with fluoride levels less than 1000 ppm F (250 ppm F was tested in three studies and 500 ppm F was also tested in three studies but one of the studies tested both concentrations). Six studies tested toothpaste with fluoride levels above 1500 ppm F (2400/2500 ppm F).

The brushing frequency did not vary greatly among studies, with only 12 studies among the 74 reporting other than daily frequencies (this was assumed when data were not reported): a frequency of less than once a day in five studies where supervised toothbrushing at school was performed, and a frequency of twice a day or more in seven studies (five of which were also studies where supervised brushing was performed). Data on the amount of toothpaste used and the duration of toothbrushing were reported in very few studies (amount reported either in 'gr' or in 'cm' dispensed over the brush). As regards the performance of some form of oral rinsing after toothbrushing, this was reported in two studies in the UK only (where toothpaste use was supervised at school) and was said to have been 'instructed' in three studies in Sweden (where toothpaste use was not supervised), but there were no reports specifying the method used for post-brushing rinse (e.g. with or without a beaker); as long as performed with water (if with a fluoride solution the trial would have been excluded), the post-brushing rinsing was considered by the reviewers as part of the method of toothpaste use and not as a separate intervention on its own.

Outcome measures
All but three of the 74 included trials reported caries increment data: 71 trials reported caries increment at the tooth surface level (D(M)FS), but d(e/m)f/s/d was not reported in any of these, and 33 trials reported caries increment at the tooth level (D(M)FT). With regard to the components of the DMFS index used, 49 trials reported DMFS data, 33 reported DFS data, and one trial reported DS data only (DFS data were chosen over DMFS data in 12 of the trials). With regard to the types of teeth/surfaces assessed, results based on all tooth surface types were reported in all 71 trials that reported caries increment data, but results have also been reported separately for first molars, anterior/posterior teeth, approximal surfaces, occlusal and other surface types in many trials (see table). Thirty-three trials presented D(M)FS data at more than one follow up time; follow up of three years was the most common (reported in 44 trials). In three trials, assessments of D(M)FS increments were also made during a post-intervention follow up period.

Clinical (73 trials) and radiographic (65 trials) 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: NCA = non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor/walls) or showing frank cavitation; ER = any radiolucency in enamel/enamel-dentin junction; DR = radiolucency into dentin. Many trials presented results using one caries grade only (usually CA/ER or CA/DR), others either did not report the grade, in which
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case CA was assumed, or reported caries increment data at both levels of diagnosis, in which case CA was chosen. Data on the state of tooth eruption considered were not clearly specified in many trials. The five studies of Marthaler used partial recording as opposed to the full-mouth recording used in all others.

Other dental caries data reported: caries incidence/attack rate (13 trials, including one trial reporting caries rate in the deciduous dentition), caries progression (five trials, four of which reporting the Extrapolated Carious Surface Increment Index (ECSI)), proportion of children developing new caries (six trials), proportion of children not remaining caries-free (two trials), proportion of teeth developing new caries and failures, carious teeth, over time (one trial), proportion of caries-free teeth/surfaces which developed caries (two trials).

Data on adverse effects were (partially or fully) reported in 12 trials: stain score (three trials), proportion of children with tooth staining (seven trials), proportion of children who complained of tooth staining (one trial), oral soft tissues lesions (three trials, none of which with complete or useable data, and with the following statement in all three: "no lesions attributable to product use were noted"). Fluorosis data have not been reported in any of the trials.

Methodological quality of included studies

Based on twenty-eight studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, inter-rater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73).

In general, studies included essential features of clinical trials: randomized groups, double-blind designs and placebo controls. Nevertheless, there were differences in their methodological quality (using the reported information and additional information obtained from a few investigators).

ALLOCATION CONCEALMENT

Eleven of the trials which described the randomization process or whose investigators provided further information in answer to our enquiry could be coded A (e.g. adequate concealment of allocation). Fifty-six included trials were described as randomized but provided no description of the allocation process and were coded B. Seven trials were quasi-randomized and coded C.

BLINDING

Blind outcome assessment and use of placebo (double-blinding, score A) was described in all but two trials where blind outcome assessment was unclear but indicated (score C), and these were placebo-controlled trials. In three trials the fluoride-free toothpaste used as control was not a true placebo (flavour and/or colour somewhat different from test toothpastes). Single-blinding (blind dental caries assessment but no placebo used) was not described in any trial.

FOLLOW UP AND WITHDRAWALS

All the participants included in the final analysis/present at the end of each study, as a proportion of all the participants present at start in all studies was 72% (38,868 analysed out of 53,710 randomized), excluding the 13 studies with no data on participants randomized to relevant groups. Drop out rates could be obtained from all but one of the 74 included studies. There was considerable variation in drop out rates ranging from 4% at two years to 66% at three years. A common reason for attrition was that participants were not available for follow up examination at
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the end of the study; exclusions based on presence in all follow up examinations were reported in 26 trials, and exclusions based on compliance were reported in three trials. Other reasons for exclusions (when given) included change of residence, and characteristics of participants also used as eligibility criteria before randomization (e.g. starting use of orthodontic bands). A few trials reported the numbers excluded according to reason for attrition, but only two trials reported this by study arm.

OTHERS
Type of randomization: stratified randomization was used in the majority of trials (but only one described use of blocking).
Unit of randomization/analysis: none of the trials reported the use of cluster randomization.
Individuals were allocated to study arms in all trials, and each participant's caries increment, over a period of time was used as the unit of analysis (as the units of recording, the tooth or surface, are not independent within a given subject).
Baseline comparisons and handling of any differences: two trials did not report any baseline data, four of the trials described as 'balanced' (for which randomization may have produced nearly exact balance) did not report the actual values for the baseline characteristic 'initial caries levels' (D(M)FS/T). Some degree of imbalance was reported in a few trials (for characteristics considered most influential, usually initial caries levels) and generally either described as not significant or adjustment mentioned to have resulted in trivial differences in effect estimates. In three of the smallest trials by Held 1968, imbalances were most pronounced.
Objectivity/reliability of primary outcome measurement: diagnostic methods used (clinical or radiographic) were described in all studies, but thresholds/definitions used for caries and monitoring of diagnostic errors were not always clearly described (see 'Notes' in the 'Characteristics of included studies' table for methodological features assessed).

Results

EFFECT OF FLUORIDE TOOTHPASTE ON DENTAL CARIES INCREMENT
The effects of fluoride toothpastes on dental caries increment (as measured by the DMF index) were reported in a variety of different ways in the included studies. Where appropriate and possible these have been combined to produce pooled estimates as described in the Methods section. The results are reported separately here for:
(1) Decayed, (Missing) and Filled Surface Prevented Fraction (D(M)FS PF);
(2) Decayed, (Missing) and Filled Teeth Prevented Fraction (D(M)FT PF);
(3) D(M)FS and D(M)FT pooled using a standardised mean difference (SMD). Estimates of the effects of fluoride toothpastes on caries increment as measured by the dmft index in deciduous teeth/surfaces could not be produced for this review, as there was no study contributing data. However, there was a single trial reporting caries incidence rate data for deciduous teeth, the results of which are described below.

Three included studies (Homan 1969; Powell 1981; Slack 1964) had no (caries increment) data suitable for meta-analysis, although they are retained in the review. Standard deviations (SD) of mean caries increment data (new D(M)FS) were (partly) missing in 16 of the 71 studies which contributed data (Abrams 1980; Dolles 1980; Fogels 1979; Forsman 1974; Forsman 1974a; Hargreaves 1973; Hargreaves 1973a; Hargreaves 1973b; Held 1968; Held 1968a; Held 1968b; James 1977; Kinkel 1972; Muhler 1955; Ran 1991; Segal 1967). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries
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We have decided to exclude the trial of Ran 1991 from all analyses because the control DMFS increment was very small (0.2) in this trial, resulting in a poor estimate of PF.

(1) Effect on tooth surfaces: D(M)FS PF
For all 70 trials combined, the D(M)FS PF pooled estimate was 0.24 (95% confidence interval (CI), 0.21 to 0.28; p<0.0001), suggesting a substantial benefit from the use of fluoride toothpaste. The CIs are relatively narrow, but substantial heterogeneity in results could be observed graphically and statistically (Q= 489.89 on 69 degrees of freedom, p<0.0001).

For each study, the D(M)FS PF and 95% CIs can be viewed in the 'Other data' tables; the results of the random effects meta-analysis of D(M)FS PFs (performed in Stata) are presented in 'Additional Table 01: Meta-analyses of prevented fractions'. A forest plot showing the effects of fluoride toothpaste (PFs and 95% CIs) on D(M)FS increments resulting from this meta-analysis is available in the 5th review in this series: Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents (Comparison 01, Sub-category 01).

Metaregression and sensitivity analyses: D(M)FS PF
Univariate metaregression suggested a significant association between estimates of D(M)FS PFs and the following trial characteristics: baseline caries levels, fluoride concentration, frequency of use, as well as 'total intensity of application' (frequency times concentration). Statistical significance was just lost for the associations of frequency of application and 'intensity' with the prevented fraction when the trial of Di Maggio 1980, a study with high influence, was excluded. There was no significant association between estimates of D(M)FS PFs and the pre-specified factors background exposure to fluoridated water or background exposure to any fluoride source. Further univariate meta-regression analyses showed a significant association of mode of toothpaste use (supervised/unsupervised) and of drop out rate with the PF, but no significant association between this and allocation concealment (random/quasi-random) or length of follow up (duration of study).

The association between baseline caries and D(M)FS PF remained significant (and the regression coefficients almost unchanged) when each one of the above investigated potential effect modifiers were included in bivariate meta-regression analyses (for each covariate, significant and non-significant associations remained the same as in the previous univariate analyses, and the association of the PF with frequency of use (10.6%; CI, 0.06% to 21%; p= 0.049) and with intensity of use (7.5%; CI, 1.45% to 13.5%; p=0.015) remained significant even after the exclusion of the study by Di Maggio 1980. The association between fluoride concentration and D(M)FS PF did not remain significant when adjusted for background exposure to water fluoridation/exposure to any fluoride, frequency of use (with or without Di Maggio 1980), or intensity of application in bivariate meta-regression. Further bivariate meta-regression analyses showed that the association between frequency of toothpaste use and D(M)FS PF remained significant when adjusted for each one of the above investigated covariates, except for background exposure to water fluoridation/exposure to any fluoride. When the trial by Di Maggio was excluded the association between frequency of toothpaste use and D(M)FS PF remained significant only when adjusted for mode of toothpaste use and baseline caries, and the association between intensity of use and D(M)FS PF remained significant when adjusted for these variables or for
dropout. Mode of toothpaste use (supervised/unsupervised) or drop out rate remained significant when adjusted for each covariate, except for background exposure to water fluoridation/exposure to any fluoride.

When the effect of each covariate (baseline caries, background exposure to water fluoridation, fluoride concentration, frequency of use (without the trial by Di Maggio), mode of toothpaste use, and drop out rate) was controlled for all others there remained strong associations between PF with baseline caries (0.8% increase in PF per unit increase in caries, 95% CI, 0.3 to 1.2%; p=0.002), mode of use (10% lower PF with unsupervised brushing, 95% CI, -16 to -3%; p=0.004), drop out rate (2.9% increase in PF per 10 drop outs, 95% CI, 0.8 to 5%; p=0.008); and fluoride concentration (11% increase in PF per 1000 ppm F, 95% CI, 3 to 18; p=0.005). These results (estimates and statistical significance for each covariate in the model) were almost unchanged when we replaced both covariates 'toothbrushing frequency' and 'fluoride concentration' by the factor 'intensity of use' (again, excluding the influential study by Di Maggio), when a 7% increase in PF was indicated with increased intensity of use - equivalent to doubling the use from once to twice a day and increasing the concentration by 1000 ppmF (95% CI, 0.8 to 13%; p=0.026).

The influence of type of fluoride agent present in the toothpaste on the prevented fraction was also investigated in metaregression. This analysis was restricted to the two-arm trials that tested only one of the four main fluoride agents in toothpaste (22 trials of sodium monofluorophosphate, 19 of stannous fluoride, 10 of sodium fluoride, and five of amine fluoride). No significant differences among these or between each and the others were indicated.

Other potential effect modifiers have not been investigated either because they were not relevant for this review (e.g. blind outcome assessment, since virtually all trials were double-blind) or due to lack of data (e.g. post-brushing rinsing habit).

Metaregression results for all potential effect modifiers (univariate analyses) are given in 'Additional Table 02: Random effects metaregression analyses of prevented fractions: D(M)FS'. It should be noted that the influential study by Di Maggio 1980 is omitted from the analyses frequency of use and intensity of use with prevented fraction. Although the number of data points (studies) in this review is unusually high, reducing the possibility of spurious claims of association, these results must be interpreted with caution given the large number of comparisons made and the observational nature of the comparisons.

We performed a sensitivity analysis for the main meta-analysis of D(M)FS PFs by excluding two trials (Dolles 1980; Kleber 1996) in which non-fluoride active agents were present in both fluoride and control groups (distinct agents in each trial), making these trials different in this way from all others that had been included. The D(M)FS PF pooled estimate resulting from the exclusion of both trials was identical to the analysis that includes them. These are small trials that carry little weight, and had minimal effect in a meta-analysis that includes so many larger studies.

In order to illustrate the magnitude of the effect, numbers of children needed to treat (NNT) to prevent one D(M)FS were calculated based on the pooled D(M)FS PF and on the caries increments in the control groups of the trials that contributed data to the meta-analysis. The overall caries-inhibiting effect (%PF) derived from the pooled results of the 70 trials was 24% (95% CI, 21% to 28%), the caries increments ranged from 1.14 to 7.66 D(M)FS per year. In populations with a caries increment of 1.14 D(M)FS per year (at the lowest end of the results seen in the included studies), this implies an absolute caries reduction of 0.27 D(M)FS per year, equivalent to an NNT of 3.7 (95% CI, 3.1 to 4.2): i.e. 3.7 children need to brush with a fluoride toothpaste.
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(rather than a non-fluoride toothpaste) to avoid one D(M)FS. In populations with a caries increment of 2.6 D(M)FS per year (at the mid range of the results seen in the included studies), this implies an absolute caries reduction of 0.62 D(M)FS per year, equivalent to an NNT of 1.6 (95% CI, 1.4 to 1.8): i.e. 1.6 children need to brush with a fluoride toothpaste to avoid one D(M)FS.

Funnel plot and test for funnel plot asymmetry: D(M)FS PF
A funnel plot of the 70 trials reporting D(M)FS PFs may look asymmetrical, but the weighted regression test for asymmetry (Egger 1997) was not statistically significant (asymmetry intercept (95% CI) = -0.85 (-2.53 to 0.83) (p=0.32)). There is, therefore, no evidence of bias using this method.

The funnel plot of the 70 trials comparing fluoride toothpaste with placebo is available in 'Additional Figure 01', where D(M)FS standardized mean differences are plotted against standard errors (see 'Alternative treatment effect measure' below).

(2) Effect on whole teeth: D(M)FT PF
Fifty-three trials reported data which allowed the calculation of the D(M)FT PF. All fifty-three are also included in the analysis of D(M)FS PF. The results of these analyses are very similar to those reported above.

The pooled estimate of D(M)FT PF was 0.23 (95% CI, 0.18 to 0.28; p< 0.0001), suggesting, again, a substantial benefit of fluoride toothpaste, within relatively narrow CIs, and with substantial heterogeneity between trials (Q= 541.04 on 52 degrees of freedom, p< 0.0001).

For each study, the D(M)FT PF and 95% CI can be viewed in the 'Other data' tables. The results of the random effects meta-analyses of D(M)FT PFs performed in Stata are also presented in 'Additional Table 01: Meta-analyses of prevented fractions'.

(3) Alternative treatment effect measure: Standardised mean difference (SMD)
Due to the character of D(M)FS data, mean caries increments are closely related to their SDs (they are about the same). Thus, meta-analyses using SMDs (the difference between two means divided by an estimate of the within group standard deviation) yielded materially similar results to those using PFs (the difference in mean caries increments between the treatment and control groups divided by the mean increment in the control group). We therefore decided to present D(M)FS and D(M)FT SMDs in RevMan, since it was not possible to present the main outcome analyses with PFs in MetaView/RevMan.

For the seventy trials, the pooled D(M)FS SMD estimate was 0.31 (95% CI, 0.27 to 0.36; p< 0.0001). There was substantial heterogeneity between trials (chi-square = 271.88 on 69 degrees of freedom, p< 0.0001). Although the results of this analysis are similar to that of the random effects meta-analysis of D(M)FS PF, they are not totally consistent. This may well be due to differences between caries increment rates and standard deviations in some of the arms of the included studies.

The pooled estimate of D(M)FT SMD based on the 53 trials that contributed data was 0.28 (95% CI, 0.24 to 0.33; p< 0.0001). There was statistically significant heterogeneity (chi-square = 177.38 on 52 degrees of freedom, p< 0.0001). These results are consistent with those found in the random effects meta-analysis of D(M)FT PF.

Effect on deciduous dentition: df-rate PF (results from one trial)
There was one large trial involving 2008 children aged 6 to 9 years (Cahen 1982) reporting on the

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number of new decayed or filled teeth per 100 observed primary teeth ('df-rate'). Although the SDs (or data from which these could be derived) were missing the PF for this trial was 0.37 (95% CI not available), significant at the 0.1% level (p< 0.001).

EFFECT OF FLUORIDE TOOTHPASTE ON OTHER OUTCOMES

Some trials report data for other relevant outcomes (see 'Outcome measures' under 'Description of studies' section). Most of these are simply other measures/indices for dental caries increment in permanent teeth/surfaces and require no further consideration; seven trials report on the proportion of children developing new caries. Meta-analyses results for the proportion of children developing new caries are presented below. The few trials that report data on adverse effects are mainly early studies conducted in the 1960s reporting on tooth staining from the use of stannous fluoride toothpaste. Meta-analyses results for the proportion of children with tooth staining are also described below.

Proportion of children developing new caries

Seven trials reported results on the proportion of children developing one or more new caries (Dolles 1980; Forsman 1974; Forsman 1974a; Hanachowicz 1984; Kleber 1996; Marthaler 1974; Torell 1965). The pooled estimate (random effects meta-analysis) of the risk ratio (RR) was 0.93 (95% CI, 0.84 to 1.04; chi-square for heterogeneity 12.31 on 6 degrees of freedom, p= 0.06). This corresponds to an NNT to prevent one child from developing caries of 20 (95% CI, 8 to 100) in a population with a caries risk the same as that found in the control groups in these trials (20 children using fluoride toothpaste for two to three years will prevent new caries development in one child).

Proportion of children with tooth staining

Data on the proportion of children with extrinsic tooth staining (light to dark coloured) were fully reported in five trials of stannous fluoride toothpaste carried out in the UK (James 1967; Naylor 1967; Slack 1964; Slack 1967; Slack 1967a). These trials measured this outcome at the end of two to three years (2 trials) and during the last year of a three-year period (3 trials). The pooled estimate (random effects meta-analysis) of the risk difference (RD) between the toothpaste and placebo arms was 0.24 (95% CI, 0.19 to 0.30; chi-square for heterogeneity 17.3 on 4 degrees of freedom, p= 0.0017), i.e. clearly favouring the placebo arm. This is equivalent to a number needed to harm (NNH) of 4.2 (95% CI, 3.3 to 5.3): i.e. in a population of children with the same underlying risk of tooth staining as controls in these studies, 4.2 children using stannous fluoride containing toothpaste would be associated with one extra case of tooth staining.

Discussion

The main question addressed by this review is the effectiveness of fluoride toothpaste for the prevention of dental caries in children compared to placebo. Over 42,300 children participated in the 74 included trials. For the great majority of children the fluoride toothpaste they used was either a Sodium Monofluorophosphate (SMFP) or a Stannous Fluoride (SnF2) formulation, usually in the concentration of 1000 ppm F, followed by Sodium Fluoride (NaF) and the other fluoride formulations.

There is clear evidence that fluoride toothpastes have a caries-inhibiting effect. The pooled results of the 70 studies assessing the effect of fluoride toothpaste on the permanent dentition suggest that the use of this intervention is associated on average with a 24% reduction in decayed, missing and filled tooth surfaces (D(M)FS), and this reduction falls within narrow confidence intervals (CIs) (21 to 28%). This means that 1.6 children need to brush with a fluoride toothpaste (rather than a
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non-fluoride toothpaste) to prevent one decayed, missing or filled tooth surface, in a child population with a caries increment of 2.6 D(M)FS per year (at the mid range of control group caries rates seen in the included studies). In populations with caries increment at the lowest level seen in the included studies (1.1 D(M)FS per year), 3.7 children will need to use a fluoride toothpaste to avoid one decayed, missing or filled tooth surface.

Only one study reported the effects of fluoride toothpastes on caries increment in deciduous teeth/surfaces. This large trial involving 2008 children aged six to nine years, reported on the number of new decayed or filled teeth per 100 observed primary teeth ('df-rate'). The authors report a substantial reduction in caries increment (37%) which is reported to be highly statistically significant (p< 0.001).

A secondary aim of this review was to examine whether there was any relationship between the caries-preventive effectiveness of fluoride toothpaste and the initial level of caries severity, background exposure to other fluoride sources, fluoride concentration, and application features such as the frequency of toothpaste use. A significant influence of the variables initial level of caries, concentration of fluoride, and frequency and intensity (frequency x concentration) of fluoride toothpaste use on the prevented fraction (PF) was shown in the meta-regression analyses performed. Although the suggested greater treatment effect with increased frequency and intensity of toothpaste use was influenced by one study with particularly powerful effects after adjustments were performed in some bivariate and multivariate analyses, such relationships remained significant in various analyses.

There was a constant relative increase in the PF as trials involved children with higher initial D(M)FS scores (baseline risk of the study population), although the magnitude of the effect was small. This implies that as the caries levels of a community decline, the percentage caries reductions will decrease. This does not necessarily imply that a low baseline caries level in a community justifies reducing the concentration of fluoride in the paste or reducing the frequency with which it is used, a decision which must depend on the overall balance of risks and benefits.

The suggested greater treatment effect with increased fluoride concentration is consistent with that reported in two large clinical trials directly comparing different fluoride concentrations in toothpaste (dose-response relationship): they reported that an increase in fluoride of around 500 ppm F in toothpastes containing 1000-2500 ppm F brings an additional 6% reduction in caries (Stephen 1988; O'Mullane 1997). The influence of application frequency on treatment effect suggested in this review is also in agreement with results from recent clinical trials, which show that the habits of children and adults using fluoride toothpaste, for instance, the frequency of use, influence effectiveness (Chesters 1992; O'Mullane 1997; Chestnutt 1998; Ashley 1999). These studies indicate that brushing twice a day or more with a fluoride toothpaste confers greater caries reductions than brushing once a day or less. Furthermore, significantly greater treatment effect with increased frequency and intensity of topical fluoride application is indicated in a previous systematic review in this series (Marinho 2002). Nevertheless, although metaregression analyses including 70 trials should have sufficient power to detect such relationships, more robust investigations of these aspects of the intervention require direct, head to head comparisons of different fluoride concentrations and frequencies of application, which were not within the scope of this review.

We were unable to detect a clear relationship between background exposure to other fluoride sources and the magnitude of the treatment effect. This may have been partly influenced by potential misclassification, especially due to the incomplete reporting of data for exposure to...
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fluorides other than water. However, the lack of association between exposure to water/salt fluoridation and treatment effect, based on analysis including 56 trials (11 of which in fluoridated areas) implies that estimates of treatment effect were similar between trials conducted in fluoridated and non-fluoridated areas (fluoride toothpaste use provides additional caries reduction in subjects from fluoridated areas).

We made a thorough attempt to investigate potential sources of heterogeneity in this review, examining factors related to participants, interventions and study quality. Most of the a priori specified factors were clearly related to heterogeneity. An association with treatment effect was found for two of the other factors investigated in post hoc analyses. The 11% lower estimate of treatment effect found in trials where the use of fluoride was unsupervised is perhaps unsurprising. This is likely to reflect more intensive use of toothpaste when supervised.

We did not detect an association between the main types of fluoride compounds present in toothpaste formulations and the magnitude of the treatment effect. This comparison was restricted to the two-arm trials that tested one of the four main fluoride agents in toothpaste (22 trials of sodium monofluorophosphate, 19 of stannous fluoride, 10 of sodium fluoride, and five of amine fluoride). Although it can provide indirect evidence of relative treatment effects, this is less reliable than evidence from head to head comparisons which, again, were not within the scope of the review. Two published meta-analyses of the comparative efficacy of sodium fluoride and sodium monofluorophosphate, the fluoride toothpaste compounds that currently dominate the market internationally, report a 7% greater reduction in caries increment with the use of sodium fluoride formulated in compatible abrasive systems (Johnson 1993; Stamm 1995).

Although visual inspection suggests a degree of funnel plot asymmetry the Egger test provided no evidence of a significant relationship between trial size and effect estimate.

Unfortunately this review provides little information about the risk of adverse effects. Only five of the trials, all of stannous fluoride containing toothpaste, reported the risk of tooth staining. Stannous fluoride is seldom used in modern toothpaste formulations. No information was reported on other adverse effects. The lack of data on enamel fluorosis in particular is likely in part to reflect the type of studies considered, the age ranges of the participants in such trials (five year-olds and above), and their usual duration of two to three years. In addition, it is mainly since the late 1980s that the risks of fluoride toothpaste use by young children have become controversial, but by this time placebo-controlled trials would not obtain ethical approval. It could be argued, with regard to the public health impact of the two conditions, dental caries and fluorosis, that one public health problem has been substantially reduced and that there is little evidence that another has risen to take its place. However, the lack of direct evidence on fluorosis from clinical trials makes it more difficult for policy makers to weigh the benefits of fluoride toothpaste use in preventing caries against potential negative effects. The selection of appropriate concentrations of fluoride in toothpaste, for example, requires evaluation of how they may affect fluorosis as well as caries in young children.
Reviewers' conclusions

Implications for practice

This review suggests that the regular use of fluoride toothpaste is associated with a clear reduction in caries increment. We found evidence that this relative effect may be greater in those who have higher baseline levels of decayed, missing and filled tooth surfaces (D(M)FS). A higher D(M)FS prevented fraction was shown with increased fluoride concentration, increased frequency/intensity of use, and with supervised brushing (where a higher compliance with fluoride toothpaste use as recommended should be expected). We found no evidence that this relative effect was dependent on background exposure to fluoridated water. Unfortunately, the review provides little information on the effects of fluoride toothpaste on outcomes such as caries incidence in the deciduous dentition, and provides no useful information on the likelihood of adverse effects such as enamel fluorosis.

Implications for research

The quality of the trials included in this review is generally better than those assessing the effects of other topical fluoride interventions, although many reports lacked important methodological details. This is likely in part to be due to the fact that most are relatively old. Many characteristics considered crucial for excluding bias, such as clearly stated randomization and allocation concealment, have only been more emphasised in later years, long after most of the toothpaste trials were reported. However, given the clarity of the results, further randomized comparisons of fluoride toothpaste and placebo alone would be hard to justify. Head to head comparisons of fluoride toothpaste and other topically applied fluoride interventions (or non-fluoride caries preventive strategies) may provide more useful information. These should be carried out in preschool children and include the assessment of caries incidence in the deciduous teeth and of fluorosis in erupting permanent anterior teeth, and should be of long duration.
## Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams 1980</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 48% drop out after 3 years (study duration = 3 years). Reasons for high drop out described: change of residence, absenteeism, non-adherence to study protocol; no differential group losses.</td>
<td>1141 children analysed at 3 years (available at final examination). Age range at start: 5-12 years. Surfaces affected at start: 3.2 DFS. Background exposure to fluoride: none reported. Year study began: in/before 1976. Location: USA.</td>
<td>FT (2 groups) versus PL (both SnF2 groups = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: silica gel in one SnF2 and placebo toothpaste, Ca pyrophosphate in the other SnF2 toothpaste.</td>
<td>3yNetDFS increment - (E+U)(CA)cl+(ER)xr. Reported at 1, 2 and 3 years follow ups.</td>
<td>Participants randomized (N = B 2210). Baseline characteristics (DFS) 'balanced'. Clinical (VT) caries assessment by two examiners, diagnostic threshold = CA. Radiographic assessment (postBW) by two 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 (% of times diagnosis replicated in all 3 examinations ranged 42-97% and 77-92% for both examiners and for each respectively).</td>
<td></td>
</tr>
<tr>
<td>Andlaw 1975</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 13% drop out after 3 years (study duration = 3 years). Main reasons for attrition described: moved away,</td>
<td>740 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 6.9 DFS. Background exposure to</td>
<td>FT versus PL (SMFP group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Al oxide</td>
<td>3yNetDFS increment - (E+U)(CA)cl+(ER)xr. Reported at 3 years follow up.</td>
<td>Participants randomized (N = B 846). Baseline characteristics (age, dental age, TAR, DFS, DMFS, DFT, DMFT, ECSI) 'balanced'. Clinical (VT) caries</td>
<td></td>
</tr>
</tbody>
</table>
### Ashley 1977

<table>
<thead>
<tr>
<th>Stratified random allocation; double-blind (A); placebo-controlled; 12% dropout (for all study groups combined) after 2 years (study duration = 2 years). Natural losses; any differential group losses not assessable.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>489 children analysed at 2 years (available at final examination).</strong> Average age at start: 12 years. Surfaces affected at start: 9.1 DFS. Background exposure to fluoride: none. Year study began: 1973. Location: UK.</td>
</tr>
<tr>
<td><strong>FT versus PL (SMFP group = 1000 ppm F).</strong> School use/supervised, daily, 1g applied for 1 min, post-brushing water rinse done (non-fluoride toothpaste provided to all for home use). Abrasive system: IMP (main abrasive).</td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>---------------</td>
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<tr>
<td>Blinkhorn 1983</td>
</tr>
<tr>
<td>Brudevold 1966</td>
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<tr>
<td>Study</td>
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<tr>
<td>-------</td>
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<tr>
<td>Buhe 1984</td>
</tr>
<tr>
<td>Cahen 1982</td>
</tr>
</tbody>
</table>
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**Di Maggio 1980**
Random allocation; double-blind (A); placebo-controlled; 16% drop out (for both study groups combined) after 2 years (study duration = 2 years).
Main reason for attrition described: left institution; any differential group losses not assessable.

42 children analysed at 2 years (available at final examination).
Age range at start: 11-12 years. Surfaces affected at start: 11.7 DMFS.
Background exposure to fluoride: data not obtained for fluoridation status of site.
Year study began: 1977.
Location: France.

SMFP and placebo toothpaste, Ca carbonate/Na and Al silicates in the AmF toothpaste.
FT versus PL (SMFP-NaF group = 2500 ppm F).
2yDMFS increment - cl. Reported at 1 and 2 years follow ups.
Institution use/supervised, three times a day.
Abrasive system: not clearly specified.

**Dolles 1980**
Stratified random allocation; double-blind (A); placebo-controlled; 22% natural drop out after 2 years (study duration = 2 years).
Reasons for attrition described with numbers by group: unacceptable staining

47 children analysed at 2 years (present for all examinations).
Average age at start: 13 years. Surfaces affected at start: NR.
Background exposure to fluoride: none. Year study FT(Chlor) versus PL(Chlor) **
(NaF toothpaste = 500 ppm F).
2yDS increment - (CA)cl+(ER)xr. Reported at 2 years follow up.
Home use/unsupervised, daily frequency assumed (instructed to brush for 2 min
Proportion of children with new carious surface.

Participants randomized (N = 50).
Baseline characteristics (DMFS, DMFT) 'balanced'.
Clinical caries assessment by two examiners; diagnostic threshold NR; state of tooth eruption included NR. Diagnostic errors NR.

**Participants randomized (N = 60).**
Baseline characteristics NR.
Clinical (VT) caries assessment, diagnostic threshold = CA; state of tooth eruption included NR. Radiographic assessment

Diagnostic threshold = NR; state of tooth eruption included NR. Radiographic assessment (2 postBW) by one examiner; diagnostic threshold NR; partial recording. Inter- and intra-examiner reproducibility of clinical and radiographic caries diagnosis assessed in 10% sample ("good reproducibility. NS difference between or within examiners").
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Location: Norway.
twice a day).
Abrasive system: plastic particles.

(3,4), unacceptable taste (2,0), change of residence (0,2), other reasons/lack of co-operation(1,1); exclusions based on presence in all follow up examinations; no differential group losses.

Fanning 1968
Stratified random allocation; double-blind (A); placebo-controlled; 22% natural drop out after 2 years (study duration = 2 years); no differential group losses (46% drop out based on analysis performed for randomized block design).
844 children analysed at 2 years (422 complete replicates of each group available). Age range at start: 12-14 years (average = 13). Surfaces affected at start: 17.7 DMFS (from sample randomized). Background exposure to fluoride: none. Year study began: 1964. Location: Australia.
FT** versus PL (SnF2 group = 1000 ppm F).
Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.
2yDMFS increment - (CA)c+(ER)xr.
Reported at 2 years follow up.
Stain score.

Participants randomized (N = B 1576).
Baseline characteristics (DMFS, DMFT, SAR) 'balanced'.
Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA.
Radiographic assessment (5 BW) by two 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").

(postBW), diagnostic threshold = ER. Diagnostic errors NR. **Chlorhexidine present in both, the fluoride and the non-fluoride toothpaste groups (other outcomes measured, such as tooth staining, not considered relevant for the comparison of interest).
### Fogels 1979

- **Random allocation; double-blind (A); placebo-controlled; 40% drop out after 3 years (study duration = 3 years).**
- **Reasons for attrition described:** graduations, change of residence/school, parental requests, and ortho treatment; no differential group losses.
- 1339 children analysed at 3 years (available at final examination).
- Age range at start: 6-11 years (average = 9).
- Surfaces affected at start: 4.9 DFS. Background exposure to fluoride: none reported.
- Year study began: 1972.
- Location: USA.
- **FT (2 groups) versus PL (both SnF2 groups = 1000 ppm F).**
- Home use/unsupervised, daily frequency assumed.
- Abrasive system: silica gel in one SnF2 and placebo toothpaste, Ca pyrophosphate in the other.
- **3yNetDFS increment - (CA)cl+(ER)xr.**
- Reported at 3 years follow up.
- **MD-DFS.**
- **DMFT.**
- Oral soft tissues lesions (data NR).
- Proportion of children with tooth staining (data NR).

### Forsman 1974

- **Random allocation; double-blind (A); placebo-controlled; 18% drop out after 2 years (study duration = 2 years).**
- **Reasons for attrition described with respective total numbers:** change of residence/school, ortho treatment, did not wish.
- 559 children analysed at 2 years (available at final examination).
- Age range at start: 10-11 years. Surfaces affected at start: 5.1 DMFS.
- Background exposure to fluoride: mouthrinse.
- Year study began: in/before FT (3 groups) versus PL (the NaF and one SMFP group = 250 ppm F, another SMFP group = 1000 ppm F).
- Home use/unsupervised, daily frequency assumed.
- Abrasive system: silica in all toothpastes.
- **2yDMFS increment - (NCA)cl.**
- Reported at 2 years follow up.
- **BLMD-DFS (clin).**
- **MD-DFS (x-ray).**
- Proportion of children with...
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Forsman 1974a
Random allocation; double-blind (A); placebo-controlled; 16% drop out after 2 years (study duration = 2 years). Reasons for attrition described with respective total numbers: change of residence/school, ortho treatment, did not wish to continue; no differential group losses reported (but not assessable).

- 394 children analysed at 2 years (available at final examination).
- Age range at start: 10-12 years.
- Surfaces affected at start: 12.9 DMFS.
- Background exposure to fluoride: mouthrinse.
- Year study began: in/before 1970.
- Location: Sweden.

FT (2 groups) versus PL.
- (one SMFP group = 250 ppm F, another SMFP group = 1000 ppm F).
- Home use/unsupervised, daily frequency assumed.
- Abrasive system: Ca carbonate in all toothpastes.

2yDMFS increment - (NCA)cl.
Reported at 2 years follow up.

BLMD-DFS (clin).
MD-DFS (x-ray).
Proportion of children with new smooth surface caries.

Participants randomized (N = B 469); numbers by group NR. Baseline characteristics (dental age, DMFS) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = NCA. Radiographic assessment (postBW) by one examiner; diagnostic threshold = ER. State of tooth eruption included = NR. Diagnostic errors NR.

Gish 1966.
Stratified random allocation; double-blind (A); placebo-controlled; 34% drop out after 3 years (study duration = 5 years). Reasons for attrition NR; any differential group losses not assessable.

- 328 children analysed at 3 years (available at final examination).
- Age range at start: 6-14 years (average = 9).
- Surfaces affected at start: 3.9 DMFS.
- Background exposure to fluoride: water.
- Year study began: in/before 1963.
- Location: USA.

FT versus PL.
- (SnF2 group = 1000 ppm F).
- Home use/unsupervised, daily frequency assumed.
- Abrasive system: Ca pyrophosphate.

3yDMFS increment - cl+xr.
Reported at 1, 2, 3, 4 and 5 years follow ups.

DMFT.

Participants randomized (N = B 500); numbers by group NR. Baseline characteristics (age, DMFS) 'balanced'. Clinical (VT) caries assessment by two examiners, diagnostic threshold = NR. Radiographic assessment (5-7 BW); diagnostic threshold = NR. State of tooth eruption included = NR. Diagnostic errors NR.

Glass 1978
Stratified random allocation; double-blind (A);

- 346 children analysed at 3 years (present for all)
- FT versus PL
- (SMFP group = 1000 ppm)

3yNetDFS increment - (CA)cl+(ER)xr.

Participants randomized (N = D 533); numbers by group NR.

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Glass 1983
Stratified random allocation; double-blind (A); placebo-controlled; 16% drop out after 2.5 years (study duration = 2.5 years). Natural losses; no losses due to any adverse effects; any differential group losses not assessable.

- Placebo-controlled; 35% drop out after 3 years (study duration = 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.
- Age range at start: 6-11 years (average = 9).
- Surfaces affected at start: 4.1 DFS.
- Background exposure to fluoride: none reported.
- Location: USA.

- FT (2 groups) versus PL (both SMFP groups = 1000 ppm F).
- School use/supervised, 1g applied daily (appropriate toothpastes and toothbrushes also provided for home use).
- Abrasive system: Ca carbonate.

- Reported at 1, 2 and 3 years follow ups.
- MD-DFS.
- O-Bl-DFS.
- DFT.
- CIR.
- O-Bl-CIR.
- MD-CIR.

Participants randomized (N = B 1017); numbers by group NR.
Baseline characteristics (age, DFS, DFT, SAR, TAR) 'balanced'.
Clinical (VT) caries assessment (FOTI used) by one examiner; diagnostic threshold = CA; state of tooth eruption included = E/U.
Radiographic assessment (2 postBW) by one examiner; diagnostic threshold = ER.
Reversals were small in both groups (about 6% of DFS increments) and equally common (NS different).

Hanachowicz 1984
Stratified random allocation;

- 853 children analysed at 2.5 years (available at final examination).
- Age range at start: 7-11 years (average = 9).
- Surfaces affected at start: 2.1 DFS.
- Background exposure to fluoride: water.
- Year study began: 1976.
- Location: USA.

- FT (2 groups) versus PL (both SMFP groups = 1000 ppm F).
- School use/supervised, daily (appropriate toothpastes and toothbrushes also provided for home use).
- Abrasive system: IMP (main abrasive) in one SMFP and placebo toothpaste, Ca carbonate in the other SMFP toothpaste.

- Reported at 2.5 years follow up.
- 2.5yNetDFS increment - (CA)cl+(ER)xr.
- DFT.
- CIR.

Participants randomized (N = B 1017); numbers by group NR.
Baseline characteristics (age, DFS, DFT, SAR, TAR) 'balanced' (for DFT/DFS). Clinical (VT) caries assessment by two examiners (independently); diagnostic threshold = CA; state of tooth eruption included = E/U.
Radiographic assessment (2 postBW) by two examiners (independently); diagnostic threshold = ER. Results of one examiner chosen (findings consistent throughout).
**Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design Details</th>
<th>Participants</th>
<th>Baseline Characteristics</th>
<th>Clinical and X-ray Diagnosis Assessment</th>
</tr>
</thead>
</table>
| Hargreaves 1973                                                     | Double-blind (A); placebo-controlled; 28% dropout after 3 years (study duration = 3 years). Reasons for attrition NR; exclusions based on presence in all follow-up examinations. Any differential group losses not assessable. | 303 children analysed at 3 years (present for all examinations). Age at start: 6 years. Surfaces affected at start: 13.9 dfs (data for deciduous dentition only). Background exposure to fluoride: none reported. Year study began: 1968. Location: UK. | DMFS (U). O-DMFS. MD-DMFS. BL-DMFS. premolarDMFT. premolarDMFT. Proportion of children with new caries. | Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) by one examiner; diagnostic threshold NR. 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). Participants randomized (N = 316); numbers by group NR. Baseline characteristics (age, tar, dfs, dmfs, dft, dmft, ecsi) 'balanced' (no DFS data at start). Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) by two examiners; diagnostic threshold = ER. State of tooth eruption included =

- **Year study began:** 1979.
- **Location:** France.
- **303 children analysed at 3 years (available at final examination and cooperative). Age range at start: 10-12 years. Surfaces affected at start: 5.4 DMFS. Background exposure to fluoride: none reported. Year study began: 1979. Location: France.**

- **FT versus PL (SMFP group = 1500 ppm F).** Report at 3 years follow up. Abrasive system: Al oxide trihydrate.

- **Age range at start:** 10-12 years.
- **Surfaces affected at start:** 5.4 DMFS.
- **Baseline characteristics (DMFS) 'balanced'.**
- **Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) by one examiner; diagnostic threshold NR. 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). Participants randomized (N = C 316); numbers by group NR. Baseline characteristics (age, tar, dfs, dmfs, dft, dmft, ecsi) 'balanced' (no DFS data at start). Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) by two examiners; diagnostic threshold = ER. State of tooth eruption included =

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## Hargreaves 1973a

- **Methods:** Quasi-random allocation; double-blind (A); placebo-controlled; 5% drop out after 3 years (study duration = 3 years). Reasons for attrition NR; exclusions based on presence in all follow up examinations; any differential group losses not assessable.
- **Participants:** 284 children analysed at 3 years (present for all examinations).
- **Age at start:** 9 years.
- **Surfaces affected at start:** 6.3 DFS.
- **Background exposure to fluoride:** none reported.
- **Year study began:** 1968.
- **Location:** UK.
- **Intervention:** FT versus PL (SMFP group = 2400 ppm F).
- **Home use/unsupervised, daily frequency assumed.**
- **Abrasive system:** A1 oxide trihydrate.
- **Outcomes:** 3yNetDFS increment - (E+U)(CA)cl+(ER)xr. Reported at 3 years follow up.

## Hargreaves 1973b

- **Methods:** Quasi-random allocation; double-blind (A); placebo-controlled; 6% drop out after 3 years (study duration = 3 years). Reasons for attrition NR; exclusions based on presence in all follow up examinations; any differential group losses not assessable.
- **Participants:** 297 children analysed at 3 years (present for all examinations).
- **Age at start:** 12 years.
- **Surfaces affected at start:** 9.2 DFS.
- **Background exposure to fluoride:** none reported.
- **Year study began:** 1968.
- **Location:** UK.
- **Intervention:** FT versus PL (SMFP group = 2400 ppm F).
- **Home use/unsupervised, daily frequency assumed.**
- **Abrasive system:** A1 oxide trihydrate.
- **Outcomes:** 3yNetDFS increment - (E+U)(CA)cl+(ER)xr. Reported at 3 years follow up.

## Held 1968

- **Methods:** Stratified random allocation; double-blind (A); placebo-controlled; 65% drop out after 3 years (study duration = 3 years). Reasons for attrition NR; exclusions based on presence in all follow up examinations; any differential group losses not assessable.
- **Participants:** 63 children analysed at 3 years (available at final examination).
- **Age range at start:** 15-16 years.
- **Intervention:** FT versus PL (NaF-SnF2 group = 1000 ppm F).
- **Institution use/supervised.**
- **Outcomes:** 3yDMFS increment - (E) cl. Reported at 3 years follow up.
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Abrasive stem</th>
<th>FT versus PL</th>
<th>DMFS increment (E)</th>
<th>DMFT</th>
<th>Annual CAR</th>
<th>Clinical caries assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Held 1968a</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 64% drop out after 3 years (study duration = 3 years). Reasons for high drop out due to age range at which many leave the institutions; no differential group losses.</td>
<td>36 children analysed at 3 years (available at final examination).</td>
<td>FT versus PL (NaF-SnF2 group = 1000 ppm F).</td>
<td>Abrasive system: not clearly specified (silica used).</td>
<td>3yDMFS increment - (E) cl. Reported at 3 years follow up.</td>
<td>DMFT.</td>
<td>Annual CAR.</td>
<td>Participants randomized (N = B 101). Baseline characteristics (DMFS, DMFT) not balanced. Clinical (VT) caries assessment by one examiner; diagnostic threshold NR; state of tooth eruption included = E. Intra-examiner reproducibility checks done.</td>
<td></td>
</tr>
<tr>
<td>Held 1968b</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 62% drop out after 2 years (study duration = 3 years). Reasons for high drop out due to age range at which many leave the institutions; no differential group losses.</td>
<td>32 children analysed at 2 years (available at final examination).</td>
<td>FT versus PL (NaF group = 500 ppm F).</td>
<td>Abrasive system: not clearly specified (silica used).</td>
<td>2y*DMFS increment - (E) cl. Reported at 2 and 3 years follow ups.</td>
<td>DMFT.</td>
<td>Annual CAR.</td>
<td>Participants randomized (N = B 85). Baseline characteristics (DMFS, DMFT) not balanced. Clinical (VT) caries assessment by one examiner; diagnostic threshold NR; state of tooth eruption included = E. Intra-examiner reproducibility checks done.</td>
<td></td>
</tr>
<tr>
<td>Hodge 1980</td>
<td>Stratified random allocation;</td>
<td>799 children analysed at 3</td>
<td>FT (3 groups) versus PL</td>
<td>3yNetDFS increment - (E)</td>
<td>Participants randomized (N = B</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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Homan 1969

- Stratified random allocation; double-blind (A); placebo-controlled; 19% dropout after 1.7 years (study duration = 1.7 years).
- Reasons for attrition not described; any differential group losses not assessable.
- 1874 children analysed at 1.7 years.
- Age range at start: 7-13 years.
- Surfaces affected at start: data not available nor obtainable.
- Background exposure to fluoride: none.
- Year study began: 1965.
- Location: Australia.

(FT (3 groups) versus PL (SnF2 and APF toothpaste concentrations NR nor obtainable). Caries increment data NR (not obtainable).
- Home use/unsupervised, daily frequency assumed.
- Abrasive system: Ca pyrophosphate in one SnF2 toothpaste, calcium-free abrasive in the other SnF2 toothpaste and in the APF toothpaste; abrasive in placebo toothpaste NR.

Horowitz 1966

- Quasi-random allocation; double-blind (A);
- 638 children analysed at 3 years (available at final examination).
- Age range at start: 11-12 years.
- Surfaces affected at start: 7.3 DMFS.
- Background exposure to fluoride: none reported.
- Year study began: in/before 1976.
- Location: UK.

(SMFP group = 1000 ppm F, both SMFP-NaF groups = 1450 ppm F). (CA)cl+(DR)xr. DMFT. 3yNetDMFS increment - (E+U) (CA)cl.

Participants randomized (N = C 1059).
Howat 1978

Random allocation; double-blind (A); placebo-controlled; 12% drop out 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); any differential group losses not assessable.

Howat 1978

Random allocation; double-blind (A); placebo-controlled; 12% drop out 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); any differential group losses not assessable.

Howat 1978

Random allocation; double-blind (A); placebo-controlled; 12% drop out 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); any differential group losses not assessable.

Howat 1978

Random allocation; double-blind (A); placebo-controlled; 12% drop out 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); any differential group losses not assessable.

Howat 1978

Random allocation; double-blind (A); placebo-controlled; 12% drop out 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); any differential group losses not assessable.
| **Jackson 1967** | Quasi-random allocation; double-blind (A); placebo-controlled; 12% drop out rate after 3 years (study duration = 3 years). Natural losses; no differential group losses. | FT versus PL. (SnF2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: dicalcium pyrophosphate. | 3yDMFS 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. Participants randomized (N = C 986). Baseline characteristics (age, DMFS, DMFT, TAR, level of treatment, staining) 'balanced'. Clinical (VT) caries assessment by one 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. |
| **James 1967** | Random allocation; double-blind (A); placebo-controlled; 23% drop out rate after 3 years (study duration = 3 years). Reasons for drop out described with respective total numbers: moved away, unco-operative, not present on examination day, disliked toothpaste, staining of teeth, others; no differential group losses. | FT versus PL. (SnF2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: dicalcium pyrophosphate. | 3yDFS increment - (E) (CA)cl+(ER)xr. Reported at 3 years follow up. DMFS. DFT. DMFT. postMD-DFS. Proportion of children with tooth staining. Participants randomized (N = B 1043). Baseline characteristics (age, DFS, DFT, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by one examiner; diagnostic threshold = ER. Diagnostic errors NR. |
| **James 1977** | Stratified random allocation; double-blind (A); placebo-controlled; 19% drop | FT versus PL. (SMFP group = 2400 ppm F). | 3yDMFS increment - (CA)cl+(ER)xr. Reported at 3 years follow up. Participants randomized (N = B 964); numbers by group NR. Baseline characteristics (age, |
### Kinkel 1972

**Random allocation; double-blind (A); placebo-controlled; 25% drop out rate after 3 years (study duration = 7 years). Reasons for drop out not described; any differential group losses not assessable.**

- **Children analysed at 3 years.**
  - Average age at start: 10 years. Surfaces affected at start: 2.2 DMFS.
  - Background exposure to fluoride: data not available.
  - Year study began: in/before 1969.
  - Location: Switzerland.
  - 699 children analysed at 3 years.

**FT versus PL (SMFP group F concentration NR).**

- Home use/unsupervised, daily frequency assumed.
- Abrasive system: NR.

- **3yDMFS increment - (CA)cl+(DR)xr.**
- Reported at 1, 2, 3, 4, 5 and 7 years follow ups.
- Participants randomized (N = B 927); numbers by group NR.
- Baseline characteristics (DMFS) 'balanced'.
- Clinical (V) caries assessment; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW); diagnostic threshold = DR and ER.

### Kleber 1996

**Stratified random allocation; double-blind (A); placebo-controlled; 10% drop out after 1 year (study duration = 1 year). Main reasons for attrition: changes in residence, few exclusions for initiation of ortho treatment; no differential**

- **Children analysed at 1 year (available at final examination).**
  - Age range at start: 10-11 years (average = 10.7).
  - Surfaces affected at start: 4.2 DMFS.
  - Background exposure to fluoride: none reported.

**FT(+Alrins) versus PL(+Alrins) **

- Home use/unsupervised, daily frequency assumed.
- Abrasive system: silica.

- **1yDMFS increment - (CA)cl+(ER)xr.**
- Reported at 0.6 and 1 year follow ups.
- Participants randomized (N = B 174).
- Baseline characteristics (age, gender DMFS, DMFT) 'balanced'.
- Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; state of tooth eruption included NR. Radiographic assessment (2 postBW); diagnostic threshold = DR and ER.
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

Koch 1967

Stratified random allocation***; double-blind (A); placebo-controlled; 19% drop out after 3 years (study duration = 3 years + 2 years post-intervention period). Natural losses; no differential group losses.

124 children analysed at 3 years (present for entire trial period).
Age range at start: 8-10 years (average = 9).
Surfaces affected at start: 11.3 DFS.
Background exposure to fluoride: none reported.
Year study began: 1962.
Location: Sweden.

FT versus PL (NaF group = 1000 ppm F).
School use/supervised, daily, 1g applied for 2 min (non-fluoride toothpaste provided to all for home use).

3yDFS increment - cl(CA)(E).
Reported at 1 and 3 years follow ups (and 2 years post-treatment).

DFT.
O-DFS.
MD-DFS.
BL-DFS.
Annual CAR.
Secondary caries.

Participants randomized (N = 153).
Baseline characteristics (DFS, DFT, SAR) 'balanced'.
Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E.
Intra-examiner reproducibility checks for DFS in 10% sample (icc over 0.98); reversals very small in both groups and equally common.
*** Allocation concealment considered adequate by

Proportion of children with new DMFS.
Oral soft tissues lesions.

eruption included = E/U.
Radiographic assessment (postBW) by two examiners (independently); diagnostic threshold = ER.
Reversals were small in both groups and equally common. Results of one examiner chosen (findings consistent throughout).
**Rinsing with 500 ppm AI solutions performed daily at school in both relevant groups compared.
### Koch 1967a

**Stratified random allocation***; double-blind (A); placebo-controlled; 18% drop out after 3 years (study duration = 3 years + 2 years post-intervention period). Natural losses; no differential group losses.

- 120 children analysed at 3 years (present for entire trial period).
- Age range at start: 11-12 years (average = 11).
- Surfaces affected at start: 19.7 DFS.
- Background exposure to fluoride: none reported.
- Year study began: 1962.
- Location: Sweden.

**FT versus PL** (NaF group = 1000 ppm F).
- School use/supervised, daily, 1g applied for 2 min (non-fluoride toothpaste provided to all for home use).
- Abrasive system: methacrylate polymer (acrylic).

3yDFS increment - cl(CA)(E).
- Reported at 1 and 3 years follow ups (and 2 years post-treatment).
- DFT, O-DFS, MD-DFS, BL-DFS.
- Annual CAR.
- Secondary caries.

### Koch 1967b

**Stratified random allocation***; double-blind (A); placebo-controlled; 19% drop out after 2 years (study duration = 2 years). Natural losses; any differential group losses not assessable.

- 70 children analysed at 2 years (present for entire trial period).
- Age range at start: 13-14 years.
- Surfaces affected at start: 30.1 DFS.
- Background exposure to fluoride: none reported.
- Year study began: 1963.
- Location: Sweden.

**FT versus PL** (NaF group = 1000 ppm F).
- Home use/unsupervised, twice a day instructed frequency but daily frequency assumed, for 2 min.
- Abrasive system: methacrylate polymer (acrylic).

2yDFS increment - cl(CA)(E).
- Reported at 2 years follow up.
- DFT, O-DFS, MD-DFS, BL-DFS.
- Annual CAR.
- Secondary caries.

---

**Participants randomized (N = A 146).**
- Baseline characteristics (DFS, DFT, SAR, TAR) 'balanced'.
- Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E.
- Intra-examiner reproducibility checks for DFS in 10% sample (icc over 0.98); reversals very small in both groups and equally common.
- *** Allocation concealment considered adequate by consensus.

---

**Participants randomized (N = A 86); numbers by group NR.**
- Baseline characteristics (FS, FT, SAR, TAR) 'balanced'.
- Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E.
- Diagnostic errors NR.
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

Koch 1967c

- Stratified random allocation***; double-blind (A); placebo-controlled; 19% drop out after 3 years (study duration = 3 years). Natural losses; no differential group losses.
- 255 children analysed at 3 years (present for entire trial period).
- Age range at start: 7-10 years. Surfaces affected at start: 7.9 DFS. Background exposure to fluoride: none reported. Year study began: 1962. Location: Sweden.
- FT versus PL (NaF group = 1000 ppm F).
- 3yDFS increment - cl(CA)(E). Reported at 1 and 3 years follow ups.
- Abrasive system: methacrylate polymer (acrylic).
- Participants randomized (N = A 316).
- Baseline characteristics (FS, FT, SAR, TAR) 'balanced'.
- Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA/NCA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E. Diagnostic errors NR.
- *** Allocation concealment considered adequate by consensus.

Lind 1974

- Stratified random allocation; double-blind (A); placebo-controlled; 17% drop out rate after 3 years (study duration = 3 years). Main reasons for drop out: moved away, sickness; exclusions based on presence in one interim examination; no differential group losses.
- 1167 children analysed at 3 years (available at intermediate and final examination).
- Age range at start: 7-12 years (average = 10). Surfaces affected at start: 5.1 DMFS. Background exposure to fluoride: water. Year study began: 1970. Location: Denmark.
- FT versus PL (SMFP group = 2400 ppm F).
- 3yNetDMFS increment - (E+U)(CA)(E) + (DR)xr. Reported at 1, 2, and 3 years follow ups.
- Abrasive system: Al oxide trihydrate.
- DMFT.
- ECSI.
- Participants randomized (N = B 1407).
- Baseline characteristics (age, DMFS, DMFT) 'balanced'.
- Clinical (VT) caries assessment by two examiners; diagnostic threshold = C/NCA; radiographic assessment (2 postBW) by two examiners; diagnostic threshold = ER/DR; state of tooth eruption included = E/U.
- Inter-examiner diagnostic error reported to have no effect on results; reversal

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Mainwaring 1978

Stratified random allocation; double-blind (A); placebo-controlled; 18% drop out (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable.

1107 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 7.9 DFS. Background exposure to fluoride: none reported. Year study began: in/before 1974. Location: UK.

FT (2 groups) versus PL (both SMFP groups = 1000 ppm F).

Home use/unsupervised, for 1 min, daily frequency assumed. Abrasive system: Ca carbonate in all toothpastes.

3yNetDFS increment - (E)(CA)cl+(ER)xr. Reported at 3 years follow up.

PF-DFS. postMD-DFS. CIR.

Mainwaring 1983

Stratified random allocation; double-blind (A); placebo-controlled; 19% drop out (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 assesable.

682 children analysed at 4 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 6.9 DFS. Background exposure to fluoride: none reported. Year study began: in/before 1978.

FT (2 groups)** versus PL (SMFP group = 1000 ppm F, SMFP-NaF group = 1000 ppm F).

Home use/unsupervised, daily frequency assumed. Abrasive system: Ca carbonate in all toothpastes.

4yNetDFS increment - (CA)cl+(ER)xr. Reported at 4 years follow up.

O-DFS. MD-DFS. postMD-DFS. MD-BL-DFS.
<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation; double-blind (A); placebo-controlled; 43% drop out (for all study groups combined) after 3 years</th>
<th>Participants randomized (numbers for relevant groups NR).</th>
<th>Baseline characteristics (age, DMFS, DMFT) 'balanced' (DFS baseline data NR).</th>
<th>Clinical (V) caries assessment by one examiner; diagnostic threshold = CA and NCA; state of tooth eruption included NR.</th>
<th>Radiographic assessment (2 postBW) by one examiner; diagnostic threshold = DR and ER; partial recording. Diagnostic errors NR.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marthaler 1965</td>
<td>Random allocation; double-blind (A); placebo-controlled; 43% drop out (for all study groups combined) after 3 years (study duration = 7 years)</td>
<td>269 children analysed at 3 years (present for all examinations).</td>
<td>3yNetDFS increment - (CA)cl+(DR)xr. Reported at 1.5, 3, 5 and 7 years follow ups.</td>
<td>FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.</td>
<td>FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.</td>
</tr>
<tr>
<td></td>
<td>Exclusions based on variation in toothpaste provision and presence in follow up examinations; any differential group losses not assessable.</td>
<td>Age range at start: 6-9 years (average = 8). Surfaces affected at start: 3.3 DMFS. Background exposure to fluoride: salt (suboptimal). Year study began: 1958. Location: Switzerland.</td>
<td>postMD-DFS. antMD-DFS. BL-DFS. O-DFS. DMFT. FT. FS. MT.</td>
<td>FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.</td>
<td>FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.</td>
</tr>
<tr>
<td>Marthaler 1965a</td>
<td>Random allocation; double-blind (A); placebo-controlled; 66% drop out (for all study groups combined) after 3 years (study duration = 3 years).</td>
<td>74 children analysed at 3 years (present for all examinations).</td>
<td>3yNetDFS increment - (CA)cl+(DR)xr. Reported at 3 years follow up.</td>
<td>FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.</td>
<td>FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.</td>
</tr>
</tbody>
</table>
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

Main reason for high drop out: children leaving public school on completion of last compulsory year; exclusions based on variation in toothpaste provision and presence in follow up examinations; any differential group losses not assessable.

18.9 DMFS. Background exposure to fluoride: salt (suboptimal). Year study began: 1958. Location: Switzerland.

Marthaler 1970

Random allocation; indication of blind caries assessment (C); placebo-controlled; 18% drop out (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.

100 children analysed at 3 years (present for all examinations). Age range at start: 6-7 years (average = 7). Surfaces affected at start: 1 DMFS. Background exposure to fluoride: salt (suboptimal). Year study began: 1966. Location: Switzerland.

FT versus PL. (AmF group = 1250 ppm F). Home use/unsupervised, twice/three times a day/680 times a year estimated. Abrasive system: IMP. 3yNetDFS increment - (CA)xcl+(DR)xr. Reported at 1 and 3 years follow ups.

Marthaler 1970a

Random allocation; indication of blind caries assessment (C); placebo-controlled; 30% drop out (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.

43 children analysed at 4* years (present for all examinations). Age range at start: 7-9 years FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, 2y*NetDFS increment - (CA)xcl+(DR)xr. Reported at 2 and 4 years follow ups.

Participants randomized B (numbers for relevant groups NR). Baseline characteristics (age, DMFS, 1stMDMFS) 'balanced' (DFS baseline data NR). Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of the two examiners known from earlier work".

Baseline characteristics (age, DMFS, 1stMDMFS) 'balanced' (DFS baseline data NR). Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of the two examiners known from earlier work".

Participants randomized B (numbers for relevant groups NR). Baseline characteristics (age, DMFS, 1stMDMFS) 'balanced' (DFS baseline data NR). Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of the two examiners known from earlier work".

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(average = 8).
Surfaces affected at start: 2.3 DMFS.
Background exposure to fluoride: salt (suboptimal).
Year study began: 1966.
Location: Switzerland.

Exclusions based on: use of orthodontic bands, and presence in all follow up examinations; any differential group losses not assessable.

Random allocation; double-blind (A); placebo-controlled; 32% drop out after 6 years (study duration = 6 years).
Exclusions based on presence in all follow up examinations; no differential group losses.

109 children analysed at 6* years (present for all examinations).
Age range at start: 6-9 years (average = 7.5).
Surfaces affected at start: 2.6 DMFS.
Background exposure to fluoride: in solution/salt (suboptimal).
Year study began: 1966.
Location: Switzerland.

FT versus PL.
(AmF group = 1250 ppm F).
Home use/unsupervised, daily frequency assumed.
Abrasive system: IMP.

6y*NetDFS increment - (E)
(CA)Cl+(DR)xr.
Reported at 2 and 6 years follow ups.

PF-DFS.
potMD-DFS.
antMD-B-DFS.
DFT.

Proportion of children with new DFS.

Participants randomized (N = B 161).
Baseline characteristics (DMFS, DMFT, FS, FT, TAR) 'balanced' (DFS baseline data NR).
Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of examiners known from earlier work". *F solution used by all children after 2 years (final 4 years results not considered).
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Participants</th>
<th>Intervention</th>
<th>Duration</th>
<th>Attrition</th>
<th>Examiners</th>
<th>Clinical Assessment</th>
<th>DMFS</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Mergele 1968</td>
<td>Stratified random allocation; double-blind ('A'); placebo-controlled; 22% drop out (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.</td>
<td>387 children analysed at 3 years (available at final examination). Age range at start: 10-13 years (average = 11). Surfaces affected at start: 6.5 DMFS. Background exposure to fluoride: water. Year study began: 1964. Location: USA.</td>
<td>FT** versus 'PL' (SnF2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in fluoride toothpaste, IMP in control toothpaste.</td>
<td>3yNetDMFS increment - cl. Reported at 3 years follow up. DMFT.</td>
<td>Participants randomized (numbers for relevant groups NR). Baseline characteristics (age, SAR, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = NR. State of tooth eruption included = NR. Diagnostic errors NR. **Na N-lauroyl sarcosinate/SMFP toothpaste groups not considered (additional non-F active agent used in this group only).</td>
<td></td>
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</tr>
</tbody>
</table>
| Muhler 1955 | Stratified random allocation; double-blind (A); placebo-controlled; 22% drop out after 1 year (study duration = 1 year). Reasons for attrition NR; differential group losses. | 444 children analysed at 1 year (available at final examination). Age range at start: 6-16 years. Surfaces affected at start: 9.3 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: 1954. | FT** versus PL (SnF2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: heat-treated Ca orthophosphate. | 1yDMFS increment - cl+xr. Reported at 6 m and 1 year follow ups. DMFT. | Participants randomized (N = 568). Baseline characteristics (DMFS) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = NR. Radiographic assessment by one examiner, diagnostic threshold = NR. State of tooth eruption included = agreement of examiners known from earlier work*. Results at 6 years follow up chosen (reported for all outcomes).
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Follow-Up</th>
<th>Attrition</th>
<th>dmFS Increment</th>
<th>Clinical Assessment</th>
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</thead>
<tbody>
<tr>
<td>Muhler 1970</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 15% dropout after 1 year (study duration = 1 year)</td>
<td>436 children</td>
<td>1 year (available at final examination)</td>
<td>NR</td>
<td>1yDMFS increment - cl+xr</td>
<td>FT** versus PL (SnF2 group = 1000 ppm F)</td>
</tr>
<tr>
<td>Murray 1980</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 23% dropout after 3 years (study duration = 3 years)</td>
<td>1106 children</td>
<td>3 years (present for all examinations)</td>
<td>NR</td>
<td>3yNetDMFS increment - cl+xr</td>
<td>FT (2 groups) versus PL (both SMFP groups = 1000 ppm F)</td>
</tr>
</tbody>
</table>

NR. Criteria for caries diagnosis reported to have been carefully standardised, diagnostic errors NR.

**NaF-heat treated Ca orthophosphate toothpaste group not considered (abrasive system known to be incompatible with NaF).
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

Naylor 1967

Stratified random allocation; double-blind (A); placebo-controlled; 17% drop out (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable.

Surfaces affected at start: 9.9 DMFS.
Background exposure to fluoride: data not available for fluoridation status of site.
Year study began: 1974.
Location: UK.

973 children analysed at 3 years (available at final examination).
Age range at start: 11-12 years.
Surfaces affected at start: 9.5 DMFS.
Background exposure to fluoride: none reported.
Year study began: 1961.
Location: UK.

FT** versus PL (SnF2 group = 1000 ppm F).
Home use/unsupervised, daily frequency assumed.
Abrasive system: IMP (main abrasive) in fluoride toothpaste, dicalcium phosphate (dihydrate) in placebo toothpaste.

Participants randomized A (numbers for relevant groups NR).
Baseline characteristics (age, gender, SAR, DMFS, DMFT, postMD-DFS) 'balanced'.
Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included = E/U.
Radiographic assessment (2 postBW) by one examiner; diagnostic threshold = ER.
Reversal rate less than 4% of observed DFS increment in all groups. High accuracy of diagnosis revealed by 10%
<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation Method</th>
<th>Participants</th>
<th>Age Range at Start</th>
<th>Surfaces Affected at Start</th>
<th>Background Exposure to Fluoride</th>
<th>Year Study Began</th>
<th>Location</th>
<th>Baseline Characteristics (Age, SAR, TAR, DFS, DFT)</th>
<th>Clinical Caries Assessment (FOTI used)</th>
<th>Radiographic Assessment (2 postBW)</th>
<th>Additional Non-F Active Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naylor 1979</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 20% drop out (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable.</td>
<td>625 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 7.9 DFS. Background exposure to fluoride: none reported. Year study began: 1973. Location: UK.</td>
<td>FT** versus PL (SMFP group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca carbonate.</td>
<td>3yDFS increment - (E) (CA)cl+(ER)xr. Reported at 3 years follow up. DFT. DFT (U). O-BL-DFS. MD-DFS. CIR.</td>
<td>Participants randomized B (numbers for relevant groups NR). Baseline characteristics (age, SAR, TAR, DFS, DFT) 'balanced'. Clinical (VT) caries assessment (FOTI used) by two examiners (independently); diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by two examiners (independently); diagnostic threshold = ER. Results of one examiner chosen (findings consistent throughout). **Ca glycerophosphate/SMFP toothpaste group not considered (additional non-F active agent used in this group only).</td>
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</tr>
<tr>
<td>Peterson 1967</td>
<td>Stratified random allocation; 954 children analysed at 2</td>
<td>3yDFS increment - (E) (CA)cl+(ER)xr. Reported at 3 years follow up. DFT. DFT (U). O-BL-DFS. MD-DFS. CIR.</td>
<td>Participants randomized (N = 625 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 7.9 DFS. Background exposure to fluoride: none reported. Year study began: 1973. Location: UK. Baseline characteristics (age, SAR, TAR, DFS, DFT) 'balanced'. Clinical (VT) caries assessment (FOTI used) by two examiners (independently); diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by two examiners (independently); diagnostic threshold = ER. Results of one examiner chosen (findings consistent throughout). **Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only).</td>
<td>2y*DMFS increment - cl+xr.</td>
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</table>
### Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

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<tr>
<th>Study</th>
<th>Allocation</th>
<th>Duration</th>
<th>Dropout</th>
<th>Baseline Characteristics</th>
<th>Assessment</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Peterson 1979</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 16% dropout after 2 years (study duration = 3 years). Natural losses; exclusions based on presence in all follow-up examinations; any differential group losses not assessable.</td>
<td>3 years (available at this examination). Age range at start: 9-15 years. Surfaces affected at start: 14.3 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: in/before 1964. Location: USA.</td>
<td>712 children analysed at 2.5 years (present for all examinations). Age range at start: 8-12 years (average = 10). Surfaces affected at start: 2.9 DFS. Background exposure to fluoride: water. Year study began: 1971. Location: USA.</td>
<td>FT (2 groups) versus PL (both SMFP groups = 1000 ppm F). School use/supervised, daily, (appropriate toothpastes also provided for home use). Abrasive system: Ca carbonate in one toothpaste and in placebo toothpaste, IMP in the other SMFP toothpaste. 2.5yDFS increment - cl+ xr.</td>
<td>Participants randomized (N = 950); numbers by group NR. Baseline characteristics (DFS, MD-DFS, DFT) 'balanced'. Clinical (VT) caries assessment (FOTI used) by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; radiographic assessment (postBW) by one examiner; diagnostic threshold = ER. Diagnostic errors NR.</td>
<td>*Results for 3 years follow up not considered (not fully reported).</td>
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</tr>
<tr>
<td>Powell 1981</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; drop out</td>
<td>4 years (subjects who developed caries).</td>
<td>125 children analysed at 4 years (available at this examination).</td>
<td>FT (pp/Plsol)** (SnF2 group = 1000 ppm F).</td>
<td>Participants randomized (numbers NR). Baseline characteristics (age, background exposure to fluoride) balanced. Clinical (VT) caries assessment (FOTI used) by one examiner; diagnostic threshold = ER. Diagnostic errors NR.</td>
<td>1136); numbers by group NR. Baseline characteristics (DMFS, DMFT, dental age) 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold NR; state of tooth eruption included NR; radiographic assessment (3 BW) by one examiner; diagnostic threshold NR. Diagnostic errors NR.</td>
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<td></td>
</tr>
</tbody>
</table>
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation Method</th>
<th>Participants</th>
<th>Baseline Characteristics</th>
<th>Intervention Details</th>
<th>Follow-up Details</th>
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<tr>
<td>Ran 1991</td>
<td>Random allocation; double-blind (A); placebo-controlled; 20% dropout (for all study groups combined) after 1.5 years (study duration = 1.5 years + 0.5 year post-intervention period). Reasons for attrition/handling of exclusions NR; any differential group losses not assessable.</td>
<td>55 children analysed at 1.5 years; all male. Average age at start: 13 years. Surfaces affected at start: 6.4 DMFS. Background exposure to other fluoride: data not obtained for home use of toothpaste. Year study began: in/before 1989. Location: Israel.</td>
<td>Baseline characteristics (DMFS) with some imbalance (reported as NS difference). Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR. Intra-examiner reproducibility checks for DMFS (icc reaching 0.97).</td>
<td>FT versus PL (AmF group = 1250 ppm F). School use/supervised, fortnightly/20 times a year, 1g applied for 4 minutes, no post-brushing rinse done (no provision of any toothpaste reported for home use). Abrasive system: NR.</td>
<td>1.5yNetDMFS increment - CL. Reported at 0.5 and 1.5 years follow ups (and 0.5 year post-treatment).</td>
</tr>
<tr>
<td>Reed 1973</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 28% dropout after 2 years (study duration = 4 years). Reasons for attrition NR; any differential group losses not assessable.</td>
<td>1525 children analysed at 2 years (available at final examination). Age range at start: 6-13 years</td>
<td>Baseline characteristics (age, gender, DMFS, DMFT) 'balanced'. Radiographic (post BW) enamel caries progression assessment by one examiner; state of tooth eruption included = E. High reproducibility of radiographic diagnosis (icc = 0.91). **Prior prophylaxis with lava pumice followed by professional application of placebo solution performed every six months for 2 years in both relevant groups compared.</td>
<td>FT (3 groups) versus PL (NaF groups = 1000 ppm F, 500 ppm F, 250 ppm F). 2yDMFS increment - cl+xr. Reported at 1 and 2 years follow ups.</td>
<td>Participants randomized (N = 2104). Baseline characteristics (age, gender, DMFS, DMFT)</td>
</tr>
</tbody>
</table>
### Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Duration</th>
<th>Age Range</th>
<th>Surfaces Affected</th>
<th>Baseline Exposure to Fluoride</th>
<th>Year Study Began</th>
<th>Location</th>
<th>Attrition Rate</th>
<th>Attrition Reasons</th>
<th>DMFT Increment</th>
<th>Diagnostic Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed 1975</td>
<td>1975</td>
<td>2 years, duration = 2 years</td>
<td>8-13 years, average = 9</td>
<td>3.3 DMFS</td>
<td>None reported</td>
<td>1970</td>
<td>USA</td>
<td>39%</td>
<td>Not described; no differential group losses</td>
<td>FT versus PL</td>
<td>2yDMFS increment - cl+xr</td>
</tr>
<tr>
<td>Ringelberg 1979</td>
<td>1979</td>
<td>2.5 years, duration = 2.5 years</td>
<td>11 years</td>
<td>4.2 DMFS</td>
<td>None reported</td>
<td>1973</td>
<td>USA</td>
<td>37%</td>
<td>Not described; no differential group losses</td>
<td>FT (2 groups) versus PL (2 groups)</td>
<td>2.5yNetDMFS increment - (CA)cl + (DR)xr</td>
</tr>
</tbody>
</table>
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

Location: USA. NR for AmF and its placebo.

**Rule 1984**

- Stratified random allocation; double-blind (A); placebo-controlled; 24% drop out 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.
- 876 children analysed at 2 years (present for all examinations).
- Age range at start: 9-12 years (average = 11).
- Surfaces affected at start: 8.6 DMFS.
- Background exposure to fluoride: none reported.
- Location: USA.
- FT versus PL (SmF2 group = 1000 ppm F).
- School use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use).
- Abrasive system: silica zerogel.
- 2yDFS increment - (E+U) (CA)cl+(ER)xr. Reported at 1 and 2 years follow ups.
- 2yDFS increment - (E+U) (CA)cl+(ER)xr. Reported at 1 and 2 years follow ups.
- Oral soft tissue lesions.

**Segal 1967**

- Stratified random allocation; double-blind (A); placebo-controlled; 23% drop out after 2 years (study duration = 2 years). Reasons for attrition NR; differential group losses.
- 648 children analysed at 2 years (available at final examination).
- Age range at start: 7-12 years. Surfaces affected at start: NR.
- Background exposure to fluoride: none reported.
- Year study began: in/befpre 1964.
- Location: USA.
- FT versus PL (SnF2 group = 1000 ppm F).
- School use/supervised, daily, (appropriate toothpastes also provided for home use).
- Abrasive system: IMP (mainly).
- 2yDFS increment - (CA)cl+XR. Reported at 1 and 2 years follow ups.
- DFS (U).
- Oral soft tissue lesions.

Participants randomized (N = B 1154).
Baseline characteristics (age, gender, TAR, DMFS, DMFT, DS, DT) 'balanced' (DFS baseline data NR).
Clinical (VT) caries assessment (FOTI used) by one examiner; diagnostic threshold = CA; state of tooth eruption included = E/U.
Radiographic assessment (2 postBW) by one examiner; diagnostic threshold = ER.
Reproducibility checks done in 10% sample clinically and radiographically.

Participants randomized (N = B 845).
Baseline characteristics (SAR) 'balanced'.
Clinical (VT) caries assessment by two examiners, diagnostic threshold = CA.
Radiographic assessment as a supplementary aid; diagnostic threshold = NR.

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| Slack 1964 | Random allocation; double-blind (A); placebo-controlled; 32% drop out rate after 2 years (study duration = 2 years). Natural losses and other reasons; exclusions based on presence in all follow up examinations; no differential group losses. | 719 children analysed at 2 years (present for all examinations). Age range at start: 11-13 years. Surfaces affected at start: NR. Background exposure to fluoride: none reported. Year study began: 1962. Location: UK. | FT versus PL (SnF2 group = 1000 ppm F). Home use/unsupervised, 3 times/day instructed but daily frequency assumed. Abrasive system: IMP in fluoride toothpaste, dicalcium phosphate (dihydrate) in placebo toothpaste. Caries increment data NR (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. Participants randomized (N = 1059). Baseline characteristics 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR. Diagnostic errors NR. |
| Slack 1967 | Random allocation; double-blind (A); placebo-controlled; 21% drop out rate after 3 years (study duration = 3 years). Reasons for drop out 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. | 696 children analysed at 3 years, all female (present for all examinations). Average age at start: 11 years. Surfaces affected at start: 8.9 DFS. Background exposure to fluoride: none reported. Year study began: 1963. Location: UK. | FT versus PL (SnF2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP (dicalcium phosphate (dihydrate) in placebo toothpaste also). Consistency of clinical assessment included E/U. Inter- and intra-examiner reproducibility checks done. Participants randomized (N = 886). Baseline characteristics 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR. Diagnostic errors NR. |
### Slack 1967a

**Random allocation;** double-blind (A); placebo-controlled; 21% drop out rate after 3 years (study duration = 3 years). **Reasons for drop out 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.

757 children analysed at 3 years, all female (present for all examinations). Age range at start: 11-12 years. Surfaces affected at start: 7 DFS. Background exposure to fluoride: none reported. Year study began: 1962. Location: UK.

FT versus PL (SnF$_2$ group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: dicalcium pyrophosphate. 3yDFS increment - (E) (CA)cl. Reported at 3 years follow up.

- **757 children analysed at 3 years, all female (present for all examinations).**
- **Age range at start: 11-12 years.**
- **Surfaces affected at start: 7 DFS.**
- **Background exposure to fluoride: none reported.**
- **Year study began: 1962.**
- **Location: UK.**

### Slack 1971

**Random allocation;** double-blind ('A'); placebo-controlled; 33% drop out rate after 3 years (study duration = 3 years). **Main reasons for drop out:** moved away, left school, away on examination day, disliked toothpaste taste, brown

1110 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 11.6 DMFS. Background exposure to fluoride: none reported. Year study began: 1965.

FT (3 groups) versus 'PL' (Both SnF$_2$ groups = 1000 ppm F, APF group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP in one SnF$_2$ toothpaste and in APF 3yCrudeDMFS increment - (CA)cl+(ER)xr. Reported at 3 years follow up.

- **1110 children analysed at 3 years (available at final examination).**
- **Age range at start: 11-12 years.**
- **Surfaces affected at start: 11.6 DMFS.**
- **Background exposure to fluoride: none reported.**
- **Year study began: 1965.**

### Participants randomized (N = 1665).

Baseline characteristics (age, gender, DMFS, previous F toothpaste use) 'balanced'. Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by one examiner; diagnostic threshold = ER. Consistency of clinical diagnosis maintained by re-examination of 10% sample and calibration checks made against reserve examiner.

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Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Baseline Characteristics</th>
<th>Clinical (VT)</th>
<th>Radiographic (BW)</th>
<th>State of Tooth Eruption</th>
<th>Check of Diagnostic Errors</th>
<th>Proportion of Children with New Carious Lesions (U)</th>
<th>Reported at 6m, 1, 1.5 and 2 years follow ups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas 1966</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 32% drop out after 2 years (study duration = 2 years). Reasons for attrition NR; no differential group losses.</td>
<td>464 children analysed at 2 years (present for the entire study period). Average age at start: 7-16 years (average = 12). Surfaces affected at start: 10.7 DFS. Background exposure to fluoride: none reported. Year study began: 1961. Location: UK.</td>
<td>toothpaste, dicalcium pyrophosphate in another SnF2 toothpaste; control toothpaste abrasive NR.</td>
<td>FT (2 groups) versus PL (Both SnF2 groups = 1000 ppm F).</td>
<td>Institution use/supervised, twice a day. Abrasive system: IMP in one SnF2 and placebo toothpaste, Ca pyrophosphate in another SnF2 toothpaste.</td>
<td>2yDFS increment - cl+xr. Reported at 6m, 1, 1.5 and 2 years follow ups.</td>
<td>Consistency of clinical diagnosis revealed by 10% sample checks at each examination.</td>
<td>76.6%</td>
<td>2yDFS increment - cl+xr. Reported at 6m, 1, 1.5 and 2 years follow ups.</td>
</tr>
<tr>
<td>Torell 1965</td>
<td>Random allocation; double-blind (A); placebo-controlled; 13% drop out rate after 2 years (study duration = 2 years). Natural losses mainly; no differential group losses.</td>
<td>668 children analysed at 2 years (available at final examination). Average age at start: 10 years. Surfaces affected at start: 14.5 DMFS (from sample randomized). Background exposure to fluoride: none reported. Year study began: 1962. Location: Sweden.</td>
<td>FT (2 groups) versus PL (2 groups) (SnF2 group = 1000 ppm F, NaF group = 1100 ppm F).</td>
<td>Home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed. Abrasive system: Ca pyrophosphate in SnF2 toothpaste and its placebo,</td>
<td>2yDMFS increment - (CA)cl. Reported at 1 and 2 years follow ups.</td>
<td>Clinical (VT) caries assessment by two examiners, diagnostic threshold = CA; radiographic assessment (BW) by two examiners; diagnostic threshold = DR. State of tooth eruption included NR.</td>
<td>Check of diagnostic errors done.</td>
<td>FD</td>
<td>MD-DMFS. FS. Proportion of children with new carious lesions (U)</td>
</tr>
<tr>
<td>Study</td>
<td>Allocation</td>
<td>Duration</td>
<td>Loss Type</td>
<td>Age at Start</td>
<td>Surfaces Affected</td>
<td>Background Exposure</td>
<td>Year Study Began</td>
<td>Location</td>
<td>Sample Size</td>
</tr>
<tr>
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<tr>
<td>Torell 1965a</td>
<td>Random allocation; double-blind (A); placebo-controlled; 20% drop out rate after 2 years</td>
<td>2 years (available at final examination)</td>
<td>Natural losses mainly; differential group losses</td>
<td>10 years</td>
<td>11.7 DMFS (from sample randomized)</td>
<td>none reported</td>
<td>1962</td>
<td>Sweden</td>
<td>285 children</td>
</tr>
<tr>
<td>Torell 1965b</td>
<td>Random allocation; double-blind (A); placebo-controlled; 15% drop out rate after 2 years (study duration = 2 years).</td>
<td>2 years (available at final examination)</td>
<td>Natural losses mainly; differential</td>
<td>11 years</td>
<td>15 DMFS (from sample randomized)</td>
<td>none reported</td>
<td>1962</td>
<td>Sweden</td>
<td>368 children</td>
</tr>
<tr>
<td>Study</td>
<td>Allocation/Control</td>
<td>Age Range</td>
<td>Surfaces Affected</td>
<td>Background Exposure</td>
<td>Year Study Began</td>
<td>Location</td>
<td>Treatment</td>
<td>FT vs. PL</td>
<td>Reasons for High Drop Out</td>
</tr>
<tr>
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</tr>
<tr>
<td>Weisenstein 1972</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 42% drop out after 1.8 years</td>
<td>5-15 years (average = 9.5)</td>
<td>6.8 DMFS</td>
<td>none reported</td>
<td>1962</td>
<td>Sweden</td>
<td>FT versus PL (NaF group = 1000 ppm F)</td>
<td>Home use/unsupervised, daily frequency assumed</td>
<td></td>
</tr>
<tr>
<td>Zacherl 1970</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 43% drop out after 2.5 years</td>
<td>6-9 years</td>
<td></td>
<td>none reported</td>
<td>1969</td>
<td>USA</td>
<td>FT versus PL (SnF2 group = 1000 ppm F)</td>
<td>Home use/unsupervised, daily frequency assumed</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Allocation</td>
<td>Duration</td>
<td>Reason for High Drop Out</td>
<td>Number of Children</td>
<td>Start Age</td>
<td>Surfaces Affected</td>
<td>Background Exposure</td>
<td>Year Study Began</td>
<td>Location</td>
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<tr>
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</tr>
<tr>
<td>Zacherl 1970a</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 35% drop out after 2.5 years (study duration = 2.5 years).</td>
<td>2.5 years</td>
<td>NR; no differential group losses.</td>
<td>528</td>
<td>13-14</td>
<td>23.5 DMFS</td>
<td>none reported</td>
<td>in/before 1963</td>
<td>USA</td>
</tr>
<tr>
<td>Zacherl 1972</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 34% drop out after 2 years (study duration = 2 years).</td>
<td>2 years</td>
<td>NR; no differential group losses.</td>
<td>447</td>
<td>6-15</td>
<td>11.7 DMFS</td>
<td>none reported</td>
<td>in/before 1963</td>
<td>USA</td>
</tr>
</tbody>
</table>

**Participants randomized (N = 2677).**
Baseline characteristics (age, gender, DMFS, DMFT) 'balanced'.
Clinical (VT) caries assessment by one examiner, diagnostic threshold = NR.
Radiographic assessment (5-10 BW) by one examiner, diagnostic threshold = NR.
State of tooth eruption included = NR. Diagnostic errors NR.

**Surfaces affected at start:** 4.6 DMFS.
**Background exposure to fluoride:** none reported.
**Year study began:** in/before 1963.
**Location:** USA.

**Fluoride toothpastes for preventing dental caries in children and adolescents (THESES CHAPTER 5)**

**Daily frequency assumed. Abrasive system:** Ca pyrophosphate.

**DMFT.**
fluoride: none reported. toothpaste abrasive NR.
Year study began: in/before 1969. Location: Canada.

Zacherl 1972a
Stratified random allocation; double-blind (A); placebo-controlled; 36% drop out after 1.7 years (study duration = 1.7 years). Reasons for high drop out NR; exclusions based on presence in both examinations; no differential group losses.
894 children analysed at 1.7 years (present for both follow up examinations). Age range at start: 7-14 years (average = 9). Surfaces affected at start: 7.3 DMFS. Background exposure to fluoride: water. Year study began: in/before 1969. Location: Canada.
FT (4 groups) versus PL (SnF2 group, NaF group, SMFP group, APF group = 1000 ppm F each). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in all toothpastes. 1.7yDMFS increment - cl+xr. Reported at 1 and 1.7 years follow ups.
Participants randomized (N = 1405). Baseline characteristics (age, gender, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = NR. Radiographic assessment (5-10 BW) by one examiner; diagnostic threshold = NR. State of tooth eruption included = NR. Diagnostic errors NR.

Zacherl 1973
Stratified random allocation; double-blind (A); placebo-controlled; 34% drop out after 2 years (study duration = 2 years). Reasons for attrition NR; no differential group losses.
444 children analysed at 2 years (available at final examination). Age range at start: 5-12 years (average = 9). Surfaces affected at start: 8.5 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1970. Location: USA.
FT** versus PL (SnF2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in SnF2 toothpaste, placebo toothpaste abrasive NR. 2yDMFS increment - cl+xr. Reported at 1 and 2 years follow ups.
Participants randomized (N = 677). Baseline characteristics (age, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = NR. Radiographic assessment (5-10 BW) by one examiner; diagnostic threshold = NR. State of tooth eruption included = NR. Diagnostic errors NR.
**Na N-lauroyl
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

Zacherl 1981

- Stratified random allocation; double-blind (A); placebo-controlled; 43% drop out 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.
- 1754 children analysed at 3 years (available at final examination).
- Age range at start: 6-13 years (average = 9).
- Surfaces affected at start: 5.8 DMFS.
- Background exposure to fluoride: none reported.
- Year study began: in/before 1977.
- Location: USA.
- FT (2 groups) versus PL (SnF2 group = 1000 ppm F, NaF group = 1100 ppm F).
- Home use/unsupervised, daily frequency assumed.
- Abrasive system: Ca pyrophosphate in SnF2 and placebo toothpastes, silica in NaF toothpaste.
- 3yDMFS increment - (CA)cl+(ER)xr.
- Reported at 1, 2 and 3 years follow ups.
- DMFT.

Participants randomized (N = 3093).
Baseline characteristics (DMFS, DMFT) 'balanced'.
Clinical (VT) caries assessment (FOTI used) by one examiner, diagnostic threshold = CA.
Radiographic assessment (postBW) by one examiner; diagnostic threshold = ER.
State of tooth eruption included = NR.
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.

Drop out rate based only on groups relevant to review, on relevant follow ups, unless otherwise stated. Baseline caries experience averaged among relevant study arms, and based on the study sample analysed at the end of study period (final sample), unless otherwise stated. Age range (average age when reported) at the time the study started based on all study participants (or on groups relevant to the review when data were available).
Istm = first permanent molar; 'A' = classified as double-blind but participants may not be blind (as a 'PL' was used); Al = aluminium; Alumina = Al oxide trihydrate (Al2O3); AmF = amine

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fluoride; APF = acidulated phosphate fluoride; Ca = calcium; Ca carbonate = CaCO3; 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; Chlor = chlorhexidine digluconate; cl = clinical examination; d(e)ft/s = decayed, (extracted) and filled deciduous teeth or surface; dmft/s = decayed, missing (or extracted) and filled deciduous teeth or surface; D(M)FS/T = decayed, (missing) and filled permanent surfaces or teeth; DR = radiolucency into dentin; E = teeth erupted at baseline; ECSI = Extrapolated Caries Surface Index (assesses caries progression into enamel/dentin/pulp); ER = any radiolucency in enamel/enamel-dentin junction; F = fluoride; FR = fluoride mouthrinse; FT = fluoride toothpaste; icc = intra-class correlation coefficient (for inter-rater reliability); IMP = insoluble Na metaphosphate; M = missing permanent teeth; MD = mesio and distal surfaces; N = numbers; Na = sodium; NaF = sodium fluoride; Na bicarbonate = NaHCO3; NCA = non-cavitated enamel lesions visible as white spots or discoloured fissures; NR = not reported; NS = not significant; O = occlusal surfaces; PF = pit and fissure surfaces; PL = placebo toothpaste; 'PL' = fluoride-free toothpaste but not a true placebo (e.g. different in taste or colour from test toothpaste(s)); post BW = posterior bite-wing x-ray assessment; ppm F = parts per million of fluoride; ptc = prior tooth-cleaning performed with or without a non-fluoride paste; Silica = silicon dioxide (SiO2); SMFP = sodium monofluorophosphate; SnF2 = stannous fluoride; U = teeth unerupted at baseline; VT = visual-tactile assessment; xr = radiographic examination.
Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antia 1974</td>
<td>Random or quasi-random allocation not stated.</td>
</tr>
<tr>
<td>Bibby 1945</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Bixler 1962</td>
<td>Group of participants more than 16 years old selected. Random or quasi-random allocation not stated.</td>
</tr>
<tr>
<td>Bixler 1966</td>
<td>Group of young adults selected.</td>
</tr>
<tr>
<td>Bixler 1966a</td>
<td>Additional fluoride-based intervention associated to fluoride toothpaste. Group of participants more than 16 years old selected. Blind outcome assessment not stated.</td>
</tr>
<tr>
<td>Downer 1976</td>
<td>Additional fluoride-based intervention associated to fluoride toothpaste.</td>
</tr>
<tr>
<td>Ennever 1980</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
</tr>
<tr>
<td>Finn 1963</td>
<td>Medically compromised group of institutionalised children selected.</td>
</tr>
<tr>
<td>Gutherz 1968</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Halikis 1966</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
</tr>
<tr>
<td>Hill 1959</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Jiraskova 1965</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Jordan 1959</td>
<td>Only two clusters (schools), each randomized to one of the two interventions compared.</td>
</tr>
<tr>
<td>Kunzel 1977</td>
<td>Additional fluoride-based intervention associated to fluoride toothpaste.</td>
</tr>
<tr>
<td>Lehnhoff 1966</td>
<td>Participants more than 16 years old selected.</td>
</tr>
<tr>
<td>Lu 1985</td>
<td>Additional active agent associated to fluoride in toothpaste.</td>
</tr>
<tr>
<td>Luoma 1978</td>
<td>Additional fluoride-based intervention associated to fluoride</td>
</tr>
</tbody>
</table>
Fluoride toothpastes for preventing dental caries in children and

toothpaste.

Mergele 1968a  Medically compromised group of institutionalised young adults and children selected.

Moller 1968  Additional active agent associated to fluoride in test toothpaste.

Muhler 1955a  Random or quasi-random allocation not stated.

Muhler 1957  Random or quasi-random allocation not stated.

Muhler 1958  Participants more than 16 years old selected. Random or quasi-random allocation not stated.

Muhler 1960  Participants more than 16 years old selected. Random or quasi-random allocation not stated. Blind outcome assessment not stated.

Muhler 1962  Participants more than 16 years old selected.

Niwa 1975  Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.

Onisi 1970  Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.

Onisi 1974  Additional active agent associated to fluoride in toothpaste. Only two clusters (villages), each assigned to one of the two interventions compared.

Patz 1970  Participants more than 16 years old selected. Blind outcome assessment not stated.

Pefiley 1960  Participants more than 16 years old selected. Random or quasi-random allocation not stated. Blind outcome assessment not stated.

Piccione 1979  Blind outcome assessment not stated or indicated.

Riethe 1975  Blind outcome assessment not stated or indicated.

Stookey 1975  Random or quasi-random allocation not stated.

Wrinkler 1953  Random or quasi-random allocation clearly not used (non-random concurrent control: by matching procedure).

Zickert 1982  Additional fluoride-based intervention associated to fluoride toothpaste.
References to studies

Included studies

Abrams 1980 {unpublished data sought but not used}


Andlaw 1975 {published data only}


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Fluoride toothpastes for preventing dental caries in children and

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{unpublished data sought but not used}

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{published and unpublished data}


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{published data only}


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Forsman B. Studies on the effect of dentifrices with low fluoride content. Community Dentistry and Oral Epidemiology 1974;2:166-75.
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**Hargreaves 1973b**


**Held 1968**


**Held 1968a**


**Held 1968b**


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Fluoride toothpastes for preventing dental caries in children and


**Hodge 1980**


**Homan 1969**


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**James 1967**


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{published data only}


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{published data only}


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Marthaler TM. Karieshemmung durch Aminfluoridzahnpasten nach 7 jahriger Studiendauer [Caries inhibition with amino fluoride toothpastes following a 7-year-long study]. SSO Schweizerische Monatsschrift Fuer Zahnheilkund 1968;78:134-47.


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Slack 1967


Slack 1967a


Slack 1971


Thomas 1966


Torell 1965


Fluoride toothpastes for preventing dental caries in children and adults


Torell 1965a


Torell 1965b


Weisenstein 1972


Zacherl 1970


Zacherl 1970a


Zacherl 1972


Zacherl 1972a


Zacherl 1973

* unpublished data sought but not used

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Fluoride toothpastes for preventing dental caries in children and adults


Zacherl 1981

{unpublished data sought but not used}


Excluded studies

Antia 1974

{unpublished data sought but not used}


Axelsson 1976

{published data only}


Bibby 1945

{published data only}


Bixler 1962

{published data only}


Bixler 1966

{published data only}


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Fluoride toothpastes for preventing dental caries in children and adults

**Bixler 1966a**


**Downer 1976**


**Ennever 1980**

**Finn 1963**

**Gish 1965**

**Gutherz 1968**

**Halikis 1966**

**Hill 1959**

**Jiraskova 1965**

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Fluoride toothpastes for preventing dental caries in children and adults


Jordan 1959


Kunzel 1977


Lehnhoff 1966


Lu 1985

(published data only)

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Luoma 1978


Mergele 1968a


Moller 1968


Muhler 1955a


Muhler 1957


Muhler 1958


Muhler 1960

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**Muhler 1962**


**Niwa 1975**


**Onisi 1970**


**Onisi 1974**


**Patz 1970**


**Peffley 1960**


**Piccione 1979**


Review Manager 4.2.2 25/09/2003
Fluoride toothpastes for preventing dental caries in children and

Riethe 1975


Stookey 1975


Wrinkler 1953


Zickert 1982


Studies awaiting assessment

Cichocka 1981


Kinkel 1968


Kinkel 1974


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Fluoride toothpastes for preventing dental caries in children and adults


Kobylanska 1975

Onishi 1967

Takeuchi 1968

Weisenstein 1967

Wilson 1978

* indicates the primary reference for the study
Fluoride toothpastes for preventing dental caries in children and

Other references

Additional references

Ashley 1999

Bentley 1999

Bratthall 1996

Burt 1992

Burt 1998

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deliefde 1998

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Fluoride toothpastes for preventing dental caries in children and

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Horowitz 1992


ICW-CCT 2002


Johnson 1993


Krasse 1996


Levy 1994


Lewis 1996


Marinho 1997


Marinho 2002

Fluoride toothpastes for preventing dental caries in children and

Marthaler 1994


Marthaler 1996


Murray 1991


Murray 1991a


Nadanovsky 1995


O'Mullane 1994


O'Mullane 1997


Ripa 1989


Ripa 1991


Rojas-Sanchez 1999

Rojas-Sanchez F, Kelly SA, Drake KM, Eckert GJ, Stookey GK, Dunipace AJ. Fluoride intake from

Rolla 1991

Sharp 1998

Stamm 1995

Stephen 1988

Stookey 1994

Thompson 1999

van Rijkom 1998

Whitford 1992
Fluoride toothpastes for preventing dental caries in children and adults

Table of comparisons

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<th>01 Fluoride Toothpaste versus Placebo</th>
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<tr>
<td>01 D(M)FS increment (prevented fraction) - nearest to 3 years (70 trials)</td>
</tr>
<tr>
<td>02 D(M)FT increment (prevented fraction) - nearest to 3 years (53 trials)</td>
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<tr>
<td>03 D(M)FS increment (SMD) - nearest to 3 years (70 trials)</td>
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<td>04 D(M)FT increment (SMD) - nearest to 3 years (53 trials)</td>
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<tr>
<td>05 Developing one or more new caries (6 trials)</td>
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<td>06 Acquiring extrinsic tooth staining (5 trials)</td>
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**Other data tables**

**01 Fluoride Toothpaste versus Placebo**

**01 D(M)FS increment (prevented fraction) - nearest to 3 years (70 trials)**

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<td>(16% to 27%)</td>
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<td>Di Maggio 1980</td>
<td>61%</td>
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<td>Dolles 1980</td>
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| Zacherl 1981 | 32%   | (20% to 44% |
Other data tables

01 Fluoride Toothpaste versus Placebo

02 D(M)FT increment (prevented fraction) - nearest to 3 years (53 trials)

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Review Manager 4.2.2 25/09/2003
Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)

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<tr>
<td>Koch 1967b</td>
<td>30%</td>
<td>(-3% to 63%)</td>
</tr>
<tr>
<td>Koch 1967c</td>
<td>5%</td>
<td>(-14% to 24%)</td>
</tr>
<tr>
<td>Lind 1974</td>
<td>31%</td>
<td>(23% to 38%)</td>
</tr>
<tr>
<td>Marthaler 1965</td>
<td>33%</td>
<td>(20% to 45%)</td>
</tr>
<tr>
<td>Marthaler 1965a</td>
<td>16%</td>
<td>(-5% to 37%)</td>
</tr>
<tr>
<td>Marthaler 1974</td>
<td>33%</td>
<td>(15% to 52%)</td>
</tr>
<tr>
<td>Mergele 1968</td>
<td>6%</td>
<td>(-5% to 18%)</td>
</tr>
<tr>
<td>Muhler 1955</td>
<td>34%</td>
<td>(11% to 57%)</td>
</tr>
<tr>
<td>Muhler 1970</td>
<td>32%</td>
<td>(16% to 49%)</td>
</tr>
<tr>
<td>Naylor 1967</td>
<td>8%</td>
<td>(1% to 15%)</td>
</tr>
<tr>
<td>Naylor 1979</td>
<td>20%</td>
<td>(12% to 27%)</td>
</tr>
<tr>
<td>Peterson 1967</td>
<td>14%</td>
<td>(5% to 23%)</td>
</tr>
<tr>
<td>Peterson 1979</td>
<td>10%</td>
<td>(-7% to 26%)</td>
</tr>
<tr>
<td>Reed 1973</td>
<td>18%</td>
<td>(8% to 28%)</td>
</tr>
<tr>
<td>Reed 1975</td>
<td>26%</td>
<td>(10% to 41%)</td>
</tr>
<tr>
<td>Ringelberg 1979</td>
<td>15%</td>
<td>(1% to 30%)</td>
</tr>
<tr>
<td>Rule 1984</td>
<td>24%</td>
<td>(14% to 34%)</td>
</tr>
<tr>
<td>Slack 1967</td>
<td>-2%</td>
<td>(-14% to 11%)</td>
</tr>
</tbody>
</table>

Review Manager 4.2.2

25/09/2003
<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage</th>
<th>Confidence Interval</th>
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<tbody>
<tr>
<td>Slack 1967a</td>
<td>4%</td>
<td>(-7% to 14%)</td>
</tr>
<tr>
<td>Thomas 1966</td>
<td>31%</td>
<td>(15% to 47%)</td>
</tr>
<tr>
<td>Weisenstein 1972</td>
<td>15%</td>
<td>(1% to 28%)</td>
</tr>
<tr>
<td>Zacherl 1970</td>
<td>35%</td>
<td>(24% to 47%)</td>
</tr>
<tr>
<td>Zacherl 1970a</td>
<td>37%</td>
<td>(29% to 46%)</td>
</tr>
<tr>
<td>Zacherl 1972</td>
<td>20%</td>
<td>(6% to 34%)</td>
</tr>
<tr>
<td>Zacherl 1972a</td>
<td>21%</td>
<td>(8% to 33%)</td>
</tr>
<tr>
<td>Zacherl 1973</td>
<td>35%</td>
<td>(18% to 53%)</td>
</tr>
<tr>
<td>Zacherl 1981</td>
<td>31%</td>
<td>(20% to 42%)</td>
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</table>
### Additional tables

#### 01 Meta-analyses of prevented fractions

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. studies</th>
<th>r.e. estimate</th>
<th>95% c. i.</th>
<th>Meta-analysis p-val</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(M)FS - all studies</td>
<td>70</td>
<td>24%</td>
<td>21% to 28%</td>
<td>p&lt;0.0001</td>
<td>Q= 489.89 (69 d.f.); p&lt;0.0001</td>
</tr>
<tr>
<td>D(M)FT - all studies</td>
<td>53</td>
<td>23%</td>
<td>19% to 28%</td>
<td>p&lt;0.0001</td>
<td>Q= 541.04 (52 d.f.); p&lt;0.0001</td>
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</tbody>
</table>

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## Additional tables

### 02 Random effects meta-regression analyses of prevented fractions: D(M)FS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. studies</th>
<th>Slope estimate</th>
<th>95% c.i.</th>
<th>Slope interpretation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline caries</td>
<td>67</td>
<td>0.7%</td>
<td>(0.07% to 1.3%)</td>
<td>Increase in PF per unit increase in mean baseline caries</td>
<td>0.03</td>
</tr>
<tr>
<td>Fluoridated water</td>
<td>56</td>
<td>3.2%</td>
<td>(-4% to 11%)</td>
<td>Higher PF in presence of water fluoridation</td>
<td>0.4</td>
</tr>
<tr>
<td>Background fluorides</td>
<td>56</td>
<td>0.6%</td>
<td>(-6% to 8%)</td>
<td>Higher PF in presence of any background fluoride</td>
<td>0.9</td>
</tr>
<tr>
<td>Concentration of fluoride</td>
<td>69</td>
<td>8.5%</td>
<td>(1.3% to 16%)</td>
<td>Increase in PF per 1000 ppm F</td>
<td>0.02</td>
</tr>
<tr>
<td>Frequency of toothbrushing</td>
<td>69</td>
<td>9%</td>
<td>(-1.4% to 20%)</td>
<td>Increase in PF moving from once to twice a day</td>
<td>0.09</td>
</tr>
<tr>
<td>Intensity (freq times conc)</td>
<td>59</td>
<td>5.9%</td>
<td>(-0.07% to 12%)</td>
<td>Increase in PF equivalent to doubling from once to twice a day and increasing by 1000 ppmF</td>
<td>0.05</td>
</tr>
<tr>
<td>Mode of use</td>
<td>70</td>
<td>-11%</td>
<td>(-18% to -4%)</td>
<td>Lower PF with unsupervised toothbrushing</td>
<td>0.03</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>70</td>
<td>3.2%</td>
<td>(-7% to 13%)</td>
<td>Higher PF with poorly concealed allocation</td>
<td>0.5</td>
</tr>
<tr>
<td>Drop out</td>
<td>70</td>
<td>2.6%</td>
<td>(0.2% to 5%)</td>
<td>Increase in PF per 10 drop outs</td>
<td>0.04</td>
</tr>
<tr>
<td>Length of follow up</td>
<td>70</td>
<td>0.8%</td>
<td>(-4.2% to 5.7%)</td>
<td>Increase in PF per extra year of follow up</td>
<td>0.8</td>
</tr>
<tr>
<td>SMFP vs NaF (indirect comparison)</td>
<td>32</td>
<td>-2.6%</td>
<td>(-11.8% to 6.5%)</td>
<td>PF lower among SMFP trials</td>
<td>0.6</td>
</tr>
<tr>
<td>AmF vs NaF (indirect comparison)</td>
<td>15</td>
<td>3.2%</td>
<td>(-11.0% to 17.3%)</td>
<td>PF higher among AmF trials</td>
<td>0.7</td>
</tr>
<tr>
<td>SnF2 vs NaF (indirect comparison)</td>
<td>29</td>
<td>-4.8%</td>
<td>(14.1% to 4.5%)</td>
<td>PF lower among SnF2 trials</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Review Manager 4.2.2 25/09/2003*
Additional figures

Figure 01
Funnel Plot of \( D(M)FS \) SMDs according to standard errors of the studies included in the meta-analysis

Review: Fluoride toothpastes for preventing dental caries in children and adolescents (THESIS CHAPTER 5)
Comparison: 01 Fluoride Toothpaste versus Placebo
Outcome: 03 \( D(M)FS \) increment (SMD) - nearest to 3 years (70 trials)

\[
\begin{align*}
\text{SE(SMD)} & = 0.0 \\
-0.4 & \quad -0.3 \\
-0.2 & \quad -0.1 \\
0 & \quad 0.1 \\
2 & \quad 3 \\
4 & \quad 5 \\
\end{align*}
\]

Review Manager 4.2.2 25/09/2003
<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride Toothpaste versus Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 D(M)FS increment (prevented fraction) - nearest to 3 years (70 trials)</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 D(M)FT increment (prevented fraction) - nearest to 3 years (53 trials)</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 D(M)FS increment (SMD) - nearest to 3 years (70 trials)</td>
<td>70</td>
<td>42300</td>
<td>SMD (random), 95% CI</td>
<td>-0.31 [-0.35, -0.27]</td>
</tr>
<tr>
<td>04 D(M)FT increment (SMD) - nearest to 3 years (53 trials)</td>
<td>53</td>
<td>32371</td>
<td>SMD (random), 95% CI</td>
<td>-0.28 [-0.33, -0.23]</td>
</tr>
<tr>
<td>05 Developing one or more new caries (6 trials)</td>
<td>7</td>
<td>2878</td>
<td>RR (random), 95% CI</td>
<td>0.93 [0.84, 1.04]</td>
</tr>
<tr>
<td>06 Acquiring extrinsic tooth staining (5 trials)</td>
<td>5</td>
<td>3948</td>
<td>RD (random), 95% CI</td>
<td>0.24 [0.19, 0.30]</td>
</tr>
</tbody>
</table>
## Comparison of Fluorne Toothpaste versus Placebo

### Thesis Chapter 5

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluorine Toothpaste</th>
<th>Placebo</th>
<th>WMD (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams 1980</td>
<td>0.35 (0.29, 0.41)</td>
<td>0.17 (0.13, 0.21)</td>
<td>0.38 (0.32, 0.44)</td>
<td>1980</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Kolon 1975</td>
<td>0.33 (0.27, 0.39)</td>
<td>0.12 (0.09, 0.14)</td>
<td>0.21 (0.17, 0.25)</td>
<td>1975</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Alper 1977</td>
<td>0.37 (0.31, 0.43)</td>
<td>0.19 (0.16, 0.23)</td>
<td>0.18 (0.14, 0.22)</td>
<td>1977</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Bora 1983</td>
<td>0.32 (0.27, 0.37)</td>
<td>0.16 (0.13, 0.19)</td>
<td>0.16 (0.12, 0.20)</td>
<td>1983</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Bush 1964</td>
<td>0.30 (0.25, 0.35)</td>
<td>0.15 (0.12, 0.18)</td>
<td>0.15 (0.12, 0.18)</td>
<td>1964</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Callen 1982</td>
<td>0.30 (0.25, 0.35)</td>
<td>0.15 (0.12, 0.18)</td>
<td>0.15 (0.12, 0.18)</td>
<td>1982</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>O'Maggie 1980</td>
<td>0.30 (0.25, 0.35)</td>
<td>0.15 (0.12, 0.18)</td>
<td>0.15 (0.12, 0.18)</td>
<td>1980</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>O'Maggie 1982</td>
<td>0.32 (0.27, 0.37)</td>
<td>0.19 (0.16, 0.23)</td>
<td>0.19 (0.16, 0.23)</td>
<td>1982</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>O'Maggie 1984</td>
<td>0.35 (0.29, 0.41)</td>
<td>0.17 (0.13, 0.21)</td>
<td>0.18 (0.14, 0.22)</td>
<td>1984</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>O'Maggie 1986</td>
<td>0.37 (0.31, 0.43)</td>
<td>0.19 (0.16, 0.23)</td>
<td>0.17 (0.13, 0.21)</td>
<td>1986</td>
<td>9</td>
<td>9</td>
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<tr>
<td>O'Maggie 1988</td>
<td>0.32 (0.27, 0.37)</td>
<td>0.19 (0.16, 0.23)</td>
<td>0.19 (0.16, 0.23)</td>
<td>1988</td>
<td>9</td>
<td>9</td>
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<tr>
<td>O'Maggie 1990</td>
<td>0.30 (0.25, 0.35)</td>
<td>0.15 (0.12, 0.18)</td>
<td>0.15 (0.12, 0.18)</td>
<td>1990</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>O'Maggie 1992</td>
<td>0.32 (0.27, 0.37)</td>
<td>0.19 (0.16, 0.23)</td>
<td>0.19 (0.16, 0.23)</td>
<td>1992</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>O'Maggie 1994</td>
<td>0.35 (0.29, 0.41)</td>
<td>0.17 (0.13, 0.21)</td>
<td>0.18 (0.14, 0.22)</td>
<td>1994</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

### Summary of Studies

- **Total (N=95)**: 25520
- **Test for heterogeneity**: $\chi^2 = 295.36$, df = 70, $p < 0.00001$
- **Total WMD (random) 95% CI**: 0.38 (0.32, 0.44)
- **Test for overall effect**: $Z = 1.445 (0.98, 1.91)$, $p < 0.00001$
### Fluoride toothpastes versus Placebo

#### Study or sub-category

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Fluoride toothpaste Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>% Difference (95% CI)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minh 1979</td>
<td>1.09 (0.2)</td>
<td>0.75 (0.2)</td>
<td>50.7% (45.2-56.1)</td>
<td>1979</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Byrd 1981</td>
<td>1.07 (0.2)</td>
<td>0.75 (0.2)</td>
<td>43.9% (38.3-49.6)</td>
<td>1981</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tannahill 1979</td>
<td>1.05 (0.2)</td>
<td>0.75 (0.2)</td>
<td>40.0% (34.5-45.5)</td>
<td>1979</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tannahill 1978</td>
<td>1.03 (0.2)</td>
<td>0.75 (0.2)</td>
<td>37.0% (31.4-42.6)</td>
<td>1978</td>
<td>0</td>
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</tr>
<tr>
<td>Tannahill 1977</td>
<td>1.01 (0.2)</td>
<td>0.75 (0.2)</td>
<td>34.1% (28.5-39.7)</td>
<td>1977</td>
<td>0</td>
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<tr>
<td>Tannahill 1976</td>
<td>0.99 (0.2)</td>
<td>0.75 (0.2)</td>
<td>31.3% (25.7-36.9)</td>
<td>1976</td>
<td>0</td>
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<tr>
<td>Tannahill 1975</td>
<td>0.97 (0.2)</td>
<td>0.75 (0.2)</td>
<td>28.4% (22.8-34.0)</td>
<td>1975</td>
<td>0</td>
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<tr>
<td>Tannahill 1974</td>
<td>0.95 (0.2)</td>
<td>0.75 (0.2)</td>
<td>25.5% (20.0-31.0)</td>
<td>1974</td>
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<tr>
<td>Tannahill 1973</td>
<td>0.93 (0.2)</td>
<td>0.75 (0.2)</td>
<td>22.6% (17.1-28.1)</td>
<td>1973</td>
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<tr>
<td>Tannahill 1972</td>
<td>0.91 (0.2)</td>
<td>0.75 (0.2)</td>
<td>20.7% (15.2-26.2)</td>
<td>1972</td>
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<tr>
<td>Tannahill 1971</td>
<td>0.89 (0.2)</td>
<td>0.75 (0.2)</td>
<td>18.8% (13.3-24.3)</td>
<td>1971</td>
<td>0</td>
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<tr>
<td>Tannahill 1970</td>
<td>0.87 (0.2)</td>
<td>0.75 (0.2)</td>
<td>17.0% (11.5-22.5)</td>
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<tr>
<td>Tannahill 1969</td>
<td>0.85 (0.2)</td>
<td>0.75 (0.2)</td>
<td>15.1% (9.6-20.6)</td>
<td>1969</td>
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<tr>
<td>Tannahill 1968</td>
<td>0.83 (0.2)</td>
<td>0.75 (0.2)</td>
<td>13.2% (7.7-18.7)</td>
<td>1968</td>
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<tr>
<td>Tannahill 1967</td>
<td>0.81 (0.2)</td>
<td>0.75 (0.2)</td>
<td>11.3% (5.8-16.8)</td>
<td>1967</td>
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<tr>
<td>Tannahill 1966</td>
<td>0.79 (0.2)</td>
<td>0.75 (0.2)</td>
<td>9.5% (4.0-15.0)</td>
<td>1966</td>
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<tr>
<td>Tannahill 1965</td>
<td>0.77 (0.2)</td>
<td>0.75 (0.2)</td>
<td>7.6% (2.1-13.1)</td>
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<td>Tannahill 1964</td>
<td>0.75 (0.2)</td>
<td>0.75 (0.2)</td>
<td>5.7% (0.2-11.1)</td>
<td>1964</td>
<td>0</td>
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</tbody>
</table>

#### Total (%CI)

<table>
<thead>
<tr>
<th>Total (%CI)</th>
<th>Mean (SD)</th>
<th>% Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5%</td>
<td>0.93 (0.2)</td>
<td>25.3% (19.8-30.8)</td>
</tr>
</tbody>
</table>

#### Test for heterogeneity: Chi² = 17.94 (df = 6; P < 0.001), I² = 70.2%
CHAPTER 6

FLUORIDE MOUTHRINSES FOR PREVENTING DENTAL CARIES IN CHILDREN AND ADOLESCENTS
Fluoride mouthrinses for preventing dental caries in children and adolescents (THESIS CHAPTER 6)

Reviewers
Marinho VCC, Higgins JPT, Logan S, Sheiham A

Dates
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Fluoride mouthrinses for preventing dental caries in children and

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Systematic Reviews Training Unit, Institute of Child Health (UCL), UK
Medical Research Council, UK

External sources of support
CAPES - Ministry of Education, BRAZIL

Contribution of reviewers
All authors contributed to the development of the protocol. Valeria Marinho (VM) wrote the protocol, conducted searches, selected studies and extracted data. Julian Higgins (JH) duplicated the study selection and data extraction in a sample of studies, and Stuart Logan (SL) or Aubrey Sheiham (AS) were consulted where necessary. VM entered and analysed the data in consultation with JH. VM prepared the full review and all authors were active in its revision and approval.

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Potential conflict of interest
None known.
Abstract

Background
Fluoride mouthrinses have been used extensively as a caries-preventive intervention in school-based programmes and individually at home.

Objectives
To determine the effectiveness and safety of fluoride mouthrinses in the prevention of dental caries in children and to examine factors potentially modifying their effect.

Search strategy
We searched the Cochrane Oral Health Group's Trials Register (May 2000), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2000), MEDLINE (1966 to January 2000), plus several other databases. We handsearched journals, reference lists of articles and contacted selected authors and manufacturers.

Selection criteria
Randomised or quasi-randomised controlled trials with blind outcome assessment, comparing fluoride mouthrinse with placebo or no treatment in children up to 16 years during at least 1 year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS).

Data collection & analysis
Inclusion decisions, quality assessment and data extraction were duplicated in a random sample of one third of studies, and consensus achieved by discussion or a third party. Authors were contacted for missing data. The primary measure of effect was the prevented fraction (PF) that is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed where data could be pooled. Potential sources of heterogeneity were examined in random effects metaregression analyses.

Main results
Thirty-six studies were included. For the 34 that contributed data for meta-analysis (involving 14,600 children) the D(M)FS pooled PF was 26% (95% confidence interval (CI), 23% to 30%; p < 0.0001). Heterogeneity was not substantial, but confirmed statistically (p = 0.008). No significant association between estimates of D(M)FS prevented fractions and baseline caries severity, background exposure to fluorides, rinsing frequency and fluoride concentration was found in metaregression analyses. A funnel plot of the 34 studies indicated no relationship between prevented fraction and study precision. There is little information concerning possible adverse effects or acceptability of treatment in the included trials.

Reviewers' conclusions
This review suggests that the supervised regular use of fluoride mouthrinse at two main strengths and rinsing frequencies is associated with a clear reduction in caries increment in children. In populations with caries increment of 0.25 D(M)FS per year, 16 children will need to use a fluoride mouthrinse (rather than a non-fluoride rinse) to avoid one D(M)FS; in populations with a caries increment of 2.14 D(M)FS per year, 2 children will need to rinse to avoid one D(M)FS. There is a need for complete reporting of side effects and acceptability data in fluoride mouthrinse trials.
Background

The prevention of dental caries in children and adolescents is generally regarded as a priority for dental services and considered more cost effective than its treatment (Burt 1998). Fluoride therapy has been the centrepiece of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray 1991). These were introduced when caries was highly prevalent and severe, and when even modest prevention activities led to considerable reductions in disease levels. In the last 20 years, with the substantial decline in dental caries rates in many western countries, an increase in dental fluorosis levels in some countries, and intensive research on the mechanism of action of fluoride highlighting the primary importance of its topical effect, greater attention has been paid to the appropriate use of other fluoride-based interventions (Glass 1982; Featherstone 1988; Ripa 1991; O'Mullane 1994; Marthaler 1996; Featherstone 1999).

The use of topically applied fluoride products in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades. By definition, the term 'topically applied fluoride' is used to describe those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect, and are therefore not intended for ingestion. The most important anti-caries effect of fluoride is considered to result from its action on the tooth/plaque interface, through promotion of remineralisation of early caries lesions and by reducing tooth enamel solubility (Featherstone 1988). Fluoride containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most commonly used at present, either alone or in combination. Various products are marketed in different countries and a variety of caries-preventive programmes based on these have been implemented. Toothpastes are by far the most widespread form of fluoride usage (Murray 1991a; Ripa 1991) and although the reasons for the decline in the prevalence of dental caries in children from different countries continues to be debated (Nadanovsky 1995; Krasse 1996; Marthaler 1996; de Liefde 1998), it has been mainly attributed to the gradual increase in, and regular home use of fluoride in toothpaste (Glass 1982; Ripa 1991; Rolla 1991; Marthaler 1994; O'Mullane 1994; Bratthall 1996).

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

The evidence on the effect of topical fluorides on the prevention of dental caries in children has been extensively reviewed in a number of traditional narrative reviews. A small number of reviews focusing on the evaluation of specific fluoride active agents within specific delivery systems have used a quantitative meta-analytical approach to synthesise studies results (Clark 1985; Johnson 1993; Helfenstein 1994; Stamm 1995; van Rijkom 1998). However, a systematic quantitative evaluation of the available evidence on the effect of the main modalities of topically applied fluoride has never been undertaken.

This review is one in a series of systematic reviews of topical fluoride interventions and assesses the effectiveness of fluoride rinses in the prevention of dental caries in children.

FLUORIDE MOUTH RINSES
Fluoride mouthrinses have been used extensively for the past 30 years to prevent dental caries in children. The use of rinses was especially widespread in organised school-based programmes in countries experiencing high caries prevalence in the 1970s and 1980s. Doubts about the effectiveness of fluoride mouthrinse as a population strategy began in the mid 1980s in view of the decline in dental caries, and their presumed cost effectiveness was challenged (Stamm 1984; Disney 1990). The current view is that fluoride mouthrinsing programmes are only appropriate for high caries groups of children. While supervised, school-based, weekly rinsing programmes using 900 ppm F solutions remain a popular procedure in America in non-fluoridated communities (Horowitz 1996), in Scandinavia and in several other countries these have been discontinued based on the above-noted caries decline and the widespread use of fluoride toothpastes (Seppa 1989). Mouthrinses containing 230 ppm F are available commercially for daily home use in some countries. Rinses containing 100 ppm F are also available for over the counter (OTC) sales and recommended for twice daily use. Fluoride mouthrinses have thus moved from being a tool mainly advocated in the public health setting and, through the force of commercial marketing, have gained greater prominence in the personal dental products market. By virtue of the widespread use of other oral mouthrinse products, from simple breath fresheners to products formulated to counter inflammatory periodontal (gum) diseases, it has been argued that the procedure could in fact be cost effective if those already using non-fluoride mouthrinses convert to the use of fluoride rinses (Stamm 1993).

Although the procedure is not recommended for children under 6 years of age, due to the risk of acute and chronic fluoride ingestion, there are data implicating fluoride mouthrinse use by pre-school children as a risk factor for dental fluorosis (enamel defects caused by young children chronically ingesting excessive amounts of fluoride during the period of tooth formation) because some young children might swallow substantial amounts (Ripa 1991; Stookey 1994). Accidental swallowing of the usual 10 ml rinse volume of a 0.05% (230 ppm F) NaF solution for daily use by a 5 to 6 year-old child will result in ingestion of 2.3 mg of fluoride (the average dosage ingested would be twice the optimum level in a fluoridated area). Although this dose is far below the probable toxic dose (PTD) of fluoride, estimated to be 5 mg/kg body weight (Whitford 1992), or approximately 100 mg of fluoride for a 5 to 6 year-old child (20 kg), this amount would be available in just 434 ml of the standard daily rinsing solution.

The effect of fluoride mouthrinses on the incidence of caries in children has been extensively investigated during the past four decades in a large number of clinical trials. Besides sodium fluoride solutions, mouthrinses containing other fluoride compounds in several concentrations and rinsing frequencies have been tested. The evidence from primary studies on the effectiveness of fluoride mouthrinses has been reviewed in numerous review articles and textbook chapters (Torell 1974; Birkeland 1978; Bohannon 1985; Leverett 1989; Ripa 1991; Ripa 1992; Petersson 1993). In one review article a meta-analytical approach has been used to synthesise the results of US studies carried out in fluoride deficient communities (Stamm 1984). To date, no systematic reviews of the available evidence from clinical trials on the effectiveness and safety of fluoride mouthrinses have been reported.

**Objectives**

(1) To determine the effectiveness and safety of fluoride rinses in preventing dental caries in the child/adolescent population.
(2) To examine whether the effect of fluoride rinses is influenced by the level of caries severity.
(3) To examine whether the effect of fluoride rinses is influenced by the background exposure to
fluoride in water (or salt), toothpastes or reported fluoride sources other than the study option(s).

(4) To examine whether the effect of fluoride rinses is influenced by fluoride concentration or application features, such as frequency of use.

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials (RCTs) using or indicating blind outcome assessment, in which fluoride mouthrinse is compared concurrently to a placebo or no treatment group during at least 1 year/school year.

RCTs with open outcome assessment or no indication of blind assessment, or lasting less than 1 year/school year, or controlled trials where random or quasi-random allocation is not used or indicated were excluded.

Types of participants

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

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

Types of interventions

Topical fluoride in the form of mouthrinses only, using any fluoride agent, at any concentration (ppm F), amount, frequency of use, duration of application, and with any technique of application, prior- or post-application (in which the rinse is swished and expectorated, not swallowed). The control group is placebo or no treatment resulting in the following comparison: fluoride rinse compared with a placebo or no treatment.

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

Types of outcome measures

The primary outcome measure in this review is caries increment, as measured by change from baseline in the decayed, missing and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. Dental caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis. (See 'Methods of the review' for the different ways of reporting the decayed, missing and filled teeth or surfaces (D(M)FT/S) scores in clinical trials of caries preventives).

The following outcomes were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions; tooth loss; dental pain/discomfort; specific side effects (fluorosis, tooth staining/discoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting); unacceptability of preventive treatment as measured by drop outs during the trial (in non-placebo controlled studies); use of health service resources (such as visits to dental care units, length of dental treatment time).

Studies reporting only on plaque/gingivitis, calculus, dentin hypersensitivity or fluoride
physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc.) were excluded.

Search strategy for identification of studies

With a comprehensive search, we attempted to identify all relevant studies irrespective of language, from 1965 onwards.

ELECTRONIC SEARCHING

Up to 1998
Relevant studies were identified (for the series of topical fluoride reviews) by searching several databases from date of inception: MEDLINE (1966 to 1997), EMBASE (1980 to 1997), SCISEARCH (1981 to 1997), SSCI SEARCH (1981 to 1997), ISTP (1982 to 1997), BIOSIS (1982 to 1997), CINAHL (1982 to 1997), ERIC (1966 to 1996), DISSERTATION ABSTRACTS (1981 to 1997) and LILACS/BBO (1982 to 1997). Two overlapping but complementary subject search phrases (below) with very low specificity (but high sensitivity), using 'free text 'and controlled vocabulary', were formulated within Silverplatter MEDLINE around two main concepts, fluoride and caries, and combined with all three levels of the Cochrane Optimal Search Strategy for Randomised Controlled Trials (RCTs). These subject search phrases were customised for searching EMBASE and the other databases:

(a) \[("DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS" all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or DMF*) and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR SMFP OR MFP OR MONOFLUOR*) or ("CARIOSTATIC-AGENTS" explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or 'DENTIFRICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or CARIOSTA* or PROPHYLA* or ANTICARI* or ANTI CARI* or VARNISH* or LACQUER* or DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRICE* or MOUTHRINS* or MOUTH RINS* or RINS* or MOUTH WASH* or MOUTHWASH*)].

(b) \[("FLUORIDES/all subheadings") or ("FLUORIDES-TOPICAL/ ALL SUBHEADINGS") or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLOUOR* OR DURAPHAT) and (CARI*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT* in TI, in AB, in MESH)) or ("CARIOSTATIC-AGENTS/all subheadings") or ("DENTIFRICES") or ("MOUTHWASHES/all subheadings") or ("MOUTHWASH* or MOUTH WASH*) or (MOUTHWASH* or MOUTH WASH*)].

RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISSERTATION ABSTRACTS, and LILACS/BBO. All the strategies (subject search and methodological filters) developed to search each database are fully described in a report produced for the Systematic Reviews Training Unit (Marinho 1997), and are available on request. These were used for the development of a register of topical fluoride clinical trials for the systematic reviews, as the Cochrane Oral Health Group's Trials Register was not yet developed in 1997/98.

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 1997), the Community of Science database (1998), which included ongoing trials funded by the National Institute of Dental Research (NIDR), the System for Information on Grey Literature in Europe (SIGLE) database (1980-1997), and OLD MEDLINE (1963-1965) were searched using...
From 1999 to 2001
The following strategy was used to search LILACS/BBO in 1999 (1982-98), where free text subject search terms were combined with a methodological filter for RCTs:

[(fluor$ or ppmf or ppm f or amf or snf or naf or apf or mfp or smfp or monofluor$ or duraphat$) and (carie$ or dfm$ or cpo$ or tooth$ or teeth$ or dent$ or dient$ or anticarie$ or cario$ or mouthrin$s or rinse$ or bochech$ or enjuag$ or verniz$ or varnish$ or barniz$ or laca$ or gel or gels) and [random$ or aleatori$ or acaso$ or azar$ or blind$ or mask$ or cego$ or cega$ or ciego$ or ciega$ or placebo$ or(clinic$ and (trial$ or ensaio$ or estud$)) or (control$ and (trial$ or ensaio$ or estud$))].

A supplementary and more specific subject search phrase (including 'free text' and 'controlled vocabulary' terms), refined exclusively for this review, formulated around three concepts: mouthrinse, fluoride and caries, was used to search Silverplatter MEDLINE (up to January 2000) without methodological filters:

[(CARTE* or (DENT* near CAVIT*) or TOOTH* DECAY* or DMF* or (explode "DENTAL-CARIES"/ALL SUBHEADINGS))
and (FLUOR* or APF* or NAF* or AMINE F OR SNF* or ACIDULATED* PHOSPHATE* FLUORID* or ACIDULATED* FLUORID* or PHOSPHATE* FLUORID* or SODIUM* FLUORID* or AMINE* FLUORID* or STANNOUS* FLUORID* or (explode "FLUORIDES"/ALL SUBHEADINGS))
and (RINS* or MOUTH* RINS* or WASH* or MOUTH* WASH*) or (MOUTH RINS* or MOUTHWASH*)) or (explode "MOUTHWASHES"/all subheadings)].

This strategy was adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and has also been run on CENTRAL (The Cochrane Library Issue 2, 2000) to double-check.

The metaRegister of Controlled Trials was searched in October 2001 for ongoing RCTs using the terms 'fluoride' and 'caries'.

REFERENCE SEARCHING
All eligible trials retrieved from the searches, meta-analyses and review articles were scanned for relevant references. Reviews had been identified mainly by a MEDLINE search strategy specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic, when The Cochrane Library database: Cochrane Database of Systematic Reviews (CDSR), and the CRD databases: Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED), were also searched. Reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions were also consulted.

FULL TEXT SEARCHING
Prospective handsearching of those journals (seven) identified as having the highest yield of eligible RCTs/controlled clinical trials (CCTs) were carried out, from January 1999 until January 2000: British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (from 1990 to December 1999), as this was the journal with the
highest yield of eligible reports.

PERSONAL CONTACT
Searching for unpublished studies (or 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published during the last two decades in order to obtain information on possible unpublished studies eligible for inclusion. All the authors of studies who had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies.

Based on information extracted mainly from included studies, a list of manufacturers of fluoride mouthrinses was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group, in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Six fluoride rinses manufacturers were contacted (October 2000) and information on any unpublished trials requested: Colgate-Palmolive, Gaba AG, Johnson & Johnson, Oral-B, Procter & Gamble, Warner-Lambert.

Methods of the review

IDENTIFICATION OF REPORTS PRODUCED BY THE SEARCHES
Because multiple databases were searched, the downloaded set of records from each database, starting with MEDLINE, was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS, BBO, CENTRAL, SIGLE and NIDR databases were not imported to Reference Manager and were scanned without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filter were imported to Reference Manager for inspection, in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register and the metaRegister of Controlled Trials were also checked outside Reference Manager.

All records electronically identified by the searches were printed off and scanned on the basis of title first, then by abstract (when this was available in English or in languages known by the reviewer) and/or keywords by one reviewer, Valeria Marinho (VM). Obviously irrelevant records were discarded and the full text of all remaining were obtained. Records were considered irrelevant according to study design/duration, participants, or interventions/comparisons (if it could be determined that the article was not a report of a randomised/quasi-randomised controlled trial; or the trial was of less than 6 to 8 months duration; or the trial was exclusively in adults; or the trial did not address a fluoride rinse intervention; or the trial did not compare fluoride mouthrinse to placebo or no treatment).

All potentially relevant reports identified when searching other sources (reference lists of relevant studies, review articles and book chapters, journal handsearch, personal contact) were also obtained. (Reports that might be identified by contacting manufacturers will be obtained to feature in updates of this review).

It was considered essential to identify and check all reports related to the same study; in case of any discrepancy, authors were contacted.
SELECTION OF STUDIES
With the inclusion criteria form previously prepared and pilot tested, one reviewer (VM) assessed all studies for inclusion in the review, and a second reviewer, Julian Higgins (JH), independently duplicated the process for a sample of those (approximately 30%). In addition, any study that could not be classified by the first reviewer was independently assessed by the second. A third reviewer was consulted, Stuart Logan (SL) or Aubrey Sheiham (AS), to resolve any disagreement. It was decided in advance to exclude any trial where agreement could not be reached (but this did not occur). Trial reports thought to be potentially relevant in languages not known by the reviewers were translated and the reviewer (VM) completed the inclusion form with reference to the translator. Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met.

QUALITY ASSESSMENT
The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Collaboration Reviewers' Handbook (Clarke 2000) used in the Cochrane Review Manager software (RevMan). Allocation concealment for each trial was rated as belonging to one of three categories:
(A) Adequately concealed (an adequate method to conceal allocation is described).
(B) Concealment unclear ('random' allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
(C) Inadequately concealed (an inadequate method of allocation concealment is described).
Excluded: random (or quasi-random) allocation clearly not used in the trial, or 'random' allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:
(A) Double-blind (blind outcome assessment and use of placebo described).
(B) Single-blind (blind outcome assessment stated and no placebo used).
(C) Blinding indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment, e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind outcome assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).
Excluded: clearly open outcome assessment used or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, of x-rays registered independently of clinical examination, of use of a placebo, and of examiners clearly not involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated the process for a random sample of approximately one third of those. Any disagreement was discussed and where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not be resolved an effort was made to contact authors directly to clarify the method used to conceal allocation or whether assessment of the main outcome had been carried out blind.

Checking of interobserver reliability was limited to these validity assessments.
Other methodological characteristics of the trials such as completeness of follow up (proportion excluded) and handling of exclusions (extent to which reasons for attrition are explicitly reported, or losses are independent of treatment allocated) were not used as thresholds for inclusion. However, all assessments of study quality are described in the table of included studies, and were coded for possible use in metaregression/sensitivity analyses.

DATA EXTRACTION
Data from all included studies were extracted by one reviewer (VM) using a pilot tested data extraction form. A second reviewer (JH) extracted data from a random sample of approximately one third of included studies. Again, data that could not be coded by the first reviewer were independently coded by the second, any disagreement was discussed and a third reviewer consulted to achieve consensus where necessary. (In future updates all reports will be data extracted and quality assessed in duplicate.) Data presented only in graphs and figures were extracted whenever possible, but were included only if two reviewers independently had the same result. Attempts were made to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary.

Additional information related to study methodology or quality that was extracted included: study duration (years of follow up); comparability of baseline characteristics: methods used pre-randomisation in sizing/balancing (stratification based on relevant variables) or used post-randomisation in analysing/adjusting for possible differences in prognostic factors between groups; objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors); any cointervention and/or contamination. Information on sponsoring institutions and manufacturers involved was also recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries severity at start (average DMFS, DFS, or other measure), background exposure to other fluoride sources (in water, topical applications, etc.), year study began, location where study was conducted (country), setting where participants were recruited, and dental treatment level (F/DMF).

Characteristics of the intervention that were extracted included: mode of application (how the intervention was delivered), methods (technique/device) of application, prior- and post-application, fluoride active agents and concentrations used, frequency and duration of application, and amount applied.

Different ways of assessing/reporting caries increment in the trials (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units of measurement (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (permanent/deciduous teeth/surfaces, first molar teeth, approximal surfaces, etc.), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiographic), and approaches adopted to account or not for reversals in caries increment (in a net or observed/crude caries increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow ups).

As we were aware that caries increment could be reported differently in different trials we developed a set of a priori rules to choose the primary outcome data for analysis from each study: data on permanent teeth would be chosen over data on deciduous teeth; data on surface level would be chosen over data on tooth level; DFS data would be chosen over DMFS data, and this
Fluoride mouthrinses for preventing dental caries in children and adolescents (T)

would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted' only, and this over data for 'erupting' only; data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological' only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated lesions; net caries increment data would be chosen over crude (observed) increment data; and follow up nearest to 3 years (often the one at the end of the treatment period) would be chosen over all other lengths of follow up, unless otherwise stated. When no specification was provided with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices described above were assumed.

The 'Table of included studies' provides a description of all the main outcome data reported from each study with the primary measure chosen featuring at the top. Where assessments of caries increments were made during a post-intervention follow-up period, the length of time over which outcomes were measured after the intervention ended was noted. All other relevant outcomes assessed/reported in the trials are also listed in this table.

ANALYSES

Handling of missing main outcome data
It was decided that missing standard deviations for caries increments that were not revealed by contacting the original researchers would be inputed through linear regression of log standard deviations on log mean caries increments. This is a suitable approach for caries prevention studies since, as caries increments follow an approximate Poisson distribution, they are closely related (similar) to their standard deviations (van Rijkom 1998).

Handling of results of studies (main outcome) with more than one treatment arm
In the studies with more than one relevant intervention group and a common control group, such as those comparing different active fluoride agents or concentrations of fluoride ions to a placebo/no treatment group, raw results (the numbers, mean caries increments and standard deviations) from all relevant experimental groups were combined in order to obtain a measure of treatment effect. This enables the inclusion of all relevant data in the primary meta-analysis, although may slightly compromise the secondary investigations of dose response.

Choice of measure of effect and meta-analyses of main outcome
The chosen measure of treatment effect was the prevented fraction (PF), that is (mean increment in the controls minus mean increment in the treated group) divided by mean increment in the controls. For an outcome such as caries increment (where discrete counts are considered to approximate to a continuous scale and are treated as continuous data) this measure was considered more appropriate than the mean difference or standardised mean difference, since it allows combination of different ways of measuring caries increment and a meaningful investigation of heterogeneity between trials. It is also simple to interpret. The meta-analyses were conducted as inverse variance weighted averages. Variances were estimated using the formula presented in Dubey 1965 which was more suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable. Random effects meta-analyses were performed throughout.

With the use of prevented fraction, it was not possible to perform the main outcome analyses in RevMan/MetaView (when the review was first published). However, the raw results of the studies (mean/SD/n) were entered in RevMan and mean differences were presented without meta-analyses. Where meta-analyses using standardised mean differences yielded materially similar results to those
using prevented fractions, we have also presented these within MetaView. Deciduous and permanent teeth are analysed separately throughout.

For illustrative purposes the results were also presented as the number of children needed to treat (NNT) to prevent one carious teeth/surface. These were calculated by combining the overall prevented fraction with an estimate of the caries increment in the control groups of the individual studies.

Assessment of heterogeneity and investigation of reasons for heterogeneity

Heterogeneity was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95% confidence intervals and by formal tests of homogeneity undertaken prior to each meta-analysis (Thompson 1999).

In addition to aspects of study quality, three potential sources of heterogeneity were specified a priori as investigations of these formed part of the primary objectives of the review. We hypothesised that: (1) the effect of fluoride mouthrinses differs according to the baseline levels of caries severity; (2) the effect of fluoride mouthrinses differs according to exposure to other fluoride sources (in water, in toothpastes, etc.); and (3) the effect of fluoride mouthrinses differs according to concentration of fluoride and frequency of application. The association of these factors with estimated effects (D(M)FS PFs) were examined by performing random effects metaregression analyses in Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998).

To allow such investigation, relevant data were dealt with as follows: data on 'baseline levels of caries' were calculated from the study sample analysed (final sample) and in connection with the caries increment index chosen, unless otherwise stated, and were averaged among all relevant study groups. Data on 'background exposure to other fluoride sources' combined data on the use of fluoride toothpaste and the consumption of fluoridated water (or salt) and were grouped into two categories: one for studies which were based on samples provided with non-fluoride toothpaste and which were from non-fluoridated areas (non-exposed), and another for studies based on samples using fluoride toothpaste or studies in fluoridated communities or both. When use or non-use of fluoride toothpaste was not clearly indicated in studies carried out in developed countries, it was assumed that fluoride toothpaste was widely used from the middle of the 1970s (Ripa 1989); this information was sought from authors (or obtained from other sources) when missing from studies carried out in other locations. When data on the year a study had begun was not provided this was calculated as a 'probable date' by subtracting the duration of the study (in years) plus one extra year, from the publication date of the study. Data on 'concentration applied' and 'frequency of rinsing' have not been categorised, but a 'total intensity of application per year' covariate was produced by multiplying frequency of application (per year) by fluoride concentration of mouthrinse applied (in ppm F). In multiple arm studies we averaged this intensity score over fluoride treatment groups. Incomplete data for frequency of mouthrinsing was dealt with as follows: in studies of supervised daily rinse at school where participants were provided with mouthrinse for home use, rinsing frequency of 365 times a year was to be assumed if not precisely reported. Rinsing frequency of 320 times a year was assumed in studies of 'unsupervised' daily rinse at home (even if instructions to rinse more than once a day were given); frequency of 160 times (days) a year was assumed when it was not precisely reported in studies of supervised daily rinse at school where children were not provided with any rinse for home use; frequency of 30 times a year was assumed for weekly rinse at school, and of 17 times a year for fortnightly rinse at school.

Further potential sources of heterogeneity were investigated by metaregression. These 'post hoc' analyses are clearly identified and the results should be treated with caution. Sensitivity analyses
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were performed where appropriate.

Investigation of publication and other biases
A funnel plot (plots of effect estimates versus the inverse of their standard errors) was drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, though may also represent a true relationship between trial size and effect size. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger et al (Egger 1997).

Measures of effect and meta-analysis of other outcomes
For outcomes other than caries increment, continuous data were to be analysed according to differences in mean treatment effects and their standard deviations. Dichotomous outcome data were analysed by calculating relative risks (RR) or, for adverse effects of fluoride treatment, risk differences (RD). RevMan 4.1 was used for estimation of overall treatment effects. Again, a random effects model was used to calculate a pooled estimate of effect. As a general rule only (relevant) outcomes with useable data are shown in the analyses tables.

Description of studies

SEARCH RESULTS
Searching the core database in Reference Manager (using 'mouthwash*' or 'rins*' or 'sodium fluoride*' or 'amine fluoride*' or 'amine fluoride solution' or 'acidulated fluorophosphate*' or 'acidulated phosphate fluoride*' or 'fluorophosphate*' or 'stannous fluoride*' as keywords combined with 'rins' or 'wash' or 'fluoride solution' in titles and notes) retrieved 2263 records from MEDLINE, EMBASE, BIOSIS, SCISEARCH, SSCISEARCH, CINAHL, ERIC, ISTP and DISSERTATION ABSTRACTS. There were 211 records scanned outside Reference Manager produced by searching LILACS (48 records), BBO (47 records), CENTRAL (86 records), SIGLE (6 records), and NIDR/Community of Science Database (24 records). When LILACS and BBO were searched for the second time with a modified search strategy the yield was 210 records (142 and 68 records respectively) also scanned outside Reference Manager. Searching OLD MEDLINE produced 545 records. Thus, 3229 records yielded by the original electronic searches for topical fluoride trials were scanned, but many of these were duplicates not merged in the core database. The specific MEDLINE search for fluoride mouthrinse trials performed without a randomised controlled trial (RCT) filter produced 763 records, and the search performed in the Cochrane Oral Health Group's Trials Register produced 139 records. The search for ongoing studies in the metaRegister of Controlled Trials produced five records.

Searching other non-electronic sources (reference lists of potentially relevant reports, review articles or book chapters, journals, and contacting authors) produced 112 additional records for inspection. One of the six manufacturers of fluoride mouthrinses contacted, GABA, provided a list of 409 records from a search performed in GALIDENT (Database of GABA Library in Dentistry) using the keyword 'amine fluoride'. However, search results from these and, if provided, from other manufacturers will be taken into account in updates of this review.

From the search results above a total of 282 records were considered potentially eligible, and sought for further assessment.

STUDY SELECTION RESULTS
Two hundred and eighty-two reports were sought for detailed assessment for inclusion, of which

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nine full text reports could not be obtained (most of these were incomplete references to non-
English reports). One hundred and forty-four reports were considered immediately irrelevant for
this review, either due to the types of study design described (historical controls or other non-
experimental designs) or as a result of the types of intervention compared with, or used in addition
to fluoride mouthrinse (including head-to-head studies without a placebo or no treatment group).
Ninety-two studies (129 reports) are considered/cited in this review. These comprise 60 reports
relating to 36 included studies, 55 reports relating to 43 excluded studies, and 14 reports relating
to 13 studies waiting assessment, either because they require translation (seven reports in Swedish
of seven studies, two reports in Russian of one study, and one report/study each in Danish,
Hungarian, Japanese, and Thai), or because additional information could not be obtained yet for
one study in abstract form (Kawall 1981). There were no reports of ongoing studies.

Listed either under excluded or included studies are 27 non-English reports (21 studies). Two of
these studies (two non-English reports) were excluded either on the basis of the English abstract
alone or due to the availability of a full text English report of the same study, and one report/study
was included based on an English publication related to the same study. There remained 24 non-
English reports that have been fully assessed (18 studies): 11 in Portuguese (by the contact
reviewer), five in Spanish (by the contact reviewer), three in German (by a German translator, with
the reviewer), three in Russian (by a Russian translator, with the reviewer), two in Japanese (by a
Japanese translator, with the reviewer).

EXCLUDED STUDIES
See 'Characteristics of excluded studies' for the description of reasons for rejecting each study.

The 43 studies in this section were excluded for a variety of reasons. Seven studies were clearly not
randomised/quasi-randomised. Five studies used open outcome assessment. One study randomised
two clusters, each to one of the two study arms. Five studies did not mention or indicate
random/quasi-random allocation nor blind outcome assessment, two studies did not mention
random/quasi-random allocation and did not mention or indicate blind outcome assessment, and
two other studies did not mention random/quasi-random allocation nor blind outcome assessment.
Two studies did not mention random or quasi-random allocation (but used/indicated blind outcome
assessment); the attempt to contact the author(s) of these studies was unsuccessful and they were
excluded. In one study, the length of follow up was 6 months and relevant outcomes were not
reported.

Sixteen studies had other active agents or other interventions in addition to fluoride mouthrinse:
eight of these did not state or indicate blind outcome assessment and/or random or quasi-random
allocation; two others had only one cluster for each study arm, another was not randomised/quasi-
randomised and the length of follow up for the main outcome assessment was less than 1
year/school year; and another had an 'inappropriate placebo' (not an inactive treatment). In two
studies, the fluoride solution was swallowed after rinsing.

INCLUDED STUDIES
See 'Characteristics of included studies' table for details of each study.

There are 36 trials included. The study conducted by Horowitz 1971 has been treated as two
independent trials, since the results for the two age groups in the study have been reported
separately as distinct studies. There were also completely distinct studies published as such
concomitantly by the same author: Koch 1967a and Koch 1967b. All 60 reports were published
between 1965 and 1998. The 36 trials were conducted between 1962 and 1994: 10 in the 1960s,
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19 in the 1970s, six in the 1980s, and one in the 1990s. Thirteen trials were conducted in USA, four in UK, five in Sweden, two in Denmark, two in Canada, two in New Zealand, three in Brazil, and one in each of the following countries: Finland, The Netherlands, South Africa, Chile and Puerto Rico. Fifteen studies had more than one publication, one of these had seven published reports. Nine studies acknowledged assistance (product provision, etc.) and/or financial support from fluoride mouthrinse manufacturers. Of a total of 18 studies whose authors were sent request letters for unpublished information, replies related to 11 studies were obtained.

Design and methods
Fifteen studies had more than one fluoride mouthrinse treatment group compared to a control (multitreatment studies); among these one trial had two treatment groups and two placebo control groups. Six trials used a factorial design to investigate the effects of multiple topical fluoride interventions. With regard to type of control group used, four trials used a no treatment control group, and the remaining 32 used a placebo control group. The study duration (indicated by the total length of follow up as well as the treatment duration) ranged from 2 to 3 years among included trials; only three lasted less than 2 years (1.6 years). Studies were large with only three trials allocating less than 100 children to relevant groups. The total number of children participating in the trials (given by the sample analysed at the end of the trial periods) was 15,171 and ranged from 95 in the smallest trial to 1238 in the largest trial (on average, 421 participants per trial). All participants were recruited from school settings.

Participants
All included trials reported that the participants were aged 14 or less at the start, with similar numbers from both sexes (where these data were reported). The ages of the children at the start of the trials ranged from 5 to 14 years (where these data were reported); at least 18 trials included children who were 12, at least five trials included 5/6 year-olds. Caries prevalence at baseline, reported in all but two of the studies, ranged from 0.94 to 14.7 D(M)FS. With regard to 'background exposure to other fluoride sources', all but two studies reported exposure or not to water fluoridation: four studies were conducted in fluoridated communities and 30 studies were not. Among the studies conducted in non-fluoridated areas, no (or very low) exposure to fluoride toothpaste or to other fluoride sources was clearly reported in eight studies, and substantial exposure to fluoride toothpaste (over 95%) was reported in six studies; exposure or not to fluoride toothpaste had to be assumed in 16 studies based on study location and year started, as described above. Information on dental treatment level was reported in the study conducted in Denmark, in one of the two studies conducted in Canada, and in one study from USA.

Interventions
All 36 included trials reported supervised use of mouthrinse in school programmes (two of which also tested their use at home). Rinsing with Sodium Fluoride (NaF) was tested in 32 trials, Acidulated Phosphate Fluoride (APF) in four trials, Stannous Fluoride (SnF2) in two, and Sodium Monofluorophosphate (SMFP), Amine Fluoride (AmF) and Amonium Fluoride (NH4F) were each tested in a different study. The fluoride concentration used in the mouthrinses ranged from 100 ppm F (0.02% NaF) to 3000 ppm F (0.66% NaF), and the frequency of application ranged from 3 to 330 times a year, but these were unusually low and high concentrations and frequencies. The concentration of 230 ppm F (180 and 250 ppm F in a few studies) was used in 18 studies, and the concentration of 900 ppm F (1000 ppm F in a few studies) was used in 19 studies. It can be seen that when rinsing was performed once a week or once every 2 weeks, a rinse usually employing 900 ppm F was used (16 trials). Conversely, when rinsing was performed once (or twice) a day, the fluoride concentration used was 230 ppm F, or around this concentration (13 trials). The only study (Duany 1981) where information on rinsing frequency was not available is likely to have used...
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daily rinses for all three low concentrations of fluoride tested (this was one of the four studies testing the 100 ppm F rinsing solutions). The usual amounts of mouthrinse used per application was 5 or 10 ml, and usual rinsing time was 1 or 2 minutes (reported in 21 studies). The performance of some form of prior tooth prophylaxis (brushing without paste or with a non-fluoride paste before rinsing) was reported in four studies (not considered a separate intervention on its own).

Outcome measures

Caries increment: All but two of the 36 trials reported caries increment data (or data from which these could be derived) at the tooth surface level (D(M)FS), and 13 trials reported caries increment at the tooth level (D(M)FT); d(e/m)fs/d data were not reported in any trial. With regard to the components of the DMFS index used (and types of teeth/surfaces assessed), 20 trials reported DMFS data (one trial for premolars and molars only and 19 trials for all tooth surface types), and 16 trials reported DFS data (one trial for approximal surfaces of premolars and molars only and 15 trials for all tooth surface types). No choice had to be made between DMFS or DFS data in any one trial. Sixteen trials presented D(M)FS data at more than one follow-up time (which ranged from 1.6 to 3 years); follow up of either 2 or 3 years was reported in 26 trials. In three trials, assessments of D(M)FS increments were also made during a post-intervention follow-up period.

Clinical (35 trials) and radiographic (20 trials) 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: NCA = non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor/walls) or showing frank cavitation; ER = any radiolucency in enamel/enamel-dentin junction; DR = radiolucency into dentin. Many trials presented results using one caries grade only (usually CA/ER or CA/DR), others did not report the grade, or reported caries increment data at both levels of diagnosis, in which case CA was chosen. Data on the state of tooth eruption considered were not clearly specified in many trials.

Other dental caries data reported: caries incidence/attack rate (five trials), proportion of children developing new caries (three trials).

Data on adverse effects: stain score (one trial), proportion of children with tooth staining (two trials, incomplete data), signs of sensitivity in oral soft tissue (two trials, with the following statement in one: "no cases of mucosal hypersensitivity after periodical examinations of every subject"; no baseline data given in the other), any side effects (three trials, none of which with complete or useable data, and with the following statement in all three: "no adverse side effects observed"). Fluorosis data have not been reported in any of the trials.

Data for unacceptability of treatment (as measured by drop outs/exclusions) were reported in two of the non-placebo controlled trials. Actual unacceptability to the taste was reported in one trial, with the following statement: "only an insignificant number withdrew because of unacceptance to the taste".

Methodological quality of included studies

Based on 28 studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, interrater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa =

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0.61) and very good for blinding (kappa = 0.73).

There were clear differences in the quality of the studies in this review (using the reported information and additional information obtained from investigators).

**ALLOCATION CONCEALMENT**

Three of the trials which described the randomisation process could be coded A (e.g. adequate concealment of allocation). Twenty-nine included trials were described as randomised but provided no description of the allocation process and were coded B. Four trials were quasi-randomised and coded C.

**BLINDING**

Twenty-nine trials were classified as double-blind (score A). Single-blinding (blind dental caries assessment but no placebo used) was described in three trials (score B). Blind outcome assessment was unclear/indicated in four trials (score C), one of which was a non-placebo controlled trial.

**FOLLOW UP AND WITHDRAWALS**

All the participants considered at the end of each study as a proportion of all the participants present at start in all studies was 65% (12,980 analysed out of 20,066 randomised); this excludes six studies with no data by group on participants randomised. Drop out rates could not be obtained for four of the 36 included studies. There was considerable variation in drop out rates ranging from 10% at 3 years to 62% at 2.5 years.

Reasons for exclusions (when given) included moving away, absent for follow-up examinations, and refusal to participate or poor compliance. A few trials reported the numbers excluded according to reason for attrition.

**OTHER METHODOLOGICAL FEATURES**

Type of randomisation: stratified random allocation was used in at least 22 trials.

Units of randomisation: cluster randomisation was used in one trial (Ruiken 1987) where schools were used as units of randomisation and children used as units of analysis. Individuals were allocated to study arms in all other trials, and each participant's caries incidence, over a period of time was used as the unit of analysis.

Baseline comparisons and handling of any differences: one trial did not report any baseline data, another described as 'balanced' (for which randomisation may have succeeded to produce nearly exact balance) did not report any of the actual values for the baseline characteristics (such as initial caries levels). Some degree of imbalance was reported in a few trials (for characteristics considered most influential, usually initial caries levels) and generally either described as not significant or that adjustment had resulted in trivial differences in effect estimates.

Objectivity/reliability of primary outcome measurement: diagnostic methods used (clinical or radiographic) were described in all studies, but thresholds/definitions used for caries and monitoring of diagnostic errors were not always reported (see 'Notes' in the 'Characteristics of included studies' table for methodological features assessed).

**Results**
EFFECT OF FLUORIDE MOUTHRINSE ON DENTAL CARIES INCREMENT

The effects of fluoride mouthrinses on dental caries increment (as measured by the DMF index) were reported in a variety of ways in the included studies. Where appropriate and possible these have been combined to produce pooled estimates as described in the Methods section. The results are reported separately here for:

1. decayed, (missing) and filled surface prevented fraction (D(M)FS PF);
2. decayed, (missing) and filled teeth prevented fraction (D(M)FT PF);
3. D(M)FS and D(M)FT pooled using a standardised mean difference (SMD).

Estimates of the effects of fluoride mouthrinse on caries increment in deciduous teeth/surfaces (as measured by the dmf index) could not be produced for this review, as there was no study contributing data.

Two included studies (Brandt 1972; de Liefde 1989) did not contribute data suitable for meta-analysis, although they are retained in the review. Standard deviations (SD) of mean caries increment data (new D(M)FS) were (partly) missing in 12 of the 34 studies which contributed data (Bastos 1989; DePaola 1977; Driscoll 1982; Finn 1975; Gallagher 1974; Heidmann 1992; Laswell 1975; McConchie 1977; Moreira 1972; Poulsen 1984; Ruiken 1987; van Wyk 1986). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries increment), (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses. Similarly, this same regression equation was used to estimate missing standard deviation data for three of the 13 trials reporting D(M)FT data (Bastos 1989; Finn 1975; McConchie 1977).

(1) Effect on tooth surfaces: D(M)FS PF

For all 34 trials combined, the D(M)FS PF pooled estimate was 0.26 (95% confidence interval (CI), 0.23 to 0.30; p < 0.0001), suggesting a substantial benefit from the use of fluoride mouthrinse. The CIs are relatively narrow, and although not substantial, heterogeneity in results could be observed statistically (Q = 55.62 on 33 degrees of freedom, p = 0.008).

For each study, the D(M)FS PF and 95% CIs can be viewed in the 'Other data' tables; the results of the random effects meta-analysis of D(M)FS PFs (performed in Stata) are presented in 'Additional Table 01: Meta-analyses of prevented fractions'. Meta-analysis results are not presented stratified by type of control group (placebo/no treatment) in this review, because only four non-placebo controlled trials are included, but this factor might represent a strong indicator of study quality and source of heterogeneity in the topical fluoride reviews, as suggested in the first review in this series (Marinho 2002). Nevertheless, forest plots showing the effects of fluoride mouthrinses (PFs and 95% CIs) on D(M)FS increments resulting from a meta-analysis stratified by type of control group are available in the 5th review in this series (whose results invigorate the discussion of the influence of this factor on effect estimates): Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents (Comparison 01, Sub-categories 04 for placebo-controlled mouthrinse trials, and 07 for rinse trials using no treatment controls).

Metaregression and sensitivity analyses: D(M)FS PF

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

Further univariate metaregression analyses showed no significant association between estimates of D(M)FS prevented fractions and allocation concealment (random/quasi-random), blinding of outcome assessment (blind/blind likely or unclear), type of control group (placebo/no treatment), drop out rate, or length of follow up (duration of study).

Other potential effect modifiers have not been investigated (e.g. mode of mouthrinse use, since virtually all trials were conducted in school settings under supervision).

Metaregression results for potential effect modifiers, are given in 'Additional Table 02: Random effects metaregression analyses of prevented fractions: D(M)FS'. It should be noted that the influential study by DePaola 1977 is omitted from the analysis intensity of application with prevented fraction.

We performed a sensitivity analysis for the main meta-analysis of D(M)FS prevented fraction, to take account of the additional uncertainty related to the cluster randomised trial by Ruiken 1987. We inflated the variance of the prevented fraction estimate by an amount equal to \(1 + (m-1) \times ICC\), where \(m\) is the average cluster size and ICC the intraclass correlation coefficient. A conservative value of 0.1 for the ICC was used since we could not find an ICC from this or any similar trial. The D(M)FS PF pooled estimate was 0.26 (95% CI, 0.23 to 0.30; \(p < 0.0001\)). These results are identical to the analysis ignoring the cluster randomised design, since the estimate for this trial is similar to the meta-analysis result and altering its weight has minimal effect.

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

In order to illustrate the magnitude of the effect, numbers of children needed to treat (NNT) to prevent one D(M)FS were calculated based on the pooled D(M)FS PF and on the caries increments in the control groups of the trials that contributed data to the meta-analysis. The overall caries-inhibiting effect (%PF) derived from the pooled results of the 34 trials was 26% (95% CI, 23% to 30%); the caries increments ranged from 0.25 to 7.02 D(M)FS per year. In populations with a caries increment of 0.25 D(M)FS per year (at the lowest end of the results seen in the included studies), this implies an absolute caries reduction of 0.065 D(M)FS per year, equivalent to an NNT of 16 (95% CI, 14 to 18): i.e. 16 children need to rinse with a fluoride mouthrinse (rather than a non-fluoride mouthrinse) to avoid one D(M)FS. In populations with a caries increment of 2.14 D(M)FS per year (at the mid range of the results seen in the included studies), this implies an absolute caries reduction of 0.56 D(M)FS per year, equivalent to an NNT of 1.8 (95% CI, 1.6 to 2): i.e. two children need to rinse with a fluoride mouthrinse to avoid one D(M)FS.

Funnel plot and test for funnel plot asymmetry: D(M)FS PF
A funnel plot of the 34 trials reporting D(M)FS PFs does not look asymmetrical, and the weighted regression test for asymmetry (Egger 1997) was not statistically significant (asymmetry intercept (95% CI) = -0.84 (-2.02 to 0.35) (\(p = 0.16\)). There is, therefore, no evidence of bias.

The funnel plot of the 34 trials comparing fluoride mouthrinse with placebo/no treatment is available in 'Additional Figure 01', where D(M)FS standardized mean differences are plotted against...
standard errors (see 'Alternative treatment effect measure' below).

(2) Effect on whole teeth: D(M)FT PF
Thirteen trials reported data which allowed the calculation of the D(M)FT PF. All 13 are also included in the analysis of D(M)FS PF. The results of this analysis are very similar to those reported above.

The pooled estimate of D(M)FT PF was 0.24 (95% CI, 0.18 to 0.30; p < 0.0001), suggesting, again, a substantial benefit of fluoride mouthrinse, within relatively narrow CIs. Heterogeneity between trials (Q = 26.04 on 12 degrees of freedom, p = 0.01) was not substantial, although statistically significant.

For each study, the D(M)FT PF and 95% CI can be viewed in the 'Other data' tables. The results of the random effects meta-analysis of D(M)FT PFs performed in Stata are also presented in 'Additional Table 01: Meta-analyses of prevented fractions'.

(3) Alternative treatment effect measure: Standardised mean difference (SMD)
Due to the character of D(M)FS data, mean caries increments are closely related to their SDs (they are about the same). Thus, meta-analyses using SMDs (the difference between two means divided by an estimate of the within group standard deviation) yielded materially similar results to those using PFs (the difference in mean caries increments between the treatment and control groups divided by the mean increment in the control group). We therefore decided to present D(M)FS and D(M)FT SMDs in RevMan, since it was not possible to present the main outcome analyses with PFs in MetaView/RevMan.

For the 34 trials, the pooled D(M)FS SMD estimate was 0.30 (95% CI, 0.24 to 0.36; p < 0.0001). There was heterogeneity between trials (chi squared = 93.00 on 33 degrees of freedom, p < 0.0001). The results of this analysis are similar to that of the random effects meta-analysis of D(M)FS PF (the slight inconsistency may well be due to differences between caries increment rates and standard deviations in some of the arms of the included studies).

The pooled estimate of D(M)FT SMD based on the 13 trials that contributed data was 0.28 (95% CI, 0.20 to 0.37; p < 0.0001). There was statistically significant heterogeneity (chi squared = 26.13 on 12 degrees of freedom, p = 0.01). These results are also consistent with those found in the random effects meta-analysis of D(M)FT PF.

Effect on deciduous dentition
None of the included trials reported on caries increment in deciduous teeth/surfaces.

EFFECT OF FLUORIDE MOUTHRINSE ON OTHER OUTCOMES
A few trials report data for other relevant outcomes (see 'Outcome measures' under 'Description of studies' section). Some of these are simply other measures/indices for dental caries increment in permanent teeth/surfaces and require no further consideration; three trials report on the proportion of children developing new caries. Meta-analyses results for the proportion of children developing new caries are presented below. The few trials that report on adverse effects give no usable or incomplete data for analysis. Data for unacceptability of treatment (as measured by drop outs) were reported in two of the non-placebo controlled trials. Meta-analyses results for these are also described below.

Proportion of children developing new caries
Three trials reported results on the proportion of children developing one or more new caries (Finn 1975; Heidmann 1992; Torell 1965). The pooled estimate (random effects meta-analysis) of the odds ratio was 0.61, with no heterogeneity in the results (95% CI, 0.41 to 0.90; chi squared for heterogeneity 3.76 on 2 degrees of freedom, p = 0.15). This corresponds to an NNT to prevent one child from developing caries of 9 (95% CI, 6 to 39) in a population with a caries risk the same as that found in the control groups in these trials (nine children using fluoride mouthrinse for 2 to 3 years will prevent new caries development in one child).

Unacceptability of treatment (drop outs/exclusions)
The pooled estimate of the odds ratio of dropping out from the mouthrinse as opposed to the non-treatment arm in the two non-placebo controlled trials that reported drop outs (Craig 1981; Moreira 1981) was 1.26 (95% CI, 0.60 to 2.64). There was no heterogeneity in these results (chi squared = 1.43 on 1 degree of freedom, p < 0.23).

Discussion

The main aim of this review was to estimate the effects on dental caries of using fluoride mouthrinse in children compared to placebo or no treatment. Over 14,600 children were included in the trials comparing a fluoride mouthrinse with a placebo or no treatment. For almost all children the fluoride rinse they received was a Sodium Fluoride (NaF) formulation, provided in supervised school-based mouthrinsing programmes, often either on a daily or weekly/fortnightly basis. Fluoride mouthrinsing at these two rinse frequencies and two main different strengths (230 ppm F/900 ppm F) has proven a versatile method of self applied topical fluoride use, and an effective method when used regularly over time under supervision.

An average caries reduction in terms of decayed, missing and filled tooth surfaces (DMFS) of about 26% can be expected from the use of this method. The meta-analysis of the 34 studies assessing the effect of fluoride mouthrinse on the permanent dentition suggests that this reduction falls within narrow confidence intervals (23 to 30%). This would correspond to a number needed to treat (NNT) of 1.8 to avoid one DMFS per year in a child population with a caries increment of 2.14 DMFS per year (in the middle range of control group rates for included studies), or an NNT of 15.4 for children from a population with a caries increment of 0.25 DMFS per year (at the lowest end of the observed range). This means that two children need to rinse with a fluoride mouthrinse (rather than a non-fluoride mouthrinse) to prevent one decayed, missing or filled tooth surface, in a child population with a high caries increment per year. In populations with caries increment as low as 0.25 DMFS per year, 16 children will need to use a fluoride mouthrinse to avoid one DMFS.

A secondary aim of this review was to examine whether there was any relationship between the caries-preventive effectiveness of fluoride mouthrinse and a number of factors including the initial level of caries severity, background exposure to fluoride, and fluoride concentration and frequency of use. We were unable to detect a clear relationship between any of these factors and the magnitude of the treatment effect in spite of substantial variation between trials in these factors. This result should, however, be interpreted with caution. Even a meta-analysis including 34 trials has limited power to detect such relationships and, like all analyses of observational data, is subject to the problem of potential confounding. For some factors such as 'background exposure to fluoride' there is, in addition, the problem of potential misclassification due to the poor quality of the reported data on exposure to fluoride other than in water. We were forced to make a number of assumptions, for instance classifying 'use of fluoride toothpaste' for 16 of the studies on the basis...
of the year when the study was conducted and its location. We were also forced to treat this as a
dichotomous variable (before/after mid 1970s), although it is likely that use of fluoridated
toothpaste gradually increased during the 1960s, 1970s, and 1980s. Similarly we grouped exposure
to fluoride in toothpaste and fluoride in water into a single dichotomous variable which is likely to
group studies whose participants had quite different levels of baseline exposure. These problems
may bias any estimates of effect towards the null hypothesis. Nevertheless, these results suggest
that fluoride mouthrinse may still be of benefit after the advent of fluoride toothpaste, and in both
fluoridated and non-fluoridated areas.

We did observe a significantly greater treatment effect with increased total intensity (frequency
times concentration) of mouthrinse application. Although plausible, this relationship was however
dependent on the inclusion of one study with particularly powerful effects (DePaola 1977). After
exclusion of this study in a sensitivity analysis no significant association was seen with this factor.
It should be noted that in the majority of studies where mouthrinse was performed once a week (or
once every 2 weeks), a rinse employing higher fluoride concentrations (usually 900 ppm F) was
used (16 trials). Conversely, in most studies where rinsing was performed once (or twice) a day a
lower fluoride concentration (usually 230 ppm F) was used (13 trials). Moreover, in five multiarm
studies investigating both combinations of concentrations-frequencies (and in seven studies testing
the two main fluoride concentrations) we averaged this intensity score over fluoride treatment
groups to combine study results, a decision that may have slightly affected this particular
investigation of heterogeneity (and that of dose-response). Nevertheless, looking specifically at the
effectiveness of the two most commonly used fluoride mouthrinse regimens there might be little to
choose when the weaker (low concentration) is used as a daily rinse and the stronger (high
concentration) as a weekly or fortnightly rinse. This does not necessarily imply that when both
concentrations are used daily, or both are used as weekly/fortnightly rinses, they will have a similar
effect. A weaker solution may well give poorer results when used less frequently. More robust
investigations of these aspects of the intervention require direct, head-to-head comparisons of
different fluoride concentrations, frequencies and intensities, which were not within the scope of
this review.

We made a thorough attempt to investigate sources of heterogeneity in this review, examining
factors related to participants, interventions and study quality. None of the factors investigated was
clearly related to heterogeneity. Even though the type of control group (placebo/no treatment)
might represent a strong indicator of study quality and source of heterogeneity in the topical
fluoride reviews (Marinho 2002), a relationship between type of control group and prevented
fraction was not observed in this review, possibly due to the fact that only four non-placebo
controlled trials were included. Moreover, it should be pointed out that a generally high attrition
rate has been observed across the fluoride rinse trials (mean of 32%). Overall only 65% of all the
participants at start remained at the end of the studies and results are often based on compliant
subjects who actually completed the study. Thus, the issue of longer term compliance should not be
disregarded when administering such procedure.

We performed a sensitivity analysis for the main meta-analysis to take account of the additional
uncertainty we should have about the cluster randomised trial by Ruiken et al (Ruiken 1987). This
showed results (PF) identical to the analysis ignoring the cluster randomised design since the
estimate for this trial is similar to the meta-analysis result and altering its weight has minimal effect.

A degree of funnel plot asymmetry may be suggested by visual inspection, but the Egger test
provided no evidence of a significant relationship between trial size and effect estimate.
We found little information about the effects of fluoride mouthrinses on other outcomes such as the proportion of children developing new caries or on acceptability of fluoride rinsing. We found little useful information about some possible adverse effects of the procedure. This lack of direct evidence from clinical trials on relevant outcomes other than caries increment makes it more difficult for clinicians and policy makers to weigh the benefits of fluoride mouthrinse use in preventing caries against possible shortcomings of the procedure, be it provided in community dental health programmes or in the home environment.
Reviewers' conclusions

Implications for practice

This review suggests that the regular and supervised use of fluoride mouthrinse by children is associated with a clear reduction in caries increment. Compared to control groups, daily and weekly/fortnightly rinse programmes result on average in 26% fewer decayed, missing, or filled permanent tooth surfaces. We found no evidence that this relative effect was dependent on baseline caries level or exposure to other fluoride sources, fluoride concentration and mouthrinsing frequency, although this result should be interpreted with caution. A higher decayed, (missing) and filled surface (D(M)FS) prevented fraction was shown with increased intensity of application (frequency times concentration). This relationship was dependent on the inclusion of one study with particularly powerful effect. Unfortunately the review does not provide useful information on the likelihood of significant side effects with the use of fluoride mouthrinse, and inconclusive information on acceptability.

Implications for research

The quality of the trials included in this review is variable and many reports lacked important methodological details. This is likely in part to be due to the fact that most are relatively old. Many characteristics considered crucial for excluding bias, such as clearly stated randomisation and allocation concealment, have only been more emphasised in later years, after most of the mouthrinse trials were reported. However, given the clarity of the results, further randomised comparisons of fluoride mouthrinse and placebo alone would be hard to justify. Head-to-head comparisons of fluoride rinses and other preventive strategies may provide more useful information. It is important that future trials should include the assessment of other relevant outcomes such as potential side effects and those related to acceptability of treatment. The evaluation of possible differences in effect associated to fluoride rinse application features, such as frequency/concentration of application, should be based on trials that directly address the comparison of such features.
### Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashley 1977</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 12% drop out (after 2 years (study duration = 2 years). Natural losses; any differential group losses not assessable.</td>
<td>488 children analysed at 2 years (available at final examination). Average age at start: 12 years. Surfaces affected at start: 9.1 DFS. Exposure to other fluoride: no. Year study began: 1973. Location: UK.</td>
<td>FR+ptc versus PL+ptc** (NaF group = 100 ppm F). School use/supervised, daily, 20 ml applied for 1 min.</td>
<td>2yNetDFS increment - (E+U)(NCA)cl+(ER)xr. Reported at 2 years follow up. PF-DFS. MD-BL-DFS. MD-DFS. DFS (U).</td>
<td>Participants randomised B (numbers for relevant groups NR). Baseline characteristics (age, DFS, DMFS, DMFT) 'balanced'. 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. Intraexaminer reproducibility checks for incremental caries data (icc for clinical 0.95, for radiographic 0.8); reversal rate between 12% and 7% of observed DFS increment in study groups. ** Prior toothbrushing with non-fluoride toothpaste in both groups.</td>
</tr>
<tr>
<td>Bastos 1989</td>
<td>Stratified quasi-random allocation; double-blind (A); placebo-controlled; 45% drop out after 2.5 years (study duration = 2.5 years). Reasons for high drop out</td>
<td>420 children analysed at 2.5 years (after exclusions, available at final examination). Age range at start: 9-12 years (average = 10).</td>
<td>FR (2 groups)** versus PL (SMFP group = 900 ppm F, NaF group = 900 ppm F). School use/supervised, weekly, 10 ml applied for 1 week.</td>
<td>2.5yDMFS increment - (CA)(E). Reported at 1, 1.5 and 2.5 year follow ups. DMFT (E/U).</td>
<td>Participants randomised (N = C 766). Baseline characteristics (DMFS, DMFT, dental age) 'balanced'. Clinical (VT) caries</td>
</tr>
</tbody>
</table>
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Blinkhorn 1983

Stratified random allocation; double-blind (A); placebo-controlled; 10% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers: 57 left school, 12 withdrawn by parents, 6 absent at final examination; no differential group losses.

374 children analysed at 3 years (available at final examination).

Age range at start: 11-12 years.

Surfaces affected at start: 8.2 DMFS.

Exposure to other fluoride: no.

Year study began: 1972.

Location: UK.

FR+ptc versus PL+ptc** (NaF group = 230 ppm F).

School use/supervised, daily, for half min.

3yNetDFS increment - (E+U)(CA)cl+(DR)xr.

Reported at 3 years follow up.

PF-DFS.

MD-DFS.

MD-BL-DFS.

AntDMFT.

PostMDFT.

DFS (U).

Side effects (incomplete data).

Participants randomised (N = B 414).

Baseline characteristics (DMFS, DMFT, SAR) 'balanced' (DFS baseline data NR).

Clinical (V) caries assessment by 1 examiner, diagnostic threshold = CA.

Radiographic assessment (1 postBW) by 1 examiner; diagnostic threshold = DR.

State of tooth eruption included = E/U.

Intraexaminer reproducibility checks for incremental clinical and radiographic caries data in 10% sample (icc score 0.9).

** Prior toothbrushing with

O-DFS.

BL-DFS.

MD-DFS.

DMFS (U).

AntDMFS.

PostDMFS.

assessment by 2 examiners, diagnostic threshold = CA.

State of tooth eruption included = E/U. Consistency of diagnosis assessed by duplicate examinations annually. Reversals were less than 5% of DMFS increments in all groups and equally common.

** Study group of sodium monofluorophosphate solution containing 4% of ethanol not considered.
**Brandt 1972**

Random allocation; double-blind (A); placebo-controlled; 22% drop out after 2 years (study duration = 2 years). Reasons for attrition described with numbers by group: change of residence (18, 12), absent at final examination (5, 7); plus exclusions based on compliance, presence in all examinations, and for statistical analysis; no differential group losses.

246 children analysed at 2 years (after exclusions based on compliance, present at all examinations). Average age at start: 11.5 years. Surfaces affected at start: 7.9 DMFS (for sample present at all examinations). Exposure to other fluoride: none assumed. Year study began: 1969. Location: UK.

FR versus PL (NaF group = 900 ppm F). School use/supervised, twice a week, 10ml applied for 1 min. 2yDFS scores* - (E+U). Reported at 2 years follow up.

**Craig 1981**

Stratified random allocation; single-blind (B); non-placebo-controlled; 11% drop out after 2 years (study duration = 2 years). Main reason for drop out: 12 children left the participating school; no differential losses between groups.

97 children analysed at 2 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 10.6 DFS. Exposure to other fluoride: toothpaste. Year study began: 1977. Location: New Zealand.

FR+ptc versus NT+ptc** (NaF group = 900 ppm F). School use/supervised, fortnightly, 10 ml applied for 2 min. 2yDFS increment - (CA). Reported at 1 and 2 years follow ups.

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Participants randomised (N = B 314).
Baseline characteristic (DMFS) with some imbalance.
Clinical caries assessment, diagnostic threshold NR.
Radiographic assessment; diagnostic threshold = NR.
State of tooth eruption included = E/U. Diagnostic errors NR.
* Only retrospective matched pair analyses results reported (results for unadjusted analyses not available, data not suitable).

Participants randomised (N = B 109).
Baseline characteristics (DFS, dental age) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA.
State of tooth eruption included NR. Reproducibility checks for incremental clinical caries data in 15% sample at each examination (reversal rate less than 4% for both examiners).
** Prior professional
<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation; double-blind (A); placebo-controlled; drop out rate NR nor obtainable (study duration = 3 years). Reasons for attrition NR; any differential group losses not assessable.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FR versus PL (NaF group = 900 ppm F). School use/supervised, fortnightly. 2yDMFS final scores* - (CA). Reported at 3 years follow up. DMFT.</td>
</tr>
<tr>
<td>DePaola 1977</td>
<td>475 children analysed at 2 years (available at final examination). Age range at start: 10-12 years (average = 11.7). Surfaces affected at start: 6.1 DFS. Exposure to other fluoride: none assumed***. Year study began: in/before 1974. Location: USA.</td>
</tr>
<tr>
<td></td>
<td>FR (2 groups) versus PL (NH4F group = 1000 ppm F, NaF group = 1000 ppm F). School use/supervised, daily, 5 ml applied for 1 min. 2yNetDFS increment - (CA)cl+xr. Reported at 2 years follow up. DFS (U). Side effects (incomplete data).</td>
</tr>
</tbody>
</table>

Participants randomised (B) (numbers NR). Baseline characteristics/values NR. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included NR; diagnostic errors NR. * Only results of combined non-randomised and randomised groups reported (separate results for placebo group not available, data not suitable).
<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation; double-blind (A); placebo-controlled; drop out</th>
<th>271 children analysed at 2 years (after exclusions, present for both examinations).</th>
<th>FR versus PL (NaF group = 230 ppm F).</th>
<th>2yNetDFS increment - (CA)c+x. School use/supervised, daily, 10 ml applied for 1 min.</th>
<th>2.5yNetDMFS increment. School use/supervised, 10 ml applied for 1 min.</th>
<th>3yDMFS increment.</th>
<th>Participants randomised (N = B 966). Baseline characteristics (DMFS) 'balanced'. Clinical caries assessment (VT) by 2 examiners; diagnostic threshold = CA; state of tooth eruption included NR; differences between examiners assessment NS (but reproducibility assessment NR). Results presented separately by examiner (combined results considered). Baseline characteristics (DMFS) 'balanced'. Other data NR nor obtainable.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DePaola 1980</td>
<td>Random allocation; double-blind (A); placebo-controlled; drop out rate NR nor obtainable (study duration = 2 years + 1 year post-study period). Exclusions based on compliance and presence in both follow-up examinations; any differential group losses not assessable.</td>
<td>524 children analysed at 2.5 years (present for entire trial period). Average age at start: 12.8 years. Surfaces affected at start: 4.8 DMFS. Exposure to other fluoride: water (and toothpaste assumed). Year study began: 1977. Location: USA.</td>
<td>FR (2 groups) versus PL. NaF Group 1: 230 ppm F, daily. NaF Group 2: 900 ppm F, weekly.</td>
<td>2.5yNetDMFS increment. Reported at 1.5 and 2.5 years follow ups. O-DMFS. MD-DMFS. BL-DMFS.</td>
<td>2.5yNetDMFS increment. School use/supervised, 10 ml applied for 1 min.</td>
<td>3yDMFS increment.</td>
<td>Participants randomised (N = B 966). Baseline characteristics (DMFS) 'balanced'. Clinical caries assessment (VT) by 2 examiners; diagnostic threshold = CA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold NR; diagnostic errors NR.</td>
</tr>
<tr>
<td>Driscoll 1982</td>
<td>Random allocation; double-blind (A); placebo-controlled; 46% drop out after 2.5 years (study duration = 2.5 years). Main reasons for high drop out rate: children moving out or withdrawn by parents; no differential group losses.</td>
<td>936 children analysed at 3 years. Age range at start and</td>
<td>FR (3 groups) versus PL (NaF groups = 100 ppm F, 225 ppm F, 450 ppm F).</td>
<td>2.5yNetDMFS increment. Reported at 1.5 and 2.5 years follow ups. O-DMFS. MD-DMFS. BL-DMFS.</td>
<td>2.5yNetDMFS increment. School use/supervised, 10 ml applied for 1 min.</td>
<td>3yDMFS increment.</td>
<td>Participants randomised (N = B 966). Baseline characteristics (DMFS) 'balanced'. Clinical caries assessment (VT) by 2 examiners; diagnostic threshold = CA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold NR; diagnostic errors NR.</td>
</tr>
<tr>
<td>Duany 1981</td>
<td>Random allocation; double-blind (A); placebo-controlled; drop out</td>
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<tr>
<td>Study</td>
<td>Allocation Method</td>
<td>Age Range</td>
<td>Surfaces Affected at Start</td>
<td>Exposure to Other Fluoride</td>
<td>Year Study Began</td>
<td>Location</td>
<td>Duration</td>
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<tr>
<td>Finn 1975</td>
<td>Stratified random allocation; indication of blind caries assessment (C); placebo-controlled; 45% drop out after 2 years (study duration = 2 years). Main reason for high drop out rate: 276 children transferred to non-participating schools; exclusions based on presence in both follow-up examinations; any differential group losses not assessable.</td>
<td>8-13 years (average = 11.7)</td>
<td>7 DMFS</td>
<td>no</td>
<td>in/before 1977</td>
<td>Puerto Rico</td>
<td>3 years</td>
</tr>
<tr>
<td>Gallagher 1974</td>
<td>Stratified quasi-random allocation; double-blind (A); placebo-controlled; 27% drop out after 2 years (study duration = 2 years). Natural losses; exclusions based on</td>
<td>11-13 years</td>
<td>7.3 DMFS (from FR (2 groups) versus PL (APF group = 200 ppm F, NaF group = 100 ppm F)).</td>
<td>no</td>
<td>in/before 1972</td>
<td>USA</td>
<td>2 years</td>
</tr>
</tbody>
</table>

Participants randomised (N = 820); numbers by group NR. Baseline characteristics (DMFS, DMFT, age, gender) 'balanced' (DFS baseline data NR). Clinical (VT) caries assessment by 1 examiner, diagnostic threshold NR. Radiographic assessment (2-4 postBW+ 4 anterior) by 1 examiner; diagnostic threshold NR. State of tooth eruption included NR. Diagnostic errors NR. Reversals ranged between 6% and 16% of observed DMFS increment in study groups for combined clin+xr findings, rates being higher in the test groups.
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<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Randomisation</th>
<th>Baseline Characteristics</th>
<th>Exposure to Other Fluoride</th>
<th>Year Study Began</th>
<th>Location</th>
<th>Dental Treatment Level (F/DMF)</th>
<th>Sample Size</th>
<th>Age Range at Start</th>
<th>Surfaces Affected at Start</th>
<th>School Use/Supervision</th>
<th>Caries Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heidmann 1992</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 17% drop out after 3 years (study duration = 3 years). Reasons for attrition NR; any differential group losses not assessable.</td>
<td>Sample randomised. Exposure to other fluoride: none assumed. Year study began: 1970. Location: Canada. Dental treatment level (F/DMF): 42%.</td>
<td>Baseline characteristics (DMFS, SAR) 'balanced'. Clinical (VT) caries assessment by dentists at public dental service, diagnostic threshold = CA. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER.</td>
<td>None assumed.</td>
<td>1970</td>
<td>Canada</td>
<td>42%</td>
<td>1083</td>
<td>6-12 years (average = 9)</td>
<td>1.5 DMFS</td>
<td>School use/supervised, fortnightly.</td>
<td>Proportion of children with new postMDDMFS.</td>
</tr>
<tr>
<td>Heifetz 1973</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 56% drop out after 2 years (study duration = 2 years). Reasons for high drop out rate</td>
<td>Participants randomised (N = B 947); numbers by group NR. Baseline characteristics (DMFS) 'balanced'. Clinical (VT) caries assessment by examiners,</td>
<td>Baseline characteristics (DMFS) 'balanced'. Clinical (VT) caries assessment by dentists at public dental service, diagnostic threshold = CA. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included = E/U. Diagnostic errors NR. Reproducibility of diagnosis assessed by duplicate radiographic examination of 10% random sample (kappa value 0.72).</td>
<td>None assumed.</td>
<td>1973</td>
<td>Denmark</td>
<td>98%</td>
<td>413</td>
<td>10-12 years</td>
<td>1.5 DMFS</td>
<td>School use/supervised,</td>
<td>Proportion of children with new postMDDMFS.</td>
</tr>
</tbody>
</table>

DF. assessment by 1 examiner, diagnostic threshold NR. State of tooth eruption included = E/U. Diagnostic errors NR.

** Both groups had been using FR before study started.
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described: high transiency of the population, dissatisfaction with taste, exclusions based on compliance and presence in both follow-up examinations; any differential group losses not assessable.

Heifetz 1982
Random allocation; double-blind (A); placebo-controlled; 34% drop out after 3 years (study duration = 3 years). Reasons for attrition NR; any differential group losses not assessable.

598 children analysed at 3 years (present for entire trial period). Age range at start: 10-12 years. Surfaces affected at start: 6.2 DMFS. Exposure to other fluoride: toothpaste. Year study began: 1976. Location: USA.

FR (2 groups) versus PL. NaF Group 1: 230 ppm F, daily. NaF Group 2: 900 ppm F, weekly. School use/supervised, 10ml applied for 1 min.

3yNetDMFS increment - (CA)(E)clin. Reported at 1, 2 and 3 years follow ups.

O-DMFS. MD-DMFS. BL-DMFS.

Horowitz 1971
Stratified random allocation; 256 children analysed at 1.6 years (present for entire trial period). Age range at start: 10-12 years. Surfaces affected at start: 6.2 DMFS. Exposure to other fluoride: toothpaste. Year study began: 1976. Location: USA.

FR versus PL.

1.6yNetDMFS increment - Participants randomised (N = B 912); numbers by group NR. Baseline characteristics (DMFS) 'balanced'. Clinical caries assessment (VT) by 2 examiners; diagnostic threshold = CA (FOTI assessment - loss of translucency on transillumination - for approximal surfaces.) State of tooth eruption included = E: differences between examiners assessment NS (but reproducibility assessment NR). Results presented separately by examiner (combined results considered).
Horowitz 1971a

Stratified random allocation; double-blind (A); placebo-controlled (PL); 48% drop out after 1.6 years (study duration = 1.6 years). Main reason for high drop out rate described (transiency of schools' neighbourhoods); exclusions based on presence in follow-up examinations; no differential group losses. 208 children analysed at 1.6 years (present for entire trial period). Age range at start: 6-7 years. Surfaces affected at start: 0.9 DMFS (sample available at end). Exposure to other fluoride: none assumed. Year study began: 1967. Location: USA. FR versus PL (NaF group = 900 ppm F). School use/supervised, weekly, 10 ml applied for 1 min. (E+U). Reported at 1 and 1.6 years follow ups. DMFT (E/U). DMFS (U). 1.6yNetDMFS increment - (E+U). Participants randomised (N = B 381). Baseline characteristics (DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold NR. State of tooth eruption included = E/U. Diagnostic errors NR.

Koch 1967

Stratified random allocation***; double-blind (A); placebo-controlled; 23% drop out after 3 years (study duration = 3 years + 2 years post-intervention period). Natural losses; no differential group losses. 167 children analysed at 3 years (present for entire trial period). Age range at start: 9-11 years (average = 10). Surfaces affected at start: 14.5 DFS. Exposure to other fluoride: no. Year study began: 1962. Location: Sweden. FR versus PL (NaF group = 2250 ppm F). School use/supervised, fortnightly, 10 ml applied for 2 min. 3yDFS increment - (CA)(E)cl. Reported at 1 and 3 years follow ups (and 2 years post-treatment). DFT. O-DFS. MD-DFS. BL-DFS. CAR (annual). Secondary caries. Participants randomised (N = A 217). Baseline characteristics (DFS, DFT, SAR) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E.
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Koch 1967a
Stratified random allocation***; double-blind (A); placebo-controlled; 27% drop out after 3 years (study duration = 3 years). Natural losses; no differential group losses.
251 children analysed at 3 years (present for entire trial period).
Age range at start: 6-8 years (average = 7).
Surfaces affected at start: 5.6 DFS.
Exposure to other fluoride: none assumed.
Year study began: 1962.
Location: Sweden.
FR versus PL (NaF group = 2250 ppm F).
School clinic/supervised, 3 times a year, 10 ml applied for 2 min.
3yDFS increment - (CA)(E)cl.
Reported at 1 and 3 years follow ups.
DFT.
CAR (annual).
Secondary caries.

Koch 1967b
Stratified random allocation***; double-blind (A); placebo-controlled; 36% drop out after 3 years (study duration = 3 years). Natural losses; no differential group losses.
251 children analysed at 3 years (present for entire trial period).
Age range at start: 7-11 years.
Surfaces affected at start: 7 DFS.
Exposure to other fluoride: none assumed.
Year study began: 1962.
FR versus PL (NaF group = 230 ppm F).
School clinic/supervised, 3 times a year, 10 ml applied for 2 min.
3yDFS increment - (CA)(E)cl.
Reported at 2 years follow up.
DFT.
CAR (annual).
Secondary caries.

Oral tissue inflammation (incomplete data).

Intraexaminer reproducibility checks for DFS in 10% sample (icc over 0.98); reversals very small in both groups and equally common.
*** Allocation concealment considered adequate by consensus.
Participants randomised (N = A 344).
Baseline characteristics (DFS, DFT, SAR, TAR) 'balanced'.
Clinical (VT) caries assessment by 4 examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E. Diagnostic errors NR.
*** Allocation concealment considered adequate by consensus.
Participants randomised (N = A 392).
Baseline characteristics (DFS, DFT, SAR, TAR) 'balanced'.
Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but...
Fluoride mouthrinses for preventing dental caries in children and adolescents (THESIS CHAPTER 6)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/Methodology</th>
<th>Participants</th>
<th>Location</th>
<th>Baseline Characteristics</th>
<th>Clinical Assessment</th>
<th>State of Tooth Eruption</th>
<th>Diagnostic Errors</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laswell 1975</td>
<td>Random allocation;</td>
<td>323 children</td>
<td>Sweden</td>
<td>DMFS, age balanced</td>
<td>Clinical (VT)</td>
<td>E/U</td>
<td>NR</td>
<td>FR (2 groups) versus PL</td>
</tr>
<tr>
<td></td>
<td>indication of blind</td>
<td></td>
<td></td>
<td></td>
<td>caries assessment</td>
<td></td>
<td></td>
<td>APF Group 1: 200 ppm F, daily.</td>
</tr>
<tr>
<td></td>
<td>caries assessment</td>
<td></td>
<td></td>
<td></td>
<td>(C);</td>
<td></td>
<td></td>
<td>APF Group 2: 1000 ppm F, weekly.</td>
</tr>
<tr>
<td></td>
<td>placebo-controlled;</td>
<td></td>
<td></td>
<td></td>
<td>placebo-controlled;</td>
<td></td>
<td></td>
<td>School use/supervised</td>
</tr>
<tr>
<td></td>
<td>44% drop out after 2.4 years (study duration = 2.4 years). Main reason for high drop out rate NR. Exclusions based on presence in follow-up examinations and on compliance; no differential group losses.</td>
<td></td>
<td></td>
<td></td>
<td>38% drop out after 2 years (study duration = 2 years + 1 year post-intervention period). Main reason for high drop out rate: children moved out of participating schools (plus absenteeism). Exclusions based on compliance; any differential group losses not assessable.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McConchie 1977</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 38% drop out after 2 years (study duration = 2 years + 1 year post-intervention period). Main reason for high drop out rate: children moved out of participating schools (plus absenteeism). Exclusions based on compliance; any differential group losses not assessable.</td>
<td>743 children</td>
<td>USA</td>
<td>DMFS, age balanced</td>
<td>Clinical (VT)</td>
<td>E/U</td>
<td>NR</td>
<td>FR (2 groups) versus PL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>caries assessment</td>
<td></td>
<td></td>
<td>(SnF2 groups = 200 ppm F, and 100 ppm F).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>placebo-controlled;</td>
<td></td>
<td></td>
<td>School use/supervised, daily, 20 ml applied in 2 successive rinses 30 seconds each (non-fluoride toothpaste provided to all for home use, but no rinse provided).</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>30% drop out after 2 years (study duration = 2 years + 1 year post-intervention period).</td>
<td></td>
<td></td>
<td>Children with tooth staining/pigmentation, unacceptance to the taste, side effects (incomplete</td>
</tr>
</tbody>
</table>

Not reported; state of tooth eruption included = E/U. *** Allocation concealment considered adequate by consensus.
<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation Method</th>
<th>Blinding</th>
<th>Control Group</th>
<th>Duration</th>
<th>Dropout Rate</th>
<th>Reason for Dropout</th>
<th>Age at Start</th>
<th>Surfaces at Start</th>
<th>Other Fluoride</th>
<th>Year</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molina 1987</td>
<td>Random allocation; double-blind (A); placebo-controlled; 62% drop out after 2.5 years (study duration = 2.5 years). Main reason for high drop out rate: children moved out of participating schools (during 1985 earthquake). No differential group losses.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chile</td>
</tr>
<tr>
<td>Moreira 1972</td>
<td>Stratified quasi-random allocation; double-blind (A); non-placebo-controlled; 39% drop out after 2 years (study duration = 2 years). Reasons for attrition NR; no differential group losses (but exclusions may have been based on 'statistical reasons', made 'at random' to keep groups of equal sizes, after natural losses).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Brazil</td>
</tr>
<tr>
<td>Moreira 1981</td>
<td>Stratified quasi-random allocation; single-blind (B); non-placebo-controlled; 29% drop out after 2.5 years (study duration = 2.5 years).</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study</td>
<td>Design and Participants</td>
<td>Exposure to Other Fluoride</td>
<td>Year Study Began</td>
<td>Location</td>
<td>Children Analysed</td>
<td>Average Age at Start</td>
<td>Surfaces Affected at Start</td>
<td>DMFS</td>
<td>Exposure to Other Fluoride</td>
<td>Year Study Began</td>
<td>Location</td>
</tr>
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</tr>
<tr>
<td>Packer 1975</td>
<td>Random allocation; indication of blind caries assessment (C); placebo-controlled; 39% drop out after 2.4 years (study duration = 2.4 years). Main reason for high drop out rate NR. Exclusions based on presence in follow-up examinations and on compliance; no differential group losses.</td>
<td>Water</td>
<td>1974</td>
<td>Brazil</td>
<td>285 children</td>
<td>8.7</td>
<td>6.6</td>
<td>FR (2 groups) versus PL</td>
<td>2.4 years</td>
<td>USA</td>
<td>139 children</td>
</tr>
<tr>
<td>Petersson 1998</td>
<td>Random allocation; double-blind (A); placebo-controlled; drop out rate NR nor obtainable (study duration = 3 years). Reasons for attrition NR. Any differential group losses not assessable.</td>
<td>No</td>
<td>1994</td>
<td>Sweden</td>
<td>365 children</td>
<td>7-10</td>
<td>36</td>
<td>FR versus PL</td>
<td>3 years</td>
<td>USA</td>
<td>139 children</td>
</tr>
<tr>
<td>Poulsen 1984</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 8% drop out after 3 years (study)</td>
<td></td>
<td></td>
<td>Brazil</td>
<td>200 ppm F, daily</td>
<td>200 ppm F, weekly</td>
<td>200 ppm F, daily</td>
<td>School use/supervised (non-fluoride toothpaste provided to all for home use, but no rinse provided).</td>
<td>2.4yNetDFS increment - (E+U). Reported at 2.4 years follow up.</td>
<td>200 ppm F, weekly</td>
<td>Brazil</td>
</tr>
</tbody>
</table>
**Radike 1973**  
Stratified random allocation; double-blind (A); placebo-controlled; 18% drop out after 1.6 years (study duration = 1.6 years). Reasons for attrition NR; no differential group losses.  
726 children analysed at 1.6 years (available at final examination).  
Age range at start: 8-13 years (average = 10.4).  
Surfaces affected at start: 4.9 DMFS.  
Exposure to other fluoride: water.  
Year study began: in/before 1970.  
Location: USA.  
Dental treatment level (F/DMF): 50%.  
FR versus PL (SnF2 group = 250 ppm F).  
School use/supervised, daily, 60 ml applied in 3 successive rinses of 10, 30, and 30 seconds each (non-fluoride toothpaste provided to all for home use, but no rinse provided).  
Children with tooth staining/pigmentation (incomplete data).  
 Participants randomised (N = 890).  
Baseline characteristics (DMFS, DMFT, age, gender) 'balanced'.  
Clinical (VT) caries assessment by dentists at public dental service, diagnostic threshold = CA.  
Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = DR.  
State of tooth eruption included (E/U).  
Reproducibility of diagnosis assessed by duplicate radiographic examination of 10% random sample (kappa value 0.72).

**Ringelberg 1979**  
Stratified random allocation; double-blind (A);  
527 children analysed at 2.5 years (available at final examination).  
FR (2 groups) versus PL (2 groups) (AmF group = 250 ppm F).  
2.5yNetDMFS increment - cl+dxr.  
Participants randomised (N = 878).
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placebo-controlled; 40% drop out after 2.5 years (study duration = 2.5 years). Reason(s) for attrition NR; no differential group losses.

Rugg-Gunn 1973
Stratified random allocation; double-blind (A); placebo-controlled; 12% drop out after 3 years (study duration = 3 years). Reasons for attrition described with examination).
Average age at start: 11 years. Surfaces affected at start: 4.3 DMFS. Exposure to other fluoride: no. Year study began: 1973. Location: USA.
School use/supervised, 10ml applied for 1 min.
Reported at 1.5 and 2.5 years follow ups.
PostMD-DFS.
Participants randomised (N = B 491).
Baseline characteristics (DMFS, DMFT, gender, exposure to fluoride toothpaste) 'balanced'. Diagnostic errors NR.

Ringelberg 1982
Stratified random allocation; double-blind (A); placebo-controlled; 39% drop out after 2 years (study duration = 2 years). Reason(s) for high drop out related to "migratory" nature of community; no differential group losses.
1238 children analysed at 2 years (available at final examination). Average age at start: 12.5 years. Surfaces affected at start: 4.7 DMFS. Exposure to other fluoride: toothpaste assumed. Year study began: in/before 1979. Location: USA.
School use/supervised, 10ml applied for 1 min.
Reported at 2.5 years follow up.
DMFT.
Stain score.
Participants randomised (N = B 2014).
Baseline characteristics (DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (5 BW) by 2 examiners; diagnostic threshold = DR. State of tooth eruption included NR. Reversal rate between 4 and 9% of observed caries increment in the groups.
<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiken 1987</td>
<td>Cluster random allocation; indication of blind caries assessment (C); non-placebo-controlled; 59% drop out after 3 years (study duration = 3 years). Main reasons for attrition: natural losses and results reported only for children with readable x-rays; any differential group losses not assessable.</td>
</tr>
<tr>
<td></td>
<td>Exposure to other fluoride: no. Year study began: in/before 1969. Location: UK.</td>
</tr>
<tr>
<td></td>
<td>PF-DMFS. FS-DMFS. AntMD-DMFS. PostMD-DMFS. DMFS (U). Signs of sensitivity in oral mucosa.</td>
</tr>
<tr>
<td></td>
<td>207 children analysed at 3 years (present at final examination, for which there were readable x-rays). Average age at start: 8 years. Surfaces affected at start: 2.7 DFS. Exposure to other fluoride: toothpaste, tablets. Year study began: 1981. Location: The Netherlands. FR versus NT (NaF group = 900 ppm F). School use/supervised, weekly, 10ml applied for 1 min. 3yNetDFS increment - cl+xr. Reported at 3 years follow up.</td>
</tr>
<tr>
<td></td>
<td>Clinical (V) caries assessment by 1 examiner. diagnostic threshold = CA/NCA. Radiographic assessment (2postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included = E/U. Intraexaminer reproducibility checks for incremental caries data in 10% sample (icc score 0.9 for DMFS). Reversal rate 4% and 7% of observed DMFS increment in control and study groups respectively.</td>
</tr>
<tr>
<td></td>
<td>Schools (N = 29) randomised (and 2nd grade children in these taken as units of analysis); number of children by group NR. Baseline characteristics (DFS, erupted surfaces, age) described as 'balanced'. Clinical (V) caries assessment by 2 examiners; diagnostic threshold = CA/NCA; state of tooth eruption included NR. Radiographic assessment (2postBW) by 2 examiners; diagnostic threshold = DR/ER; partial recording.</td>
</tr>
<tr>
<td>Study</td>
<td>Random allocation;</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Spets-Happonen 1991</td>
<td>double-blind (A);</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation;</th>
<th>494 children analysed at 2 years (available at final examination).</th>
<th>FR (2 groups) versus NT</th>
<th>2yDMFS increment - (CA)c1. Reported at 1 and 2 years follow ups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torell 1965</td>
<td>single-blind (B);</td>
<td>494 children analysed at 2 years (available at final examination).</td>
<td>NaF Group 1: 230 ppm F, 10 ml applied daily.</td>
<td>Participants randomised (N = 597). Baseline characteristics (DMFS, MD-DMFS).</td>
</tr>
<tr>
<td></td>
<td>non-placebo-controlled; 17% drop out rate after 2 years</td>
<td>Average age at start: 10</td>
<td></td>
<td>** Chlorhexidine present in both, the fluoride and the non-fluoride mouthrinse (thus, other outcomes, such as tooth staining, not relevant for the comparison of interest). Prior toothbrushing without toothpaste done.</td>
</tr>
</tbody>
</table>

Diagnostic errors NR. Participants randomised (numbers NR). Baseline characteristics (DMFS, gender) with some imbalance, but "adjustment made no difference in the results". Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA (FOTI assessment - loss of translucency on transillumination - for approximal surfaces of anterior teeth); state of tooth eruption included NR. Radiographic assessment; diagnostic threshold = DR; kappa 0.7 and 0.79 for inter- and intra-examiner reliability. ** Chlorhexidine present in both, the fluoride and the non-fluoride mouthrinse (thus, other outcomes, such as tooth staining, not relevant for the comparison of interest). Prior toothbrushing without toothpaste done.
Stratified random allocation; double-blind (A); placebo-controlled; 38% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers, main reasons: changing of school and scholastic failure; no differential group losses.

van Wyk 1986

569 children analysed at 3 years (available at final examination). Age range at start: 12-13 years. Surfaces affected at start: 1.6 DFS. Exposure to other fluoride: no. Year study began: 1981. Location: South Africa.

FR (2 groups) versus PL (NaF groups = 900 ppm F and 230 ppm F). School use/supervised, weekly, 10ml applied for 1 min.

Proportion of children with new carious lesions - (U)xr.

MD-DMFS.

FS.

2yNetDFS increment - (CA)cl. Reported at 1, 2 and 3 years follow ups.

Participants randomised (N = 925). Baseline characteristics (DFS, gender) balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA. State of tooth eruption included NR. Intra-examiner reproducibility checks for incremental caries data in 40% sample (icc score 0.91).

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

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

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aasenden 1972</td>
<td>Fluoride solution swallowed after rinsing (even though no systemic effect should be anticipated for this age group).</td>
</tr>
<tr>
<td>Badersten 1975</td>
<td>Additional non-fluoride based intervention associated to fluoride mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Birkeland 1973</td>
<td>Length of follow up of less than 1 year/school year. Relevant outcomes not reported. Blind outcome assessment not stated.</td>
</tr>
<tr>
<td>Bohannan 1985a</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Boyd 1985</td>
<td>Additional fluoride-based intervention associated to fluoride mouthrinse. Clearly not randomised or quasi-randomised. Length of follow up of less than 1 year/school year.</td>
</tr>
<tr>
<td>Bristow 1975</td>
<td>Additional interventions associated to fluoride mouthrinse. Only two clusters (schools), each assigned to one of the two study groups.</td>
</tr>
<tr>
<td>Brodeur 1989</td>
<td>Open outcome assessment.</td>
</tr>
<tr>
<td>Castellanos 1983</td>
<td>Open outcome assessment reported after contacting author.</td>
</tr>
<tr>
<td>Chikte 1996</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Clark 1985a</td>
<td>Clearly not randomised or quasi-randomised (concurrent control group taken from another study).</td>
</tr>
<tr>
<td>Corpus 1973</td>
<td>Clearly not randomised or quasi-randomised (systematic allocation according to participants' characteristics). Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>de Canton 1983</td>
<td>Additional fluoride and non-fluoride based interventions associated to fluoride mouthrinse. Random or quasi-random allocation not stated.</td>
</tr>
<tr>
<td>Disney 1989</td>
<td>Additional non-fluoride based intervention associated to fluoride</td>
</tr>
</tbody>
</table>
Fluoride mouthrinses for preventing dental caries in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esteva Canto 1991</td>
<td>Clearly not randomised or quasi-randomised. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Fernandez 1979</td>
<td>Open outcome assessment. Random or quasi-random allocation not stated or indicated.</td>
</tr>
<tr>
<td>Frankl 1972</td>
<td>Fluoride solution swallowed after rinsing (even though no systemic effect should be anticipated for this age group).</td>
</tr>
<tr>
<td>Gray 1980</td>
<td>Additional fluoride-based intervention associated to fluoride mouthrinse.</td>
</tr>
<tr>
<td>Heifetz 1979</td>
<td>Additional fluoride-based intervention associated to fluoride mouthrinse. Note - Inappropriate 'placebo' used.</td>
</tr>
<tr>
<td>Irmisch 1974</td>
<td>Additional active agent associated to fluoride in mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Ivanova 1990</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Kasakura 1966</td>
<td>Random or quasi-random allocation not stated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Kitsugi 1978</td>
<td>Additional intervention associated to fluoride mouthrinse.</td>
</tr>
<tr>
<td>Kunzel 1978</td>
<td>Only two clusters (schools), each assigned to one of the two study groups. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Louw 1995</td>
<td>Random or quasi-random allocation to groups not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Luoma 1978</td>
<td>Additional fluoride-based intervention associated to fluoride mouthrinse.</td>
</tr>
<tr>
<td>McCormick 1970</td>
<td>Random or quasi-random allocation not stated. Note - Only post-treatment effects reported.</td>
</tr>
<tr>
<td>Mendonca 1995</td>
<td>Open outcome assessment reported after contacting author.</td>
</tr>
<tr>
<td>Morozova 1983</td>
<td>Additional intervention associated to fluoride mouthrinse. Random or</td>
</tr>
</tbody>
</table>
quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.

Ramos 1995  Open outcome assessment.

Roberts 1948  Clearly not randomised or quasi-randomised (concurrent control group selected by matching procedure).

Rodriguez Miro 1983  Additional active agent associated to fluoride in mouthrinse. Only three clusters (school classes), each assigned to one of the three interventions compared.

Suntsov 1991  Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated. Note - Only post-treatment effects reported.

Swerdloff 1969  Length of follow up of less than 1 year/school year.

Weisz 1960  Clearly not randomised or quasi-randomised (concurrent control group taken from a different population). Open outcome assessment.

Widenheim 1989  Clearly not randomised or quasi-randomised (concurrent control group taken from a different population). Open outcome assessment.

Wilson 1978  Random or quasi-random allocation not stated.

Wycoff 1991  Clearly not randomised or quasi-randomised. Blind outcome assessment not stated or indicated.

Zickert 1982  Additional fluoride-based intervention associated to fluoride mouthrinse.
References to studies

Included studies

Ashley 1977


Bastos 1989

Bastos JR, Viegas AR, Lopes ES. Comparison between the use of 0.2% sodium fluoride solutions, 0.7% sodium monofluorophosphate solutions and 0.7% sodium monofluorophosphate solutions in 4% alcohol, in weekly rinsing, in the prevention of dental caries. Results after 12 months [Comparacao entre o uso de solucoes de fluoreto de sodio a 0,2%, monofluorfosfato de sodio a 0,7% e monofluorfosfato de sodio a 0,7% em alcool a 4%, em bochechos semanais, na prevencao de carie dentaria. Resultados de 12 meses]. Revista da Associacao Paulista de Cirurgioes Dentistas 1981;35:390-5.

* Bastos JRM. Comparacao entre uso de unidades de fluoreto de sodio a 0.2%, monofluorfosfato de sodio a 0.7% e monofluorfosfato de sodio a 0.7% em alcool a 4%, em bochechos, na prevencao da carie dentaria [dissertation]. Sao Paulo (SP): Universidade de Sao Paulo, 1979.

Bastos JRM, Lopes ES. Bochechos com fluoretos: efeito anticariogenico de bochechos semanais com solucoes de fluoreto de sodio ou monofluor fosfato de sodio, após 32 meses em escolares de 9-12 anos de idade [Fluoride mouthwashes: anticaries effectiveness of a weekly mouthrinsing program using sodium fluoride or sodium monofluorophosphate after 32 months in schoolars from 9 to 12 years old]. Revista da Associacao Paulista de Cirurgioes Dentistas 1989;43:34-6.

Bastos JRM, Viegas AR, Lopes ES. Solucoes de fluoreto de sodio a 0,2 por cento, monofluorfosfato de sodio a 0,7 por cento e monofluorfosfato a 0,7 por cento, em alcool a 4 por cento, em bochechos semanais, na prevencao da carie dentaria: resultados de 20 meses [Weekly mouthwashing in caries prevention using solution of NaF 0.2 percent, 0.7 percent in alcohol 0.4 percent: results after 20 months (comparative study)]. Revista da Associacao Paulista de Cirurgioes Dentistas 1986;40:443-5.

Blinkhorn 1983


Brandt 1972

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Craig 1981


Pearce EI, Craig EW, Suckling GW. Stability of fluoride levels in surface layer of normal enamel during a 21-month fluoride mouthrinsing program. Community Dentistry and Oral Epidemiology 1980;8:396-400.

de Liefde 1989


DePaola 1977

{published data only}


DePaola 1980

{unpublished data sought but not used}


Driscoll 1982

{unpublished data sought but not used}


Duany 1981

{published data only}


Finn 1975

{published data only}


Review Manager 4.2.2 25/09/2003
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**Gallagher 1974**

**Heidmann 1992**


**Heifetz 1973**

**Heifetz 1982**


**Horowitz 1971**


**Horowitz 1971a**


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Fluoride mouthrinses for preventing dental caries in children and adults

Koch 1967


Koch 1967a


Koch 1967b


Laswell 1975


**Fluoride mouthrinses for preventing dental caries in children and**

---

**McConchie 1977**  
(published data only)


**Molina 1987**  
(unpublished data sought but not used)

Molina MX, Rodriguez FG, Urbina T, Vargas S. Efecto de enjuagatorios semanales con una solucion neutra de NaF al 0.2% en la incidencia de caries en primeros molares definitivos [Effect of weekly mouthrinses with 0.2% neutral NaF solution on caries incidence in first permanent molars]. Odontologia Chilena 1989;37:176-82.

* Molina XM, Rodriguez GP, Sepulveda MM, Urbina TR, Vargas SJ. Efecto en la incidencia de caries dentarias, de enjuagatorios semanales con solucion neutra de fluoruro de sodio al 0,2 en escolares de enseganca basica fiscal [Increase of caries in a school children group that participated in a weekly mouth wash program with sodium fluoride 0.2]. Revista de la Facultad de Odontologia de la Universidad de Chile 1987;5:18-27.

**Moreira 1972**  
(published and unpublished data)


* Moreira BH, Tumang AJ. Prevencao da carie dentaria atraves de bochechos com solucoes de fluoreto de sodio a 0,1%. Resultados apos dois anos de estudos [Prevention of dental caries by means of mouthwashes with 0.1 solutions of sodium fluoride. Results of a 2 year study]. Revista Brasileira de Odontologia 1972;29:37-42.

**Moreira 1981**  
(published and unpublished data)


**Packer 1975**  
(published data only)


**Petersson 1998**  
(unpublished data sought but not used)


**Poulsen 1984**  
(published and unpublished data)
Fluoride mouthrinses for preventing dental caries in children and adults


Radike 1973

(published data only)


Ringelberg 1979

(published data only)


Ringelberg 1982

(unpublished data sought but not used)


Rugg-Gunn 1973

(published data only)


Ruiken 1987

(unpublished data sought but not used)


Spets-Happonen 1991

(unpublished data sought but not used)
Fluoride mouthrinses for preventing dental caries in children and adults


Torell 1965


van Wyk 1986

van Wyk I, van Wyk CW. The effectiveness of a 0.2 percent and a 0.05 percent neutral NaF mouthrinsing programme. Journal of the Dental Association of South Africa 1986;41:35-40.

Excluded studies

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Arcieri RM, Saliba NA, Saliba O. Avaliacao da reducao na incidencia da carie dentaria, devida a bochechos com solucao de fluoreto de sodio a 0.2% [Appraisal of the reduction of the incidence of dental caries, due to mouthwashes with a 0.2% sodium fluoride solution]. Revista da Associacao Paulista de Cirurgioes Dentistas 1981;35:126-31.

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Bohannan 1985a

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Fluoride mouthrinses for preventing dental caries in children and adults


Boyd 1985


Bristow 1975


Brodeur 1989


Castellanos 1983

Castellanos RA. Estudo comparativo do efeito de solucao de NaF a 0,5%, atraves de bochecho, escovacao e ambos, na prevencao da carie dental [Comparative study of the effect of a .5% NaF solution by mouthwash, toothbrushing or both, in the prevention of dental caries]. Revista de Saude Publica 1983;17:461-75.

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{published data only}

Clark 1985a

Corpus 1973

de Canton 1983

DePaola 1967

Disney 1989

Esteva Canto 1991

Fernandez 1979
Fernandez RAC. Estudo comparativo do efeito de solucao de NaF a 0.5% atraves de bochecho, escovacao e ambos, na prevencao da carie dental [dissertation]. Sao Paulo (SP): Universidade de Sao Paulo, 1979.

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Fluoride mouthrinses for preventing dental caries in children and adults

Gray 1980 {published data only}

Heifetz 1979 {published data only}


Irmisch 1974 {published data only}


Ivanova 1990 {published data only}

Kani 1973 {published data only}

Kasakura 1966 {published data only}

Kitsugi 1978 {published data only}

Kunzel 1978 {published data only}
Fluoride mouthrinses for preventing dental caries in children and adults


Louw 1995


Luoma 1978


McCormick 1970


Mendonca 1995


Morozova 1983

Fluoride mouthrinses for preventing dental caries in children and adults

Ramos 1995


Roberts 1948


Rodriguez Miro 1983


Suntsov 1991


Swerdloff 1969


Weisz 1960


Widenheim 1989


Wilson 1978

Wilson CJ, Triol CW, Volpe AR. The clinical anticaries effect of a fluoride dentifrice and
Fluoride mouthrinses for preventing dental caries in children and


**Wycoff 1991** {published data only}


**Zickert 1982** {published data only}


**Studies awaiting assessment**

**Ainamo 1981** {published data only}


**Cichocka 1981** {published data only}


**Forsman 1965** {published data only}


**Hall 1964** {published data only}


**Hansson 1965** {published data only}


**Kawall 1981** {published data only}

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Fluoride mouthrinses for preventing dental caries in children and


Mounttin 1975


Nenyei 1971


Nystrom 1961


Ollinen 1963


Shimada 1978


Torell 1963


Torell 1969


* indicates the primary reference for the study
Other references

Additional references

Birkeland 1978

Bohannan 1985

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Clarke 2000

da Liefde 1998

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Disney JA, Bohannan HM, Klein SP, Bell RM. A case study in contesting the conventional wisdom: school-based fluoride mouthrinse programs in the USA. Community Dentistry and Oral Epidemiology 1990;18:46-54.

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Fluoride mouthrinses for preventing dental caries in children and adults.

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Helfenstein 1994


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Krasse 1996


Leverett 1989


Marinho 1997


Marinho 2002

Marthaler 1994

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Nadanovsky 1995

O'Mullane 1994

Petersson 1993

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Fluoride mouth rinses for preventing dental caries in children and adults


Ripa 1992

Rolla 1991

Seppa 1989

Sharp 1998

Stamm 1984

Stamm 1993

Stamm 1995

Stookey 1994

Thompson 1999

Torell 1974
van Rijkom 1998


Whitford 1992

Table of comparisons

01 Fluoride Mouthrinse versus Placebo/No-treatment
   01 D(M)FS increment (prevented fraction) - nearest to 3 years (34 trials)
   02 D(M)FT increment (prevented fraction) - nearest to 3 years (13 trials)
   03 D(M)FS increment (SMD) - nearest to 3 years (34 trials)
   04 D(M)FT increment (SMD) - nearest to 3 years (13 trials)
   05 Developing one or more new caries (3 trials)
   06 Unacceptability of treatment as measured by leaving study early (2 trials)
### Other data tables

#### 01 Fluoride Mouthrinse versus Placebo/No-treatment

#### 01 D(M)FS increment (prevented fraction) - nearest to 3 years (34 trials)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashley 1977</td>
<td>14%</td>
<td>(1% to 27%)</td>
</tr>
<tr>
<td>Bastos 1989</td>
<td>28%</td>
<td>(18% to 39%)</td>
</tr>
<tr>
<td>Blinkhorn 1983</td>
<td>24</td>
<td>(11% to 38%)</td>
</tr>
<tr>
<td>Craig 1981</td>
<td>32%</td>
<td>(-4% to 67%)</td>
</tr>
<tr>
<td>DePaola 1977</td>
<td>42%</td>
<td>(32% to 51%)</td>
</tr>
<tr>
<td>DePaola 1980</td>
<td>22%</td>
<td>(5% to 38%)</td>
</tr>
<tr>
<td>Driscoll 1982</td>
<td>38%</td>
<td>(21% to 54%)</td>
</tr>
<tr>
<td>Duany 1981</td>
<td>13%</td>
<td>(-5% to 31%)</td>
</tr>
<tr>
<td>Finn 1975</td>
<td>17%</td>
<td>(4% to 29%)</td>
</tr>
<tr>
<td>Gallagher 1974</td>
<td>14%</td>
<td>(5% to 23%)</td>
</tr>
<tr>
<td>Heidmann 1992</td>
<td>5%</td>
<td>(-19% to 30%)</td>
</tr>
<tr>
<td>Heifetz 1973</td>
<td>32%</td>
<td>(20% to 45%)</td>
</tr>
<tr>
<td>Heifetz 1982</td>
<td>35%</td>
<td>(20% to 50%)</td>
</tr>
<tr>
<td>Horowitz 1971</td>
<td>16%</td>
<td>(-17% to 50%)</td>
</tr>
<tr>
<td>Horowitz 1971a</td>
<td>43%</td>
<td>(19% to 68%)</td>
</tr>
<tr>
<td>Koch 1967</td>
<td>23%</td>
<td>(13% to 34%)</td>
</tr>
<tr>
<td>Koch 1967a</td>
<td>25%</td>
<td>(9% to 41%)</td>
</tr>
<tr>
<td>Koch 1967b</td>
<td>2%</td>
<td>(-21% to 25%)</td>
</tr>
<tr>
<td>Laswell 1975</td>
<td>35%</td>
<td>(10% to 60%)</td>
</tr>
</tbody>
</table>

Review Manager 4.2.2
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<table>
<thead>
<tr>
<th>Author</th>
<th>Percentage</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>McConchie 1977</td>
<td>18%</td>
<td>(7% to 29%)</td>
</tr>
<tr>
<td>Molina 1987</td>
<td>30%</td>
<td>(16% to 44%)</td>
</tr>
<tr>
<td>Moreira 1972</td>
<td>17%</td>
<td>(-6% to 39%)</td>
</tr>
<tr>
<td>Moreira 1981</td>
<td>25%</td>
<td>(8% to 42%)</td>
</tr>
<tr>
<td>Packer 1975</td>
<td>35%</td>
<td>(6% to 64%)</td>
</tr>
<tr>
<td>Petersson 1998</td>
<td>14%</td>
<td>(-30% to 59%)</td>
</tr>
<tr>
<td>Poulsen 1984</td>
<td>12%</td>
<td>(-10% to 34%)</td>
</tr>
<tr>
<td>Radike 1973</td>
<td>33%</td>
<td>(22% to 44%)</td>
</tr>
<tr>
<td>Ringelberg 1979</td>
<td>23%</td>
<td>(7% to 39%)</td>
</tr>
<tr>
<td>Ringelberg 1982</td>
<td>22%</td>
<td>(6% to 39%)</td>
</tr>
<tr>
<td>Rugg-Gunn 1973</td>
<td>36%</td>
<td>(27% to 44%)</td>
</tr>
<tr>
<td>Ruiken 1987</td>
<td>33%</td>
<td>(16% to 49%)</td>
</tr>
<tr>
<td>Spets-Happonen 1991</td>
<td>26%</td>
<td>(-17% to 70%)</td>
</tr>
<tr>
<td>Torell 1965</td>
<td>35%</td>
<td>(26% to 43%)</td>
</tr>
<tr>
<td>van Wyk 1986</td>
<td>30%</td>
<td>(20% to 40%)</td>
</tr>
</tbody>
</table>
### Other data tables

**01 Fluoride Mouthrinse versus Placebo/No-treatment**

**02 D(M)FT increment (prevented fraction) - nearest to 3 years (13 trials)**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prevented fraction</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastos 1989</td>
<td>34%</td>
<td>(21% to 48%)</td>
</tr>
<tr>
<td>Blinkhorn 1983</td>
<td>25%</td>
<td>(12% to 37%)</td>
</tr>
<tr>
<td>Finn 1975</td>
<td>22%</td>
<td>(6% to 37%)</td>
</tr>
<tr>
<td>Horowitz 1971</td>
<td>25%</td>
<td>(-8% to 58%)</td>
</tr>
<tr>
<td>Horowitz 1971a</td>
<td>52%</td>
<td>(26% to 77%)</td>
</tr>
<tr>
<td>Koch 1967</td>
<td>11%</td>
<td>(1% to 21%)</td>
</tr>
<tr>
<td>Koch 1967a</td>
<td>13%</td>
<td>(-10% to 35%)</td>
</tr>
<tr>
<td>Koch 1967b</td>
<td>-4%</td>
<td>(-29% to 21%)</td>
</tr>
<tr>
<td>McConchie 1977</td>
<td>18%</td>
<td>(3% to 33%)</td>
</tr>
<tr>
<td>Molina 1987</td>
<td>26%</td>
<td>(11% to 40%)</td>
</tr>
<tr>
<td>Radike 1973</td>
<td>31%</td>
<td>(20% to 42%)</td>
</tr>
<tr>
<td>Ringelberg 1979</td>
<td>18%</td>
<td>(3% to 33%)</td>
</tr>
<tr>
<td>Rugg-Gunn 1973</td>
<td>32%</td>
<td>(24% to 40%)</td>
</tr>
</tbody>
</table>
### Additional tables

#### 01 Meta-analyses of prevented fractions

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. studies</th>
<th>r.e. estimate</th>
<th>95% c.i.</th>
<th>Meta-analysis p-val</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(M)FS - all studies</td>
<td>34</td>
<td>26%</td>
<td>23% to 30%</td>
<td>p&lt;0.0001</td>
<td>Q= 55.62 (33 d.f.); p=0.008</td>
</tr>
<tr>
<td>D(M)FT - all studies</td>
<td>13</td>
<td>24%</td>
<td>18% to 30%</td>
<td>p&lt;0.0001</td>
<td>Q= 26.04 (12 d.f.); p=0.011</td>
</tr>
</tbody>
</table>
## Additional tables

### 02 Random effects metaregression analyses of prevented fractions: D(M)FS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. studies</th>
<th>Slope estimate</th>
<th>95% c.i.</th>
<th>Slope interpretation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline caries</td>
<td>33</td>
<td>0.3%</td>
<td>(-0.7% to 1.3%)</td>
<td>Increase in PF per unit increase in mean baseline caries</td>
<td>0.6</td>
</tr>
<tr>
<td>Fluoridated water area</td>
<td>32</td>
<td>7%</td>
<td>(-3.9% to 17.8%)</td>
<td>Higher PF in presence of water fluoridation</td>
<td>0.2</td>
</tr>
<tr>
<td>Fluoride dentrifice use</td>
<td>32</td>
<td>-0.7%</td>
<td>(-9.5% to 8%)</td>
<td>Lower PF in presence of fluoride dentrifice use</td>
<td>0.9</td>
</tr>
<tr>
<td>Background fluorides</td>
<td>32</td>
<td>1.4%</td>
<td>(-6.3% to 9%)</td>
<td>Higher PF in presence of background fluoride</td>
<td>0.7</td>
</tr>
<tr>
<td>Rinsing frequency</td>
<td>33</td>
<td>1%</td>
<td>(-3.3% to 5.5%)</td>
<td>Increase in PF per 100 extra applications/year</td>
<td>0.6</td>
</tr>
<tr>
<td>Fluoride concentration in solution</td>
<td>34</td>
<td>1%</td>
<td>(-3.7% to 5.7%)</td>
<td>Increase in PF per 1000 extra applications/year</td>
<td>0.7</td>
</tr>
<tr>
<td>Intensity (freq times conc)</td>
<td>32 (excludes DePaola 1977)</td>
<td>11.5%</td>
<td>(-10% to 33%)</td>
<td>Increase in PF equivalent to doubling from 100 to 200 applications and increasing by 1000 ppmF</td>
<td>0.3</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>34</td>
<td>-7%</td>
<td>(-18% to 5%)</td>
<td>Lower PF with adequately concealed allocation</td>
<td>0.3</td>
</tr>
<tr>
<td>Blind outcome assessment</td>
<td>34</td>
<td>8%</td>
<td>(-11% to 13%)</td>
<td>Higher PF with blind outcome assessment indicated (not clearly stated)</td>
<td>0.9</td>
</tr>
<tr>
<td>Double blinding</td>
<td>34</td>
<td>3.5%</td>
<td>(-5.4% to 13%)</td>
<td>Higher PF with lack of double-blinding</td>
<td>0.4</td>
</tr>
<tr>
<td>Control group</td>
<td>34</td>
<td>6.3%</td>
<td>(-4.2% to 17%)</td>
<td>Higher PF for no-treatment compared with placebo</td>
<td>0.2</td>
</tr>
<tr>
<td>Drop out</td>
<td>31</td>
<td>0.6%</td>
<td>(-1.8% to 3%)</td>
<td>Increase in PF per 10 drop outs</td>
<td>0.6</td>
</tr>
<tr>
<td>Length of follow up</td>
<td>34</td>
<td>0.2%</td>
<td>(-6.9% to 7.4%)</td>
<td>Increase in PF per extra year of follow up</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Additional figures

Figure 01
Funnel Plot of D(M)FS SMDs according to standard errors of the studies included in the meta-analysis

Review: Fluoride mouthrinses for preventing dental caries in children and adolescents (THESIS CHAPTER 6)
Comparison: 01 Fluoride Mouthrinse versus Placebo/No-treatment
Outcome: 03 D(M)FS increment (SMD) - nearest to 3 years (34 trials)
<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride Mouthrinse versus Placebo/No-treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 D(M)FS increment (prevented fraction) - nearest to 3 years (34 trials)</td>
<td>34</td>
<td>14663</td>
<td>SMD (random), 95% CI</td>
<td>-0.30 [-0.36, -0.24]</td>
</tr>
<tr>
<td>02 D(M)FT increment (prevented fraction) - nearest to 3 years (13 trials)</td>
<td>13</td>
<td>5105</td>
<td>SMD (random), 95% CI</td>
<td>-0.28 [-0.37, -0.20]</td>
</tr>
<tr>
<td>03 D(M)FS increment (SMD) - nearest to 3 years (34 trials)</td>
<td>36</td>
<td>1805</td>
<td>OR (random), 95% CI</td>
<td>0.61 [0.41, 0.90]</td>
</tr>
<tr>
<td>04 D(M)FT increment (SMD) - nearest to 3 years (13 trials)</td>
<td>13</td>
<td>5105</td>
<td>SMD (random), 95% CI</td>
<td>-0.28 [-0.37, -0.20]</td>
</tr>
<tr>
<td>05 Developing one or more new caries (3 trials)</td>
<td>3</td>
<td>1805</td>
<td>OR (random), 95% CI</td>
<td>0.61 [0.41, 0.90]</td>
</tr>
<tr>
<td>06 Unacceptability of treatment as measured by leaving study early (2 trials)</td>
<td>2</td>
<td>315</td>
<td>OR (random), 95% CI</td>
<td>1.26 [0.60, 2.64]</td>
</tr>
</tbody>
</table>
Review:
Com panson
Outcome

Fiuoode m outhnnses for preventing dental c a n e s m children and ad o lesce rts (THESIS CHAPTER 6)
01 Fluonde Mouthrmse versus Placebo/N o-lreatm ent
03 tXMIFS increment (SMD) - nea rest to 3 y e ars (34 Inals)
Fluonde Mouthrmse
Mean (SD)

Study
or sutxcategory
Ashley 1977
B astos 1989
Bknldiom 1983
Craig 1981
DePaola 1977
DePaola 1980
Dfiscol 1982
Duany 1981
Firm 1975
G alag h er 1974
Heidmann 1992
Heifetz 1973
Heifetz 1982
Horowitz 1971
Horowitz 1971a
Koch 1967
Koch 1967a
Koch 1967b
Laswell 1975
McConchie 1977
Molina 1987
Moreira 1972
Moreira 1981
Packer 1975
P etersson 1998
Poulsen 1984
Radike 1973
Ringelberg 1979
Ringelberg 1982
Rugg-Gunn 1973
Ruiken 1987
Spets-H apponen 1991
Tore» 1965
van Wyk 1988

2 45
280
190
49
317
179
37 3
711
292
3 06
538
2 59
394
133
98
85
117
114
2 26
4 96
14 5
150
73
18 8
69
1 91
348
341
989
2 22
129
44
3 32
377

4 . 8114 . 21)
17. 0. 022 1155.5.544))
4 .7 2 (4 .1 9 )
1 .7 7 (2 .7 3 )
4 .4 1 1 4 .2 9 )
7 .1 4 (6 .7 0 )
1 .4 0 (2 .2 8 )
2 . 82 (4 . 39)
n . 2 2 ( 5 .1 8 )
1 0 .0 6 (6 .7 5 )
0 .7 0 (1 .5 6 )
5 .1 0 1 5 .2 4 )
2 .6 5 (3 .8 3 )
1 .0 8 (1 .9 6 )
1 .6 5 (2 .7 7 )
1 6 .1 3 (6 .8 2 )
4 .6 0 (4 .0 0 )
4 .8 2 (4 .1 6 )
1 .0 5 (1 .9 5 )
4 .7 2 (4 .4 5 )
3 .5 7 (3 .4 1 )
5 . 1 6 1 4 .6 8 )
4 .2 0 (3 .3 3 )
1 .7 2 (3 .9 3 )
2 . 7 5 (4 . 46)
2 . 4 8 1 3 .1 3 )
2 .0 2 (2 .4 6 )
4 .8 2 (5 .4 6 )
2 .6 0 (5 .4 6 )
6 .5 7 (4 .7 9 )
4 .4 1 (4 .2 9 )
2 .5 0 (3 .2 0 )
6 . 54 15. 17)
5 .2 6 (4 .7 3 )

SMD (random)
95% Cl

Placebo(NT
Mean (SD)

WeighI
%
3 .4 1
3. 10
3 .1 1
I . S3
3 .2 1
2 .7 4
3 .2 7
3 .7 3
3 .2 3
3 .6 0
4 .0 9
3. 14
3 . SO
2 .6 8
2 .4 1
2 .1 1
2 .6 4
2 .6 5
2 ,7 4
3 .7 0
2 .8 3
2 .0 3
2 . 10
2 .6 7
1 .9 4
3 .0 9
3 .7 7
3 .3 9
3 .8 6
3 .2 4
2 .3 2
1 .5 1
3 .2 5
3 .4 3

5 . o l 1 4 .6 4 )
9 .7 9 (6 .6 5 )
6 .2 5 (5 .5 5 )
2 .5 9 (2 .7 0 )
7 .5 5 (5 .7 7 )
9 . 1 1 (7 .5 1 1
2 .2 4 (2 .9 6 )
3 .2 4 ( 4 . 2 6 )
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Favours Pfacebo/NT

Fluonde m outhnnses 'o r preventing dental ca n e s m children and adolescents (THESIS CHAPTER 6)
01 Fluonde Mouthrmse versus Placebo/No-treatm enl
04 D(M)FT increment (SMD) - nea rest to 3 yea rs (13 Inals)

StiKjy
or sub-category
B astos 1989
Bfenkhom 1983
Finn 1975
Horowitz 1971
Horowitz 1971a
Koch 1967
Koch 1967a
Koch 1967b
McConchie 1977
Molina 1987
Radike 1973
Ringelberg 1979
Rugg-Gunn 1973

N
280
190
292
133
90
85
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114
496
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348
341
222

Fluonde m outhnnse
Mean (SD)
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2 .6 5 (2 .3 1 )
3 .3 4 (3 .6 8 )
0 .5 4 ( 1 .1 5 )
0 .7 9 (1 .6 8 )
7 . 48 ( 2 . 77)
2 .5 8 ( 2 .7 0 )
2 .9 0 (2 .6 7 )
2 .5 6 (3 .1 8 )
2 .3 7 (2 .3 2 )
1 . 3 9 1 1 .6 6 )
2 . 70 ( 2 .9 4 )
3 .7 4 (2 .4 9 )

2 861
Total (95% Cl)
T est tor hetero g en ety Chi* » 26.13. df *• 1 2 ( P - 0 . 0 1 ) . I * - 5 4 1%
T est for overal effect: Z * 6 45 (P < 0 00001 )

Placebo/NT
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SMD (random)
95% Cl

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0 .7 2 (1 .0 0 )
1 .6 3 (2 .6 2 )
8 .4 1 (2 .9 0 )
2 .9 5 (2 ,8 9 )
2 .7 8 (2 .8 1 )
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R eview :
C o m p a n so n ;

Fluoride m o u th n n s e s fo r p rev e n tin g den tal c a rie s in children a n d a d o le s c e n ts (T H E S IS C H A P T E R 6)
01 Flu o n d e M o u th n n se v e rs u s P la c e b o /N o -tre a tm e n t

O u tc o m e

05 D eveloping o n e o r m o re n ew c a n e s (3 tn als)

S tu d y
o r su b -c a te g o ry
Firm 1975
H eid m an n 1992
T o r e l l 9 55

T re a tm e n t
rv/N

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%

Control

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5 1 /3 3 2

Weight

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9 5 % Cl

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T o tal e v e n ts . 47 (Fluoride m o U h rin se ), 31 (NT)
T e st f o r h e tero g en eity : C h i' = 1 .4 4 . df = 1 (P = 0 .2 3 ). !» = 3 0 .7 %
T e s t f o r o v e r a l effect. Z = 0 .6 2 (P = 0 .54)
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F luonde m o u th n n s e s fo r p re v en tin g den tal c a n e s in children a n d a d o le s c e n ts (T H E S IS C H A P T E R 6)
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1050
T o tal (9 5 % C l)
T o tal e v e n ts ; 4 6 3 (T reatm en t), 3 6 5 (C ontrol)
T e s t fo r h ete ro g e n e ity : Chi= = 3 .7 6 , df = 2 (P = 0 .1 5 ). I ' = 46 8%
T e s t fo r o v e r a l effect: Z = 2 .4 9 (P = 0.01)

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Favoifs Ptacebo/NT

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CHAPTER 7

TOPICAL FLUORIDE (TOOTHPASTES, MOUTHRINSES, GELS OR VARNISHES) FOR PREVENTING DENTAL CARIES IN CHILDREN AND ADOLESCENTS
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents (THESIS CHAPTER 7)

Reviewers
Marinho VCC, Higgins JPT, Logan S, Sheiham A

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Date of last minor update: / / 
Date next stage expected: 15/10/2005
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Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing

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Systematic Reviews Training Unit, Institute of Child Health (UCL), UK
Medical Research Council, UK

External sources of support
CAPES - Ministry of Education, BRAZIL

Contribution of reviewers
All authors contributed to the development of the protocol and execution of the review. Valeria Marinho (VM) wrote the protocol, designed and implemented the search strategies, contacted authors, selected studies, assessed validity, and extracted data. Julian Higgins (JH) duplicated study selection, quality assessment, and data extraction in a sample of studies and Stuart Logan (SL) or Aubrey Sheiham (AS) were consulted where necessary. VM entered and analysed the data in consultation with JH. VM prepared the full review. All authors contributed to its revision, interpretation of results and approval.

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Potential conflict of interest
None known.
Abstract

Background
Topical fluoride therapy (TFT) in the form of varnish, gel, mouthrinse or toothpaste has been used extensively as a caries-preventive intervention for over three decades.

Objectives
To determine the effectiveness and safety of fluoride varnishes, gels, mouthrinses, and toothpastes in the prevention of dental caries in children and to examine factors potentially modifying their effect.

Search strategy
We searched the Cochrane Oral Health Group's Trials Register (May 2000), CENTRAL (The Cochrane Library Issue 2, 2000), MEDLINE (1966 to January 2000), plus several other databases. We handsearched journals, reference lists of articles and contacted selected authors and manufacturers.

Selection criteria
Randomized or quasi-randomized controlled trials with blind outcome assessment, comparing fluoride varnish, gel, mouthrinse, or toothpaste with placebo or no treatment in children up to 16 years during at least 1 year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS).

Data collection & analysis
Inclusion decisions, quality assessment and data extraction were duplicated in a random sample of one third of studies, and consensus achieved by discussion or a third party. Authors were contacted for missing data. The primary measure of effect was the prevented fraction (PF) that is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed where data could be pooled. Potential sources of heterogeneity were examined in random effects metaregression analyses.

Main results
There were 144 studies included. For the 133 that contributed data for meta-analysis (involving 65,169 children) the D(M)FS pooled prevented fraction estimate was 26% (95% CI, 24% to 29%; p < 0.0001). There was substantial heterogeneity, confirmed statistically (p < 0.0001), but the direction of effect was consistent. The effect of topical fluoride varied according to type of control group used, type of TFT used, mode/setting of TFT use, initial caries levels and intensity of TFT application, but was not influenced by exposure to water fluoridation or other fluoride sources. D(M)FS PF was on average 14% (95% CI, 5% to 23%; p = 0.002) higher in non-placebo controlled trials, 14% (95% CI, 2% to 26%; p = 0.025) higher in fluoride varnish trials compared with all others, and -10% (95% CI, -17% to -3%; p = 0.003) lower in trials of unsupervised home use compared with self applied supervised and operator-applied. There was a 0.7% increase in the PF per unit increase in baseline caries (95% CI, 0.2% to 1.2%; p = 0.004).

Reviewers' conclusions
The benefits of topical fluorides have been firmly established on a sizeable body of evidence from randomized controlled trials. While the formal examination of sources of heterogeneity between
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries has been important in the overall conclusions reached, these should be interpreted with caution. We were unable to reach definite conclusions about any adverse effects that might result from the use of topical fluorides, because data reported in the trials are scarce.
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries

Background

Dental caries and its consequences pose important and uncomfortable problems in all industrialized societies and in a large number of developing countries. Although the prevalence and severity of dental caries in most industrialized countries have decreased substantially in the past two decades, reaching averages as low as 1.1 decayed, missing and filled teeth (DMFT) in 12 year olds, nearly half of those without any tooth decay or fillings (Marthaler 1996), this largely preventable disease is still common, increases significantly with age, and remains a public health problem for a significant proportion of the world population (Burt 1998). In the United Kingdom, 30% of 3.5 to 4.5 year olds (Moynihan 1996), and 50% of 12 year olds (Downer 1995) had experienced caries in 1993. In 2000, the figures were 40% for 5 year olds in Great Britain (Pitts 2001) and 38% for 12 year olds in England and Wales (Pitts 2002). These findings demonstrate the continuing need for effective preventive strategies and treatment services for these age groups in a country that has experienced a substantial caries decline. In general, dental caries levels vary considerably between and within different countries, but children in the lower socio-economic status (SES) groups have higher caries levels than those in the upper SES groups, and these differences are consistent in industrialized and in urbanized developing countries (Chen 1995).

Fluoride therapy has been the cornerstone of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray 1991). Fluoride controls the initiation and progression of carious lesions. Intensive laboratory and epidemiological research on the mechanism of action of fluoride in preventing caries indicates that fluoride's predominant effect is topical, which occurs mainly through promotion of remineralization of early caries lesions and by reducing sound tooth enamel demineralization (Featherstone 1988). Various modes of fluoride use have evolved, each with its own recommended concentration, frequency of use, and dosage schedule. The use of topically applied fluorides in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades and fluoride containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most widely used at present, either alone or in different combinations. By definition, the term 'topically applied fluoride' describes those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect and are therefore not intended for ingestion. Fluoride gels and varnishes are typical methods of professional topical fluoride application and both delivery systems have been used in preventive programs. Fluoride gels have also been used as a self applied intervention in such programs. Fluoride rinses and toothpastes are the main forms of self applied fluoride therapy. The intensive use of fluoride mouthrinising in school programs has been discontinued in many developed countries because of doubts regarding its cost-effectiveness at a low prevalence of dental caries and are being replaced by selective fluoride therapy directed to high risk children. Such procedures usually involve the combined use of fluoride toothpastes with gels or varnishes. Toothpaste is by far the most widespread form of fluoride usage (Murray 1991a, RIPA 1991) and the decline in the prevalence of dental caries in developed countries has been mainly attributed to its increased use (Glass 1982; Rolla 1991; Marthaler 1994; O' MULLANE 1995; Marthaler 1996).

However, there is currently a debate regarding the appropriate use of fluorides. The questions being asked relate to the actual effectiveness and the potential risks (mainly in terms of fluorosis) that may be expected from the various fluoride-based caries preventive measures in an era of decreased caries prevalence and widespread availability of fluoride from multiple sources (Ripa 1991). In this context, even the need for selective professional fluoride applications has been questioned (Seppa 1998). The persistence of this debate and the variations in the use of the main...
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries suggests the need to search for meaningful ways to summarize the empirical findings on this topic systematically.

Much of the experimental research on the effectiveness of individual fluoride modalities in preventing dental caries was conducted before the 1990s, when dental caries was more common and more severe. Modalities were usually tested separately and with the assumption that the method would provide the main source of fluoride. The studies have been extensively reviewed and synthesized in a number of traditional narrative reviews which often provide very different estimates of effectiveness, probably due to differences in how the literature to be included was selected, and rarely explore the causes of variability in reported effectiveness in a formal way. To date, a few published reviews focusing mainly on the evaluation of specific fluoride active agents within specific delivery systems have used a quantitative meta-analytical approach to synthesize studies' results (Stamm 1984; Clark 1985; Johnson 1993; Helfenstein 1994; Stamm 1995; van Rijkom 1998; Bartizek 2001; Strohmenger 2001; Chaves 2002). However, there has been no systematic investigation evaluating and comparing the overall effectiveness of the main forms of topical fluoride therapy currently used in caries prevention and examining formally the main factors that may influence their effectiveness. Moreover, none of the existing reviews have attempted to identify all relevant experimental research.

Objectives

The primary objective of this review is to determine the effects of topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels and varnishes in the prevention of dental caries in children and adolescents. The secondary objective is to examine whether the effectiveness of TFT is influenced by the initial level of caries severity, the background exposure to other fluoride sources, the mode/setting of TFT use, and the form of TFT used.

The specific objectives are:
1. To determine the effectiveness and safety of topical fluoride therapy in the form of toothpastes, mouthrinses, gels and varnishes in preventing dental caries in the child/adolescent population.
2. To examine whether the effect of TFT is influenced by the level of caries severity.
3. To examine whether the effect of TFT is influenced by the background exposure to ambient levels of fluoride in water (or salt), or reported fluoride sources other than the study option(s).
4. To examine whether the effect of TFT is influenced by the mode/setting of use (self applied supervised use of TFT in preventive programmes, self applied 'unsupervised' use of TFT at home, and operator-applied use of TFT), and if this does occur, whether there is a differential effect on caries prevention among the different forms of TFT used in each mode/setting.
5. To examine whether the effect of TFT is influenced by the form of TFT used.

Criteria for considering studies for this review

Types of studies
Randomized or quasi-randomized controlled trials using or indicating blind outcome assessment, in which one form of topical fluoride therapy (TFT) (either as toothpaste, mouthrinse, gel or varnish) is compared concurrently to a placebo or no TFT group during at least 1 year/school year. Randomized or quasi-randomized controlled trials using within-group paired comparison designs (e.g. split-mouth trials of fluoride varnish, as the effect of the varnish could spread across the mouth leading to contamination of control sites), or with open outcome assessment or no indication of blind assessment, or lasting less than 1 year/school year, or controlled trials where
random or quasi-random allocation was not used or indicated were excluded.

Types of participants
Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started).
Studies where participants were selected on the basis of special (general or oral) health conditions were excluded.

Types of interventions
Topical fluoride therapy in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration (ppm F), amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year. The control group is placebo (for any method of fluoride application) or no treatment (except for brushing or flossing methods of application) resulting in the following comparison: Any single TFT described above compared with a placebo or no TFT.
Studies where the intervention consisted of any caries preventive agent/procedure in addition to any of the forms of TFT described above were excluded (e.g. fluoride-based measures used in combination, anti-plaque or anti-calculus agents, sealants, oral hygiene interventions, xylitol chewing gums, glass ionomers).

Types of outcome measures
The primary outcome measure in this review is caries increment, as measured by change from baseline in the decayed, (missing) and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. For studies in younger children the outcome measure of interest is caries increment in deciduous tooth surfaces, as measured by change in the decayed, (missing/extraction indicated), and filled surface d(e/m)fs index. Dental caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis. (See 'Methods of the review' for the different ways of reporting the decayed, (missing) and filled teeth or surfaces (D(M)FT/S) scores in clinical trials of caries preventives.)
The following outcomes were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions; tooth loss; proportion of children developing new caries; dental pain/discomfort; specific side effects (fluorosis, tooth staining/discoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting); unacceptability of preventive treatment as measured by drop outs during the trial (in non-placebo controlled studies); use of health service resources (such as visits to dental care units, length of dental treatment time). Studies reporting only on changes in plaque/calculus formation, plaque regrowth/vitality, plaque/salivary bacterial counts, or gingival bleeding/gingivitis, dentin hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc.) were excluded.

Search strategy for identification of studies
With a comprehensive search, we attempted to identify all relevant studies irrespective of language, from 1965 onwards.

ELECTRONIC SEARCHING
• Up to 1998
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries

Relevant studies were identified (for the series of topical fluoride reviews) by searching several databases from date of inception: MEDLINE (1966 to 1997), EMBASE (1980 to 1997), SCISEARCH (1981 to 1997), SSCISEARCH (1981 to 1997), ISTP (1982 to 1997), BIOSIS (1982 to 1997), CINAHL (1982 to 1997), ERIC (1966 to 1996), DISserTATION ABSTRACTS (1981 to 1997) and LILACS/BBO (1982 to 1997). Two overlapping but complementary subject search phrases (below) with low specificity (but high sensitivity), using 'free text' and 'controlled vocabulary', were formulated within Silverplatter MEDLINE around two main concepts, fluoride and caries, and combined with all three levels of the Cochrane Optimal Search Strategy for Randomized Controlled Trials (RCTs). These subject search phrases were customised for searching EMBASE and the other databases:

(a) ["DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS" all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or DMF*] and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR SMFP OR MFP OR MONOFLUOR*) or ("CARIOSTATIC-AGENTS" explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or "DENTIFRICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or CARIOSTA* or PROPHYLAXIS* or ANTICARI* or VARNISH* or LACUER* or DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRIC* or MOUTH RINS* or MOUTH RIN* or MOUTHWASH* or MOUTH WASH*).

(b) [(explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPICAL/ ALL SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MF OR SMFP OR MONOFLUOR* OR DURAPHAT)] and (CARI* or DMF* or TOOTH* or TEETH* or DENT* in TI, in AB, in MESH) or (explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or (explode MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or (MOUTH RINS* or MOUTH RIN* or VARNISH* or LACUER*)].

RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISserTATION ABSTRACTS, and LILACS/BBO. All the strategies (subject search and methodological filters) developed to search each database are fully described in a report produced for the Systematic Reviews Training Unit (Marinho 1997), and are available on request. These were used for the development of a register of topical fluoride clinical trials for the systematic reviews, as the Cochrane Oral Health Group's Trials Register was not yet developed in 1997/98.

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 1997), the Community of Science database (1998), which included ongoing trials funded by the National Institute of Dental Research (NIDR), the System for Information on Grey Literature in Europe (SIGLE) database (1980 to 1997), and OLD MEDLINE (1963 to 1965) were searched using the terms 'fluor' and 'carie' truncated. (Grey literature search had also been carried out by searching the Index to Scientific and Technical Proceedings (ISTP) and DISserTATION ABSTRACTS).

From 1999 to 2001
The following strategy was used to search LILACS/BBO in 1999 (1982 to 1998), where free text subject search terms were combined with a methodological filter for RCTs:

[(fluor$ or ppmf or ppm f or amf or snf or naf or apf or mfp or smfp or monofluor$ or duraphat$) and (cari$ or dmf$ or cpo$ or tooth$ or teeth$ or dent$ or dient$ or anticarie$ or cario$ or mouthrins$ or mouth rins$ or rinse$ or bochech$ or enjuag$ or verniz$ or vernish$ or barniz$ or laca$ or gel or gels)] and [random$ or aleator$i$ or acaso$ or azar$ or blind$ or mask$ or cego$ or...
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries or placebo or (clinical and (trial or ensaio or estudo)) or (control and (trial or ensaio or estudo)).

Four supplementary and more specific subject search phrases (including 'free text' and 'controlled vocabulary' terms), refined exclusively for the reviews on the effects of individual fluoride modalities, formulated around three concepts each (the relevant topical fluoride therapy (TFT), fluoride and caries) were used to search Silverplatter MEDLINE (up to January 2000) without methodological filters:

\[(\text{CARIE}^* \text{ or } (\text{DENT}^* \text{ near } \text{CAVIT}^*) \text{ or } \text{TOOTH}^* \text{ DECAY}^* \text{ or } \text{DMF}^* \text{ or } (\text{explode } "\text{DENTAL-CARIES}"/ \text{ALL SUBHEADINGS})) \]

and (FLUOR* or APF* or NAF* or AMINE F OR SNF* or ACIDULATED* PHOSPHATE* FLUORID* or ACIDULATED* FLUORID* or PHOSPHATE* FLUORID* or SODIUM* FLUORID* or AMINE* FLUORID* or STANNOUS* FLUORID* or (explode "FLUORIDES"/ \text{ALL SUBHEADINGS}))

and

(1) (TOOTHPASTE* or TOOTH* PASTE* or DENTIFRICE* or PASTE*) or (explode "DENTIFRICES"/ \text{all subheadings}].
(2) ((RINS* or MOUTH* RINS* or WASH* or MOUTH* WASH*) or (MOUTHRINS* or MOUTHWASH*)) or (explode "MOUTHWASHES"/ \text{all subheadings}]
(3) (FLUOR* or ... or ELMEX* or (explode "FLUORIDES"/ \text{ALL SUBHEADINGS})
and (GEL* or TRAY*].
(4) (FLUOR* or (DURAPHAT* or FLUOR PROTECTOR*) or (explode "FLUORIDES"/ \text{ALL SUBHEADINGS}) and (VARNISH*) or (LACQUER* or LAQUER*) or (VERNIZ*) or (LACKER*) or (LAKK*) or (SILANE* or POLYURETHANE*]

These strategies were adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and have also been run on CENTRAL (The Cochrane Library Issue 2, 2000) to double check.

The metaRegister of Current Controlled Trials was searched in October 2001 for ongoing RCTs using the terms 'fluoride' and 'caries'.

REFERENCE SEARCHING
All eligible trials retrieved from the searches, meta-analyses and review articles located up to January 2000 were checked for relevant references. Reviews had been identified mainly by a MEDLINE search strategy specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic, when The Cochrane Library database: Cochrane Database of Systematic Reviews (CDSR), and the CRD databases: Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED), were also searched. Reference lists of relevant chapters from preventive dentistry textbook on topically applied fluoride interventions were also consulted.

FULL TEXT SEARCHING
Prospective handsearching of the seven journals identified as having the highest yield of eligible RCTs/controlled clinical trials (CCTs) was carried out, from January 1999 until January 2000: British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (1990 to December 1999), as this was the journal with the highest yield of eligible reports.
PERSONAL CONTACT
Searching for unpublished studies (or 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published during the last two decades in order to obtain information on possible unpublished studies eligible for inclusion. All the authors of studies who had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies.

Based on information extracted mainly from included studies, a list of manufacturers of fluoride toothpastes, mouthrinses, gels and varnishes was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group, in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Fourteen manufacturers were contacted (October 2000) and information on any unpublished trials requested: Bristol-Myers Co, Colgate-Palmolive, Davies Rose-Hoyt Pharmaceutical Division, Gaba AG, Ivoclar North America, John O Butler Company, Johnson & Johnson, Oral-B Laboratories, Pharmascience, Procter & Gamble, Smithkline Beecham, Synthelabo, Unilever/Gibbs, Warner-Lambert.

Methods of the review

MANAGEMENT OF RECORDS PRODUCED BY THE SEARCHES
Because multiple databases were searched, the downloaded set of records from each database, starting with MEDLINE, was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS, BBO, CENTRAL, SIGLE and NIDR databases were not imported to Reference Manager and were checked without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filter were imported to Reference Manager for inspection, in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register and the metaRegister of Current Controlled Trials were also checked outside Reference Manager. In order to facilitate importing of all records located from searching other (non-electronic) sources to Reference Manager, we tried to locate these in MEDLINE as well. Those references that could not be downloaded in this way were entered manually. (Reports that might be identified by contacting manufacturers will be obtained to feature in updates of this review.)

RELEVANCE ASSESSMENT
All records identified by the searches were printed off and checked on the basis of title first, then by abstract (when this was available in English or in languages known by the reviewer) and/or keywords by one reviewer, Valeria Marinho (VM). Records that were obviously irrelevant were discarded and the full text of all remaining records was obtained. Records were considered irrelevant according to study design/duration, participants, or interventions/comparisons (if it could be determined that the article was not a report of a randomized/quasi-randomized controlled trial; or the trial was of less than 6 to 8 months duration; or the trial was exclusively in adults; or the trial did not address one of the four topical fluoride therapies (TFTs); or the trial did not compare a TFT to placebo or no treatment).
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries

SELECTION OF STUDIES FOR INCLUSION
With the inclusion criteria form previously prepared and pilot tested, one reviewer (VM) assessed all studies for inclusion in the review, and a second reviewer, Julian Higgins (JH), independently duplicated the process for a sample of those (approximately 30%). In addition, any study that could not be classified by the first reviewer was independently assessed by the second. A third reviewer was consulted, Stuart Logan (SL) or Aubrey Sheiham (AS), to resolve any disagreement. It was decided in advance to exclude any trial where agreement could not be reached (but this did not occur). Trial reports thought to be potentially relevant in languages not known by the reviewers were translated and the reviewer (VM) completed the inclusion form with reference to the translator. Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met.

It was considered essential to identify and check all reports related to the same study; in case of any discrepancy, authors were contacted.

QUALITY ASSESSMENT
The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Reviewers' Handbook (Clarke 2000) used in the Cochrane Review Manager software (RevMan). Allocation concealment for each trial was rated as belonging to one of three categories:
(A) Adequately concealed (an adequate method to conceal allocation is described).
(B) Concealment unclear ('random' allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
(C) Inadequately concealed (an inadequate method of allocation concealment is described).
Excluded: random (or quasi-random) allocation clearly not used in the trial, or 'random' allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:
(A) Double-blind (blind outcome assessment and use of placebo described).
(B) Single-blind (blind outcome assessment stated and no placebo used).
(C) Blinding indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment, e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind outcome assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).
Excluded: clearly open outcome assessment used or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, or x-rays registered independently of clinical examination, of use of a placebo, and of examiners clearly not involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated the process for a random sample of approximately one third. Any disagreement was discussed and where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not be resolved an effort was made to contact authors directly to clarify the method used to conceal allocation or whether assessment of the main outcome had been carried out blind.

Checking of interobserver reliability was limited to these validity assessments.
Other methodological characteristics of the trials such as completeness of follow up (proportion excluded) and handling of exclusions (extent to which reasons for attrition are explicitly reported, or losses are independent of treatment allocated) were not used as thresholds for inclusion. However, all assessments of study quality are described in the table of included studies (refer to individual reviews of fluoride gels, varnishes, mouthrinses and toothpastes) and were coded for possible use in metaregression or sensitivity analyses.

**DATA EXTRACTION**

Data from all included studies were extracted by one reviewer (VM) using a pilot tested data extraction form. A second reviewer (JH) extracted data from a random sample of approximately one third of included studies. Again, data that could not be coded by the first reviewer were independently coded by the second, any disagreements were discussed and a third reviewer consulted to achieve consensus where necessary. (In future updates all reports will be data extracted and quality assessed in duplicate.) Data presented only in graphs and figures were extracted whenever possible, but were included only if two reviewers independently had the same result. Attempts were made to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. Papers in languages not known by the reviewers were data extracted with help from appropriate translators.

Additional information related to study methodology or quality that was extracted included: study duration (years of follow up); comparability of baseline characteristics: methods used pre-randomization in sizing/balancing (stratification based on relevant variables) or used post-randomization in analysing/adjusting for possible differences in prognostic factors between groups; objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors); any co-intervention and/or contamination. Information on sponsoring institutions and manufacturers involved was also recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries severity at start (average DMFS, DFS, or other measure), background exposure to fluoride sources other than the study option(s) (in water, topical applications, etc.), year study began, place where study was conducted (country), setting where participants were recruited, and dental treatment level (F/DMF). Characteristics of the interventions that were extracted included: fluoride modality(s), mode of application (how the intervention was delivered), methods (technique/device) of application, prior- and post-application, fluoride active agents and concentrations used, frequency and duration of application, and amount applied.

Different ways of assessing/reporting caries increment in the trials (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units of measurement (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (permanent/deciduous teeth/surfaces, first molar teeth, approximal surfaces, etc.), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiographical), and approaches to account or not for reversals in caries increment adopted (in a net or observed/crude caries increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow ups), and where assessments of caries increments were made during a post-intervention follow-up period, the length of time over which outcomes were measured after the intervention ended was noted.
As we were aware that caries increment could be reported differently in different trials we
developed a set of a priori rules to choose the primary outcome data for analysis from each study:
data on permanent teeth would be chosen over data on deciduous teeth; data on surface level
would be chosen over data on tooth level; DFS data would be chosen over DMFS data, and this
would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data
for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over
data for 'erupted' only, and this over data for 'erupting' only; data from 'clinical and radiological
examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological'
only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated
lesions; net caries increment data would be chosen over crude (observed) increment data; and
follow up nearest to 3 years (often the one at the end of the treatment period) would be chosen
over all other lengths of follow up, unless otherwise stated. When no specification was provided
with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth
and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices
described above were assumed.

All other relevant outcomes assessed/reported in the trials were also recorded/listed.

ANALYSES

• Handling of missing main outcome data
It was decided that missing standard deviations for caries increments that were not revealed by
contacting the original researchers would be imputed through linear regression of log standard
deviations on log mean caries increments. This is a suitable approach for caries prevention studies
since, as they follow an approximate Poisson distribution, caries increments are closely related
(similar) to their standard deviations (van Rijkom 1998).

• Handling of results of studies (main outcome) with more than one treatment arm
In the studies with more than one relevant intervention group (but of the same modality of TFT)
and a common control group, such as those comparing different concentrations of fluoride ions in a
mouthrinse for example to a placebo/no treatment group, raw results (the numbers, mean caries
increments and standard deviations) from all relevant experimental groups were combined in order
to obtain a measure of treatment effect (this enables the inclusion of all relevant data for each form
of TFT in the primary meta-analysis, although may slightly compromise any secondary
investigations of dose response). In the studies comparing two or more relevant modalities of TFT
to a common placebo/no treatment group, we have divided the control group into approximately
equally sized smaller groups to provide a pairwise comparison for each modality. Means and
standard deviations were unchanged.

• Choice of measure of effect and meta-analyses of main outcome
The chosen measure of treatment effect was the prevented fraction (PF), that is (mean increment in
the controls minus mean increment in the treated group) divided by mean increment in the controls.
For an outcome such as caries increment (where discrete counts are considered to approximate to a
continuous scale and are treated as continuous data) this measure was considered more appropriate
than the mean difference or standardised mean difference, since it allows combination of different
ways of measuring caries increment and a meaningful investigation of heterogeneity between trials.
It is also simple to interpret. The meta-analyses were conducted as inverse variance weighted
averages. Within-study variances were estimated using the formula presented in Dubey 1965 which
was more suitable for use in a weighted average, and for large sample sizes the approximation
should be reasonable. Random effects meta-analyses were performed throughout in RevMan
4.2.1/RevMan Analyses.

Deciduous and permanent teeth were analysed separately throughout.

For illustrative purposes, when overall results were significant, the results were also presented as the number of children needed to treat (NNT) to prevent one carious tooth/surface. These were calculated by combining the overall prevented fraction with an estimate of the caries increment in the control groups of the individual studies.

- **Assessment of heterogeneity and investigation of reasons for heterogeneity**

Heterogeneity in the results of the trials was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95% confidence intervals and by formal tests of homogeneity (Thompson 1999).

In addition to aspects of study quality, four potential sources of heterogeneity were specified a priori as investigations of these formed part of the primary objectives of the review. We hypothesised that: (1) the effect of TFT differs according to the baseline levels of caries severity; (2) the effect of TFT differs according to exposure to other fluoride sources (in water, in toothpastes, etc.); (3) the effect of TFT differs according to mode of use; and (4) forms of TFT used. The association of these factors with estimated effects (D(M)FS PFs) were examined by performing random effects meta-regression analyses in Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998). The random effects regression model described in detail elsewhere (Thompson 1999) relates treatment effect to study characteristics assuming a normal distribution for the residual errors with both a within- and an additive between-study component of variance. The between-studies variance was estimated by an iterative procedure, using an estimate that is based on a restricted maximum likelihood method.

To allow such investigation, relevant data were dealt with as follows: data on 'baseline levels of caries' were calculated from the study sample analysed (final sample) and in connection with the caries increment index chosen, unless otherwise stated, and were averaged among all relevant study groups.

Data on 'background exposure to other fluoride sources' combined data on the use of fluoride toothpaste or any fluoride other than the study option(s) and the consumption of fluoridated water (or salt) and were grouped into two categories: one for studies which were based on samples provided with non-fluoride toothpaste/reporting no/low use of other fluorides and which were from non-fluoridated areas (non exposed), and another for studies based on samples using any fluoride other than the study option(s) or studies in fluoridated communities or both. When background exposure to fluoride toothpaste was not clearly indicated in studies carried out in developed countries, it was assumed that fluoride toothpaste was widely used from the middle of the 1970s (Ripa 1989); this information was sought from authors (or obtained from other sources) when missing from studies carried out in other locations. When data on the year a study had begun was not provided this was calculated as a 'probable date' by subtracting the duration of the study (in years) plus one extra year, from the publication date of the study. Background exposure to fluoride rinses, gels, tablets, etc. should be reported to be involving the majority in a study to be considered as such, otherwise it was assumed these had not been used. Exposure to water fluoridation should be above 0.3 ppm F; when information on the fluoridation status of a site was not available/obtainable, no assumptions were made.

Data on the 'fluoride application mode of use and forms of TFT' were classified as self applied unsupervised use (of toothpaste or mouthrinse at home), self applied supervised use (of gel, mouthrinse or toothpaste in school-based programmes), and operator-applied use (of gel or
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental varnish). The four modalities of TFT were categorised as such.

Further potential sources of heterogeneity were investigated by metaregression based on previous investigations of covariates carried out in the individual TFT reviews. These included investigations of the potential influence of fluoride concentration and frequency of use. (Data on 'concentration applied' and 'frequency of use' have not been categorised, but a 'total intensity of application per year' covariate was produced by multiplying frequency of application (per year) by fluoride concentration (in ppm F).) In multiple arm studies we have averaged this intensity score over fluoride treatment groups. These 'post hoc' analyses are clearly identified and the results should be treated with caution. Sensitivity analyses were performed as appropriate.

- **Investigation of publication and other biases**
  A funnel plot (plots of effect estimates versus the inverse of their standard errors) was drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, though may also represent a true relationship between trial size and effect size. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger et al (Egger 1997).

- **Measures of effect and meta-analysis of other outcomes**
  For outcomes other than caries increment, continuous data were to be analysed according to differences in mean treatment effects and their standard deviations. Dichotomous outcome data were to be analysed by calculating risk ratios (RR) or, for adverse effects of fluoride treatment, risk differences (RD). RevMan 4.2 was used for estimation of overall treatment effects. Again, a random effects model was used to calculate a pooled estimate of effect. As a general rule only (relevant) outcomes with useable data were shown in the analyses tables.

**Description of studies**

**SEARCH RESULTS**

Our initial multiple database search (1997/98) produced the following total number of records, according to database searched: MEDLINE, 4599; EMBASE, 5052; BIOSIS, 421; SCISEARCH, 514; SSCISEARCH, 169; ISTP, 66; CINAHL, 133; ERIC, 60; DISSEITATION ABSTRACTS, 95, LILACS, 48, BBO, 47, CENTRAL, 86, SIGLE, 6. Searching OLD MEDLINE produced 545 records, and the Community of Science database, 24 records. In the second stage of searches (1999), searching LILACS and BBO with a modified search strategy produced 210 records (142 and 68 records respectively). The more specific MEDLINE searches (by individual modalities of topical fluoride therapy (TFT)) performed without a randomized controlled trial (RCT) filter produced 2441 records, and the searches performed in the Cochrane Oral Health Group's Trials Register (May 2000) produced 479 records. Searching the metaRegister of Current Controlled Trials for ongoing studies produced 5 records. Searching the metaRegister of Current Controlled Trials for ongoing studies produced 5 records. Many records retrieved through electronic search were duplicates merged later in the core database, and many appeared more than once in different databases and/or searches performed (overlapped). Searching other non-electronic sources (reference lists of potentially relevant reports, review articles or book chapters, relevant journals, and contacting authors) produced 171 additional records for inspection. (Any search results produced by contacting manufacturers will feature in updates of this review.)

**RELEVANCE ASSESSMENT RESULTS**

When the records produced from all the above searches were screened, a total of 713 reports were considered potentially eligible and further assessment was sought.
STUDY SELECTION RESULTS
Seven hundred and thirteen reports were sought for detailed assessment for inclusion, of which 19 full text reports could not be obtained (most of these were incomplete references to non-English reports and unpublished studies conducted decades ago by toothpaste manufacturers). Two hundred and ninety-three reports (293) were considered immediately irrelevant for this review, largely as a result of the types of intervention compared with, or used in addition to the relevant topical fluoride treatments (including head to head studies without a placebo or no treatment group), and due to the types of study design described (historical controls or other non-experimental designs).

Thus, 287 studies (401 reports) are considered/cited in this review. These comprise 214 reports relating to 144 included studies, 157 reports relating to 115 excluded studies, two reports relating to two ongoing (fluoride varnish) studies, and 28 reports relating to 26 studies waiting assessment (either because they require translation, because translation and contact with the authors have not ascertained whether all inclusion criteria have been met, or because additional information has not been obtained yet for two studies in abstract form).

Listed either under excluded or included studies are 91 reports (25%) in languages other than English: 39 in German, 14 in Portuguese, seven in Spanish, seven in Russian, five in Japanese, four in French, three in Hungarian, three in Danish, two in Dutch, two in Italian, two in Polish, one in Czech, one in Bulgarian, one in Norwegian. The reports in Portuguese, Spanish and Italian have been assessed by the contact reviewer, and the others by the reviewer with a translator (some reports have not been translated due to the availability of a full text English report of the same study, or because sufficient information was available in the English abstract to exclude the study).

EXCLUDED STUDIES
See 'Characteristics of excluded studies' for the description of reasons for rejecting each study.

We have excluded 33 fluoride varnish studies, 11 fluoride gel studies, 38 fluoride mouthrinse studies, and 33 fluoride toothpaste studies.

All 115 studies were excluded for a variety of reasons. Twenty-eight studies had non-fluoride or other fluoride-based interventions, or active agents in addition to the ones considered in this review. In one study a fluoride intervention was associated to the control group, and in two studies the fluoride rinsing solution was supposed to be swallowed. Five studies involved children with specific health problems, and eight studies included participants older than 16 years of age. In two studies, the length of follow up was 6 months (and relevant outcomes were not reported in one of these). Ten (fluoride varnish) studies used the within-subject paired design, or 'split-mouth' design. The remaining studies were excluded for reasons related to random allocation or blind assessment of outcome as described in the Methods section.

INCLUDED STUDIES
See 'Characteristics of included studies' tables of individual reviews of fluoride gels, varnishes, mouthrinses, and toothpastes for details of each study.

There are 144 trials included. The studies conducted by Forsman 1974; Hargreaves 1973; Horowitz 1971a; Koch 1967; Koch 1967c; Marthaler 1970; Marthaler 1970b; Zacherl 1970; Held 1968; Marthaler 1965; and Torell 1965 have been treated as two (or more) independent trials each, because the results for the two (or more) age groups, and/or study sites, and/or comparisons involved were reported separately as distinct studies. There were also completely distinct studies.
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental disease has been studied extensively. Zacherl 1972/Zacherl 1972a; Koch 1967a/Koch 1967b; Koch 1967e/Koch 1967f; and Slack 1967/Slack 1967a. All 214 reports were published between 1955 and 1999. The 144 trials were conducted between 1954 and 1996: three in the 1950s, the great majority in the 1960s and 1970s, 16 in the 1980s, and four in the 1990s. The majority of studies were conducted in industrialized countries, especially USA, UK, European and Scandinavian countries, but there were at least 14 conducted in other countries. Twenty-two studies had at least one report published in languages other than English and 12 studies had only non-English publications (one of these, Treide 1988, reported data for deciduous teeth only).

There are 74 toothpaste trials included, followed by 36 mouthrinse trials, 25 gel trials, and nine varnish trials (the same trials are included in the separate reviews of fluoride toothpaste, mouthrinse, gel and varnish respectively). Fifty-eight studies had more than one topical fluoride treatment group compared to a control. Forty-six studies compared different characteristics of the same modality of TFT (e.g. different concentrations of fluoride ions in a mouthrinse) and eight studies (which have been entered as 16 comparisons/studies) compared two or more relevant modalities of TFT to a common control group (in two of these, entered as four studies, different features of each modality were compared concomitantly). One hundred and twenty-five trials used a placebo control group and the remaining 19 used a no treatment control group. Study duration ranged from 1 to 6 years, with the great majority of studies lasting 2 or 3 years. Studies were generally large with only 15 allocating less than 100 children to relevant study groups, nearly all recruited from school settings.

There was substantial variation in the characteristics of participants and interventions in the trials included. While the majority of studies reported on exposure or not to fluoridation, background exposure to fluoride toothpaste (or other fluoride sources) was clearly reported in very few studies. Caries prevalence at baseline was generally reported. All fluoride varnish and gel trials reported whether or not applications were carried out by professionals, and with two exceptions, all fluoride toothpaste, mouthrinse and gel trials (of self applied gel) reported whether or not TFT use was carried out under supervision (by dental personnel, trained non-dental personnel, or by mothers and dental personnel in preventive programmes; or 'unsupervised' at home). Fluoride concentrations and application frequencies varied greatly among TFT modalities and within each modality, and were reported in the great majority of studies.

All but five of the 144 trials reported caries increment data (or data from which these could be derived) at the tooth surface level (D(M)FS was reported in 135 trials, defs in one of these, and d(e/m)fs in the other four trials). Data at the tooth level for the permanent dentition (D(M)FT) were reported in 79 of the 139 trials that reported any caries increment data; only one of the five trials that reported caries increment data for deciduous teeth (dmfs) reported these data at the tooth level (dmft). With regard to the components of the DMFS index used, 92 trials reported DMFS data and 56 trials reported DFS data. Sixty-five trials presented D(M)FS data at more than one follow-up time. 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: NCA = non-cavitated incipient enamel lesions clinically visible as white spots or discoloured fissures; CA = lesions showing loss of enamel continuity that can be recorded clinically (undermined enamel, softened floor/walls) or showing frank cavitation; ER = any radiolucency in enamel/enamel-dentin junction; DR = radiolucency into dentin. Many trials presented results using one caries grade only (usually CA/ER or CA/DR), others either did not report the grade, or reported caries increment data at both levels of diagnosis, in which case CA was chosen. Data on the state of tooth eruption considered were not clearly specified in many trials. The seven studies of Marthaler used partial recording as opposed to the full mouth recording used in all others.
The 'Table of included studies' in the individual reviews of fluoride gels, varnishes, mouthrinses, and toothpastes provides a description of all the main outcome data reported from each study with the primary measure chosen featuring at the top.

Other dental caries data reported in a few trials: caries incidence/attack rate, caries progression, proportion of children developing new caries, proportion of children not remaining caries-free, proportion of teeth developing new caries and failures (carious teeth) over time, proportion of caries-free teeth/surfaces which developed caries.

Data on adverse effects were reported in a few trials (partially reported or unusable data in many of these): stain score, proportion of children with tooth staining, signs of sensitivity in oral soft tissue, adverse symptoms (nausea/vomiting), etching of enamel. Fluorosis data have not been reported in any of the trials. Data for unacceptability of treatment (as measured by dropouts/exclusions) were reported in 10 non-placebo controlled trials.

ONGOING STUDIES

See 'Characteristics of ongoing studies' table (in the fluoride varnish review) for details of each study.

We have identified two ongoing randomized trials of fluoride varnish, one from UK and the other from USA.

Methodological quality of included studies

Based on 28 studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, interrater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73).

As expected, there was a considerable variation in the quality of the studies in this review (using the reported information and additional information obtained from investigators). One hundred and nine trials included in this review were described as randomized but provided no sufficient description on how the 'random' allocation was done, and 21 trials were considered to be quasi-randomized. Double-blinding was described in 118 trials, single-blinding (blind outcome assessment but no placebo used) was described in 14 trials, and blind outcome assessment was indicated in 12 trials.

Seventy-two per cent (72%) of the participants originally enrolled in these studies were included in the final analysis (60,423 analysed out of 85,093 initially randomized). These data exclude 27 of the 144 included studies which provided no information on the number of participants randomized to relevant groups. Drop-out rates were obtained from all but 11 of the 144 included studies and ranged from 4% at 2 years to 66% at 3 years. The most common reason for attrition was that participants were not available for follow-up examination at the end of the study.

Cluster randomization was used in two trials (Bravo 1997; Ruiken 1987) where school classes (in the first trial) and schools (in the second trial) were used as units of randomization and children used as units of analysis. Individuals were allocated to study arms in all other trials, and each participant's caries incidence, over a period of time was used as the unit of analysis.
Results

EFFECT OF TOPICAL FLUORIDES ON DENTAL CARIES INCREMENT
The effects of fluoride toothpaste, mouthrinse, gel and varnish on dental caries increment (as measured by the DMF index) were reported in a variety of ways in the included studies. Where appropriate and possible these have been combined to produce pooled estimates as described in the Methods section. The results are reported separately here for:
(1) Decayed, (Missing) and Filled Surfaces Prevented Fraction (D(M)FS PF), with results from analyses of associations between this and study characteristics;
(2) Decayed, (Missing) and Filled Teeth Prevented Fraction (D(M)FT PF);
(3) decayed, (missing/extraction indicated), and filled surfaces Prevented Fraction (d(m/e)fs PF).
Estimates of the effects of topical fluoride therapy (TFT) are therefore presented for caries increment in the permanent and in the deciduous dentitions.

Five included studies (Brandt 1972; de Liefe 1989; Homan 1969; Powell 1981; Slack 1964) did not contribute (caries increment) data suitable for meta-analysis, although they are retained in the review (characteristics of each are described in the 'Table of included studies' of the relevant individual reviews, and the basic findings reported or obtained from the authors are described below). Standard deviations (SD) of mean caries increment data in the permanent dentition (new D(M)FS) were (partly) missing in 34 of the 135 studies which contributed data (Abadia 1978; Abrams 1980; Bastos 1989; Bijella 1981; Clark 1985; DePaola 1977; Dolles 1980; Driscoll 1982; Finn 1975; Fogels 1979; Forsman 1974; Forsman 1974a; Gallagher 1974; Hargreaves 1973; Hargreaves 1973a; Hargreaves 1973b; Heidmann 1992; Held 1968; Held 1968a; Held 1968b; James 1977; Kinkel 1972; Laswell 1975; Mestrinho 1983; Muhler 1955; Poulsen 1984; Ran 1991; Ran 1991a; Ruiken 1987; Segal 1967; van Wyk 1986). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries increment), (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses. Similarly, this regression equation was used to estimate missing standard deviation data for 15 of the 79 trials reporting D(M)FT data (Abrams 1980; Bastos 1989; Bijella 1981; Clark 1985; Fogels 1979; Hargreaves 1973; Hargreaves 1973a; Hargreaves 1973b; Heidmann 1992; Held 1968; Held 1968a; Held 1968b; James 1977; Kinkel 1972; Laswell 1975; McConchie 1977; Mestrinho 1983; Modeer 1984; Moreira 1972; Muhler 1955; Poulsen 1984; Ran 1991; Ran 1991a; Ruiken 1987; Segal 1967; van Wyk 1986). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries increment), (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses. Similarly, this regression equation was used to estimate missing standard deviation data for 15 of the 79 trials reporting D(M)FT data (Abrams 1980; Bastos 1989; Bijella 1981; Clark 1985; Fogels 1979; Hargreaves 1973; Hargreaves 1973a; Hargreaves 1973b; Heidmann 1992; Held 1968; Held 1968a; Held 1968b; James 1977; Kinkel 1972; Laswell 1975; McConchie 1977; Mestrinho 1983; Muhler 1955). Standard deviation data were missing in four of the five trials reporting mean caries increment data in the deciduous dentition (Clark 1985; Englander 1978; Frostell 1991; Treide 1988). The 'd(e/m)fs' for these trials were also estimated with the regression equation. Only one of the studies reporting d(e/m)fs data is also included in the analysis of D(M)FS PF (Clark 1985).

There were eight included studies that had a common control group and tested two different modalities of TFT (Ashley 1977; Blinkhorn 1983; DePaola 1980; Mainwaring 1978; Marthaler 1970; Marthaler 1970a; Ran 1991, Ringelberg 1979). These have been entered as 16 comparisons/studies (dividing up the control groups into approximately equally sized smaller groups to provide a pairwise comparison for each modality; means and standard deviations were unchanged).

We have decided to exclude the trials of Ran 1991/Ran 1991a (fluoride gel and toothpaste comparisons respectively with a common control group) from all analyses because the control DMFS increment was very small (0.2) in these comparisons, resulting in a poor estimate of PF.
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental decay

(1) Effect on permanent tooth surfaces: D(M)FS PF
The random effects meta-analysis of all 133 trials combined suggested a clear benefit from the use of topical fluorides. The D(M)FS PF pooled estimate was 0.26 (95% confidence interval (CI), 0.23 to 0.29; p < 0.00001). However, substantial heterogeneity in results could be observed graphically and statistically (chi square = 745.25 on 132 degrees of freedom, p < 0.00001). The [method of moments-based] estimate of among-trial variance in the random effects meta-analysis was 0.018, corresponding to a standard deviation of 0.134. Thus, an approximate, though anti-conservative, interval in which at most 95% of underlying PFs might lie is from 0.262 - 1.96*0.134 to 0.262 + 1.96*0.134, that is from 0.00 to 0.53. This provides strong evidence of a generalizable beneficial effect of topical fluoride therapy.

(a) Metaregression, subgroup and sensitivity analyses: D(M)FS PF
Metaregression analyses were performed to examine potential associations between study factors and the estimated treatment effect of topical fluorides. Univariate metaregression suggested a significant association between estimates of D(M)FS PFs and the following pre-specified trial characteristics: baseline caries levels, mode/setting of TFT use (unsupervised self applied home use/supervised self applied use in school-based programmes/operator-applied use), and type of TFT used (fluoride varnish/gel/mouthrinse/toothpaste). Further univariate metaregression analyses showed a significant association between estimates of D(M)FS prevented fractions and type of control group (placebo/no treatment), language of publication (English/other than English only), method of application (paint or tray/brush or rinse), fluoride concentration, and 'total intensity of application', but statistical significance for 'intensity of application' (frequency x concentration) was lost when the trial of Di Maggio 1980, a study with an unusually large PF, and hence of high influence, was excluded, in a sensitivity analysis. Univariate metaregression did not reveal any statistically significant associations between estimates of D(M)FS prevented fractions and the pre-specified factors background exposure to fluoridated water or background exposure to other fluoride sources. In addition, no statistically significant associations were revealed in univariate metaregression between estimates of D(M)FS PFs and allocation concealment (random/quasi-random), blinding of outcome assessment (blind/blind likely or unclear), drop-out rate, length of follow up, frequency of use, mode of use (operator/self applied) or fluoride agent used (APF/AmF/NaF/SMFP/SnF2).

The difference between TFT types (indirect comparisons) shown in the univariate analysis relates to a greater benefit of TFT with the use of fluoride varnish. This modality has been found to be significantly different (coefficient, 0.20; 95% CI, 0.08 to 0.33; p = 0.001) from the other three types of TFT (fluoride gel/mouthrinse/toothpaste), while differences among these three modalities were not obvious. The analysis involved all 133 included trials (seven fluoride varnish trials, 22 fluoride gel trials, 34 fluoride rinse trials and 70 toothpaste trials). When the analysis was restricted to 126 trials of fluoride gel, mouthrinse and toothpaste, no significant differences among these or between each and the others were indicated either, although failure to identify such differences may be due to low power. The unadjusted pooled estimate of treatment effects from the seven fluoride varnish trials was 0.46 (95% CI, 0.30 to 0.63; p < 0.0001); from the 22 fluoride gel trials was 0.28 (95% CI, 0.19 to 0.37; p < 0.0001), from the 34 fluoride mouthrinse trials was 0.26 (95% CI, 0.23 to 0.30; p < 0.0001), and from the 70 fluoride toothpaste trials was 0.24 (95% CI, 0.21 to 0.28; p < 0.0001). These results have been reported and examined in detail in separate component reviews in this series focusing on the effectiveness of each TFT modality.

Metaregression results also clearly indicated a greater treatment effect in trials with no treatment rather than placebo control groups (coefficient, 0.16; 95% CI, 0.08 to 0.23; p < 0.0001). The
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental disease

The pooled estimate of treatment effect on D(M)FS PF from the 17 trials with a no treatment control group was 0.40 (95% CI, 0.31 to 0.49; p < 0.0001), while that from the 116 placebo-controlled trials was 0.24 (95% CI, 0.22 to 0.27; p < 0.0001). However, heterogeneity among the 116 trials with placebo control groups was not substantially less (Q = 575.336 on 115 degrees of freedom, p < 0.0001) than that observed when all trials were included in the meta-analysis.

Statistical significance was not lost when both factors, TFT types and type of control group, were used in the metaregression model; i.e. greater treatment effects were still shown for fluoride varnish trials compared with the other modalities of topical fluorides (coefficient, 0.14; 95% CI, 0.02 to 0.26; p = 0.025) and in trials with no treatment rather than placebo control groups (coefficient, 0.14; 95% CI, 0.05 to 0.23; p = 0.002). In addition, little change could be observed in the metaregression results when all univariate metaregression analyses were performed in the subset of 117 placebo controlled trials. Because both these covariates have been identified as strong predictors of treatment effect, we decided to adjust all metaregression analyses for type of TFT (all four levels) and type of control group. In addition, we have decided to present the results of the D(M)FS PF meta-analyses subgrouped by type of control group and TFT types.

The random effects meta-analyses of D(M)FS PFs, subgrouped by type of control group and TFT types, are presented in RevMan Analyses. The pooled estimate of treatment effect on D(M)FS PF from the three placebo-controlled fluoride varnish trials was 0.40 (95% CI, 0.09 to 0.72; p = 0.01), from the 13 placebo-controlled fluoride gel trials was 0.21 (95% CI, 0.14 to 0.28; p < 0.00001), from the 30 placebo-controlled fluoride mouthrinse trials was 0.26 (95% CI, 0.22 to 0.29; p < 0.00001), and from the 70 placebo-controlled fluoride toothpaste trials was 0.24 (95% CI, 0.21 to 0.28; p < 0.00001). Pooled estimates from the trials with no treatment control groups were: 0.52 (95% CI, 0.35 to 0.69; p < 0.00001) for fluoride varnish, 0.38 (95% CI, 0.23 to 0.53; p < 0.00001) for fluoride gel, and 0.33 (95% CI, 0.26 to 0.40; p < 0.00001) for fluoride rinse; there were no non-placebo controlled fluoride toothpaste trials. [Differences between the subgroup results from metaregression may differ from differences between the results of separate meta-analyses in separate subgroups due to an assumption of similar residual heterogeneity among PFs made in the metaregression analyses.]

We repeated the metaregression analyses adjusting for type of control group and all four levels of TFT types. The association between baseline caries and D(M)FS PF remained significant (and the regression coefficients almost unchanged) when both factors were included in the model (coefficient, 0.007; 95% CI, 0.002 to 0.01; p = 0.004). Lack of statistically significant associations remained between estimates of D(M)FS prevented fractions and background exposure to fluoridated water (coefficient, 0.03; 95% CI, -0.03 to 0.09; p = 0.36) or background exposure to any fluoride source (coefficient, -0.02; 95% CI, -0.07 to 0.04; p = 0.56). For the three modes/settings of TFT use categories, univariate meta-regression analysis had indicated a lower treatment effect with unsupervised home use of TFT (some toothpaste trials only) (coefficient, -0.08; 95% CI, -0.13 to -0.03; p = 0.002) compared with self applied supervised use or operator-applied use, and no significant differences between these two. This association (unsupervised use of TFT and D(M)FS PF) remained when adjusted first by type of control group (coefficient, -0.06; 95% CI, -0.11 to -0.01; p = 0.025), and then by TFT type (coefficient, -0.10; 95% CI, -0.17 to -0.03; p = 0.003). A higher treatment effect with supervised use of self applied TFT in school programmes (virtually all mouthrinse trials, and some toothpaste and gel trials) compared with unsupervised use and operator-applied TFT, not shown in the univariate analysis, appeared when adjusting for type of control group (coefficient, 0.06; 95% CI, 0.01 to 0.11; p = 0.015) and...
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries increased and became highly significant when TFT types were added to the model (coefficient, 0.11; 95% CI, 0.05 to 0.17; p < 0.0001). A lower treatment effect with operator-applied TFT also appeared in the model (coefficient, -0.13; 95% CI, -0.27 to -0.00; p = 0.049). Within each subgroup, statistically significant differences in treatment effect between fluoride varnishes and gels remained in the operator-applied mode of TFT use, and no statistically significant differences were shown among the three TFT types in the self-applied supervised mode of use, or between fluoride rinse and toothpaste in the unsupervised mode of use (only two fluoride mouthrinse trials in this subgroup however). Associations between prevented fraction and language of publication remained when adjusting for type of control group and TFT types, where a higher PF was shown for trials reported only in languages other than English (coefficient, 0.11; 95% CI, 0.02 to 0.19; p = 0.02), but associations of D(M)FS PFs with method of application or with fluoride concentration became non-significant when adjusted by type of control group and TFT types. The associations between D(M)FS PFs with frequency of application and intensity of application became significant when type of control group and TFT types were included in the metaregression (with or without the trial of Di Maggio 1980).

The association between type of control group and D(M)FS prevented fraction remained significant when each investigated potential effect modifier was included in all bivariate or multivariate metaregression analyses (with or without the trial of Di Maggio 1980). The associations seen between TFT types (differences in treatment effect between fluoride varnish and that of other TFTs) and D(M)FS prevented fraction also remained significant throughout, except when adjusted by background exposure to fluorides (association between PF and exposure to other fluoride sources remaining non-significant in the model), or by fluoride concentration (association between PF and fluoride concentration becoming non-significant in the model), irrespective of exclusion or not of the trial of Di Maggio 1980. However, associations between language of publication and prevented fraction did not remain after excluding the trial of Di Maggio 1980 from the analyses (in univariate and multivariate metaregression). Further sensitivity analysis removing all but the 12 trials published only in languages other than English produced a D(M)FS pooled estimate of 0.34 (95% CI, 0.20 to 0.48; p < 0.0001), with substantial heterogeneity in results (Q = 122.181 on 11 degrees of freedom, p < 0.0001).

When the effect of each relevant covariate (type of control group, all four levels of TFT types, all three levels of mode/setting of TFT use, background exposure to any fluoride, baseline caries, and intensity of application) was controlled for all others in the metaregression model there remained strong associations between DM(F)S PF and type of control group (0.13 higher PF with no treatment control, 95% CI, 0.05 to 0.21; p = 0.002), baseline caries (0.008 increase in PF per unit increase in caries, 95% CI, 0.004 to 0.012; p < 0.0001), total intensity of application (0.00002 increase in PF per extra equivalent to 100 more applications 1000 ppmF higher, 95% CI, 0.000008 to 0.00004; p = 0.002), mode/setting of TFT use (-0.08 lower PF with unsupervised home use compared with supervised use in preventive programmes, 95% CI, -0.15 to -0.02; p = 0.01; and both not significantly different from operator-applied use), and TFT type (-0.20 lower PF with toothpaste compared to fluoride varnish, 95% CI, -0.39 to -0.02; p = 0.033; and both not significantly different from mouthrinse or gel).

All metaregression results, in each case adjusting for type of control group and all four levels of TFT types, are provided in 'Additional Table 01: Random effects metaregression analyses of prevented fractions: D(M)FS'. The influential study by Di Maggio 1980 is omitted from three analyses: intensity of application and frequency of application with prevented fraction, and language of publication with prevented fraction.
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing denta

It should be noted that although the number of data points (comparisons) in this review is unusually high, reducing the possibility of spurious claims of association, all metaregression results should be interpreted with a degree of caution given the large number of comparisons made and the observational nature of the comparisons.

The additional uncertainty we should have about the cluster randomized trials by Bravo 1997 and Ruiken 1987 had been taken account of in sensitivity analyses performed in previous component reviews, where the variances of the prevented fraction estimates were inflated (using a conservative value for the intraclass correlation coefficient (ICC)). The adjusted results were virtually identical to the analyses, ignoring the cluster randomized design, since the estimates for the trials were similar to the meta-analyses results and altering their weight had minimal effect.

In order to illustrate the magnitude of the overall effect of topical fluorides, numbers of children needed to treat (NNT) to prevent one D(M)FS were calculated based on the pooled D(M)FS PF and on the caries increments in the control groups of the trials that contributed data to the meta-analysis. The overall caries-inhibiting effect (% PF) derived from the pooled results of the 133 trials was 26% (95% CI, 23% to 29%); the caries increments in the included trials ranged from 0.2 to 7.7 D(M)FS per year. In populations with a caries increment of 0.2 D(M)FS per year (at the lowest end of the results seen in the included studies), this implies an absolute caries reduction of 0.052 D(M)FS per year, equivalent to an NNT of 20 (95% CI, 18 to 22): i.e. 20 children need to use topical fluorides to avoid one D(M)FS. In populations with a caries increment of 2.5 D(M)FS per year (at the mid range of the results seen in the included studies), this implies an absolute caries reduction of 0.65 D(M)FS per year, equivalent to an NNT of 2 (95% CI, 2 to 2): i.e. 2 children need to use TFT to avoid one D(M)FS.

(b) Funnel plot and test for funnel plot asymmetry: D(M)FS PF
A funnel plot of the 133 trials reporting D(M)FS PFs may look asymmetrical, but the weighted regression test for asymmetry (Egger 1997) was not statistically significant (asymmetry intercept = -0.41 (95% CI, -1.38 to 0.55; p = 0.4)). There is, therefore, no evidence of bias using this method.

The funnel plot of the 133 trials comparing TFT with placebo/no treatment is available in 'Additional Figure 01'.

Basic findings from studies which did not contribute data for the D(M)FS PF meta-analysis are as follows:
Brandt 1972 - "Preventive effect on the incidence of caries from fluoride mouthrinsing was shown" (compared with placebo).
de Liefde 1989 - "No preventive effect from mouthrinsing was shown" (compared with placebo).
Homan 1969 - "Negative outcome (no significant differences between fluoride toothpastes tested and placebo)".
Powell 1981 - "Inhibitory effect on initial lesion progression was shown for fluoride dentifrice" (compared with non-fluoride dentifrice).
Slack 1964 - "No evidence to support the use of the fluoride dentifrice in the control of caries" (compared with non-fluoride dentifrice).

(2) Effect on permanent teeth: D(M)FT PF
Seventy-nine trials reported data which allowed the calculation of the D(M)FT prevented fraction. All 79 are also included in the analysis of D(M)FS PF. The pooled estimate of D(M)FT prevented fraction was 0.26 (95% CI, 0.21 to 0.30; p < 0.00001). There was substantial heterogeneity between trials (chi square = 845.06 on 78 degrees of freedom, p < 0.00001). The results of this
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental decay analysis are very similar to those reported in the analysis of D(M)FS PF.

As with the estimates of the effects of TFT on D(M)FS PF, univariate metaregression suggested that the estimates from trials using no treatment as opposed to placebo controls were substantially higher (coefficient, 0.21; 95% CI, 0.09 to 0.34; p = 0.001). The pooled estimate of the D(M)FT prevented fraction from the seven trials with a no treatment control group (fluoride gel and varnish trials only) was 0.45 (95% CI, 0.32 to 0.58; p < 0.0001), while that from the 72 placebo-controlled trials (all four modalities) was 0.24 (95% CI, 0.20 to 0.28; p < 0.0001). When the meta-analysis was confined to those trials with placebo controls, there remained substantial heterogeneity (Q = 591.33 on 71 degrees of freedom, p < 0.0001).

Differences between TFT types (indirect comparisons) shown for D(M)FS PF in metaregression analyses were also suggested for D(M)FT PF. Fluoride varnish has been found to be significantly different from the other types of TFT (coefficient, 0.28; 95% CI, 0.08 to 0.33; p = 0.01); differences among the other three modalities (fluoride gel/mouthrinse/toothpaste) were not obvious. Although no significant differences between fluoride varnish and gel were shown when all TFT types were in the model, these became significant when adjusted for type of control group (in which case, differences between fluoride varnish and mouthrinse became non-significant). The pooled estimate of treatment effect from the three fluoride varnish trials was 0.53 (95% CI, 0.23 to 0.82; p < 0.0001); from the 10 fluoride gel trials was 0.32 (95% CI, 0.19 to 0.46; p < 0.0001), from the 13 fluoride mouthrinse trials was 0.24 (95% CI, 0.18 to 0.30; p < 0.0001), and from the 53 fluoride toothpaste trials was 0.23 (95% CI, 0.19 to 0.28; p < 0.0001). It should be noted that there were only placebo-controlled fluoride toothpaste and mouthrinse trials reporting DMFT data.

The random effects meta-analyses of D(M)FT prevented fractions are presented in RevMan Analyses, also subgrouped by type of control group and TFT types.

(3) Effect on deciduous tooth surfaces: d(e/m)fs PF

Five trials reported data which allowed the calculation of the 'd(e/m)fs' prevented fraction. Only one of these (Clark 1985) is also included in the analysis of D(M)FS PF. The pooled estimate of d(m/e)fs prevented fraction was 0.33 (95% CI, 0.22 to 0.44; p < 0.0001), suggesting a substantial benefit of TFT in the deciduous dentition. There was no statistically significant heterogeneity between trials (chi square = 6.13 on 4 degrees of freedom, p = 0.19). These results should be viewed with a degree of caution given the fact that standard deviations (SDs) were imputed (regression equation) in four of the five trials. In addition, the test for heterogeneity has low power to detect excess variability between the results of the trials when only a few trials are included.

Univariate metaregression suggested no significant association between estimates of d(e/m)fs prevented fractions and type of control group (placebo/no treatment). Because the meta-analysis included only five trials (three fluoride varnish trials and two fluoride gel trials), no further exploration of competing explanations for heterogeneity in treatment effects was considered. Metaregression would have had very limited power to detect any association under these circumstances. However, we have decided to present the meta-analysis results stratified by type of control group and TFT type, since there is clear evidence for the influence of these factors on treatment effects. In fact, the pooled estimate of the d(e/m)fs prevented fraction from the two trials with a no treatment control group was 0.41 (95% CI, 0.26 to 0.55; p < 0.0001) while that from the three placebo-controlled trials was 0.27 (95% CI, 0.8 to 0.48; p < 0.004), and the pooled estimate of treatment effect from the three fluoride varnish trials was 0.33 (95% CI, 0.19 to 0.48; p < 0.0001) while that from the two fluoride gel trials was 0.26 (95% CI, -0.11 to 0.63; p = 0.18).
The random effects meta-analyses of d(e/m)fs prevented fractions are presented in RevMan Analyses, subgrouped by type of control group and TFT types.

Numbers of children needed to treat (NNT) to prevent one defs were calculated based on the pooled d(e/m)fs prevented fraction and on the caries increments in the control groups of the five trials in the meta-analysis. In populations with a caries increment of 0.8 defs per year (at the lowest end of the results seen in the included studies), this implies an absolute caries reduction of 0.26 defs per year, equivalent to an NNT of 3.8 (95% CI, 2.8 to 5.7): i.e. 4 children need to use topical fluorides to avoid one defs. In populations with a caries increment of 1.9 defs per year (at the highest range of the results seen in the included studies), this implies an absolute caries reduction of 0.63 defs per year, equivalent to an NNT of 1.6 (95% CI, 1.2 to 2.4); i.e. 2 children need to use topical fluorides to avoid one defs.

EFFECT OF TOPICAL FLUORIDES ON OTHER OUTCOMES

Some trials report data for other relevant outcomes (see 'Included studies' under 'Description of studies' section). Some of these are simply other measures/indices for dental caries increment in permanent teeth/surfaces and require no further consideration; 12 trials report on the proportion of children developing new caries. Meta-analyses results for the proportion of children developing new caries are presented below.

The few trials that report data on adverse effects either give no useable or incomplete data for analysis, or are so closely related to specific TFT types (already reported in the separate reviews of each) that it would not be meaningful to address these again in this review.

Data for unacceptability of treatment (as measured by drop outs) were reported in 10 of the non-placebo controlled trials that reported drop outs. Meta-analysis results for these are also described below.

• Proportion of children developing new caries
Thirteen trials reported results on the proportion of children developing one or more new caries (Dolles 1980; Finn 1975; Forsman 1974; Forsman 1974a; Gisselsson 1999; Hanachowicz 1984; Heidmann 1992; Holm 1979; Holm 1984; Kleber 1996; Marthaler 1974; Torell 1965; Torell 1965a). The pooled estimate (random effects meta-analysis) of the risk ratio was 0.88, with substantial heterogeneity in the results (95% CI, 0.82 to 0.95; chi square for heterogeneity 53.88 on 12 degrees of freedom, p < 0.00001). [Using alternative measures of effect has not reduced heterogeneity substantially.] This corresponds to an NNT to prevent one child from developing caries of 15 (95% CI, 10 to 34) in a population with a caries risk the same as that found in the control groups in these trials (15 children using TFT for 2 to 3 years will prevent new caries development in one child).

• Unacceptability of treatment (dropouts/exclusions)
The pooled estimate of the relative risk of dropping out from the TFT as opposed to the non-treatment arm in the 10 non-placebo controlled trials that reported drop outs (Abadia 1978; Bryan 1970; Craig 1981; Cobb 1980; Englander 1967; Holm 1979; Horowitz 1971; Ingraham 1970; Modeer 1984; Moreira 1981) was 1.20 (95% CI, 0.85 to 1.70). There was substantial heterogeneity in these results (chi square = 40.85 on 9 degrees of freedom, p < 0.00001).

Discussion
The first question addressed by this review was whether the use of topical fluoride therapy (TFT) in the form of toothpaste, mouthrinse, gel or varnish for the prevention of dental caries in children is overall better than not using a topical fluoride intervention. The review as a whole contains information from over 65,000 children included in the trials comparing a topical fluoride intervention with a placebo or no treatment, and suggests that the use of topical fluorides is associated with a clear reduction in caries increment in both the permanent and the deciduous dentition. For the great majority of children (approximately two thirds) the topical fluoride modality they used was toothpaste, followed by mouthrinse, gel and varnish applications.

There is strong evidence of a generalizable beneficial effect of topical fluoride therapy. The random effects meta-analysis of 133 trials combined assessing the effect of topical fluorides on the permanent dentition suggests a caries inhibiting effect of 26% on average; an approximate, though anti-conservative, interval in which at most 95% of underlying effects might lie is from 0% to 53%. The average caries reduction of 26% would correspond to a number needed to treat (NNT) of 2 to avoid one decayed, filled or missing tooth surface (DMFS) per year in a child population with a caries increment of 2.5 D(M)FS per year (in the middle range of control group rates for included studies), or an NNT of 20 for children from a population with a caries increment of 0.2 D(M)FS per year (at the lowest end of the observed range). Only five studies reported the effects of topical fluoride therapy on caries increment in deciduous tooth surfaces, two of these tested self applications of fluoride gel with a toothbrush and three studies tested fluoride varnish applications. The random effects meta-analysis of the five studies combined suggests that the use of topical fluoride applications is associated on average with a 33% (95% confidence interval (CI), 22% to 44%) reduction in decayed, missing and filled tooth surfaces. This would correspond to an NNT of 2 to avoid one defs per year in a child population with a caries increment of 1.9 defs per year (at the highest end of the control group rates), or an NNT of 4 for children from a population with a caries increment of 0.8 defs per year (at the lowest end of the observed range). It should be noted that although the variation among the results of the 133 studies assessing the effectiveness of topical fluoride on the permanent dentition is substantial, the results of the few studies on the effectiveness of topical fluoride on deciduous tooth surfaces are less heterogeneous. On the other hand, the confidence intervals are relatively wide for the effect on deciduous tooth surfaces, since relatively few trials were included in the meta-analysis (1685 participants).

A secondary objective of this review was to exploit power to look at potential sources of heterogeneity between studies across all four types of topical fluoride interventions and at indirect comparisons of the different TFT types. It was examined extensively whether there was any relationship between the caries-preventive effectiveness of topical fluoride therapy and a number of factors, including initial level of caries, background exposure to extraneous fluoride sources, mode/setting of TFT use and type of topical fluoride intervention used. A significant influence of the pre-specified factors/variables initial level of caries, mode/setting of use, and type of topical fluoride on the prevented fraction (PF) was shown in the metaregression analyses performed. Among the other potential sources of heterogeneity investigated, a significant influence of type of control group was shown.

We have detected a constant relative increase in the PF of 1% on average as trials involved children with higher initial D(M)FS scores (baseline risk of the study population). Although the magnitude of the effect was small, this implies that as the caries levels of a community decline, the percentage caries reductions will decrease. On the other hand, we were unable to detect a clear relationship between background exposure to other fluoride sources and the magnitude of the treatment effect. Although this may have been partly influenced by potential misclassification, especially due to the incomplete reporting of data for exposure to fluorides other than water, the lack of association
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries

between background exposure to water fluoridation and treatment effect, based on analysis including 116 trials (20 of which were in fluoridated areas), implies that estimates of treatment effect were similar between trials conducted in fluoridated and non-fluoridated areas i.e. use of topical fluoride may provide additional caries reduction in subjects from fluoridated areas.

There is evidence of a 14% greater caries inhibiting effect with the use of fluoride varnish compared with the other TFT types (gels, mouthrinses and toothpastes), while no significant differences in treatment effects among these or between any one of these and the others were suggested. However, relatively few fluoride varnish trials were included and very few among these were placebo-controlled trials, making it difficult to rule out the possibility of an overestimation of the size of the effect, due to the preponderance of no treatment control studies of lower methodological quality in this subgroup. Further, conclusions about differences in effect due to differences between topical fluoride interventions are on a strongest ground if participants are randomized to one type of TFT or another within a study and a consistent relationship is found across similar studies, but surely such investigations could not be performed in a review including only placebo/no-treatment comparisons. Therefore, these results should be interpreted with caution since the investigation of differences between subgroups is effectively a non-randomized comparison, and is prone to all the difficulties in inferring causality in observational studies. Nevertheless, the adjusted indirect comparisons resulting from the metaregression analyses performed in this review had the advantage that other possible explanations for heterogeneity in different trials, including prognostic factors of participants (such as baseline caries levels and background exposure to fluorides), intervention and actual trial characteristics, could be partially taken into account. Another advantage was that uncertainty could be incorporated in the analyses results by providing wider confidence intervals.

We observed a 10% decrease in the PF with the unsupervised home use of topical fluoride interventions (basically toothpaste) compared with supervised and with operator-applied use in the adjusted metaregression analysis. In addition, the effect of self applied supervised use of TFT appeared to be 11% greater than that of operator-applied and unsupervised home use of TFT. These differences in treatment effect between trials of supervised use and both unsupervised use and operator-applied use are perhaps unsurprising. They are likely to reflect the more intensive use of topical fluoride interventions under supervised schemes. As regards the suggested greater treatment effect with increased frequency and intensity of topical fluoride application in this review, this had been indicated in two other reviews in this series (Marinho 2002; Marinho 2003) and should probably be more relevant in the context of each specific review. It should be pointed out that metaregression analyses including 130 trials should have sufficient power to detect such relationships, but more robust investigations of these aspects of the topical fluoride interventions also require direct, head to head comparisons of different frequencies/intensities of application, which were not within the scope of this review.

Treatment effects estimates from the trials that employed a no-treatment control group were on average 14% more beneficial than from those with a placebo control group. The strong evidence on differences in effect estimates by type of control group shown in this review (which included 116 placebo controlled trials and 17 no-treatment control comparisons in the analysis) was also indicated in a previous systematic review in this series (Marinho 2002). Blind assessment of outcome was an inclusion criterion used across all reviews but clearly participants could not have been blinded in trials with no treatment controls. Although it is unclear why this should have been associated with differences in outcome in these particular circumstances, type of control group can be considered a useful 'proxy' for the use or not of double-blinding in included studies, a key methodological feature that may represent the best indicator of study quality in these reviews. With
regards to the key quality domain of allocation concealment, no association with treatment effect could be demonstrated for this, possibly due to the fact that the randomization process was poorly described in the studies included.

We observed a significantly greater treatment effect in non-English language trials in the post hoc metaregression analyses performed. Although plausible (Juni 2002), this relationship was dependent on the inclusion of one study with particularly powerful effects (Di Maggio 1980). After exclusion of this study in a sensitivity analysis no significant association was seen with this factor. It should be noted however that comprehensive searching and data extraction from as many trials as possible published in any language was an important component of this review in an attempt to reduce biases and imprecision. Although the exclusion of trials published in languages other than English may have little impact on the summary effect estimate of a review that includes so many trials, such studies carried out in a variety of countries should maximise the ability of users of the review to judge its applicability for specific decisions on the appropriate use of topical fluorides.

Although visual inspection of the funnel plot may suggest a degree of asymmetry, the Egger formal test for asymmetry provided no evidence of a significant relationship between trial size and effect estimate. Therefore, there is no evidence that the smaller studies in the meta-analysis of D(M)FS PFs tend to show larger treatment effects in this review.

We found little useful information about the risk of adverse effects in the topical fluoride reviews, and the few results available are discussed in the context of each relevant separate review in this series.
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries

Reviewers' conclusions

Implications for practice
The use of topical fluoride therapy is associated with a clear reduction in caries increment in children. While we found evidence that the relative effect of topical fluoride may be greater in those who have higher baseline levels of decayed, missing and filled tooth surfaces (D(M)FS), we found no evidence that the effect of topical fluoride was dependent on background exposure to fluoridated water or other fluoride sources. In addition, a higher D(M)FS prevented fraction was shown with increased total intensity of fluoride application, with self-applied supervised use (where a higher compliance with topical fluoride interventions as recommended should be expected), and with the use of fluoride varnishes compared with the other topical fluoride modalities. Research on the effects of fluoride varnish has been of lower methodological quality however. The effect of topical fluoride also varied according to type of control group used; the D(M)FS prevented fraction was higher with no treatment compared with placebo. Unfortunately, little information is available on the effects of topical fluoride therapy on outcomes such as caries incidence in the deciduous dentition and on the likelihood of adverse effects. The general lack of evidence on outcomes other than caries increment in children's permanent teeth makes it more difficult for policy makers to weigh the benefits of topical fluoride use in preventing caries against potential negative effects.

Implications for research
This systematic review included placebo controlled trials as well as trials with no treatment controls on the effects of topical fluoride therapy (TFT) on dental caries in children. There is sufficient evidence to establish that this factor (type of control group) represents an important source of heterogeneity and a strong indicator of study quality in the topical fluoride reviews. Although many reports lacked important methodological details, the review findings are quite strong, based on a sizeable body of randomized evidence. In this review, the meta-analyses were stratified by both type of control group and type of topical fluoride intervention (all four levels). Here, a test of differences between subgroups in multivariate meta-regression analyses was effectively an indirect comparison of the effects of the various topical fluoride interventions. Although such a test can provide indirect evidence of relative treatment effects, it may be less reliable than evidence from randomized controlled trials that compare the interventions directly (head to head comparisons). We need therefore to be cautious about drawing conclusions about the relative efficacy of the TFT interventions based on such evaluation of the magnitude of treatment effects across studies. Fortunately, direct evidence from head to head comparisons is available for the various topical fluoride interventions and this will be the subject of the next systematic review in this series.
## Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
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</thead>
<tbody>
<tr>
<td>Aasenden 1972</td>
<td>Fluoride solution swallowed after rinsing (even though no systemic effect should be anticipated for this age group).</td>
</tr>
<tr>
<td>Antia 1974</td>
<td>Random or quasi-random allocation not stated.</td>
</tr>
<tr>
<td>Badersten 1975</td>
<td>Additional non-fluoride based intervention associated to fluoride mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Bellini 1981</td>
<td>Additional fluoride based intervention associated to fluoride gel. Blind outcome assessment not stated and unlikely. Note - no relevant outcome reported.</td>
</tr>
<tr>
<td>Bibby 1945</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Billy-Pryga 1983</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
</tr>
<tr>
<td>Birkeland 1973</td>
<td>Length of follow up of less than 1 year/school year. Relevant outcomes not reported. Blind outcome assessment not stated.</td>
</tr>
<tr>
<td>Bixler 1962</td>
<td>Group of participants more than 16 years old selected. Random or quasi-random allocation not stated.</td>
</tr>
<tr>
<td>Bixler 1966</td>
<td>Group of young adults selected.</td>
</tr>
<tr>
<td>Bixler 1966a</td>
<td>Additional fluoride-based intervention associated to fluoride toothpaste. Group of participants more than 16 years old selected. Blind outcome assessment not stated.</td>
</tr>
<tr>
<td>Bohannan 1985a</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Boyd 1985</td>
<td>Additional fluoride based intervention associated to fluoride gel/rinse. Clearly not randomized or quasi-randomized. Blind outcome assessment not stated. Length of follow up of less than 1 year/school year.</td>
</tr>
<tr>
<td>Bristow 1975</td>
<td>Additional interventions associated to fluoride mouthrinse. Only two clusters (schools), each assigned to one of the two study groups.</td>
</tr>
</tbody>
</table>
### Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Brodeur 1989</td>
<td>Open outcome assessment.</td>
</tr>
<tr>
<td>Castellanos 1983</td>
<td>Open outcome assessment reported after contacting author.</td>
</tr>
<tr>
<td>Chikte 1996</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Clark 1985a</td>
<td>Clearly not randomized or quasi-randomized (concurrent control group taken from another study).</td>
</tr>
<tr>
<td>Corpus 1973</td>
<td>Clearly not randomized or quasi-randomized (systematic allocation according to participants' characteristics). Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>de Canton 1983</td>
<td>Additional fluoride and non-fluoride based interventions associated to fluoride mouthrinse. Random or quasi-random allocation not stated.</td>
</tr>
<tr>
<td>Disney 1989</td>
<td>Additional non-fluoride based intervention associated to fluoride mouthrinse. Random or quasi-random allocation not stated or indicated.</td>
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<tr>
<td>Downer 1976</td>
<td>Additional fluoride-based intervention associated to fluoride toothpaste.</td>
</tr>
<tr>
<td>Ennever 1980</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
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<tr>
<td>Esteva Canto 1991</td>
<td>Clearly not randomized or quasi-randomized. Blind outcome assessment not stated or indicated.</td>
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<tr>
<td>Fernandez 1979</td>
<td>Open outcome assessment. Random or quasi-random allocation not stated or indicated.</td>
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<tr>
<td>Finn 1963</td>
<td>Medically compromised group of institutionalised children selected.</td>
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<tr>
<td>Frankl 1972</td>
<td>Fluoride solution swallowed after rinsing (even though no systemic effect should be anticipated for this age group).</td>
</tr>
<tr>
<td>Gray 1980</td>
<td>Additional fluoride-based intervention associated to fluoride mouthrinse.</td>
</tr>
<tr>
<td>Grodzka 1982</td>
<td>No random or quasi-random allocation used. Open outcome assessment reported after contacting author.</td>
</tr>
<tr>
<td>Gutherz 1968</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
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<td>Study</td>
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<td>Halikis 1966</td>
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<tr>
<td>Heifetz 1979</td>
<td>Additional fluoride based intervention associated to fluoride gel/rinse.</td>
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<tr>
<td></td>
<td>Note - inappropriate 'placebo' used.</td>
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<tr>
<td>Hetzer 1973</td>
<td>Additional non-fluoride based intervention associated to fluoride varnish.</td>
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<td></td>
<td>Random or quasi-random allocation not stated or indicated.</td>
</tr>
<tr>
<td>Heuser 1968</td>
<td>No random or quasi-random allocation used (non-random concurrent control).</td>
</tr>
<tr>
<td></td>
<td>Blind outcome assessment not stated and unlikely. Varnish applied once in 15 months.</td>
</tr>
<tr>
<td>Hill 1959</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
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<td></td>
<td>Blind outcome assessment not stated or indicated.</td>
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<td>Hochstein 1975</td>
<td>Medically compromised group of children selected. No random or quasi-random allocation used (non-random concurrent control). Open outcome assessment.</td>
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<td>Irmisch 1974</td>
<td>Additional active agent associated to fluoride in mouthrinse. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
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<tr>
<td>Ivanova 1990</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
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<tr>
<td></td>
<td>Blind outcome assessment not stated and unlikely.</td>
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<tr>
<td>Jiraskova 1965</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
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<td></td>
<td>Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Jordan 1959</td>
<td>Only two clusters (schools), each randomized to one of the two interventions compared.</td>
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<td>Kani 1973</td>
<td>Random or quasi-random allocation not stated.</td>
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<td>Kasakura 1966</td>
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<td>Kitsugi 1978</td>
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<tr>
<td>Kolehmainen 1979</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and placebo groups.</td>
</tr>
<tr>
<td>Kolehmainen 1981</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and placebo groups.</td>
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<tr>
<td>Kukleva 1983</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
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<td>Open outcome assessment reported after contacting author.</td>
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<td>Kukleva 1998</td>
<td>Random or quasi-random allocation not stated or indicated.</td>
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<td>Review Manager 4.2.2 25/09/2003</td>
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</table>
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing

outcome assessment reported after contacting author.

Kunin 1991  Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.

Kunzel 1977  Additional fluoride-based intervention associated to fluoride toothpaste.

Kunzel 1978  Only two clusters (schools), each assigned to one of the two study groups. Blind outcome assessment not stated or indicated.

Lagutina 1978  Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.

Lehnhoff 1966  Participants more than 16 years old selected.

Lieser 1978  No random or quasi-random allocation used (non-random concurrent control - by matching procedure). Blind outcome assessment not stated and unlikely.

Lindquist 1989  Fluoride based intervention associated to control group.

Louw 1995  Random or quasi-random allocation to groups not stated or indicated. Blind outcome assessment not stated or indicated.

Lu 1985  Additional active agent associated to fluoride in toothpaste.

Luoma 1978  Additional fluoride-based intervention associated to fluoride mouthrinse/toothpaste.

Maiwald 1973  Random or quasi-random allocation not stated or indicated.

Maiwald 1978  Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.

Mari 1988  Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.

Mari 1988a  Random or quasi-random allocation not stated or indicated. Note - two clusters, each assigned to one of the two groups.

McCormick 1970  Random or quasi-random allocation not stated. Note - only post-treatment effects reported.

Mellberg 1978  Blind outcome assessment not stated and unlikely in any element /phase of assessment.

Mendonca 1995  Open outcome assessment reported after contacting author.

Mergele 1968a  Medically compromised group of institutionalised young adults and children selected.

Moller 1968  Additional active agent associated to fluoride in test toothpaste.
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing
dental caries

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
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<tr>
<td>Morozova 1983</td>
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<td>Muhler 1955a</td>
<td>Random or quasi-random allocation not stated.</td>
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<td>Muhler 1957</td>
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<td>Muhler 1958</td>
<td>Participants more than 16 years old selected. Random or quasi-random allocation not stated.</td>
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<td>Muhler 1960</td>
<td>Participants more than 16 years old selected. Random or quasi-random allocation not stated. Blind outcome assessment not stated.</td>
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<tr>
<td>Muhler 1962</td>
<td>Participants more than 16 years old selected.</td>
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<td>Murray 1977</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and placebo groups.</td>
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<td>Niwa 1975</td>
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<td>Onisi 1970</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated.</td>
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<td>Onisi 1974</td>
<td>Additional active agent associated to fluoride in toothpaste. Only two clusters (villages), each assigned to one of the two interventions compared.</td>
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<td>Pashaev 1977</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups. Random or quasi-random allocation not stated. Blind outcome assessment not stated and unlikely.</td>
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<td>Patz 1970</td>
<td>Participants more than 16 years old selected. Blind outcome assessment not stated.</td>
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<tr>
<td>Peflley 1960</td>
<td>Participants more than 16 years old selected. Random or quasi-random allocation not stated. Blind outcome assessment not stated.</td>
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<td>Petersson 1998</td>
<td>No random or quasi-random allocation used (non-random concurrent controls - by matching procedure). Blind outcome assessment not stated and unlikely.</td>
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<td>Piccione 1979</td>
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<tr>
<td>Ramos 1995</td>
<td>Open outcome assessment.</td>
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<td>Riethe 1975</td>
<td>Blind outcome assessment not stated or indicated.</td>
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<td>Riethe 1977</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
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<tr>
<td>Roberts 1948</td>
<td>Clearly not randomized or quasi-randomized (concurrent control group selected by matching procedure).</td>
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<tr>
<td>Rodriguez Miro 1983</td>
<td>Additional active agent associated to fluoride in mouthrinse. Only three clusters (school classes), each assigned to one of the three interventions compared.</td>
</tr>
<tr>
<td>Rodriguez Miro 1988</td>
<td>Additional non-fluoride based intervention associated to fluoride varnish.</td>
</tr>
<tr>
<td>Ruszynska 1978</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
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<tr>
<td>Salem 1979</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
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<tr>
<td>Schmidt 1970</td>
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</tr>
<tr>
<td>Seppa 1982</td>
<td>Split-mouth design - sites within a participant's mouth were allocated to treatment and control groups.</td>
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<tr>
<td>Shobha 1987</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. Note - main outcome data not reported in control group (and not obtainable).</td>
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<td>Spears 1978</td>
<td>No random or quasi-random allocation used (non-random concurrent control). Blind outcome assessment not stated and unlikely. Note - dramatic drop-out rate during the study period.</td>
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<td>Stadtler 1982</td>
<td>Medically compromised group of institutionalised children selected.</td>
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<tr>
<td>Stookey 1975</td>
<td>Random or quasi-random allocation not stated.</td>
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<td>Suntozov 1991</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. Note - only post-treatment effects reported.</td>
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<td>Swerdloff 1969</td>
<td>Length of follow up of less than 1 year/school year.</td>
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<tr>
<td>Szoke 1989</td>
<td>Additional fluoride or non-fluoride based intervention associated to fluoride gel. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
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<tr>
<td>Szwejda 1971</td>
<td>No random or quasi-random allocation used (concurrent control taken</td>
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</table>
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing from another study).

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
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<tr>
<td>Todorashko 1983</td>
<td>Additional fluoride based intervention associated to fluoride varnish. Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely.</td>
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<tr>
<td>van Eck 1984</td>
<td>No random or quasi-random allocation used (non-random concurrent control - by matching procedure).</td>
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<td>Weisz 1960</td>
<td>Clearly not randomized or quasi-randomized (concurrent control group taken from a different population). Open outcome assessment.</td>
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<tr>
<td>Widenheim 1989</td>
<td>Clearly not randomized or quasi-randomized (concurrent control group taken from a different population). Open outcome assessment.</td>
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<tr>
<td>Wilson 1978</td>
<td>Random or quasi-random allocation not stated.</td>
</tr>
<tr>
<td>Winter 1975</td>
<td>No random or quasi-random allocation used (non-random concurrent control). Blind outcome assessment not stated and unlikely.</td>
</tr>
<tr>
<td>Wrinkler 1953</td>
<td>Random or quasi-random allocation clearly not used (non-random concurrent control: by matching procedure).</td>
</tr>
<tr>
<td>Wycoff 1991</td>
<td>Clearly not randomized or quasi-randomized. Blind outcome assessment not stated or indicated.</td>
</tr>
<tr>
<td>Zickert 1982</td>
<td>Additional fluoride-based intervention associated to fluoride mouthrinse/toothpaste.</td>
</tr>
<tr>
<td>Zimmer 1999</td>
<td>No random or quasi-random allocation used (non-random concurrent control). Blind outcome assessment not used.</td>
</tr>
</tbody>
</table>
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{published data only}


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{published and unpublished data}


**Ulvestad 1978**

{published data only}


**Wacinska 1987**

{published data only}


**Weisenstein 1967**

{published data only}


**Wojtowicz 1986**

{published data only}

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Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing

Ongoing studies

Mancunian
Davies G. The Mancunian Fluoride Varnish Project. Ongoing trial.

PECC

* indicates the primary reference for the study
Other references

Additional references

**Bartizek 2001**


**Burt 1998**


**Chaves 2002**


**Chen 1995**


**Clark 1985**


**Clarke 2000**


**Downer 1995**


**Dubey 1965**


**Egger 1997**

Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing


Featherstone 1988


Glass 1982


Helfenstein 1994


Johnson 1993


Juni 2002


Marinho 1997


Marinho 2002


Marinho 2003


Marthaler 1994

Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing... 84

Marthaler 1996


Moynihan 1996


Murray 1991


Murray 1991a


O'Mullane 1995


Pitts 2001


Pitts 2002


Ripa 1989


Ripa 1991

Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing

Rolla 1991

Seppa 1998

Sharp 1998

Stamm 1984

Stamm 1995

Strohmenger 2001

Thompson 1999

van Rijkom 1998
**Table of comparisons**

01 Topical Fluoride versus Placebo/No-treatment

01 D(M)FS increment (PF) - nearest to 3 years (133 trials)
- 01 Fluoride Toothpaste versus Placebo
- 02 Fluoride Gel versus Placebo
- 03 Fluoride Varnish versus Placebo
- 04 Fluoride Mouthrinse versus Placebo
- 05 Fluoride Gel versus No-treatment
- 06 Fluoride Varnish versus No-treatment
- 07 Fluoride Mouthrinse versus No-treatment

02 D(M)FT increment (PF) - nearest to 3 years (79 trials)
- 01 Fluoride Toothpaste versus Placebo
- 02 Fluoride Gel versus Placebo
- 03 Fluoride Varnish versus Placebo
- 04 Fluoride Mouthrinse versus Placebo
- 05 Fluoride Gel versus No-treatment
- 06 Fluoride Varnish versus No-treatment

03 d(e)fs increment (PF) - nearest to 3 years (5 trials)
- 01 Fluoride Gel versus Placebo
- 02 Fluoride Varnish versus Placebo
- 03 Fluoride Varnish versus No-treatment

04 Developing one or more new caries (12 trials)
05 Unacceptability of treatment as measured by leaving study early (10 trials)
## Additional tables

### 01 Random effects metaregression analyses of prevented fractions: D(M)FS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. studies</th>
<th>Slope estimate</th>
<th>Slope interpretation</th>
<th>p-value</th>
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<tr>
<td>F Gel vs F Varnish (indirect comparison)</td>
<td>29</td>
<td>-15%</td>
<td>(-28% to -1.6%) PF lower among Fluoride Gel trials</td>
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<td>F Mouthrinse vs F Varnish (indirect comparison)</td>
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<td>F Toothpaste vs F Varnish (indirect comparison)</td>
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<td>(-27% to -0.6%) PF lower among Fluoride Toothpaste trials</td>
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<td>Control group</td>
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<td>(5% to 23%) Higher PF for no-treatment compared with placebo</td>
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<td>Mean baseline caries</td>
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<td>Fluoridated water</td>
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<td>Background fluorides</td>
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<td>(-6.7% to 3.7%) Lower PF in presence of any background fluoride</td>
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<td>Operator vs unsupervised (indirect comparison)</td>
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<td>Self applied supervised vs unsupervised (indirect comparison)</td>
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<td>Intensity (frequency x concentration)</td>
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<td>(1% to 3.9%) Increase in PF equivalent to doubling from 100 to 200 applications and increasing by 1000 ppmF</td>
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<td>Frequency of application</td>
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<td>3%</td>
<td>(0.4% to 5.7%) Increase in PF per 100 extra applications/year</td>
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<th>Interpretation</th>
<th>p-Value</th>
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<td>Blind outcome assessment</td>
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<td>Double-blinding</td>
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<td>Length of follow up</td>
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<td>Decrease in PF per extra year of follow up</td>
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<td>APF vs AmF (indirect comparison)</td>
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<td>-3.9%</td>
<td>PF lower among APF trials</td>
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<td>NaF vs AmF (indirect comparison)</td>
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<td>SMFP vs AmF (indirect comparison)</td>
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<td>SnF2 vs AmF (indirect comparison)</td>
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<td>PF lower among SnF2 trials</td>
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Additional figures

Figure 01
Funnel Plot of D(M)FS PFs according to standard errors of the studies included in the meta-analysis

Review: Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents
Comparison: 01 Topical Fluoride versus Placebo/No-treatment
Outcome: 01 D(M)FS increment (PF) - nearest to 3 years (133 trials)
### Comparison or outcome

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<th>Statistical method</th>
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<td>65179</td>
<td>Prevented Fraction (random),</td>
<td>0.26 [0.23, 0.29]</td>
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<td>RR (random), 95% CI</td>
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<td>05 Unacceptability of treatment as measured by leaving study early</td>
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<td>2897</td>
<td>RR (random), 95% CI</td>
<td>1.20 [0.85, 1.70]</td>
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<td>(10 trials)</td>
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<td>van Wyk</td>
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<td>1968</td>
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<td>1968</td>
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<td>1969</td>
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<tr>
<td>1969</td>
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<tr>
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<td>1970</td>
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<td>1970</td>
<td>Parker</td>
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<td>0.3000 (0.1200)</td>
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<td>Lennard</td>
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<td>0.3000 (0.1300)</td>
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<tr>
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<td>Galleger</td>
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<td>1970</td>
<td>Rugg-Guerr</td>
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Subtotal (95% CI): 7340.79
Test for heterogeneity: Chi² = 50.11, df = 29 (P = 0.0009), I² = 59.1%
Test for overall effect: Z = 13.52 (P < 0.00001)

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
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<th>Mean Effect SIZE</th>
<th>95% CI</th>
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Subtotal (95% CI): 7340.79
Test for heterogeneity: Chi² = 50.11, df = 29 (P = 0.00001), I² = 59.1%
Test for overall effect: Z = 13.52 (P < 0.00001)

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<tr>
<th>Year</th>
<th>Study</th>
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Subtotal (95% CI): 7340.79
Test for heterogeneity: Chi² = 50.11, df = 29 (P = 0.00001), I² = 59.1%
Test for overall effect: Z = 13.52 (P < 0.00001)
Review: Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents (THESSIS CHAPTER 7)

Comparison: One topical fluoride versus Placebo

Outcome: G2 DMFT increment (PP) - near to 3 years (738) teeth

### Study

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<th>N</th>
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<th>SE</th>
<th>Effect Size</th>
<th>Weight</th>
<th>Prevented Fraction (random)</th>
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<th>Quality</th>
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# Test for overall effect

- Z = -4.00 (P < 0.0001)
- Z = -4.00 (P < 0.0001)
- Z = -4.00 (P < 0.0001)
- Z = -4.00 (P < 0.0001)
- Z = -4.00 (P < 0.0001)
- Z = -4.00 (P < 0.0001)
- Z = -4.00 (P < 0.0001)
- Z = -4.00 (P < 0.0001)

# Results

- Test for heterogeneity: Chi^2 = 539.95, df = 52 (P < 0.0001), P < 0.05
- Test for overall effect: Z = 4.00 (P < 0.0001)
- Test for heterogeneity: Chi^2 = 539.95, df = 52 (P < 0.0001), P < 0.05
- Test for overall effect: Z = 4.00 (P < 0.0001)
- Test for heterogeneity: Chi^2 = 539.95, df = 52 (P < 0.0001), P < 0.05
- Test for overall effect: Z = 4.00 (P < 0.0001)
### Test for heterogeneity not applicable

- **Chi**² = 8.45, df = 78 (P < 0.0001), I² = 90.8%
- **Total (95% Cl):** 2.16 3.4 1.67 5.7

### Test for overall effect: Z = 5.00 (P < 0.0001)
- **Subtotal (95% Cl):** 5.05 5.9

### Test for overal effect: Z = 11.50 (P < 0.0001)
CHAPTER 8

ONE TOPICAL FLUORIDE (TOOTHPASTES, OR MOUTHRINSES, OR GELS, OR VARNISHES) VERSUS ANOTHER FOR PREVENTING DENTAL CARIES IN CHILDREN AND ADOLESCENTS
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes)

Cover sheet
Title
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents (THESIS CHAPTER 8)

Reviewers
Marinho VCC, Higgins JPT, Sheiham A, Logan S

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One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes)

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Contribution of reviewers
All authors contributed to the development of the protocol and execution of the review. Valeria Marinho (VM) wrote the protocol, designed and implemented the search strategies, tracked down all full articles, contacted authors, selected studies, assessed validity, and extracted data. Julian Higgins (JH) duplicated study selection, quality assessment, and data extraction in a sample of studies and Stuart Logan (SL) or Aubrey Sheiham (AS) were consulted where necessary. VM entered and analysed the data in consultation with JH. VM prepared the full review. All authors contributed to its revision, interpretation of results and approval.

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The authors wish to thank the Systematic Reviews Training Unit (UCL) and the Cochrane Oral Health Group for the continuous support. Many thanks are due to the investigators who have kindly provided additional information about their trials or supplied reports of trials, as well as to those who helped with the translations or provided comments and editorial input to this review.

Potential conflict of interest
None known.
Abstract

Background
Topical fluorides in the form of toothpaste, mouthrinse, varnish and gel are effective caries preventive measures. However, there is uncertainty about the relative value of these interventions.

Objectives
To compare the effectiveness of one form of topical fluoride intervention with another when used for the prevention of dental caries in children.

Search strategy
We searched the Cochrane Oral Health Group's Trials Register (May 2000), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2000), MEDLINE (1966 to January 2000), plus several other databases. We handsearched journals, reference lists of articles and contacted selected authors and manufacturers.

Selection criteria
Randomized or quasi-randomized controlled trials with blind outcome assessment, comparing fluoride varnish, gel, mouthrinse, or toothpaste with each other in children up to 16 years during at least 1 year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS).

Data collection & analysis
Inclusion decisions, quality assessment and data extraction were duplicated in a random sample of one third of studies, and consensus achieved by discussion or a third party. Authors were contacted for missing data. The primary measure of effect was the prevented fraction (PF) that is the difference in mean caries increments between the 'experimental' and 'control' groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed where data could be pooled.

Main results
There were 17 studies included, and 15 contributed data for the meta-analyses. Fluoride toothpaste was not significantly different from mouthrinse (pooled DMFS PF 0%; 95% CI -18% to 19%; p = 0.94), or gel (pooled DMFS PF 0%; 95% CI -21% to 21%; p = 1), or both gel and mouthrinse (pooled DMFS PF 1%; 95% CI -13% to 14%; p = 0.94); heterogeneity was substantial. Results from the single trial comparing toothpaste with varnish (in deciduous teeth) were inconclusive (dfs PF 5%; CI not obtainable). The pooled results from the comparisons of fluoride varnish with mouthrinse was a non-significant difference favouring varnish (DMFS PF 10%; 95% CI, -12% to 32%; p = 0.40), but this result was not robust to sensitivity analysis performed, and heterogeneity was considerable. Results from the single trial comparing varnish with gel (14%, 95% CI, -12% to 40%; p = 0.30) and the single trial comparing gel with mouthrinse (-14% DMFS PF; 95% CI -40% to 12%; p = 0.30) were inconclusive (favoured varnish and mouthrinse respectively).

Reviewers' conclusions
Fluoride toothpastes in comparison to mouthrinses or gels appear to have a similar degree of effectiveness for the prevention of dental caries in children. There is no clear suggestion that fluoride varnish is more effective than mouthrinses and the evidence for the comparative effectiveness of fluoride varnishes and gels, and mouthrinses and gels is inconclusive. No
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an

conclusions about adverse effects could be reached, because no data were reported on in the trials. Acceptance is likely to be greater for fluoride toothpaste.
Background

Dental caries and its consequences pose important and uncomfortable problems in all industrialized societies and in a large number of developing countries. Although the prevalence and severity of dental caries in most industrialized countries have decreased substantially in the past two decades, reaching averages as low as 1.1 decayed, missing and filled teeth (DMFT) in 12 year olds, nearly half of those without any tooth decay or fillings (Marthaler 1996), this largely preventable disease is still common, increases significantly with age, and remains a public health problem for a significant proportion of the world population (Burt 1998). In the United Kingdom, 30% of 3.5 to 4.5 year olds (Moynihan 1996), and 50% of 12 year olds (Downer 1995) had experienced caries in 1993. In 2000, the figures were 40% for 5 year olds in Great Britain (Pitts 2001) and 38% for 12 year olds in England and Wales (Pitts 2002). These findings demonstrate the continuing need for effective preventive strategies and treatment services for these age groups in a country that has experienced a substantial caries decline. In general, dental caries levels vary considerably between and within different countries, but children in the lower socio-economic status (SES) groups have higher caries levels than those in the upper SES groups, and these differences are consistent in industrialized and in urbanized developing countries (Chen 1995).

Fluoride therapy has been the cornerstone of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray 1991). Fluoride controls the initiation and progression of carious lesions. Intensive laboratory and epidemiological research on the mechanism of action of fluoride in preventing caries indicates that fluoride's predominant effect is topical, which occurs mainly through promotion of remineralization of early caries lesions and by reducing sound tooth enamel demineralization (Featherstone 1988). Various modes of fluoride use have evolved, each with its own recommended concentration, frequency of use, and dosage schedule. The use of topically applied fluorides in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades and fluoride containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most widely used at present, either alone or in different combinations. By definition, the term 'topically applied fluoride' describes those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect and are therefore not intended for ingestion. Fluoride gels and varnishes are typical methods of professional topical fluoride application and both delivery systems have been used in preventive programs. Fluoride gels have also been used as a self applied intervention in such programs. Fluoride mouthrinses and toothpastes are the main forms of self applied fluoride therapy. The intensive use of fluoride mouthrinsing in school programs has been discontinued in many developed countries because of doubts regarding its cost-effectiveness at a low prevalence of dental caries and are being replaced by selective fluoride therapy directed to high risk children. Such procedures usually involve the combined use of fluoride toothpastes with gels or varnishes. Toothpaste is by far the most widespread form of fluoride usage (Murray 1991a; Ripa 1991) and the decline in the prevalence of dental caries in developed countries has been mainly attributed to its increased use (Glass 1982; Rolla 1991; Marthaler 1994; O'Mullane 1995; Marthaler 1996).

However, there is currently a debate regarding the appropriate use of fluorides. The lower caries prevalence now prevailing in many countries and the widespread availability of fluoride from multiple sources have raised the question of whether topically applied fluorides are still effective in reducing caries, and safe, mainly in terms of the potential risk of fluorosis (mottled enamel) (Ripa 1991). In this context, even the need for selective professional fluoride applications has been questioned (Seppa 1998). The persistence of this debate and the variations in the use of the main
forms of topically applied fluorides suggest the need to search for meaningful ways to summarize the empirical findings on this topic systematically.

If topical fluorides remain effective it will then become relevant to assess which form is best by directly comparing the various treatments currently used, since no consensus on which one, if any, is the most effective can be found in the literature. It is of clinical importance not only to assess the relative effectiveness of the modalities used for professional topical fluoride applications (varnishes and gels), but also to compare the effect of fluoride mouthrinses with that of professionally-applied fluoride gels or varnishes, and the effect of fluoride toothpastes with that of any other commonly used topical fluoride intervention, since toothpaste use is the most popular method of fluoride application. If the various topical fluoride treatments are shown to be equally effective in controlled trials, the choice of modality will then depend on safety, acceptance and ease of application (and cost).

Over the past half-century, numerous clinical trials have investigated the anti-caries effect of each topical fluoride intervention, and their effectiveness has been widely recognised. It appears that most of the trials have focused on topical fluoride in one form or another and that a small number of such trials have investigated the relative effectiveness of the main topical fluoride modalities. Although the evidence on the effect of topical fluorides on the prevention of dental caries in children has been extensively reviewed in a number of reviews, there has been no systematic investigation directly comparing the different topical fluoride interventions currently used in caries prevention.

With regard to the clinical effectiveness of topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels and varnishes three basic questions can be asked:
1- Is TFT effective in preventing dental caries in children and adolescents?
2- Is one of these forms of TFT more effective than another?
3- Are combinations of these TFT forms more effective than one form used alone?
This review attempts to answer the second question; the other two questions are addressed in separate reviews.

Objectives

The primary objective of this systematic review is to assess the evidence on the comparative effectiveness of topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels and varnishes in the prevention of dental caries in children and adolescents. The specific objectives are:
(1) To determine whether there is a differential effect between any two forms of TFT described above (how each intervention compares with the other).
(2) To determine whether there is a differential effect between professionally-applied topical fluoride varnishes and professionally-applied gels.
(3) To determine whether there is a differential effect between fluoride mouthrinses and professionally-applied TFT (varnishes or gels).
(4) To determine whether there is a differential effect between fluoride toothpastes and any other modality of TFT (mouthrinses, gels or varnishes).

Criteria for considering studies for this review

Types of studies
Randomized or quasi-randomized controlled trials using or indicating blind outcome assessment, in
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an

which one form of TFT (either as toothpaste, mouthrinse, gel or varnish) is compared with another (head to head), during at least one calendar or school year.

Randomized or quasi-randomized controlled trials using within group paired comparison designs (e.g. split-mouth trials involving fluoride varnish, as the effect of the varnish could spread across the mouth leading to contamination of control sites), or with open outcome assessment or no indication of blind assessment, or lasting less than one calendar or school year, or controlled trials where random or quasi-random allocation was not used or indicated were excluded.

* 

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

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

Types of interventions
Topical fluoride therapy in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration (ppm F), amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year.

Any of the six possible pair-wise comparisons of the four modalities are eligible for inclusion in the review.

Studies where the intervention consisted of any caries preventive agent/procedure (e.g. same or other fluoride-based measures, anti-plaque or anti-calculus agents, sealants, oral hygiene interventions, xylitol chewing gums, glass ionomers) used in addition to any form of TFT described above were excluded.

Types of outcome measures
The primary outcome measure in this review is caries increment, as measured by change from baseline in the decayed, (missing) and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. For studies in younger children the outcome measure of interest is caries increment in deciduous tooth surfaces, as measured by change in the decayed, (missing/extraction indicated), and filled surface d(e/m)fs index. Dental caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis. (See 'Methods of the review' for the different ways of reporting the decayed, (missing) and filled teeth or surfaces (D(M)FT/S) scores in clinical trials of caries preventives).

The following outcomes were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions; tooth loss; proportion of children developing new caries; dental pain/discomfort; specific side effects (fluorosis, tooth staining/discoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting); unacceptability of preventive treatment as measured by dropouts during the trial (in non-placebo controlled studies); use of health service resources (such as visits to dental care units, length of dental treatment time). Studies reporting only on changes in plaque/calculus formation, plaque regrowth/vitality, plaque/salivary bacterial counts, or gingival bleeding/gingivitis, dentin hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels,
Search strategy for identification of studies

With a comprehensive search, we attempted to identify all relevant studies irrespective of language, from 1965 onwards.

ELECTRONIC SEARCHING

• Up to 1998

Relevant studies were identified (for the series of topical fluoride reviews) by searching several databases from date of inception: MEDLINE (1966 to 1997), EMBASE (1980 to 1997), SCISEARCH (1981 to 1997), SSCISEARCH (1981 to 1997), ISTP (1982 to 1997), BIOSIS (1982 to 1997), CINAHL (1982 to 1997), ERIC (1966 to 1996), DISSERTATION ABSTRACTS (1981 to 1997) and LILACS/BBO (1982 to 1997). Two overlapping but complementary subject search phrases (below) with low specificity (but high sensitivity), using 'free text' and 'controlled vocabulary', were formulated within Silverplatter MEDLINE around two main concepts, fluoride and caries, and combined with all three levels of the Cochrane Optimal Search Strategy for Randomized Controlled Trials (RCTs). These subject search phrases were customised for searching EMBASE and the other databases:

(a) ["DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS" all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or DMT* and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR SMFP OR MFP OR MONOFLUOR*) or ("CARIOSTATIC-AGENTS" explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or "DENTIFRICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or CARIOSTA* or PROPHYLAXIS* or ANTICARI* or ANTI CARI* or VARNISH* or LACQUER* or DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRIC* or MOUTHRINS* or MOUTH RINS* or RINS* or MOUTHWASH* or MOUTH WASH*)].

(b) [(explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPICAL/ ALL SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT) and ((CARIE*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT* in TI, in AB, in MESH)) or (explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or (explode MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or (MOUTHRINS* or MOUTH RINS*) or (VARNISH* or LACQUER*)].

RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISSERTATION ABSTRACTS, and LILACS/BBO. All the strategies (subject search and methodological filters) developed to search each database are fully described in a report produced for the Systematic Reviews Training Unit (Marinho 1997), and are available on request. These were used for the development of a register of topical fluoride clinical trials for the systematic reviews, as the Cochrane Oral Health Group's Trials Register was not yet developed in 1997/98.

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 1997), the Community of Science database (1998), which included ongoing trials funded by the National Institute of Dental Research (NIDR), the System for Information on Grey Literature in Europe (SIGLE) database (1980 to 1997), and OLD MEDLINE (1963 to 1965) were searched using the terms 'fluor' and 'carie' truncated. (Grey literature search had also been carried out by
searching the Index to Scientific and Technical Proceedings (ISTP) and DISSERTATION ABSTRACTS).

- From 1999 to 2001

The following strategy was used to search LILACS/BBO in 1999 (1982 to 1998), where free text subject search terms were combined with a methodological filter for RCTs:

\[ (\text{fluor} S \text{ or ppmf or ppm f or amf or snf or naf or apf or mfp or smfp or monofluorS or duraphatS}) \]

\[ \text{and (carie} S \text{ or dmfS or cpoS or toothS or teethS or dentS or dentS or anticarieS or carioS or mou} \text{thrinsS or mouth rinsS or rinseS or bochechS or enjuagS or vernizS or varnishS or barnizS or lacaS or gel or gels}) \]

\[ \text{and (randomS or aleatoriS or acasoS or azarS or blindS or maskS or cegoS or ciegoS or ciegaS or placeboS or(clinicS and (trialS or ensaioS or estudS)) or (controlS and (trialS or ensaioS or estudS)))}. \]

Four supplementary and more specific subject search phrases (including 'free text' and 'controlled vocabulary' terms), refined exclusively for the reviews on the effects of individual fluoride modalities, formulated around three concepts each (the relevant topical fluoride therapy (TFT), fluoride and caries) were used to search Silverplatter MEDLINE (up to January 2000) without methodological filters:

\[ (\text{CARIE} S \text{ or (DENT* near CAVIT*) or TOOTH* DECAY* or DMF* or (explode "DENTAL-CARIES"/ ALL SUBHEADINGS))} \]

\[ \text{and (FLUOR* or APF* or NAF* or AMINE F OR SNF* or ACIDULATED* PHOSPHATE* FLUORID* or ACIDULATED* FLUORID* or PHOSPHATE* FLUORED* or SODIUM* FLUORID* or AMINE* FLUORID* or STANNOUS* FLUORID* or (explode "FLUORIDES"/ ALL SUBHEADINGS))} \]

\[ \text{and (TOOTHPASTE* or TOOTH* PASTE* or DENTIFRICE* or PASTE*) or (explode "DENTIFRICES"/ ALL subheadings)).} \]

\[ (2) ((RINS* or MOUTH* RINS* or WASH* or MOUTH* WASH*) or (MOUTHRINS* or MOUTHWASH*)) or (explode "MOUTHWASHES"/ all subheadings)]. \]

\[ (3) (FLUOR* or ...or ELMEX* or (explode "FLUORIDES"/ ALL SUBHEADINGS)) \]

\[ \text{and (GEL* or TRAY*)}. \]

\[ (4) (FLUOR* or (DURAPHAT* or FLUOR PROTECTOR*) or (explode "FLUORIDES"/ ALL SUBHEADINGS)) \] \]

\[ \text{and (VARNISH*) or (LACQUER* or LAQUER*) or (VERNIZ*) or (LACKER*) or (LAKK*) or (SILANE* or POLYURETHANE*)]. \]

These strategies were adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and have also been run on CENTRAL (The Cochrane Library Issue 2, 2000) to double check.

The metaRegister of Current Controlled Trials was searched in October 2001 for ongoing RCTs using the terms 'fluoride' and 'caries'.

REFERENCE SEARCHING

All eligible trials retrieved from the searches, meta-analyses and review articles located up to January 2000 were checked for relevant references. Reviews had been identified mainly by a MEDLINE search strategy specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic, when The Cochrane Library database: Cochrane Database of Systematic Reviews (CDSR), and the CRD databases: Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED), were also searched. Reference lists of relevant chapters from preventive dentistry...
textbooks on topically applied fluoride interventions were also consulted.

FULL TEXT SEARCHING
Prospective handsearching of the seven journals identified as having the highest yield of eligible RCTs/controlled clinical trials (CCTs) was carried out, from January 1999 until January 2000: British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (1990 to December 1999), as this was the journal with the highest yield of eligible reports.

PERSONAL CONTACT
Searching for unpublished studies (or 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published during the last two decades in order to obtain information on possible unpublished studies eligible for inclusion. All the authors of studies who had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies.

Based on information extracted mainly from included studies, a list of manufacturers of fluoride toothpastes, mouthrinses, gels and varnishes was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group, in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Fourteen manufacturers were contacted (October 2000) and information on any unpublished trials requested: Bristol-Myers Co, Colgate-Palmolive, Davies Rose-Hoyt Pharmaceutical Division, Gaba AG, Ivoclar North America, John O Butler Company, Johnson & Johnson, Oral-B Laboratories, Pharmascience, Procter & Gamble, Smithkline Beecham, Synthelabo, Unilever/Gibbs, Warner-Lambert.

Methods of the review

MANAGEMENT OF RECORDS PRODUCED BY THE SEARCHES
Because multiple databases were searched, the downloaded set of records from each database, starting with MEDLINE, was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS, BBO, CENTRAL, SIGLE and NIDR databases were not imported to Reference Manager and were checked without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filter were imported to Reference Manager for inspection, in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register and the metaRegister of Current Controlled Trials were also checked outside Reference Manager. In order to facilitate inspection of all records located from searching other (non-electronic) sources (reference lists of relevant studies, review articles and book chapters, journal handsearch, personal contact), we also tried to locate them in MEDLINE and to import them to Reference Manager. Those references that could not be downloaded in this way were entered manually.

RELEVANCE ASSESSMENT
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an

All records identified by the searches were printed off and checked on the basis of title first, then by abstract (when this was available in English or in languages known by the reviewer) and/or keywords by one reviewer, Valeria Marinho (VM). Records that were obviously irrelevant were discarded and the full text of all remaining records was obtained. Records were considered irrelevant according to study design/duration, participants, or interventions/comparisons (if it could be determined that the article was not a report of a randomized/quasi-randomized controlled trial; or the trial was of less than 6 to 8 months duration; or the trial was exclusively in adults; or the trial did not address at least two of the relevant topical fluoride treatments; or the trial did not compare one topical fluoride with another).

SELECTION OF STUDIES FOR INCLUSION
With the inclusion criteria form previously prepared and pilot tested, one reviewer (VM) assessed all studies for inclusion in the review, and a second reviewer, Julian Higgins (JH), independently duplicated the process for a sample of those (approximately 30%). In addition, any study that could not be classified by the first reviewer was independently assessed by the second. A third reviewer was consulted, Stuart Logan (SL) or Aubrey Sheiham (AS), to resolve any disagreement. It was decided in advance to exclude any trial where agreement could not be reached (but this did not occur). Trial reports thought to be potentially relevant in languages not known by the reviewers were translated and the reviewer (VM) completed the inclusion criteria form with reference to the translator. Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met.

It was considered essential to identify and check all reports related to the same study; in case of any discrepancy, authors were contacted.

QUALITY ASSESSMENT
The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Reviewers' Handbook (Clarke 2000) used in the Cochrane Review Manager software (RevMan). Allocation concealment for each trial was rated as belonging to one of three categories:
A. Adequately concealed (an adequate method to conceal allocation is described).
B. Concealment unclear ('random' allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
C. Inadequately concealed (an inadequate method of allocation concealment is described).
Excluded: random (or quasi-random) allocation clearly not used in the trial, or 'random' allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:
A. Double-blind (blind outcome assessment and use of placebo/blinding of participants described).
B. Single-blind (blind outcome assessment stated and no placebo used/participants not blind).
C. Blinding indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment, e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind outcome assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).
Excluded: clearly open outcome assessment used or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, of x-rays
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an
registered independently of clinical examination, of use of a placebo, and of examiners clearly not
involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated
the process for a random sample of approximately one third. Any disagreement was discussed and
where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not
be resolved an effort was made to contact authors directly to clarify the method used to conceal
allocation or whether assessment of the main outcome had been carried out blind.

Checking of interobserver reliability was limited to these validity assessments.

Other methodological characteristics of the trials such as completeness of follow up (proportion
excluded) and handling of exclusions (extent to which reasons for attrition are explicitly reported,
or losses are independent of treatment allocated) were not used as thresholds for inclusion.
However, all assessments of study quality are described in the table of included studies, and were
coded for possible use in metaregression/sensitivity analyses. [For example, sensitivity analyses
could be performed to assess the impact of blind outcome assessment and concealment of
allocation, since studies where blinding is not clearly stated (but likely) and studies reporting
inadequate allocation concealment are also included in this review].

DATA EXTRACTION
Data from all included studies were extracted by one reviewer (VM) using a pilot tested data
extraction form. A second reviewer (JH) extracted data from a random sample of approximately
one third of included studies. Again, data that could not be coded by the first reviewer were
independently coded by the second, any disagreements were discussed and a third reviewer
consulted to achieve consensus where necessary. (In future updates all reports will be data
extracted and quality assessed in duplicate.) Data presented only in graphs and figures were
extracted whenever possible, but were included only if two reviewers independently had the same
result. Attempts were made to contact authors through an open-ended request in order to obtain
missing information or for clarification whenever necessary. Papers in languages not known by the
reviewers were data extracted with help from appropriate translators.

Additional information related to study methodology or quality that was extracted included: study
duration (years of follow up); comparability of baseline characteristics: methods used pre­
randomization in sizing/balancing (stratification based on relevant variables) or used post­
randomization in analysing/adjusting for possible differences in prognostic factors between groups;
objectivity/reliability of primary outcome measurement (diagnostic methods and
thresholds/definitions used and included, and monitoring of diagnostic errors); any co-intervention
and/or contamination. Information on sponsoring institutions and manufacturers involved was also
recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries
severity at start (average DMFS, DFS, or other measure), background exposure to fluoride sources
other than the study option(s) (in water, topical applications, etc), year study began, place where
study was conducted (country), setting where participants were recruited, and dental treatment
level (F/DMF). Characteristics of the interventions that were extracted included: fluoride
modality(s), mode of application (how the intervention was delivered), methods (technique/device)
of application, prior- and post-application, fluoride active agents and concentrations used,
frequency and duration of application, and amount applied.
Different ways of assessing/reporting caries increment in the trials (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units of measurement (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (permanent/deciduous teeth/surfaces, first molar teeth, approximal surfaces, etc), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiographic), and approaches to account or not for reversals in caries increment adopted (in a net or observed/crude caries increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow ups), and where assessments of caries increments were made during a post-intervention follow up period, the length of time over which outcomes were measured after the intervention ended was noted.

As we were aware that caries increment could be reported differently in different trials we developed a set of a priori rules to choose the primary outcome data for analysis from each study: data on permanent teeth would be chosen over data on deciduous teeth; data on surface level would be chosen over data on tooth level; DFS data would be chosen over DMFS data, and this would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted' only, and this over data for 'erupting' only; data from 'clinical and radiographical examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological' only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated lesions; net caries increment data would be chosen over crude (observed) increment data; and follow up nearest to 3 years (often the one at the end of the treatment period) would be chosen over all other lengths of follow up, unless otherwise stated. When no specification was provided with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices described above were assumed.

All other relevant outcomes assessed/reported in the trials were also recorded/listed.

ANALYSES
Handling of missing main outcome data
It was decided that missing standard deviations for caries increments that were not revealed by contacting the original researchers would be imputed through linear regression of log standard deviations on log mean caries increments. This is a suitable approach for caries prevention studies since, as they follow an approximate Poisson distribution, caries increments are closely related (similar) to their standard deviations (van Rijkom 1998).

Handling of results (main outcome) of studies with more than one treatment arm
For studies with more than two-arms, where the same TFT form is compared in two or more 'experimental' groups (for example, different active agents or concentrations of fluoride ion are compared for the same modality of TFT to a common 'control' group), raw results (the numbers, mean caries increments and standard deviations) from all relevant 'experimental' groups were combined in order to obtain a measure of treatment effect (this enables the inclusion of all relevant data for each form of TFT in the meta-analyses).

Choice of measure of effect and meta-analyses of main outcome
The chosen measure of treatment effect was the prevented fraction (PF), that is (mean increment in
the 'controls' minus mean increment in the 'experimental' group) divided by mean increment in the
'controls'. For an outcome such as caries increment (where discrete counts are considered to
approximate to a continuous scale and are treated as continuous data) this measure was considered
more appropriate than the mean difference or standardised mean difference, since it allows
combination of different ways of measuring caries increment and a meaningful investigation of
heterogeneity between trials. It is also simple to interpret.

The meta-analyses were conducted as inverse variance weighted averages. Within-study variances
were estimated using the formula presented in Dubey 1965 which was more suitable for use in a
weighted average, and for large sample sizes the approximation should be reasonable. Random
effects meta-analyses were performed throughout in RevMan 4.2/RevMan Analyses.

Deciduous and permanent teeth were analysed separately throughout.

For illustrative purposes, when overall results were significant, the results were also presented as
the number of children needed to treat (NNT) to prevent one carious teeth/surface. These were
calculated by combining the overall prevented fraction with an estimate of the caries increment in
the 'control' groups of the individual studies.

Assessment of heterogeneity and investigation of reasons for heterogeneity
Heterogeneity in the results of the trials was assessed by inspection of a graphical display of the
estimated treatment effects from the trials along with their 95% confidence intervals and by formal
tests of homogeneity (Thompson 1999).

Statistically significant heterogeneity was investigated using metaregression when a meta-analysis
included a sufficiently large number of studies. In addition to aspects of study quality, potential
sources of heterogeneity investigated would include baseline levels of caries severity and exposure
to fluoride sources other than the study options. The association of these factors with estimated
effects (D(M)FS PFs) would be examined by performing random effects metaregression analyses in
Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998).

Investigation of publication and other biases
A funnel plot (plots of treatment effect estimates versus the inverse of their standard errors) was
drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to
sample size, though may also represent a true relationship between trial size and effect size. A
formal investigation of the degree of asymmetry was performed using the method proposed by
Egger et al (Egger 1997).

Measures of effect and meta-analysis of other outcomes
For outcomes other than caries increment, continuous data would be analysed according to
differences in mean treatment effects and their standard deviations. Dichotomous outcome data
were analysed by calculating risk ratios (RR) or, for adverse effects of fluoride treatment, risk
differences (RD). RevMan 4.2 was used for estimation of overall treatment effects. Again, a
random effects model was used to calculate a pooled estimate of effect. NNT was calculated when
overall results were significant. As a general rule only (relevant) outcomes with useable data were
shown in the analyses tables.

Description of studies

Review Manager 4.2.2 26/09/2003
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an

SEARCH RESULTS
Our initial multiple database search (1997/98) produced the following total number of records, according to database searched: MEDLINE, 4599; EMBASE, 5052; BIOSIS, 421; SCISEARCH, 514; SSCISEARCH, 169; ISTP, 66; CINAHL, 133; ERIC, 60; DISSERTATION ABSTRACTS, 95; LILACS, 48, BBO, 47; CENTRAL, 86; SIGLE, 6. Searching OLD MEDLINE produced 545 records, and the Community of Science database, 24 records. In the second stage of searches (1999), searching LILACS and BBO with a modified search strategy produced 210 records (142 and 68 records respectively). The more specific MEDLINE searches (by individual modalities of topical fluoride therapy (TFT)) performed without a randomized controlled trial (RCT) filter produced 2441 records, and the searches performed in the Cochrane Oral Health Group's Trials Register (May 2000) produced 479 records. Searching the metaRegister of Current Controlled Trials for ongoing studies produced 5 records. Many records retrieved through electronic search were duplicates merged later in the core database, and many appeared more than once in different databases and/or searches performed (overlapped).

Searching other non-electronic sources (reference lists of potentially relevant reports, review articles or book chapters, relevant journals, and contacting authors) produced 171 additional records for inspection. (Any search results produced by contacting manufacturers will feature in updates of this review).

RELEVANCE ASSESSMENT RESULTS
When all the records produced by the searches above were screened, a total of 713 reports were identified as potentially eligible and further assessment was sought.

STUDY SELECTION RESULTS
Two (2) full text reports could not be obtained (these were incomplete references of unpublished studies/grey literature). Six hundred and seventy-five (674) reports were considered immediately irrelevant for this review, largely as a result of the types of intervention compared with (or used in addition to) a relevant TFT (including placebo or no treatment control trials without a relevant head to head comparison(s) of one TFT with another), and due to the types of study design described.

Thus, 28 studies (37 reports) are considered/cited in this review. These comprise 24 reports relating to 17 included studies, 10 reports relating to nine excluded studies, and three reports relating to two studies waiting assessment (either because they require translation (Polish) or because additional information has not been obtained for one study in abstract form). There are no reports of ongoing studies. Six non-English reports (five studies) listed either under included or excluded studies have been fully assessed: Two in French (by a French translator, with the contact reviewer), one in Portuguese (by the contact reviewer), and three in Russian (by a translator, with the reviewer).

EXCLUDED STUDIES
See 'Characteristics of excluded studies' for the description of reasons for rejecting each study.

We have excluded two studies comparing fluoride varnish with gel, three comparing varnish with mouthrinse, three comparing toothpaste with mouthrinse, and one comparing fluoride varnish, gel and mouthrinse (there were no excluded studies comparing varnish with toothpaste or gel with toothpaste).

These nine studies were excluded for a variety of reasons. One study used open outcome
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an assessment. One study randomized three clusters, each to one of the three groups compared. Four studies did not mention or indicate random or quasi-random allocation and blind outcome assessment; one of these also did not report main outcome data for one group and another reported post-treatment effects only. One study did not mention or indicate random or quasi-random allocation (but described blind outcome assessment); attempts to contact the authors of this study were unsuccessful and it was excluded. Two studies had other intervention in addition to one of the relevant TFTs, and one of these did not describe the use of blind outcome assessment.

INCLUDED STUDIES
See 'Characteristics of included studies' table for details of each study.

There are 17 trials included. The study conducted by Marthaler 1970 was treated as two independent trials because the results for the two age groups involved were reported separately as distinct studies. The study by Koch 1967 presented results by age group for one treatment arm but not the other, so we treated it as a single study, combining the age subgroups for the toothpaste arm. The 17 trials were conducted between 1962 and 1994: four during the 1960s, nine in the 1970s, three in the 1980s and one in the 1990s. Two trials were conducted in USA, three in UK, two in Switzerland, five in Sweden, two in Denmark, two in Finland, and one in Israel. Four studies had more than one publication, two of these had four published reports each. All 24 reports were published between 1965 and 1995. Five studies acknowledged assistance (product provision, etc.) and/or financial support from manufacturers. Of a total of four studies whose authors were sent request letters for unpublished information, replies related to two studies were obtained.

Design and methods
All the 17 included studies used parallel group designs. Five studies had more than two arms; in three of these there were two groups of one of the modalities of TFT being compared, and in the other two studies there were two groups (study arms) of each of the two modalities being compared. There was no study comparing more than two relevant modalities of TFT. Ten trials used inactive/placebo interventions for the head to head comparisons (i.e. were organized on a double-blind basis) and the remaining seven used no treatment (simple head to head comparisons of the TFTs only). Study duration ranged from 1 to 3 years, with only two studies lasting less than 2 years. Studies were generally large with only four allocating less than 190/200 children to relevant study groups (and eight studies involving over 300 participants); all but one study recruited children from school settings.

Interventions
There are six trials comparing fluoride toothpaste with mouthrinse, four comparing toothpaste with gel (one involving operator-applied gel, and three self applied gel), one comparing toothpaste with varnish, four comparing varnish with mouthrinse, one comparing varnish with gel (operator-applied gel), and one comparing mouthrinse with gel (self applied gel). The fluoride concentration in the 11 trials with a toothpaste arm was similar (ranged from 1000 to 1200 ppm F in the toothpastes), and in four of these toothbrushing was performed under supervision (at school). In all six trials with a fluoride varnish arm the varnish application was semi-annual, and all but one tested a 22,600 ppm F (Duraphat). The fluoride concentration in all six trials with a fluoride gel arm was also similar (12,300/12,500 ppm F), but frequency of gel application varied from twice (operator-applied) to 25 times a year (self applied). There was variation in both the fluoride concentration (100, 230/250, 900 ppm F) and frequency of application (daily, weekly, fortnightly) in the trials involving fluoride mouthrinsing.

Participants
Participants were aged 14 or less at the start (in all trials), with similar numbers from both sexes (where these data were reported). At least 10 trials included children who were around 12 at start, and only one trial (Petersson 1985) involved pre-school children. Caries prevalence at baseline, reported in all but two of the studies, ranged from 0.9 to 15 D(M)FS and was 0.9 dfs in the study by Petersson. Fifteen studies reported exposure or not to water fluoridation, and only one of these was conducted in a fluoridated community. Background exposure to fluoride toothpaste (or other sources of topical fluoride) was not clearly reported in the majority of studies.

Outcome measures
Caries increment: all trials reported caries increment data (or data from which these could be derived) at the tooth surface level (D(M)FS was reported in 16 trials, and dfs in one trial), and three trials reported caries increment at the tooth level (D(M)FT). With regard to the components of the DMFS index used (and types of teeth/surfaces assessed), six trials reported DMFS data (for all tooth surface types), 10 trials reported DFS data (for all tooth surface types) and one trial reported DS data (for approximal surfaces of premolars and molars only). No choice had to be made between DMFS or DFS data in any one trial. Eight trials presented D(M)FS data at more than one follow up time. In one trial, assessment of D(M)FS increments were also made during a post-intervention follow up period. Many trials presented results using one caries grade only (usually CA/ER or CA/DR), others either did not report the grade, or reported caries increment data at both levels of diagnosis, in which case CA was chosen. Data on the state of tooth eruption considered were not clearly specified in many trials.

The table 'Characteristics of included studies' provides a description of all the main outcome data reported from each study with the primary measure chosen featuring at the top.

Other dental caries data reported: caries incidence/attack rate (two trials), caries progression (one trial), and proportion of children developing new caries (two trials).

Data on adverse effects: stain score (one trial), signs of sensitivity in oral soft tissue (one trial), any side effects (one trial, without complete or useable data, and with the following statement: "no side effects observed in both groups"). Fluorosis data have not been reported in any of the trials.

Data for unacceptability of treatment (as measured by dropouts/exclusions) were reported in eight trials.

Methodological quality of included studies
Based on 28 studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, interrater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73).

There was a considerable variation in the quality of the studies in this review (using the reported information and additional information obtained from investigators).

ALLOCATION CONCEALMENT
Fourteen trials were described as randomized but provided no description on how the 'random' allocation was done and were coded B, two trials were considered to be quasi-randomized and were coded C, in one trial allocation concealment was considered adequate by consensus (coded
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an

A).

BLINDING
Double-blinding was described in eight trials (Code A), single-blinding (blind outcome assessment described but no placebo used) was described in seven trials (code B), and blind outcome assessment was indicated in two trials (code C) which described the use of placebo.

LOSS TO FOLLOW UP
Seventy-three per cent (73%) of the participants originally enrolled in the studies were included in the final analysis (3243 analysed out of 4423 initially randomized). These data exclude six of the 17 included studies, which provided no information on the number of participants randomized to relevant groups. Drop-out rates were obtained from all but one of the 17 included studies and ranged from 2% at 2 years to 39% at 3 years. The most common reason for attrition was that participants were not available for follow up examination at the end of the study.

OTHER METHODOLOGICAL FEATURES
Cluster randomization was used in three trials which compared fluoride varnishes to fluoride mouthrinses (Brunn 1985; Kirkegaard 1986; Seppa 1987) where school classes were used as units of randomization and children used as units of analysis. Individuals were allocated to study arms in all other trials, and each participant's caries incidence, over a period of time was used as the unit of analysis.

Baseline comparisons and handling of any differences: one trial described as 'balanced' (for which randomization may have succeeded to produce nearly exact balance) did not report any of the actual values for the baseline characteristics (such as initial caries levels). Some degree of imbalance was reported in a few trials (for characteristics considered most influential, usually initial caries levels) and generally either described as not significant or that adjustment had resulted in trivial differences in effect estimates.

Objectivity/reliability of primary outcome measurement: diagnostic methods used (clinical or radiographic) were described in all studies, but thresholds/definitions used for caries and monitoring of diagnostic errors were not always reported (see 'Notes' in the 'Characteristics of included studies' table for methodological features assessed).

Results

EFFECT ON DENTAL CARIES
Pooled estimates of the relative effects of topical fluoride therapy (TFT) are presented for caries increment in the permanent dentition as Decayed, (Missing) and Filled Surfaces Prevented Fraction (D(M)FS PF). Estimates for caries increment in the deciduous dentition are presented as decayed, (missing/extraction indicated), and filled surfaces Prevented Fraction (d(m/e)fs PF).

Sixteen studies provided data suitable for meta-analysis. Standard deviations (SD) of mean caries increment data (new D(M)FS) were missing in two of the 16 studies (Axelsson 1987; Ran 1991). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation $\log (SD \text{ caries increment}) = 0.64 + 0.55 \log (\text{mean caries increment})$, (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses. The single study reporting caries increment in deciduous tooth surfaces (Petersson 1985) did not
provide standard deviations of mean caries increment (new dfs) either, and is not included in the analysis of D(M)FS PF (no caries increment data for the permanent dentition).

We have decided to exclude the trial of Ran 1991 (comparing fluoride toothpaste with gel) from any analysis because the DMFS increment in the fluoride gel arm of the trial was very small, resulting in a poor estimate of PF. Thus, 15 studies are included in the meta-analyses.

The results are reported separately here for the following main comparisons:
(1) Fluoride varnish versus gel (1 trial)
(2) Fluoride varnish versus mouthrinse (4 trials)
(3) Fluoride varnish versus toothpaste (1 trial, incomplete data, for deciduous tooth surfaces only)
(4) Fluoride toothpaste versus gel (3 trials)
(5) Fluoride toothpaste versus mouthrinse (6 trials)
(6) Fluoride gel versus mouthrinse (1 trial)
(7) Fluoride toothpaste versus any TFT - D(M)FS data available for comparisons with fluoride gel (3 trials) and fluoride mouthrinse (6 trials), but not for comparison with fluoride varnish.

Objective 1 is addressed in comparisons (1) to (6). The only comparison of fluoride gel versus varnish involved professional application of both, so comparison 1 (of fluoride varnish versus gel) under Objective 1 in effect addresses Objective 2 as well (comparative effect of operator-applied varnish and operator-applied gel). Similarly, the only comparison of fluoride gel versus mouthrinse involved self-application of fluoride gel, so comparison 2 (of fluoride mouthrinse versus varnish) under Objective 1 in effect addresses Objective 3 as well (comparative effect of fluoride mouthrinse and professionally-applied TFT). Finally, Objective 4 (comparative effect of fluoride toothpaste and other TFT) is addressed in comparison 7.

Relatively few trial reports provided data able to contribute to meta-analysis and with the exception of three trials, which were not carried out on a double-blind basis (Torell 1965; Koch 1967, Seppa 1987), all reported equivocal results for caries reductions, i.e. no demonstrated differential effect. Apart from the division of trials into those comparing fluoride toothpaste with gel or mouthrinse in comparison (7), no subgroup analyses were performed due to the lack of an appropriate volume of data. No metaregression and funnel plot analyses were performed either, on the grounds of insufficient data.

(1) Fluoride varnish versus fluoride gel
Only one trial (Seppa 1995) compared fluoride varnish with fluoride gel (n = 254). Analysis of this trial showed a non-significant effect in favour of fluoride varnish and a wide confidence interval for the estimate of effect. The D(M)FS prevented fraction was 0.14 (95% CI, -0.12 to 0.40; p = 0.30), suggesting that there is insufficient evidence from this trial to confirm or refute a differential effect in caries reduction.

(2) Fluoride varnish versus fluoride mouthrinse
Four trials compared fluoride varnish with fluoride mouthrinse (n = 952). The D(M)FS prevented fraction pooled estimate from the random effects meta-analysis of all four trials combined was 0.10 (95% CI, -0.12 to 0.32; p = 0.40), a non-significant effect in favour of fluoride varnish and a wide confidence interval for the pooled estimate of effect. Heterogeneity in the results could be observed graphically and statistically (chi squared = 11.13 on 3 degree of freedom, p = 0.01) and according to the I-squared heterogeneity statistic the extent of heterogeneity (or lack of consistency) in results is indeed large (I squared = 73%). If a fixed effects meta-analysis is performed, however, the result becomes statistically significant and the two models still come out with similar answers,
even though the differential effect is larger in the fixed effects meta-analysis. The D(M)FS prevented fraction pooled estimate from the fixed effects meta-analysis was 0.15 (95% CI, 0.04 to 0.26; \( p = 0.007 \)).

We performed further sensitivity analysis to take account of the additional uncertainty we should have about the three cluster randomized trials (Brunn 1985, Kirkegaard 1986, and Seppa 1987) in this comparison. We inflated the variance of the prevented fraction estimates in these trials by an amount equal to \((1 + (m-1) \times ICC)\), where \( m \) is the average cluster size and ICC the intraclass correlation coefficient. A conservative value of 0.1 for the ICC was used since we could not find an ICC from these or any similar trials. The D(M)FS PF pooled estimate (random effects meta-analysis) was 0.14 (95% CI, -0.06 to 0.34; \( p = 0.16 \)). It may be noted that although heterogeneity in these results could not be detected by the standard chi squared test (chi squared = 5.86 on 3 degrees of freedom, \( p = 0.12 \)), this was not due to homogeneity (I squared = 49%). Nevertheless, these results are similar to the analysis ignoring the cluster randomized design (though not identical, since the estimates for these trials differ from the meta-analysis result), showing a non-significant differential effect in favour of fluoride varnishes, but less heterogeneity in results. Again, if a fixed effects meta-analysis is performed the result becomes statistically significant and the two models still come out with similar answers (and a larger differential effect is shown again). The D(M)FS prevented fraction pooled estimate from the fixed effects meta-analysis was 0.19 (95% CI, 0.06 to 0.32; \( p = 0.005 \)).

Double-blinding (use of placebo rather than no treatment comparisons) may represent a valid indicator of study quality and source of heterogeneity in the topical fluoride reviews (Marinho 2003). If further sensitivity analysis is carried out (in the original data, ignoring the cluster randomized design) excluding the two trials which are not double-blind, no significant differences are detected. For the two double-blind trials combined (Brunn 1985, Kirkegaard 1986) the D(M)FS prevented fraction pooled estimate (random effects meta-analysis) was -0.12 (95% CI, -0.32 to 0.08; \( p = 0.23 \)), a non-significant difference in the opposite direction, in favour of fluoride mouthrinse. Heterogeneity in the results could not be observed graphically nor statistically (chi squared = 0.50 on 1 degree of freedom, \( p = 0.48 \); I squared = 0). The revised meta-analysis yielded an estimate of effect which differed from the overall estimate, indicating the results are not robust and may be distorted by the lesser quality trials. Similar findings are obtained when we use the inflated variances for these two trials: the D(M)FS prevented fraction pooled estimate (random effects meta-analysis) was -0.12 (95% CI, -0.40 to 0.17; \( p = 0.43 \)), a non-significant difference in favour of fluoride mouthrinse. Heterogeneity in the results was not detected.

(3) Fluoride varnish versus fluoride toothpaste
The single trial (Petersson 1985) comparing fluoride varnish with fluoride toothpaste (\( n = 183 \)) assessed the relative effect in terms of caries increment in deciduous surfaces and provided no standard deviations or data from which these could be derived. It reported a negligible dfs PF of -0.05 (CI not obtainable).

It may be noted that this trial also reported on the proportion of children developing one or more new caries in deciduous tooth surfaces. Exactly the same proportions were reported in both groups (no evidence of a difference).

(4) Fluoride toothpaste versus fluoride gel
Three trials compared fluoride toothpaste with fluoride gel (\( n = 1256 \)). The D(M)FS prevented fraction pooled estimate from the random effects meta-analysis of the three trials combined was 0.00 (95% CI, -0.21 to 0.21; \( p = 1.00 \)), i.e. absolutely no differences in effect and a relatively wide
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another

confidence interval. Heterogeneity was not significant according to the standard chi squared test, but the test would have minimal power to detect heterogeneity (chi squared = 3.34 on 2 degrees of freedom, p = 0.19), which is actually indicated graphically and shown to be moderately large according to the I-squared heterogeneity statistic (I squared = 40%).

(5) Fluoride toothpaste versus fluoride mouthrinse
The six trials comparing fluoride toothpaste with mouthrinse (n = 2545) showed no differences in effect and substantial heterogeneity in results (I squared = 85%). The D(M)FS prevented fraction was 0.00 (95% CI, -0.18 to 0.19; p = 0.97) and the chi squared test for heterogeneity was 32.35 on 5 degrees of freedom (p< 0.00001).

There was one trial reporting on the proportion of children developing one or more new caries in permanent tooth surfaces (Torell 1965). It reported a non-significant risk ratio (RR) of 0.90 (95% CI, 0.60 to 1.37) in favour of toothpaste.

(6) Fluoride gel versus fluoride mouthrinse
Only one trial (DePaola 1980) compared fluoride gel with fluoride mouthrinse (n = 257). It showed a non-significant effect in favour of fluoride mouthrinse and a wide confidence interval for the estimate of effect. The D(M)FS prevented fraction was -0.14 (95% CI, -0.40 to 0.12; p=0.30) suggesting that there is insufficient evidence from this trial to confirm or refute a differential effect in caries reduction.

(7) Fluoride toothpaste versus any TFT
For all nine trials combined (three comparing fluoride toothpaste with gel and six with mouthrinse; n = 3801), the D(M)FS prevented fraction pooled estimate from the random effects meta-analysis was 0.01 (95% CI, -0.13 to 0.14; p = 0.94), i.e., no significant differences were detected. Heterogeneity in results was significant (chi squared = 36.28 on 8 degrees of freedom, p<0.0001), and substantial (I squared = 78%). Results for the separate subsets comparing toothpaste with either gel or mouthrinse (described above) are consistent with no evidence of a differential effect.

EFFECT ON OTHER OUTCOMES
Data for unacceptability of treatment were reported in eight trials that reported dropouts. Each of the eight trials reported equivocal results for this outcome, i.e. no demonstrated differential effect. Meta-analysis results for these are described below.

Fluoride varnish versus fluoride mouthrinse
The pooled estimate (random effects meta-analysis) of the relative risk (RR) of dropping out from the fluoride varnish group as opposed to the mouthrinse arm in the two trials that reported dropouts was 1.19 (95% CI, 0.86 to 1.65) in favour of fluoride mouthrinse, but no significant differences were detected. Using alternative measures of effect has given similar results (OR 1.26, CI 0.82 to 1.94). Heterogeneity was not detected in these results (chi squared = 0.15 on 1 degree of freedom, p = 0.70; I squared = 0%).

Fluoride varnish versus fluoride toothpaste
There was one trial only reporting dropouts in this comparison. The relative risk (RR) of dropping out from the fluoride varnish group as opposed to the toothpaste arm of the trial was 1.28 (95% CI, 0.37 to 4.41) in favour of fluoride toothpaste, but no significant differences were detected and the confidence interval was wide.

Fluoride toothpaste versus fluoride mouthrinse
The pooled estimate (random effects meta-analysis) of the relative risk (RR) of dropping out from the fluoride toothpaste group as opposed to the fluoride mouthrinse arm in the five trials that reported dropouts was 0.89 (95% CI, 0.78 to 1.00; p = 0.05) in favour of fluoride toothpaste. Heterogeneity was not detected in these results (chi squared = 2.61 on 4 degrees of freedom, p = 0.63; I squared = 0%). Using alternative measures of effect has given similar results (OR 0.83, CI 0.70 to 1.00; RD -0.03, CI -0.06 to 0.00).

None of the trials in the other pairwise comparisons reported dropouts fully.

**Fluoride toothpaste versus any TFT**

The pooled estimate (random effects meta-analysis) of the relative risk (RR) of dropping out from the fluoride toothpaste group as opposed to the other TFT arm (fluoride varnish (one trial), mouthrinse (five trials)) in the six trials that reported dropouts was 0.88 (95% CI, 0.78 to 1.00; p = 0.05) in favour of fluoride toothpaste. Heterogeneity was not detected in these results (chi squared = 2.65 on 5 degrees of freedom, p = 0.75; I squared = 0%). Using alternative measures of effect has given similar results (OR 0.83, CI 0.70 to 0.99; RD -0.02, CI -0.05 to 0.00).

**Discussion**

Topical fluorides in the form of toothpastes, mouthrinses, varnishes and gels are effective caries preventive interventions. The effectiveness of each of these has been assessed fully in four previous systematic reviews in this series (Marinho 2002; Marinho 2002a; Marinho 2003; Marinho 2003a). Compared with placebo or no treatment the average DMFS prevented fractions ranged from 24% for fluoride toothpaste, through 26% for mouthrinses and 28% for gels, to 46% for fluoride varnish. These conclusions were made on a clearer basis in placebo controlled trials (Marinho 2003b). For example, the first review in the series focused on the effectiveness of fluoride gels and reported a pooled PF on permanent tooth surfaces of 21% based on 14 placebo-controlled studies (Marinho 2002). In terms of absolute caries reductions per year in D(M)FS increments (in populations with D(M)FS increments of around 2), these ranged from 0.46 for fluoride gel to 0.74 for fluoride varnish (mouthrinses 0.56, toothpaste 0.62). There is uncertainty, however, about the relative value of the various topical fluoride treatments.

The main question addressed by this review is how effective the use of one type of topical fluoride therapy (TFT) for the prevention of caries in children is compared to another. The 15 studies included in the meta-analyses in this review covered nearly all the range of direct head to head comparisons of possible practical value between fluoride toothpastes, mouthrinses, gels and varnishes. Yet, there is a relatively small number of trials in each main comparison/meta-analysis. The randomized evidence that we have brought together is, as far as we can ensure, the totality of the available randomized evidence comparing the relevant topical fluoride modalities directly. There is a general lack of statistical significance for virtually all meta-analyses' results in this review. Further, for the great majority of comparisons, the confidence intervals are relatively wide and the variation among the results of the studies can be substantial. This calls for a cautious interpretation of the data.

Our second objective was to assess the relative effectiveness of professionally-applied gels and varnishes. Based on the results from the single trial comparing fluoride varnish to fluoride gel there is insufficient evidence to confirm or refute a differential effect in caries reduction between these two interventions. Analysis of this trial showed a non-significant effect in favour of fluoride varnish and a wide confidence interval for the estimate of effect.
A third objective of the review was to examine whether there was a beneficial effect in terms of caries prevention from the use of fluoride mouthrinses (a self-applied TFT) compared with professionally-applied TFTs (varnishes or gels). The only available comparison of fluoride gel and mouthrinse, based on a single study, involved self-application of fluoride gel, and showed a non-significant effect in favour of fluoride mouthrinse and a wide confidence interval for the estimate of effect. Therefore, the question above is in effect addressed exclusively by the meta-analysis of five trials of fluoride mouthrinse compared with fluoride varnish. We were unable to detect a clear differential effect from these data. In addition, although the random effects meta-analysis of the five trials produced a non-significant result (of small magnitude) in favour of varnishes, when the analysis was restricted to the subset of two double-blind trials (both cluster randomized trials comparing the same fluoride varnish product used semi-annually with the same fluoride mouthrinse used fortnightly), the difference in effect was reverted in favour of mouthrinses, but still not statistically significant.

It is interesting to compare these results with those of Strohmenger 2001 that carried a systematic review on the anti-caries efficacy of fluoride varnishes, using a different and restrictive set of inclusion criteria, which resulted in the analysis of only three studies. All three of these studies were comparisons of fluoride varnishes with fortnightly fluoride mouthrinses at school, and were included in our analyses. Again, although the pooled estimate of the treatment effect in the meta-analyses by Strohmenger 2001 favoured fluoride varnish, the results were not statistically significant at the 0.05 level.

The final objective of the review was a comparison between fluoride toothpastes and any other modality of TFT (mouthrinses, gels or varnishes). The general observation is that there is no indication of an increased benefit with the use of either, toothpaste or the other TFTs. Again, data (for the permanent dentition) were available from trials involving direct comparisons of toothpaste with fluoride mouthrinse and with fluoride gel; relevant comparisons with useable data of fluoride toothpaste and varnish were lacking. Nevertheless, results for the separate subsets and for all the data combined comparing toothpaste with either gel or mouthrinse are consistent with no evidence of an important differential effect.

The results above, based on head to head comparisons in this review, are generally in line with those from a previous systematic review in this series (Marinho 2003b), based on adjusted indirect comparisons from meta-analyses of all four TFT types in which a large amount of data from placebo/no treatment trials were considered. Results from the adjusted indirect comparisons suggested no significant differences in treatment effects between gel, mouthrinse and toothpaste, but significantly lower D(M)FS prevented fractions for fluoride gel, mouthrinse or toothpaste in comparison with fluoride varnish. However, relatively few fluoride varnish trials were included in the indirect comparison analyses and very few among these were placebo-controlled trials, making it difficult to rule out the possibility of an overestimation of the size of the differential effect, due to the preponderance of no treatment control fluoride varnish studies of lower methodological quality in the review. Nevertheless, empirical evidence indicates that in most cases results of adjusted indirect comparisons are not significantly different from those from direct comparisons (Song 2003), and when direct evidence is available but insufficient, the adjusted indirect comparison may provide supplementary information (Higgins 1996). Thus, the data available for indirect comparisons could usefully strengthen conclusions based on the pooled results from the direct comparisons in this review, especially when there are concerns about the methodological quality of a few randomized trials. Methods are being developed to formally combine data from direct and indirect evidence (Higgins 2003) and we hope to be able to apply the new methods in future.
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus an

updates of this review.

As was generally the case for other reviews in this series, we found no useful information in the trials about potential adverse effects such as fluorosis, tooth staining, or oral allergic reactions. However, if children are allocated to fluoride toothpaste they appear to be more likely to stay in the study than if they are given alternative forms of topical fluoride therapy.
Reviewers' conclusions

Implications for practice
This review has found that compared with each other, fluoride toothpaste and mouthrinse, and toothpaste and gel appear to be effective to a similar degree in the prevention of dental caries in children. The benefits in terms of caries reduction from fluoride mouthrinse compared with gel, fluoride varnish compared with gel, and varnish compared with toothpaste (deciduous teeth only) are unclear. In addition, there is no clear indication from this review that any additional cariostatic effect may accrue from the use of fluoride varnish in comparison to mouthrinse. The general acceptability for fluoride toothpastes is unquestioned by these results. Arguably, fluoride varnishes lead to less fluoride ingestion, which may be of importance in young children, and require less time for application (usually at semi-annual intervals), but the general lack of data on potential adverse effects and on acceptance for virtually all TFTs, makes it more difficult to weigh the benefits of using any given topical fluoride against possible shortcomings of the procedure.

Implications for research
There is a general lack of randomized trial evidence evaluating the comparative effectiveness of the various topical fluorides for the prevention of dental caries in children, and, therefore, a modest difference in treatment effect may have been missed for most relevant comparisons. However, the lack of a clear suggestion of significant benefits from the data analysed from most direct comparisons may not indicate priority for the performance of new studies. Nevertheless, taking the available results from indirect evidence into account as well, there may be a suggestion for the performance of additional larger studies of higher methodological quality to determine whether fluoride varnishes are more effective in caries prevention than other topical fluorides, gels and mouthrinses in particular, since varnishes are already perceived to present some empirical advantages over these treatments.
### Characteristics of included studies

<table>
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<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
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<tr>
<td>Ashley 1977</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 12% drop out (for all study groups combined) after 2 years (study duration = 2 years). Natural losses; any differential group losses not assessable.</td>
<td>491 children analysed at 2 years (available at final examination). Average age at start: 12 years. Surfaces affected at start: 8.8 DFS. Exposure to other fluoride: no. Year study began: 1973. Location: UK.</td>
<td>FR+PLT versus FT+PLR&lt;br&gt;NaF group (FR) = 100 ppm F.&lt;br&gt;School mouthrinising/supervised, daily, 20 ml applied for 1 min (after toothbrushing with placebo toothpaste at school).</td>
<td>2yNetDFS increment - (E+U)(NCA)c+(ER)xr. Reported at 2 years follow up.</td>
<td>Participants randomized (numbers for relevant groups NR). Baseline characteristics (age, DFS, DMFS, DMFT) 'balanced'. Clinical (V) caries assessment by one examiner (FOTI used); diagnostic threshold = NCA. Radiographic assessment (postBW) by one 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.</td>
</tr>
<tr>
<td>Axelsson 1987</td>
<td>Random allocation; double-blind (A); placebo-controlled; 18% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers by group; no</td>
<td>93 children analysed at 3 years (available at final examination). Age range at start: 13-14 years. Surfaces affected at start: relevant data NR. Exposure to other fluoride:</td>
<td>FR+PLT versus FT+PLR&lt;br&gt;NaF group (FR) = 230 ppm F.&lt;br&gt;School mouthrinising/supervised, daily, 1g applied for 1 min (followed by rinse with placebo mouthrinse); non-fluoride toothpaste provided to all for home use. Abrasive system: IMP (main abrasive).</td>
<td>3ypostMD-DS increment - (ER)xr. Reported at 3 years follow up.</td>
<td>Participants randomized (N = 113). Baseline characteristics (DS) 'balanced'. Radiographic assessment (postBW) by two examiners; diagnostic threshold = ER. State of tooth eruption</td>
</tr>
</tbody>
</table>

*Review Manager 4.2.2 26/09/2003*
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children

**Blinkhorn 1983**
- Stratified random allocation; double-blind (A); placebo-controlled; 10% drop out after 3 years (study duration = 3 years).
- Reasons for attrition described with respective total numbers: 57 left school, 12 withdrawn by parents, 6 absent at final examination; no differential group losses.
- Location: Sweden.

374 children analysed at 3 years (available at final examination).
- Age range at start: 11-12 years.
- Surfaces affected at start: 8.3 DMFS.
- Exposure to other fluoride: no.
- Year study began: 1972.
- Location: UK.

NaF group (FT) = 1000 ppm F.
- Home toothbrushing/unsupervised, daily frequency assumed (instructed to brush twice a day).
- Abrasive system: silica.

FR+PLT versus FT+PLR
- NaF group (FR) = 230 ppm F.
- School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with placebo toothpaste at school).

SMFP group (FT) = 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by rinse with placebo mouthrinse); appropriate toothpaste provided to all for home use.
- Abrasive system: IMP (main abrasive).

3yNetDFS increment - (E+U)(CA)cl+(DR)xr.
- Reported at 3 years follow up.
- PF-DFS.
- MD-BL-DFS.
- MD-DFS.
- postMD-DFS.
- DMFT (E/U).
- anterior DMFT.
- posterior DMFT.
- DFS (U).
- Drop out.

Participants randomized (N = 414).
- Baseline characteristics (DMFS, DMFT, SAR) 'balanced' (DFS baseline data NR).
- Clinical (V) caries assessment by one examiner, diagnostic threshold = CA.
- Radiographic assessment (1 postBW) by one 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).

**Bruun 1985**
- Cluster quasi-random allocation; double-blind (A); placebo-controlled; 30% drop out after 3 years (study duration = 3 years).
- Natural losses only; any
- Location: UK.

251 children analysed at 3 years (available at final examination).
- Average age at start: 11 years.
- Surfaces affected at start: 5.2 DMFS, DFT, SAR 'balanced' (DFS baseline data NR).

FV+PLR versus FR+PLV
- NaF Group (Fluor Protector® varnish) = 7000 ppm F.
- Applied twice a year, with soft brush (prior to fluoride varnish application).

3yDFS increment - (CA)(E+U)cl.
- Reported at 3 years follow up.
- DFS(xr).

School-classes randomized (24) and children taken as units for caries increment analyses (N = 359); numbers by group NR.

Baseline characteristics...
<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Duration</th>
<th>Dropout</th>
<th>Exclusions</th>
<th>Participants</th>
<th>Intervention</th>
<th>Diagnosis</th>
<th>Results</th>
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<tbody>
<tr>
<td>DePaola 1980</td>
<td>Random allocation; double-blind (A); placebo-controlled; drop out rate NR nor obtainable (study duration = 2 years + 1 year post-study period)</td>
<td>1980-1981</td>
<td>25%</td>
<td>Compliance and presence in all follow-up examinations; any differential group losses not assessable.</td>
<td>257 children analysed at 1 year (after exclusions, present for entire study period).</td>
<td>FG+PLR versus FR+PLG</td>
<td>1y*NetDFS increment - (CA)cl+xr. Reported at 1 and 2 years follow ups (and 1 year post-treatment).</td>
<td>Participants randomized (numbers NR). Baseline characteristics (age, dental age, DFS) described as 'balanced' (values NR). Clinical (VT) caries assessment by two examiners, diagnostic threshold = CA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners (diagnostic threshold NR); diagnostic errors NR. *Intervention (gel) applied during 1st year of study only (thus, final 2 years results not considered).</td>
</tr>
<tr>
<td>Kirkegaard 1986</td>
<td>Cluster random allocation; double-blind (A); placebo-controlled; 25% drop out after 3 years (study duration = 5 years). Natural losses; no differential group losses.</td>
<td>1977-1981</td>
<td>25%</td>
<td></td>
<td>319 children analysed at 3 years (available at 3 years examination).</td>
<td>FV+PLR versus FR+PLV</td>
<td>3yNetDMFS increment - (E)cl. Reported at 3 and 5 years follow ups.</td>
<td>School-classes randomized (22) and children taken as units for caries increment analyses (N = 426). Baseline characteristics (DMFS, erupted surfaces, age) 'balanced'.</td>
</tr>
</tbody>
</table>

DFS = Decayed, Fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children

Exposure to other fluoride: toothpaste assumed.
Year study began: 1978.
Location: Denmark.

Drop out.
NaF group (FR) = 900 ppm F.
School use/supervised, fortnightly, 10 ml applied.

Clinical (VT) caries assessment by one examiner, diagnostic threshold NR.
Radiographic assessment (2 postBW) by one examiner; diagnostic threshold = DR.
State of tooth eruption included (E/U).
Reproducibility of diagnosis assessed by duplicate clinical and radiographic examination of 10% sample (reliability coefficient 0.90).

Koch 1967

Stratified random allocation***; single-blind (B); non-placebo-controlled; 19% drop out after 3 years (study duration = 3 years + 2 years post-intervention period).
Natural losses; no differential group losses.

209 children analysed at 3 years (present for entire trial period).
Age range at start: 8-12 years (average = 10).
Surfaces affected at start: 14.6 DFS.
Exposure to other fluoride: no.
Year study began: 1962.
Location: Sweden.

FR versus FT
NaF group (FR) = 2250 ppm F.
School use/supervised, fortnightly, 10 ml applied for 2 min.

3yDFS increment - (CA)(E)cl.
Reported at 1 and 3 years follow ups (and 2 years post-treatment).
DFT.
O-DFS.
MD-DFS.
BL-DFS.

CAR (annual).
Secondary caries.

Oral tissue inflammation (incomplete data).

Participants randomized (N = 258).
Baseline characteristics (DFS, DFT, SAR) 'balanced'.
Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; radiographic assessment (2 postBW) used as an aid but not reported; state of tooth eruption included = E.
Intra-examiner reproducibility checks for DFS in 10% sample (icc over 0.98); reversals very small in both groups and equally common.

*** Allocation concealment considered adequate by consensus.
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children

**Koch 1979**
- Random allocation; single-blind (B); non-placebo-controlled; 2% drop out after 2 years (study duration = 2 years).
- Natural losses (all but 3 children completed the study; moved away from the area); no differential group losses.
- 197 children analysed at 2 years (present for entire trial period).
- Average age at start: 14 years.
- Surfaces affected at start: 13.1 DFS. Exposure to other fluoride: toothpaste and 0.5ppmF in water.
- Year study began: in/before 1976.
- Location: Sweden.

**FV versus FR**
- NaF Group (Duraphat® varnish) = 22,600 ppm F. Applied twice a year (0.3 to 0.5 ml), with small brush (prior toothcleaning performed).
- NaF group (FR) = 900 ppm F.
- School use/supervised, weekly, 7 ml applied for 1 min.

**Mainwaring 1978**
- Stratified random allocation; double-blind (A); placebo-controlled; 18% drop out (for all study groups combined) after 3 years (study duration = 3 years).
- Natural losses; any differential group losses not assessable.
- 1106 children analysed at 3 years (available at final examination).
- Age range at start: 11-12 years.
- Surfaces affected at start: 8.1 DFS.
- Exposure to other fluoride: no.
- Location: UK.

**FG+PLT versus FT+PLG (2 groups)**
- APF group (FG) = 12,300 ppm F.
  - Operator-applied, with tray, twice a year, applied for 4 min (prior toothbrushing with non-fluoride toothpaste performed).
- SMFP groups (FT1&FT2) = 1000 ppm F (but flavours were different).
  - Home use/unsupervised, for 1 min, daily frequency assumed.
  - Abrasive system: Ca carbonate.

**2yDFS increment - (CA)xr. Reported at 1and 2 years follow ups.**
- DFS(cl).
- Dropout.

**Participants randomized (N = B 200).**
- Baseline characteristics (DFS) 'balanced'.
- Clinical (VT) caries assessment by one examiner;
  - diagnostic threshold = CA;
  - radiographic assessment (2 postBW) by two examiners;
  - diagnostic threshold = DR.
  
  **State of tooth eruption included NR. Diagnostic errors NR.**

**Participants randomized**
- Baseline characteristics (age, SAR, DFS) 'balanced'.
- Clinical (VT) caries assessment by one examiner;
  - diagnostic threshold = CA;
  - state of tooth eruption included = E. Radiographic assessment (2 postBW) by one 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 4% of observed
<table>
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<tr>
<th>Study</th>
<th>Allocation Method</th>
<th>Randomization</th>
<th>Duration</th>
<th>Dropout Rate</th>
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<th>Participants</th>
<th>Baseline Characteristics</th>
<th>Clinical Assessment</th>
<th>Radiographic Assessment</th>
<th>Participants</th>
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<tbody>
<tr>
<td>Marthaler 1970</td>
<td>Random allocation; indication of blind caries assessment (C); placebo-controlled; 18% drop out (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.</td>
<td>106 children analysed at 3 years (present for all examinations). Age range at start: 6-7 years. Surfaces affected: 0.9 DMFS Exposure to other fluoride: salt. Year study began: 1966, Location: Switzerland.</td>
<td>3 years</td>
<td>18%</td>
<td>1966</td>
<td>Switzerland</td>
<td>Orthodontic bands and presence in all follow-up examinations; any differential group losses not assessable.</td>
<td>Baseline characteristics (age, DMFS, Istm DMFS) balanced’. Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. 'Sufficient agreement of the two examiners known from earlier work'.</td>
<td>DFS increment in all groups. Participants randomized (numbers for relevant groups NR). Baseline characteristics (age, DMFS, IstmDMFS) 'balanced'. Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. 'Sufficient agreement of the two examiners known from earlier work'.</td>
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<tr>
<td>Marthaler 1970a</td>
<td>Random allocation; indication of blind caries assessment (C); placebo-controlled; 30% drop out (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.</td>
<td>44 children analysed at 2&amp;4* years (present for all examinations). Age range at start: 7-9 years. Surfaces affected: 2.1 DMFS. Exposure to other fluoride: salt. Year study began: 1966, Location: Switzerland.</td>
<td>4 years</td>
<td>30%</td>
<td>1966</td>
<td>Switzerland</td>
<td>Orthodontic bands and presence in all follow-up examinations; any differential group losses not assessable.</td>
<td>Baseline characteristics (age, DMFS, Istm DMFS) balanced’. Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. 'Sufficient agreement of the two examiners known from earlier work'.</td>
<td>DFS increment in all groups. Participants randomized (numbers for relevant groups NR). Baseline characteristics (age, DMFS, IstmDMFS) 'balanced'. Clinical (V) caries assessment by two examiners; diagnostic threshold = CA and NCA; state of tooth eruption included NR. Radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR and ER; partial recording. 'Sufficient agreement of the two examiners known from earlier work'.</td>
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</table>
# One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children

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<tr>
<th>Study</th>
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<th>Placebo</th>
<th>Drop out</th>
<th>Duration</th>
<th>Attrition</th>
<th>Gender</th>
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<th>Year</th>
<th>Location</th>
<th>Intervention Details</th>
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<tr>
<td>Petersson 1985</td>
<td>Quasi-random allocation; single-blind (B); non-placebo-controlled; 5% drop out after 2 years (study duration = 2 years).</td>
<td>Reason(s) for attrition NR; no differential group losses.</td>
<td></td>
<td>183 children analysed at 2 years (present for entire trial period).</td>
<td>Average age at start: 3 years. Surfaces affected at start: 0.9 dfs (data from original sample only). Exposure to other fluoride: none assumed. Year study began: 1978. Location: Sweden.</td>
<td>FV+PLT versus FT alone</td>
<td>NaF Group (Duraphat® varnish) = 22,600 ppm F. Applied twice a year. NaF group (FT) = 250 ppm F. Home use/unsupervised, daily frequency assumed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2ydfs increment - (E) (CA)c1+(DR)xr</td>
<td>Reported at 2 years follow up. O-defs. MD-defs. BL-defs. Proportion of children with one or more new defs (at CA level).</td>
</tr>
<tr>
<td>Ran 1991</td>
<td>Random allocation; single-blind (B); non-placebo-controlled; 20% drop out (for all study groups combined) after 1.5 years (study duration = 1.5 years + 0.5 year post-intervention period).</td>
<td>Reasons for attrition/handling of exclusions NR; any differential group losses not assessable.</td>
<td>86 children analysed at 1.5 years; all male.</td>
<td>Average age at start: 13 years. Surfaces affected at start: 6.0 DMFS. Exposure to other fluoride: data not obtained for home use of dentifrice. Year study began: in/before 1989. Location: Israel.</td>
<td>FG (2 groups) versus FT</td>
<td>AmF group (FG1) = 4000 ppm F, AmF group (FG2) = 12,500 ppm F. Self-applied under supervision at school, with toothbrush, 25 times a year, 1g applied for 4 min. AmF group (FT) = 1250 ppm F.</td>
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<td></td>
<td>1.5yNetDMFS increment - (CA). Reported at 0.5 and 1.5 years follow ups (and 0.5 year post-treatment).</td>
<td>Participants randomized (numbers for relevant groups NR). Baseline characteristics (DFMS) with some imbalance (reported as NS difference). Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included NR; intra-examiner reproducibility checks for</td>
<td></td>
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</tbody>
</table>
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children

**Ringelberg 1979**

Stratified random allocation; double-blind (A); placebo-controlled; 39% drop out after 2.5 years (study duration = 2.5 years). Reason(s) for attrition NR; no differential group losses.

- 711 children analysed at 2.5 years (available at final examination).
- Average age at start: 11 years.
- Surfaces affected at start: 4.0 DMFS.
- Exposure to other fluoride: no. Year study began: 1973. Location: USA.

FR+PLT (2 groups) versus FT+PLR (2 groups)

AmF group (FR1) = 250 ppm F, NaF group (FR2) = 250 ppm F. School use/supervised, daily, 10 ml applied for 1 min. AmF group (FT1) = 1250 ppm F, SnF2 group (FT2) = 1000 ppm F. Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in SnF2 toothpaste, NR for AmF toothpaste.

2.5yNetDMFS increment - (CA)cl + (DR)xr. Reported at 2.5 years follow up. DMFT. Stain score. Drop out.

**Seppa 1987**

Cluster random allocation; single-blind (B); non-placebo-controlled; 9% drop out after 2 years (study duration = 2 years). Reasons for attrition/ handling of exclusions NR; any differential group losses.

- 185 children analysed at 2 years (available at final examination).
- Age range at start: 10-13 years.
- Surfaces affected at start: 8.9 DMFS.
- Exposure to other fluoride: no. Year study began: 1973. Location: USA.

FV (2 groups) versus FR

NaF Group 1 (Duraphat® varnish) = 22,600 ppm F. NaF Group 2 (Fluor Protector® varnish) = 7000 ppm F. Both applied twice a year

2yDMFS increment - cl+xr. Reported at 2 years follow up. School-classes randomized (24) and children taken as units for caries increment analyses (N = 204); numbers by group NR. Baseline characteristics (DMFS, age) slightly 'unbalanced'.

Participants randomized (N = B 1174). Baseline characteristics (DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by two examiners, diagnostic threshold = CA. Radiographic assessment (5 BW) by two examiners; diagnostic threshold = DR. State of tooth eruption included NR. Reversal rate between 4 and 9% of observed caries increment in the groups.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>Sample Size</th>
<th>Age Range</th>
<th>Surfaces Affected</th>
<th>Exposure to Other Fluoride</th>
<th>Treatment Details</th>
<th>Baseline Characteristics</th>
<th>Follow-up Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seppa 1995</td>
<td>1984</td>
<td>Finland</td>
<td>254 children</td>
<td>10-12 years</td>
<td>7.4 DMFS</td>
<td>Toothpaste</td>
<td>NaF Group (FR) = 900 ppm F, School use/supervised, fortnightly, 10 ml applied.</td>
<td>Participants randomized (N = 289); numbers by group NR. Baseline characteristics (DMFS, MD-DMFS) 'balanced'. Clinical (VT) caries assessment by one examiner, diagnostic threshold = CA; radiographic assessment (BW) by one examiner, diagnostic threshold = DR. State of tooth eruption included NR. Diagnostic errors NR.</td>
<td></td>
</tr>
</tbody>
</table>
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children

Year study began: 1962.
Location: Sweden.

SnF2 group (FT1) = 1000 ppm F,
NaF group (FT2) = 1100 ppm F.

Home use/unsupervised, daily frequency assumed (brushing twice a day and post-brushing water rinse instructed).

Abrasive system: Ca pyrophosphate in SnF2 toothpaste, Na bicarbonate in NaF toothpaste.

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

Istm = first permanent molar; AmF = amine fluoride; APF = acidulated phosphate fluoride; BW = bite-wing x-ray assessment; Ca = calcium; Ca carbonate = CaCO3; 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; d(e)ft/s = decayed, (extracted) and filled deciduous teeth or surface; dmft s = decayed, missing (or extracted) and filled deciduous teeth or surface; D(M)FS/T = decayed, (missing) and filled permanent surfaces or teeth; DR = radiolucency into dentin; E = teeth erupted at baseline; ER = any radiolucency in enamel/enamel-dentin junction; F = fluoride; FG = fluoride gel; FR = fluoride mouthrinse; FT = fluoride toothpaste; FV = fluoride varnish; icc = intra-class correlation coefficient (for inter-rater reliability); IMP = insoluble Na metaphosphate; M = missing permanent teeth; MD = mesio and distal surfaces; N = numbers;

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.

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One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children

Na = sodium; NaF = sodium fluoride; NCA = non-cavitated enamel lesions visible as white spots or discoloured fissures; NR = not reported; NS = not significant; NT = no treatment control; O = occlusal surfaces; PF = pit and fissure surfaces; PL = placebo; postBW = posterior bite-wing x-ray assessment; ppm F = parts per million of fluoride; ptc = prior tooth-cleaning performed with or without a non-fluoride paste; Silica = silicon dioxide (SiO2); SMFP = sodium monofluorophosphate; SnF2 = stannous fluoride; U = teeth unerupted at baseline; VT = visual-tactile assessment; xr = radiographic examination.
## Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnaud 1984</td>
<td>Only three clusters (schools), each randomized to one of the three interventions compared (FR vs FT1 vs FT2).</td>
</tr>
<tr>
<td>Hamp 1984</td>
<td>Additional fluoride-based intervention associated to fluoride mouthrinse. Blind outcome assessment not stated. (FV vs FR)</td>
</tr>
<tr>
<td>Ivanova 1990</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. (FV vs FG/FV vs FR/FG vs FR)</td>
</tr>
<tr>
<td>Ivanova 1990a</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. (FV vs FG)</td>
</tr>
<tr>
<td>Karjalainen 1994</td>
<td>Additional non fluoride-based intervention associated to fluoride mouthrinse. (supervised FR vs unsupervised FT)</td>
</tr>
<tr>
<td>Ramos 1995</td>
<td>Open outcome assessment. (FV vs FR)</td>
</tr>
<tr>
<td>Shobha 1987</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. (FV vs FG) Note - Main outcome data not reported in control group (and not obtainable).</td>
</tr>
<tr>
<td>Suntosev 1991</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated and unlikely. (FV vs FR) Note - Only post-treatment effects reported.</td>
</tr>
<tr>
<td>Wilson 1978</td>
<td>Random or quasi-random allocation not stated. (FR vs FT)</td>
</tr>
</tbody>
</table>

*FG = fluoride gel; FR = fluoride mouthrinse; FT = fluoride toothpaste; FV = fluoride varnish*
References to studies

Included studies

Ashley 1977

Axelsson 1987

Blinkhorn 1983

Bruun 1985

DePaola 1980

Kirkegaard 1986

Koch 1967


One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes)


Koch 1979

Koch G, Petersson LG, Ryden H. Effect of fluoride varnish (Duraphat) treatment every six months compared with weekly mouthrinses with 0.2 per cent NaF solution on dental caries. Swedish Dental Journal 1979;3:39-44.

Mainwaring 1978


Marthaler 1970


Marthaler 1970a


Petersson 1985


Ran 1991


Ringelberg 1979


* Ringelberg ML, Webster DB, Dixon DO, LeZotte DC. The caries-preventive effect of amine

**Seppa 1987**


**Seppa 1995**


**Torell 1965**


**Excluded studies**

**Barnaud 1984**


**Hamp 1984**


**Ivanova 1990**


**Ivanova 1990a**

Ivanova EN, Frolova GI, Postoiuk SN, Liakh GA. Sostoianie polosti i rezultaty primenenii florsoderzhashchikh preparatov v profilaktike kariesa zubov u detei [The status of the oral cavity...
and results of the use of fluorine-containing preparations in preventing dental caries in children].

Karjalainen 1994

Karjalainen S, Eriksson AL, Ruokola M, Toivonen A. Caries development after substitution of
supervised fluoride rinses and toothbrushings by unsupervised use of fluoride toothpaste.

Ramos 1995

Ramos SB. Efeito de bochechos fluoretados (NaF - 0,2 por cento) e da aplicacao do verniz com
fluor (NaF - 5 por cento) na prevencao da carie dentaria: estudo comparativo em escolares da
Regiao Norte da cidade de Sao Paulo, 1992-1993 [Effect of fortnightly rinsing with a 0.2 percent
NaF solution and a fluoride varnish with 5 percent NaF in dental caries prevention: comparative
study in students of the northern region of Sao Paulo city, Brazil, 1992-1993] [dissertation]. Sao

Shobha 1987

Shobha T, Nandlal B, Prabhakar AR, Sudha P. Fluoride varnish versus acidulated phosphate

Suntsov 1991

Suntsov VG, Distel' VA, Zhorova TN, et al. Sledovaia effektivnost' profilaktiki kariesa zubov u
detei [The trace efficacy of dental caries prevention in children]. Stomatologiia Moskva

Wilson 1978

Wilson CJ, Triol CW, Volpe AR. The clinical anticaries effect of a fluoride dentifrice and

Studies awaiting assessment

Autio 1999

Autio J, Courts F. Feasibility of a fluoride varnish program in Head Start Children [abstract].

Cichocka 1981

Cichocka E. Ocena ekonomiczna wybranych metod kontaktowego fluorkowania zebow [Economic
evaluation of selected methods of contact fluoridation of the teeth]. Czasopismo Stomatologiczne

* Cichocka E. Higiena jamy ustnej a skutecznosc wybranych metod kontaktowego fluorkowania
zebow [Oral hygiene and the efficacy of selected methods of contact tooth fluoridation].
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes)


* indicates the primary reference for the study
Other references

Additional references

Burt 1998

Chen 1995

Clarke 2000

Downer 1995

Dubey 1965

Egger 1997

Featherstone 1988

Glass 1982

Higgins 1996
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes)

Higgins 2003
Higgins J. Personal communication August 4 2003.

Marinho 1997

Marinho 2002

Marinho 2002a

Marinho 2003

Marinho 2003a

Marinho 2003b

Marthaler 1994

Marthaler 1996

Moynihan 1996
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes)

Murray 1991

Murray 1991a

O'Mullane 1995

Pitts 2001

Pitts 2002

Ripa 1991

Rolla 1991

Seppa 1998

Sharp 1998

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One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes)

Song 2003

Strohmenger 2001

Thompson 1999

van Rijkom 1998
Table of comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome Measure</th>
<th>Data Points</th>
</tr>
</thead>
<tbody>
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<td>01 Fluoride varnish versus Fluoride gel</td>
<td>D(M)FS increment (PF) - nearest to 3 years</td>
<td>1 trial</td>
</tr>
<tr>
<td>02 Fluoride varnish versus Fluoride mouthrinse</td>
<td>D(M)FS increment (PF) - nearest to 3 years</td>
<td>4 trials</td>
</tr>
<tr>
<td></td>
<td>Unacceptability of treatment as measured by leaving study early</td>
<td>2 trials</td>
</tr>
<tr>
<td>03 Fluoride varnish versus Fluoride toothpaste</td>
<td>D(e)fs increment (PF) - nearest to 3 years</td>
<td>1 trial</td>
</tr>
<tr>
<td></td>
<td>Unacceptability of treatment as measured by leaving study early</td>
<td>1 trials</td>
</tr>
<tr>
<td>04 Fluoride toothpaste versus Fluoride gel</td>
<td>D(M)FS increment (PF) - nearest to 3 years</td>
<td>3 trials</td>
</tr>
<tr>
<td>05 Fluoride toothpaste versus Fluoride mouthrinse</td>
<td>D(M)FS increment (PF) - nearest to 3 years</td>
<td>6 trials</td>
</tr>
<tr>
<td></td>
<td>Unacceptability of treatment as measured by leaving study early</td>
<td>5 trials</td>
</tr>
<tr>
<td>06 Fluoride gel versus Fluoride mouthrinse</td>
<td>D(M)FS increment (PF) - nearest to 3 years</td>
<td>1 trial</td>
</tr>
<tr>
<td>07 Fluoride toothpaste versus Other topical fluoride</td>
<td>D(M)FS increment (PF) - nearest to 3 years</td>
<td>9 trials</td>
</tr>
<tr>
<td></td>
<td>Fluoride toothpaste versus fluoride gel</td>
<td>3 trials</td>
</tr>
<tr>
<td></td>
<td>Fluoride toothpaste versus fluoride mouthrinse</td>
<td>6 trials</td>
</tr>
<tr>
<td></td>
<td>Unacceptability of treatment as measured by leaving study early</td>
<td>6 trials</td>
</tr>
<tr>
<td></td>
<td>Fluoride toothpaste versus fluoride varnish</td>
<td>1 trial</td>
</tr>
<tr>
<td></td>
<td>Fluoride toothpaste versus fluoride mouthrinse</td>
<td>5 trials</td>
</tr>
</tbody>
</table>
Review: One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adults.

Total number of included studies: 17

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride varnish versus Fluoride gel</td>
<td>1</td>
<td>254</td>
<td>Prevented Fraction (random), RR (random), 95% CI</td>
<td>0.14 [-0.12, 0.40]</td>
</tr>
<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years (1 trial)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Fluoride varnish versus Fluoride mouthrinse</td>
<td>4</td>
<td>952</td>
<td>Prevented Fraction (random), RR (random), 95% CI</td>
<td>0.10 [-0.12, 0.32]</td>
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<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years (4 trials)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Unacceptability of treatment as measured by leaving study early (2 trials)</td>
<td>2</td>
<td>626</td>
<td>RR (random), 95% CI</td>
<td>1.18 [0.85, 1.64]</td>
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<tr>
<td>03 Fluoride varnish versus Fluoride toothpaste</td>
<td>0</td>
<td>0</td>
<td>Prevented Fraction (random), RR (random), 95% CI</td>
<td>Not estimable</td>
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<tr>
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<td>02 Unacceptability of treatment as measured by leaving study early (1 trial)</td>
<td>1</td>
<td>193</td>
<td>RR (random), 95% CI</td>
<td>1.28 [0.37, 4.41]</td>
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<tr>
<td>04 Fluoride toothpaste versus Fluoride gel</td>
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<td>1256</td>
<td>Prevented Fraction (random), RR (random), 95% CI</td>
<td>0.00 [-0.21, 0.21]</td>
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<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years (3 trials)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>05 Fluoride toothpaste versus Fluoride mouthrinse</td>
<td>6</td>
<td>2545</td>
<td>Prevented Fraction (random), RR (random), 95% CI</td>
<td>0.00 [-0.18, 0.19]</td>
</tr>
<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years (6 trials)</td>
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<td></td>
<td></td>
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<tr>
<td>02 Unacceptability of treatment as measured by leaving study early (5 trials)</td>
<td>5</td>
<td>2752</td>
<td>RR (random), 95% CI</td>
<td>0.89 [0.78, 1.00]</td>
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<tr>
<td>06 Fluoride gel versus Fluoride mouthrinse</td>
<td>1</td>
<td>257</td>
<td>Prevented Fraction (random), RR (random), 95% CI</td>
<td>-0.14 [-0.40, 0.12]</td>
</tr>
<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years (1 trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>07 Fluoride toothpaste versus Other topical fluoride</td>
<td>9</td>
<td>3801</td>
<td>Prevented Fraction (random), RR (random), 95% CI</td>
<td>0.01 [-0.13, 0.14]</td>
</tr>
<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years (9 trials)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 Unacceptability of treatment as measured by leaving study early (6 trials)</td>
<td>6</td>
<td>2945</td>
<td>RR (random), 95% CI</td>
<td>0.88 [0.78, 1.00]</td>
</tr>
</tbody>
</table>
### Outcome 01: DMFS increment (PF) - nearest to 3 years (1 trial)

**Comparison:** Fluoride varnish versus Fluoride gel

**Outcome:**
- Test for heterogeneity: Chi² = 114.14, df = 3 (P = 0.01), I² = 73.1%
- Test for overall effect: Z = 0.85, (P = 0.40)

**Study**
- Kirttgaard 1986
- Total events: 60 (Fluoride varnish), 50 (Fluoride mouthwash)
- Test for overall effect: Z = 0.85, (P = 0.40)

**Summary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride varnish</th>
<th>Fluoride mouthwash</th>
<th>Fluoride to other paste</th>
<th>Fluoride gel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Kirttgaard 1986</td>
<td>58/214</td>
<td>49/212</td>
<td>2/100</td>
<td>1/100</td>
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<tr>
<td>Total (95% CI)</td>
<td>11/1</td>
<td>11/1</td>
<td>1/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>

### Outcome 02: Unacceptability of treatment as measured by leaving study early (1 trial)

**Comparison:** Fluoride varnish versus Fluoride mouthwash

**Outcome:**
- Test for overall effect: Z = 0.20 (P = 0.69)

**Study**
- Kirttgaard 1986
- Total events: 60 (Fluoride varnish), 50 (Fluoride mouthwash)
- Test for overall effect: Z = 0.20 (P = 0.69)

**Summary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride varnish</th>
<th>Fluoride mouthwash</th>
<th>Fluoride to other paste</th>
<th>Fluoride gel</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Kirttgaard 1986</td>
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<tr>
<td>Total (95% CI)</td>
<td>11/1</td>
<td>11/1</td>
<td>1/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>

### Outcome 03: Fluoride varnish versus Fluoride to other paste

**Comparison:**
- 01 Unacceptability of treatment as measured by leaving study early (2 trials)

**Outcome:**
- Test for heterogeneity: Chi² = 334.14, df = 2 (P = 0.19), I² = 40.1%
- Test for overall effect: Z = 0.40 (P = 0.69)

**Study**
- Kirttgaard 1986
- Total events: 60 (Fluoride varnish), 50 (Fluoride mouthwash)
- Test for overall effect: Z = 0.40 (P = 0.69)

**Summary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride varnish</th>
<th>Fluoride mouthwash</th>
<th>Fluoride to other paste</th>
<th>Fluoride gel</th>
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<td>11/1</td>
<td>1/10</td>
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</tbody>
</table>

### Outcome 04: Fluoride to other paste versus Fluoride gel

**Comparison:**
- 01 Unacceptability of treatment as measured by leaving study early (2 trials)

**Outcome:**
- Test for heterogeneity: Chi² = 334.14, df = 2 (P = 0.19), I² = 40.1%
- Test for overall effect: Z = 0.40 (P = 0.69)

**Study**
- Kirttgaard 1986
- Total events: 60 (Fluoride varnish), 50 (Fluoride mouthwash)
- Test for overall effect: Z = 0.40 (P = 0.69)

**Summary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride varnish</th>
<th>Fluoride mouthwash</th>
<th>Fluoride to other paste</th>
<th>Fluoride gel</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Kirttgaard 1986</td>
<td>58/214</td>
<td>49/212</td>
<td>2/100</td>
<td>1/100</td>
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<td>Total (95% CI)</td>
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<td>11/1</td>
<td>1/10</td>
<td>1/10</td>
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</tbody>
</table>

### Outcome 05: Fluoride mouthwash versus Fluoride varnish

**Comparison:**
- 01 Unacceptability of treatment as measured by leaving study early (2 trials)

**Outcome:**
- Test for heterogeneity: Chi² = 334.14, df = 2 (P = 0.19), I² = 40.1%
- Test for overall effect: Z = 0.40 (P = 0.69)

**Study**
- Kirttgaard 1986
- Total events: 60 (Fluoride varnish), 50 (Fluoride mouthwash)
- Test for overall effect: Z = 0.40 (P = 0.69)

**Summary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride varnish</th>
<th>Fluoride mouthwash</th>
<th>Fluoride to other paste</th>
<th>Fluoride gel</th>
</tr>
</thead>
<tbody>
<tr>
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<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Kirttgaard 1986</td>
<td>58/214</td>
<td>49/212</td>
<td>2/100</td>
<td>1/100</td>
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<tr>
<td>Total (95% CI)</td>
<td>11/1</td>
<td>11/1</td>
<td>1/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>
### Comparison: Fluoride toothpaste versus Fluoride mouthrinse

Review: One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents (THESIS CHAPTER 8)

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride toothpaste</th>
<th>Fluoride mouthrinse</th>
<th>Prevented Fraction (random)</th>
<th>Weight %</th>
<th>Prevented Fraction (random)</th>
<th>Weight %</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axlsson 1987</td>
<td>1.0</td>
<td>0.3</td>
<td>0.3158 (0.3846)</td>
<td>4.93</td>
<td>-0.32 (-1.04, 0.41)</td>
<td>1997</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bircham 1983</td>
<td>0.85</td>
<td>0.90</td>
<td>0.2504 (0.5923)</td>
<td>14.10</td>
<td>0.03 (-0.16, 0.21)</td>
<td>1993</td>
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<tr>
<td>Ringberg 1979</td>
<td>0.84</td>
<td>0.50</td>
<td>-0.0646 (0.0590)</td>
<td>19.10</td>
<td>-0.06 (-0.26, 0.11)</td>
<td>1979</td>
<td>3</td>
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<td></td>
</tr>
<tr>
<td>Ashley 1987</td>
<td>2.46</td>
<td>2.45</td>
<td>0.0769 (0.0742)</td>
<td>19.33</td>
<td>0.04 (-0.07, 0.20)</td>
<td>1977</td>
<td>4</td>
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</tr>
<tr>
<td>Koch 1987</td>
<td>1.24</td>
<td>0.67</td>
<td>0.2775 (0.2074)</td>
<td>20.29</td>
<td>0.28 (0.27, 0.30)</td>
<td>1967</td>
<td>5</td>
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</tr>
<tr>
<td>Torell 1985</td>
<td>2.15</td>
<td>3.32</td>
<td>-0.2370 (0.0278)</td>
<td>19.05</td>
<td>-0.26 (-0.33, -0.09)</td>
<td>1965</td>
<td>6</td>
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</table>

Total (95% CI): 3.93

Test for heterogeneity: Chi² = 32.35, df = 5 (P < 0.00001), I² = 84.5%

Test for overall effect: Z = 0.04 (P = 0.97)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Favours toothpaste</th>
<th>Favours mouthrinse</th>
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<td>01</td>
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</table>

### Comparison: Other topical fluoride versus Fluoride mouthrinse

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluoride toothpaste</th>
<th>Fluoride mouthrinse</th>
<th>Prevented Fraction (random)</th>
<th>Weight %</th>
<th>Prevented Fraction (random)</th>
<th>Weight %</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
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</thead>
<tbody>
<tr>
<td>Axlsson 1987</td>
<td>1.0</td>
<td>0.3</td>
<td>0.3158 (0.3846)</td>
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<td>1997</td>
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<tr>
<td>Bircham 1983</td>
<td>0.85</td>
<td>0.90</td>
<td>0.2504 (0.5923)</td>
<td>14.10</td>
<td>0.03 (-0.16, 0.21)</td>
<td>1993</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ringberg 1979</td>
<td>0.84</td>
<td>0.50</td>
<td>-0.0646 (0.0590)</td>
<td>19.10</td>
<td>-0.06 (-0.26, 0.11)</td>
<td>1979</td>
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<td>Ashley 1987</td>
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<td>1.24</td>
<td>0.67</td>
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<td>19.05</td>
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<td>1965</td>
<td>6</td>
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</table>

Total (95% CI): 3.93

Test for heterogeneity: Chi² = 32.35, df = 5 (P < 0.00001), I² = 84.5%

Test for overall effect: Z = 0.04 (P = 0.97)
### Review
One topical fluoride toothpastes, or mouthrinses, or gels, or varnishes versus another for preventing dental caries in children and adolescents (THESIS CHAPTER 8)

### Comparison
01 Fluoride toothpaste versus Other topical fluoride

### Outcome
03 Unacceptability of treatment as measured by leaving study early (6 trials)

### Table

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Fluoride toothpaste</th>
<th>Any other TFT</th>
<th>RR (random) 95% CI</th>
<th>Weight</th>
<th>RR (random) 95% CI</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride toothpaste versus fluoride varnish (1 trial)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Petersson 1985</td>
<td>4/69</td>
<td>6/104</td>
<td>0.96</td>
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<tr>
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<td>114</td>
<td>1.04</td>
<td>1.77 (0.23, 12.47)</td>
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<tr>
<td>Total events: 4 (Fluoride toothpaste), 6 (Any other TFT)</td>
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<td></td>
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<tr>
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</table>

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Fluoride toothpaste</th>
<th>Any other TFT</th>
<th>RR (random) 95% CI</th>
<th>Weight</th>
<th>RR (random) 95% CI</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
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<tr>
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<tr>
<td>Axelsson 1987</td>
<td>7/57</td>
<td>13/54</td>
<td>2.07</td>
<td>0.13 (0.23, 1.23)</td>
<td>1987</td>
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<tr>
<td>Baschon 1983</td>
<td>21/105</td>
<td>21/109</td>
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<td>24/159</td>
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<td>Ringberg 1979</td>
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<td>Torssell 1985</td>
<td>57/392</td>
<td>69/401</td>
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<td>0.85 (0.62, 1.17)</td>
<td>1985</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>139</td>
<td>135</td>
<td>7.90</td>
<td>0.40 (0.18, 1.50)</td>
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<tr>
<td>Total events: 336 (Fluoride toothpaste), 372 (Any other TFT)</td>
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<tr>
<td>Test for heterogeneity: CHI² = 2.61, df = 4 (P = 0.69), I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 1.95 (P = 0.05)</td>
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01 02 0.5 1 2 3 5 10

Favours toothpaste  Favours other TFT
CHAPTER 9

COMBINATIONS OF TOPICAL FLUORIDE (TOOTHPASTES, MOUTHRINSES, GELS, VARNISHES) VERSUS SINGLE TOPICAL FLUORIDE FOR PREVENTING DENTAL CARIES IN CHILDREN AND ADOLESCENTS
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents (THESIS CHAPTER 9)

Reviewers
Marinho VCC, Higgins JPT, Sheiham A, Logan S

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Date of last minor update: / /
Date next stage expected: 20/10/2005
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External sources of support
CAPES - Ministry of Education, BRAZIL

Contribution of reviewers
All authors contributed to the development of the protocol and execution of the review. Valeria Marinho (VM) wrote the protocol, designed and implemented the search strategies, contacted authors, selected studies, assessed validity, and extracted data. Julian Higgins (JH) duplicated study selection, quality assessment, and data extraction in a sample of studies and Stuart Logan (SL) or Aubrey Sheiham (AS) were consulted where necessary. VM entered and analysed the data in consultation with JH. VM prepared the full review. All authors contributed to its revision, interpretation of results and approval.

Acknowledgements
The authors wish to thank the Systematic Reviews Training Unit (UCL) and the Cochrane Oral Health Group for the continuous support. Many thanks are due to the investigators who have kindly provided additional information about their trials or supplied reports of trials, as well as to those who helped with the translations or provided comments and editorial input to this review.

Potential conflict of interest
None known.
Abstract

Background
Topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, varnishes and gels are effective caries preventive measures. However, there is uncertainty about the relative value of these interventions when used together.

Objectives
To compare the effectiveness of two TFT modalities combined with one of them alone (mainly toothpaste) when used for the prevention of dental caries in children.

Search strategy
We searched the Cochrane Oral Health Group's Trials Register (May 2000), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2000), MEDLINE (1966 to January 2000), plus several other databases. We handsearched journals, reference lists of articles and contacted selected authors and manufacturers.

Selection criteria
Randomized or quasi-randomized controlled trials with blind outcome assessment, comparing fluoride varnish, gel, mouthrinse, or toothpaste in combination with each other in children up to 16 years during at least 1 year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS.

Data collection & analysis
Inclusion decisions, quality assessment and data extraction were duplicated in a random sample of one third of studies, and consensus achieved by discussion or a third party. Authors were contacted for missing data. The primary measure of effect was the prevented fraction (PF) that is the difference in mean caries increments between the 'treatment' and 'control' groups expressed as a percentage of the mean increment in the control group. Random effects meta-analyses were performed where data could be pooled.

Main results
Eleven of the 12 included studies contributed data for the meta-analyses. For the nine trials that provided data for the main meta-analysis on the effect of fluoride mouthrinses, gels or varnishes used in combination with toothpaste (involving 4026 children) the D(M)FS pooled PF was 10% (95% CI, 2% to 17%, p = 0.01) in favour of the combined regimens. Heterogeneity was not substantial in these results (I² = 32%). The separate meta-analyses of fluoride gel or mouthrinse combined with toothpaste versus toothpaste alone favour the combined regimens, but differences were not statistically significant; the significant difference in favour of the combined use of fluoride varnish and toothpaste accrues from a very small trial and appears likely to be a spurious result. Not all other combinations of possible practical value were tested in the included studies. The only other statistically significant result was in favour of the combined use of fluoride gel and mouthrinse in comparison to gel alone (pooled DMFS PF 23%; 95% CI 4% to 43%; p =0.02), based on two trials. No other combinations of TFT were consistently superior to a single TFT.

Reviewers' conclusions
Topical fluorides (mouthrinses, gels, or varnishes) used in addition to fluoride toothpaste achieve a
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus modest reduction in caries compared to toothpaste used alone. No conclusions about any adverse effects could be reached, because data were scarcely reported in the trials.
Background

Dental caries and its consequences pose important and uncomfortable problems in all industrialized societies and in a large number of developing countries. Although the prevalence and severity of dental caries in most industrialized countries have decreased substantially in the past two decades, reaching averages as low as 1.1 decayed, missing and filled teeth (DMFT) in 12 year olds, nearly half of those without any tooth decay or fillings (Marthaler 1996), this largely preventable disease is still common, increases significantly with age, and remains a public health problem for a significant proportion of the world population (Burt 1998). In the United Kingdom, 30% of 3.5 to 4.5 year olds (Moynihan 1996), and 50% of 12 year olds (Downer 1995) had experienced caries in 1993. In 2000, the figures were 40% for 5 year olds in Great Britain (Pitts 2001) and 38% for 12 year olds in England and Wales (Pitts 2002). These findings demonstrate the continuing need for effective preventive strategies and treatment services for these age groups in a country that has experienced a substantial caries decline. In general, dental caries levels vary considerably between and within different countries, but children in the lower socio-economic status (SES) groups have higher caries levels than those in the upper SES groups, and these differences are consistent in industrialized and in urbanized developing countries (Chen 1995).

Fluoride therapy has been the cornerstone of caries-preventive strategies since the introduction of water fluoridation schemes over five decades ago (Murray 1991). Fluoride controls the initiation and progression of carious lesions. Intensive laboratory and epidemiological research on the mechanism of action of fluoride in preventing caries indicates that fluoride's predominant effect is topical, which occurs mainly through promotion of remineralization of early caries lesions and by reducing sound tooth enamel demineralization (Featherstone 1988). Various modes of fluoride use have evolved, each with its own recommended concentration, frequency of use, and dosage schedule. The use of topically applied fluorides in particular, which are much more concentrated than the fluoride in drinking water, has increased over recent decades and fluoride containing toothpastes (dentifrices), mouthrinses, gels and varnishes are the modalities most widely used at present, either alone or in different combinations. By definition, the term 'topically applied fluoride' describes those delivery systems which provide fluoride to exposed surfaces of the dentition, at elevated concentrations, for a local protective effect and are therefore not intended for ingestion. Fluoride gels and varnishes are typical methods of professional topical fluoride application and both delivery systems have been used in preventive programs. Fluoride gels have also been used as a self applied intervention in such programs. Fluoride mouthrinses and toothpastes are the main forms of self applied fluoride therapy. The intensive use of fluoride mouthrinsing in school programs has been discontinued in many developed countries because of doubts regarding its cost-effectiveness at a low prevalence of dental caries and are being replaced by selective fluoride therapy directed to high risk children. Such procedures usually involve the combined use of fluoride toothpastes with gels or varnishes. Toothpaste is by far the most widespread form of fluoride usage (Murray 1991a; Ripa 1991) and the decline in the prevalence of dental caries in developed countries has been mainly attributed to its increased use (Glass 1982; Rolla 1991; Marthaler 1994; O'Mullane 1995; Marthaler 1996).

However, there is currently a debate regarding the appropriate use of fluorides. The lower caries prevalence now prevailing in many countries and the widespread availability of fluoride from multiple sources have raised the question of whether topically applied fluorides are still effective in reducing caries, and safe, mainly in terms of the potential risk of fluorosis (mottled enamel) (Ripa 1991). In this context, even the need for selective professional fluoride applications has been questioned (Seppa 1998). The persistence of this debate and the variations in the use of the main
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus... forms of topically applied fluorides suggest the need to search for meaningful ways to summarize the empirical findings on this topic systematically.

If topical fluorides remain effective it will then become relevant to assess which form is best by directly comparing the various treatments currently used and to assess how much extra benefits topical fluoride treatments used together may actually have, and whether the likely benefits are worth the effort considering potential negative effects such as fluorosis. Because the use of fluoride toothpaste is widespread in fluoridated and non-fluoridated areas, and supported by researchers and public health authorities as the method of choice among all topical fluoride interventions, there would be little justification for the use of professionally-applied or supervised self applied fluoride interventions if their combined use with toothpastes results in a marginal enhancement of effectiveness. The unanswered question today, of how much extra caries protection comes from a professionally-applied fluoride or a fluoride rinsing program on top of that provided from the regular use of fluoride toothpaste, is of clear importance and needs to be formally investigated.

Over the past half-century, numerous clinical trials have investigated the anti-caries effect of each topical fluoride intervention. It appears that most of the trials have focused on topical fluoride in one form or another and that a small number of such trials have directly investigated increased effectiveness when two or more fluoride interventions are topically applied. Although the results of studies investigating the cariostatic efficacy of the combined use of various fluorides have been assessed before (Marthaler 1971; Horowitz 1980; Marthaler 1990), there has been no systematic review of the available evidence.

With regard to the clinical effectiveness of topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels and varnishes three basic questions can be asked:
1- Is TFT effective in preventing dental caries in children and adolescents?
2- Is one of these forms of TFT more effective than another?
3- Are combinations of these TFT forms more effective than one form used alone?

This review attempts to answer the third question; the other two questions are addressed in separate reviews.

Objectives

The primary objective of this systematic review is:
(1) to determine whether there is a beneficial effect of adding topical fluoride therapy (TFT) in the form of mouthrinse, gel or varnish to fluoride toothpaste.

As secondary objectives we:
(2) evaluated the addition of each TFT modality to toothpaste separately;
(3) evaluated all other combinations of two TFT modalities compared to one of them.

Criteria for considering studies for this review

Types of studies
Randomized or quasi-randomized controlled trials using or indicating blind outcome assessment, in which one form of TFT (toothpaste, mouthrinse, varnish or gel) is compared concurrently with another in combination with it, during at least one calendar or school year.
Randomized or quasi-randomized controlled trials using within group paired comparison designs...
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus

(e.g. split-mouth trials involving fluoride varnish, as the effect of the varnish could spread across the mouth leading to contamination of control sites), or with open outcome assessment or no indication of blind assessment, or lasting less than one calendar or school year, or controlled trials where random or quasi-random allocation was not used or indicated were excluded.

Types of participants
Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started). Studies where participants were selected on the basis of special (general or oral) health conditions were excluded.

Types of interventions
Topical fluoride therapy (TFT) in the form of toothpastes, mouthrinses, gels or varnishes only, using any fluoride agent (which may be formulated with any compatible abrasive system, in the case of fluoride toothpastes), at any concentration (ppm F), amount or duration of application, and with any technique or method of application, provided the frequency of application was at least once a year. The following comparisons are of relevance (combined TFT compared with single TFT): Fluoride toothpaste plus any topical fluoride (varnish, gel, mouthrinse) compared with toothpaste alone, and any other combination of two of these modalities compared with one modality alone. Studies where the intervention consisted of any caries preventive agent/procedure (e.g. other fluoride-based measures, anti-plaque or anti-calculus agents, sealants, oral hygiene interventions, xylitol chewing gums, glass ionomers) used in addition to any form of TFT described above were excluded.

Types of outcome measures
The primary outcome measure in this review is caries increment, as measured by change from baseline in the decayed, (missing) and filled surface (D(M)FS) index, in all permanent teeth erupted at start and erupting over the course of the study. For studies in younger children the outcome measure of interest is caries increment in deciduous tooth surfaces, as measured by change in the decayed, (missing/extraction indicated), and filled surface d(e/m)fs index. Dental caries is defined here as being clinically and radiographically recorded at the dentin level of diagnosis. (See ‘Methods of the review’ for the different ways of reporting the decayed, (missing) and filled teeth or surfaces (D(M)FT/S) scores in clinical trials of caries preventives).

The following outcomes were considered relevant: coronal dental caries and dental fillings, in both the permanent and the deciduous dentitions; tooth loss; proportion of children developing new caries; dental pain/discomfort; specific side effects (fluorosis, tooth staining/discoloration, oral allergic reactions, adverse symptoms such as nausea, vomiting); unacceptability of preventive treatment as measured by dropouts during the trial (in non-placebo controlled studies); use of health service resources (such as visits to dental care units, length of dental treatment time). Studies reporting only on changes in plaque/calculus formation, plaque regrowth/vitality, plaque/salivary bacterial counts, or gingival bleeding/gingivitis, dentin hypersensitivity or fluoride physiological outcome measures (fluoride uptake by enamel or dentin, salivary secretion levels, etc.) were excluded.
Search strategy for identification of studies

With a comprehensive search, we attempted to identify all relevant studies irrespective of language, from 1965 onwards.

ELECTRONIC SEARCHING

• Up to 1998

Relevant studies were identified (for the series of topical fluoride reviews) by searching several databases from date of inception: MEDLINE (1966 to 1997), EMBASE (1980 to 1997), SCISEARCH (1981 to 1997), SSCISEARCH (1981 to 1997), ISTP (1982 to 1997), BIOSIS (1982 to 1997), CINAHL (1982 to 1997), ERIC (1966 to 1996), DISSERTATION ABSTRACTS (1981 to 1997) and LILACS/BBO (1982 to 1997). Two overlapping but complementary subject search phrases (below) with low specificity (but high sensitivity), using 'free text' and 'controlled vocabulary', were formulated within Silverplatter MEDLINE around two main concepts, fluoride and caries, and combined with all three levels of the Cochrane Optimal Search Strategy for Randomized Controlled Trials (RCTs). These subject search phrases were customised for searching EMBASE and the other databases:

(a) ["DENTAL-CARIES" explode all subheadings or "DENTAL-CARIES-ACTIVITY-TESTS" all subheadings or "DENTAL-CARIES-SUSCEPTIBILITY" all subheadings or CARIE* or DMF*) and ("FLUORIDES" explode all subheadings or "FLUORIDES,-TOPICAL" explode all subheadings or FLUOR* or AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR SMFP OR MFP OR MONOFLUOR*) or ("CARIOSTATIC-AGENTS" explode all subheadings or "DENTAL-PROPHYLAXIS" explode all subheadings or "DENTIFRICES" explode all subheadings or "MOUTHWASHES" explode all subheadings or CARIOSTA* or PROPHYLA* or ANTICARI* or ANTI CARI* or VARNISH* or LACQUER* or DURAPHAT or GEL* or TOOTHPASTE* or TOOTH PASTE* or PASTE* or DENTIFRIC* or MOUTHRINS* or MOUTH RINS* or RINS* or MOUTHWASH* or MOUTH WASH*)].

(b) [(explode FLUORIDES/ all subheadings) or (explode FLUORIDES-TOPICAL/ ALL SUBHEADINGS) or (FLUOR*) or (AMF or AMINE F OR SNF2 OR STANNOUS F OR NAF OR SODIUM F OR APF OR MFP OR SMFP OR MONOFLUOR* OR DURAPHAT)) and ((CARI*) or (DMF*) or (TOOTH*) or (TEETH*) or (DENT* in TI, in AB, in MESH)) or (explode CARIOSTATIC-AGENTS/ all subheadings) or (ANTICARI* or ANTI CARI*) or (explode MOUTHWASHES/ all subheadings) or (MOUTHWASH* or MOUTH WASH*) or (MOUTHRINS* or MOUTH RINS*) or (VARNISH* or LACQUER*)].

RCT filters were also adapted to search EMBASE, BIOSIS, SCISEARCH, DISSERTATION ABSTRACTS, and LILACS/BBO. All the strategies (subject search and methodological filters) developed to search each database are fully described in a report produced for the Systematic Reviews Training Unit (Marinho 1997), and are available on request. These were used for the development of a register of topical fluoride clinical trials for the systematic reviews, as the Cochrane Oral Health Group's Trials Register was not yet developed in 1997/98.

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 1997), the Community of Science database (1998), which included ongoing trials funded by the National Institute of Dental Research (NIDR), the System for Information on Grey Literature in Europe (SIGLE) database (1980 to 1997), and OLD MEDLINE (1963 to 1965) were searched using the terms 'fluor' and 'carie' truncated. (Grey literature search had also been carried out by searching the Index to Scientific and Technical Proceedings (ISTP) and DISSERTATION
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus

ABSTRACTS).

- From 1999 to 2001
  The following strategy was used to search LILACS/BBO in 1999 (1982 to 1998), where free text subject search terms were combined with a methodological filter for RCTs:
  
  \[(fluor\$ or ppmf or ppm f or amf or snf or naf or apf or mfp or smfp or monofluor\$ or duraphat\$)
  and (carie\$ or dmf\$ or tooth\$ or teeth\$ or dient\$ or dientc\$ or anticarie\$ or carie\$ or
  mouthrin\$s or rinse\$s or bochech\$ or enjuag\$ or verniz\$ or varnish\$ or barniz\$ or
  laca\$s or gel or gels)] and [random\$ or aleatori\$ or acaso\$ or azar\$ or blind\$ or mask\$ or cego\$ or
  cegas or ciego\$ or ciega\$ or placebo\$ or(clinic\$ and (trial\$ or ensaio\$ or estud\$)) or (control\$ and
  (trial\$ or ensaio\$ or estud\$))].

  Four supplementary and more specific subject search phrases (including 'free text' and 'controlled vocabulary' terms), refined exclusively for the reviews on the effects of individual fluoride modalities, formulated around three concepts each (the relevant topical fluoride therapy (TFT), fluoride and caries) were used to search Silverplatter MEDLINE (up to January 2000) without methodological filters:
  
  \[(CARIE* or (DENT* near CAVIT*) or TOOTH* DECAY* or DMF* or (explode "DENTAL-
  CARIES"/ ALL SUBHEADINGS))
  and (FLUOR* or APF* or NAF* or AMINE F OR SNF* or ACIDULATED* PHOSPHATE*
  FLUORID* or ACIDULATED* FLUORID* or PHOSPHATE* FLUORID* or SODIUM*
  FLUORID* or AMINE* FLUORID* or STANNOUS* FLUORID* or (explode "FLUORIDES"/
  ALL SUBHEADINGS))
  and
  (1) (TOOTHPASTE* or TOOTH* PASTE* or DENTIFRICE* or PASTE*) or (explode
  "DENTIFRICES"/ all subheadings)].
  (2) ((RINS* or MOUTH* RINS* or WASH* or MOUTH* WASH*) or (MOUTHRINS* or
  MOUTHWASH*)) or (explode "MOUTHWASHES"/ all subheadings)].
  (3) (FLUOR* or ...or ELMEX* or (explode "FLUORIDES"/ ALL SUBHEADINGS))
  and (GEL* or TRAY*]].
  (4) (FLUOR* or (DURAPHAT* or FLUOR PROTECTOR*) or (explode "FLUORIDES"/ ALL
  SUBHEADINGS)) and (VARNISH*) or (LACQUER* or LAQUER*) or (VERNIZ*) or
  (LACKER*) or (LAKK*) or (SILANE* or POLYURETHANE*]].

  These strategies were adapted to search the Cochrane Oral Health Group's Trials Register (up to May 2000), and have also been run on CENTRAL (The Cochrane Library Issue 2, 2000) to double check.

  The metaRegister of Current Controlled Trials was searched in October 2001 for ongoing RCTs using the terms 'fluoride' and 'caries'.

REFERENCE SEARCHING

All eligible trials retrieved from the searches, meta-analyses and review articles located up to January 2000 were checked for relevant references. Reviews had been identified mainly by a MEDLINE search strategy specifically carried out to provide information on available systematic reviews or meta-analyses and on the scope of the literature on the topic, when The Cochrane Library database: Cochrane Database of Systematic Reviews (CDSR), and the CRD databases: Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database.

Review Manager 4.2.2 26/09/2003
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(NHS EED), were also searched. Reference lists of relevant chapters from preventive dentistry textbooks on topically applied fluoride interventions were also consulted.

FULL TEXT SEARCHING
Prospective handsearching of the seven journals identified as having the highest yield of eligible RCTs/controlled clinical trials (CCTs) was carried out, from January 1999 until January 2000: British Dental Journal, Caries Research, Community Dentistry and Oral Epidemiology, Journal of the American Dental Association, Journal of Dental Research, Journal of Public Health Dentistry and European Journal of Oral Sciences. The handsearch of Community Dentistry and Oral Epidemiology was undertaken (1990 to December 1999), as this was the journal with the highest yield of eligible reports.

PERSONAL CONTACT
Searching for unpublished studies (or 'grey' literature such as technical reports and dissertations, or studies published in languages other than English which may not have been indexed to major databases) started by contacting experts in the field of preventive dentistry. A letter was sent to the author(s) of each included study published during the last two decades in order to obtain information on possible unpublished studies eligible for inclusion. All the authors of studies who had been contacted in order to clarify reported information to enable assessment of eligibility or obtain missing data were also asked for unpublished studies.

Based on information extracted mainly from included studies, a list of manufacturers of fluoride toothpastes, mouthrinses, gels and varnishes was created for locating unpublished trials. Letters to manufacturers were sent out by the Cochrane Oral Health Group, in the hope that companies might be more responsive to contact from the editorial base than from individual reviewers. Fourteen manufacturers were contacted (October 2000) and information on any unpublished trials requested: Bristol-Myers Co, Colgate-Palmolive, Davies Rose-Hoyt Pharmaceutical Division, Gaba AG, Ivoclar North America, John O Butler Company, Johnson & Johnson, Oral-B Laboratories, Pharmascience, Procter & Gamble, Smithkline Beecham, Synthelabo, Unilever/Gibbs, Warner-Lambert.

Methods of the review

MANAGEMENT OF RECORDS PRODUCED BY THE SEARCHES
Because multiple databases were searched, the downloaded set of records from each database, starting with MEDLINE, was imported to the bibliographic software package Reference Manager and merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. The records yielded from LILACS, BBO, CENTRAL, SIGLE and NIDR databases were not imported to Reference Manager and were checked without the benefit of eliminating duplicates. The records produced by OLD MEDLINE and by the specific MEDLINE search performed without methodological filter were imported to Reference Manager for inspection, in a database separate from the core database. The records produced by searching the Cochrane Oral Health Group's Trials Register and the metaRegister of Current Controlled Trials were also checked outside Reference Manager. In order to facilitate inspection of all records located from searching other (non-electronic) sources (reference lists of relevant studies, review articles and book chapters, journal handsearch, personal contact), we also tried to locate them in MEDLINE and to import them to Reference Manager. Those references that could not be downloaded in this way were entered manually.
RELEVANCE ASSESSMENT
All records identified by the searches were printed off and checked on the basis of title first, then by abstract (when this was available in English or in languages known by the reviewer) and/or keywords by one reviewer, Valeria Marinho (VM). Records that were obviously irrelevant were discarded and the full text of all remaining records was obtained. Records were considered irrelevant according to study design/duration, participants, or interventions/comparisons (if it could be determined that the article was not a report of a randomized/quasi-randomized controlled trial; or the trial was of less than 6 to 8 months duration; or the trial was exclusively in adults; or the trial did not address at least two of the relevant topical fluoride treatments; or the trial did not compare one topical fluoride with topical fluoride used in combination).

QUALITY ASSESSMENT
The methodological quality of the included studies was assessed according to the criteria for concealment of treatment allocation described in the Cochrane Reviewers' Handbook (Clarke 2000) used in the Cochrane Review Manager software (RevMan). Allocation concealment for each trial was rated as belonging to one of three categories:
A. Adequately concealed (an adequate method to conceal allocation is described).
B. Concealment unclear ('random' allocation stated/indicated but the actual allocation concealment method is not described or an apparently adequate concealment scheme is reported but there is uncertainty about whether allocation is adequately concealed).
C. Inadequately concealed (an inadequate method of allocation concealment is described).
Excluded: random (or quasi-random) allocation clearly not used in the trial, or 'random' allocation not stated and not implied/possible.

Blinding of main outcome assessment was also rated according to the following three categories defined for the topical fluoride reviews:
A. Double-blind (blind outcome assessment and use of placebo/blinding of participants described).
B. Single-blind (blind outcome assessment stated and no placebo used/participants not blind).
C. Blinding indicated (blind outcome assessment not stated but likely in any element/phase of outcome assessment, e.g. clinical and/or radiographic examinations performed independently of previous results, or radiographic examinations performed independently of clinical examinations with results reported separately/added later, or examiners clearly not involved in giving treatment, or use of placebo described) or reported but unclear (blind outcome assessment reported but there is information that leads to suspicion/uncertainty about whether the examination was blind).
Excluded: clearly open outcome assessment used or blind outcome assessment not reported and unlikely (no description of an examination performed independently of previous results, of x-rays registered independently of clinical examination, of use of a placebo, and of examiners clearly not involved in giving treatment).

One reviewer (VM) assessed the quality of all included studies. A second reviewer (JH) duplicated the process for a random sample of approximately one third. Any disagreement was discussed and where necessary a third reviewer was consulted to achieve consensus. Where uncertainty could not be resolved an effort was made to contact authors directly to clarify the method used to conceal allocation or whether assessment of the main outcome had been carried out blind.

Checking of interobserver reliability was limited to these validity assessments.

Other methodological characteristics of the trials such as completeness of follow up (proportion excluded) and handling of exclusions (extent to which reasons for attrition are explicitly reported,
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus

or losses are independent of treatment allocated) were not used as thresholds for inclusion. However, all assessments of study quality are described in the table of included studies, and were coded for possible use in metaregression/sensitivity analyses. [For example, sensitivity analyses could be performed to assess the impact of blind outcome assessment and concealment of allocation, since studies where blinding is not clearly stated (but likely) and studies reporting inadequate allocation concealment are also included in this review].

DATA EXTRACTION
Data from all included studies were extracted by one reviewer (VM) using a pilot tested data extraction form. A second reviewer (JH) extracted data from a random sample of approximately one third of included studies. Again, data that could not be coded by the first reviewer were independently coded by the second, any disagreements were discussed and a third reviewer consulted to achieve consensus where necessary. (In future updates all reports will be data extracted and quality assessed in duplicate.) Data presented only in graphs and figures were extracted whenever possible, but were included only if two reviewers independently had the same result. Attempts were made to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. Papers in languages not known by the reviewers were data extracted with help from appropriate translators.

Additional information related to study methodology or quality that was extracted included: study duration (years of follow up); comparability of baseline characteristics: methods used pre-randomization in sizing/balancing (stratification based on relevant variables) or used post-randomization in analysing/adjusting for possible differences in prognostic factors between groups; objectivity/reliability of primary outcome measurement (diagnostic methods and thresholds/definitions used and included, and monitoring of diagnostic errors); any co-intervention and/or contamination. Information on sponsoring institutions and manufacturers involved was also recorded.

Characteristics related to participants that were extracted included: age (range) at start, caries severity at start (average DMFS, DFS, or other measure), background exposure to fluoride sources other than the study option(s) (in water, topical applications, etc), year study began, place where study was conducted (country), setting where participants were recruited, and dental treatment level (F/DMF). Characteristics of the interventions that were extracted included: fluoride modality(s), mode of application (how the intervention was delivered), methods (technique/device) of application, prior- and post-application, fluoride active agents and concentrations used, frequency and duration of application, and amount applied.

Different ways of assessing/reporting caries increment in the trials (change from baseline as measured by the DMF index) were recorded separately and/or combined according to the components of the index chosen and units of measurement (DMFT/S, or DFT/S, or DT/S, or FT/S), types of tooth/surface considered (permanent/deciduous teeth/surfaces, first molar teeth, approximal surfaces, etc), state of tooth eruption considered (erupted and/or erupting teeth or surface), diagnostic thresholds used (cavitated/dentin lesions, non-cavitated incipient lesions), methods of examination adopted (clinical and/or radiographic), and approaches to account or not for reversals in caries increment adopted (in a net or observed/crude caries increment respectively). In addition, caries increments have been recorded whenever the authors reported them (various follow ups), and where assessments of caries increments were made during a post-intervention follow up period, the length of time over which outcomes were measured after the intervention ended was noted.
As we were aware that caries increment could be reported differently in different trials we developed a set of a priori rules to choose the primary outcome data for analysis from each study: data on permanent teeth would be chosen over data on deciduous teeth; data on surface level would be chosen over data on tooth level, DFS data would be chosen over DMFS data, and this would be chosen over DS or FS; data for 'all surface types combined' would be chosen over data for 'specific types' only; data for 'all erupted and erupting teeth combined' would be chosen over data for 'erupted' only, and this over data for 'erupting' only; data from 'clinical and radiological examinations combined' would be chosen over data from 'clinical' only, and this over 'radiological' only; data for dentinal/cavitated caries lesions would be chosen over data for enamel/non-cavitated lesions; net caries increment data would be chosen over crude (observed) increment data; and follow up nearest to 3 years (often the one at the end of the treatment period) would be chosen over all other lengths of follow up, unless otherwise stated. When no specification was provided with regard to the methods of examination adopted, diagnostic thresholds used, groups of teeth and types of tooth eruption recorded, and approaches for reversals adopted, the primary choices described above were assumed.

All other relevant outcomes assessed/reported in the trials were also recorded/listed.

ANALYSES

Handling of missing main outcome data
It was decided that missing standard deviations for caries increments that were not revealed by contacting the original researchers would be imputed through linear regression of log standard deviations on log mean caries increments. This is a suitable approach for caries prevention studies since, as they follow an approximate Poisson distribution, caries increments are closely related (similar) to their standard deviations (van Rijkom 1998).

Handling of results (main outcome) of studies with more than one treatment arm
For studies with more than two-arms, where the same TFT form(s) is(are) compared in two or more 'experimental' groups (for example, different active agents or concentrations of fluoride ion are compared for the same modality(ies) of TFT to a common 'control' group), raw results (the numbers, mean caries increments and standard deviations) from all relevant 'experimental' groups were combined in order to obtain a measure of treatment effect (this enables the inclusion of all relevant data for each form/combined forms of TFT in the meta-analyses). In the studies comparing more than two relevant combined modalities of TFT with a common fluoride toothpaste group, the toothpaste group was divided into approximately equally sized smaller groups to provide a pairwise comparison for each combination of modalities. Means and standard deviations were unchanged.

Choice of measure of effect and meta-analyses of main outcome
The chosen measure of treatment effect was the prevented fraction (PF), that is (mean increment in the 'controls' minus mean increment in the 'treated' group) divided by mean increment in the 'controls'. For an outcome such as caries increment (where discrete counts are considered to approximate to a continuous scale and are treated as continuous data) this measure was considered more appropriate than the mean difference or standardised mean difference, since it allows combination of different ways of measuring caries increment and a meaningful investigation of heterogeneity between trials. It is also simple to interpret.

The meta-analyses were conducted as inverse variance weighted averages. Within-study variances were estimated using the formula presented in Dubey 1965 which was more suitable for use in a weighted average, and for large sample sizes the approximation should be reasonable. Random
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus effects meta-analyses were performed throughout in RevMan 4.2/RevMan Analyses.

Deciduous and permanent teeth were analysed separately throughout.

For illustrative purposes, when overall results were significant, the results were also presented as the number of children needed to treat (NNT) to prevent one carious teeth/surface. These were calculated by combining the overall prevented fraction with an estimate of the caries increment in the control groups of the individual studies.

Assessment of heterogeneity and investigation of reasons for heterogeneity
Heterogeneity in the results of the trials was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95% confidence intervals and by formal tests of homogeneity (Thompson 1999).

Statistically significant heterogeneity was investigated using metaregression when a meta-analysis included a sufficiently large number of studies. In addition to aspects of study quality, potential sources of heterogeneity investigated would include baseline levels of caries severity and exposure to fluoride sources other than the study options. The association of these factors with estimated effects (D(M)FS PFs) would be examined by performing random effects metaregression analyses in Stata version 6.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998).

Investigation of publication and other biases
A funnel plot (plots of treatment effect estimates versus the inverse of their standard errors) was drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, though may also represent a true relationship between trial size and effect size. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger et al (Egger 1997).

Measures of effect and meta-analysis of other outcomes
For outcomes other than caries increment, continuous data would be analysed according to differences in mean treatment effects and their standard deviations. Dichotomous outcome data were analysed by calculating risk ratios (RR) or, for adverse effects of fluoride treatment, risk differences (RD). RevMan 4.2 was used for estimation of overall treatment effects. Again, a random effects model was used to calculate a pooled estimate of effect. NNT was calculated when overall results were significant. As a general rule only (relevant) outcomes with usable data were shown in the analyses tables.

Description of studies
SEARCH RESULTS
Our initial multiple database search (1997/98) produced the following total number of records, according to database searched: MEDLINE, 4599; EMBASE, 5052; BIOSIS, 421; SCISEARCH, 514; SSCISEARCH, 169; ISTP, 66; CINAHL, 133; ERIC, 60; DISSERTATION ABSTRACTS, 95; LILACS, 48; BBO, 47; CENTRAL, 86; SIGLE, 6. Searching OLD MEDLINE produced 545 records, and the Community of Science database, 24 records. In the second stage of searches (1999), searching LILACS and BBO with a modified search strategy produced 210 records (142 and 68 records respectively). The more specific MEDLINE searches (by individual modalities of topical fluoride therapy (TFT)) performed without a randomized controlled trial (RCT) filter
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus

produced 2441 records, and the searches performed in the Cochrane Oral Health Group's Trials Register (May 2000) produced 479 records. Searching the metaRegister of Current Controlled Trials for ongoing studies produced 5 records. Many records retrieved through electronic search were duplicates merged later in the core database, and many appeared more than once in different databases and/or searches performed (overlapped).

Searching other non-electronic sources (reference lists of potentially relevant reports, review articles or book chapters, relevant journals, and contacting authors) produced 171 additional records for inspection. (Any search results produced by contacting manufacturers will feature in updates of this review).

RESULTS OF RELEVANCE ASSESSMENT
When all the records produced by the searches above were screened, a total of 713 reports were identified as potentially eligible and further assessment was sought.

STUDY SELECTION RESULTS
One full text report could not be obtained (this was an incomplete reference of an unpublished study/grey literature). Six hundred and ninety (690) reports were considered immediately irrelevant for this review, largely as a result of the types of intervention compared with (or used in addition to) the relevant topical fluorides (including all placebo or no treatment control trials without a relevant comparison of topical fluorides in combination with each other), and due to the types of study design described.

Thus, 16 studies (22 reports) are considered/cited in this review. These comprise 15 reports relating to 12 included studies, 6 reports relating to three excluded studies, and one report relating to one study waiting assessment (because it requires translation, but look unlikely to either be a randomised trial or to add to data already acquired). There are no reports of ongoing studies. Two non-English reports in Portuguese (one study) listed under included studies have been fully assessed.

EXCLUDED STUDIES
See 'Characteristics of excluded studies' for the description of reasons for rejecting each study.

We have excluded two studies comparing fluoride mouthrinse plus toothpaste with mouthrinse alone (one of which also compared fluoride toothpaste plus mouthrinse with toothpaste alone) and one study comparing fluoride mouthrinse plus gel with mouthrinse alone. These three studies were excluded for the following reasons:
Two studies did not mention or indicate random (or quasi-random) allocation and blind outcome assessment; and one study did not mention or indicate random or quasi-random allocation but described blind outcome assessment (attempts to contact the authors of this study were unsuccessful and it was excluded).

INCLUDED STUDIES
See 'Characteristics of included studies' table for details of each study.

There are 12 trials included. The study conducted by Marthaler 1970 was treated as two independent trials because the results for the two age groups involved were reported separately as distinct studies. The 12 trials were conducted between 1966 and 1985: two during the 1960s (in Switzerland), nine in the 1970s (two in Sweden, two in USA, three in UK), and one in the 1980s (in Brazil). Three studies had more than one publication, one of these had four published reports.
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus...

All 15 reports were published between 1969 and 1995. Of a total of three studies whose authors were sent request letters for unpublished information, reply related to one study was obtained.

Design and methods
All the 12 included studies used parallel group designs and with one exception (Arcieri 1988), all had more than two relevant arms. In one of the 11 multiple arm trials (Triol 1980) there was one group (study arm) of the single topical fluoride modality (toothpaste) and three groups of toothpaste and mouthrinse combined (where different concentrations of the same fluoride agent in the mouthrinse was tested); in another (Mainwaring 1978) there were two toothpaste study-arms (testing different flavours of toothpaste) and one group of gel and toothpaste combined; and in another (Ringelberg 1979) there were two groups of each, toothpaste or mouthrinse, and of these tested in combination (using different active fluoride agents). It should be noted that two of the included studies (Arcieri 1988; Triol 1980) had only one single fluoride modality being compared with this combined with another; i.e. each study had one relevant comparison only; eight studies compared two different single topical fluoride modalities to a common group where both modalities were combined; i.e. there were two relevant comparisons (with a common group) in each; and one study (Axelsson 1987) with three relevant comparisons, where both the single fluoride group and the combined fluoride group were alternatively common to two comparisons. This study has therefore been entered as two distinct studies (Axelsson 1987/ Axelsson 1987a) because mouthrinses or varnishes tested in combination with toothpaste, each combined regimen in a separate arm, were to be compared to a common toothpaste group in the main meta-analysis. All but one study (Arcieri 1988) used inactive/placebo interventions for the single fluoride arm of the relevant comparisons. Study duration ranged from 2 to 3 years. Studies were generally large with only three allocating less than 200 children to relevant study groups; all but one study recruited children from school settings.

Interventions
There are five trials comparing fluoride toothpaste plus mouthrinse with toothpaste alone (Ashley 1977; Axelsson 1987; Blinkhorn 1983; Ringelberg 1979; Triol 1980) - and four comparing mouthrinse plus toothpaste with mouthrinse alone (Ashley 1977; Axelsson 1987; Blinkhorn 1983; Ringelberg 1979), followed by three comparing toothpaste plus gel with toothpaste alone (Mainwaring 1978; Marthaler 1970; Marthaler 1970a) - and the same three comparing fluoride gel plus toothpaste with gel alone, two comparing toothpaste plus varnish with toothpaste alone (Axelsson 1987a; Petersson 1985) - and one comparing fluoride varnish plus toothpaste with varnish alone (Petersson 1985), two comparing gel plus mouthrinse with gel alone (Arcieri 1988; DePaola 1980) - and one comparing mouthrinse plus gel with mouthrinse alone (DePaola 1980). In all but one trial testing fluoride toothpastes, the fluoride concentrations in the toothpastes were similar, ranging from 1000 to 1250 ppm F, and in three of these trials toothbrushing was performed under supervision at school. In one of the trials testing fluoride varnish, the application frequency was semi-annual (concentration 22,600 ppm F) and in the other, testing a 22,600 ppm F (Duraphat) varnish, the frequency of application was four times a year. The fluoride concentration in all five trials testing a fluoride gel was also similar (12,300/12,500 ppm F), but frequency of gel application varied from twice (operator-applied) to 22 times a year (self applied). There was variation in the fluoride concentration (100, 230/250, 900 ppm F) in the trials testing fluoride mouthrinsing, but frequency of application was either daily (in two trials) or weekly (in the other five trials).

Participants
Participants were aged 14 or less at the start (in all trials), with similar numbers from both sexes (where these data were reported). The majority of trials included children who were around 12...
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus years at start, and only one trial (Petersson 1985) involved pre-school children. Caries prevalence at baseline, reported in all but two of the studies, ranged from 1 to 10 D(M)FS (and was 0.9 dfs in the study by Petersson). All studies reported exposure or not to water fluoridation, and only one was conducted in a fluoridated community.

Outcome measures
Caries increment: all trials reported caries increment data (or data from which these could be derived) at the tooth surface level (D(M)FS was reported in 11 trials, and def's in one), and three trials reported caries increment at the tooth level (D(M)FT). With regard to the components of the DMFS index used (and types of teeth/surfaces assessed), six trials reported DFS data (for all tooth surface types), three trials reported DMFS data (for all tooth surface types) and two trials reported DS data (for approximal surfaces of premolars and molars only). No choice had to be made between DMFS or DFS data in any one trial. Trials presented results using one caries grade only (usually CA/ER or CA/DR), or did not report the grade, or reported caries increment data at both levels of diagnosis (in which case CA was chosen). Data on the state of tooth eruption considered were not clearly specified in most trials.

The table 'Characteristics of included studies' provides a description of all the main outcome data reported from each study with the primary measure chosen featuring at the top.

Other dental caries data reported: caries incidence rate (one trial), caries progression (two trials), and proportion of children developing new caries (two trials, one for the permanent dentition and another for the deciduous).

Data on adverse effects: stain score (one trial), any side effects (one trial, without complete or usable data, and with the following statement: "no side effects observed in both groups"). Fluorosis data have not been reported in any of the trials.

Data for unacceptability of treatment (as measured by dropouts/exclusions) were completely reported in six trials.

Methodological quality of included studies
Based on 28 studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between two reviewers, interrater reliability was excellent (89%) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73).

There was variation in the quality of the studies in this review (using the reported information and additional information obtained from investigators).

ALLOCATION CONCEALMENT
Ten trials were described as randomized but provided no description on how the 'random' allocation was done and were coded B, two trials were considered to be quasi-randomized and were coded C. None of the trials which described the randomization process or whose investigators provided further information in answer to our enquiry could be assigned code A (adequate concealment of allocation fully described).
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus

BLINDING
Double-blinding was described in seven trials (Code A), single-blinding (blind outcome assessment described but no placebo used) was described in three trials (code B), and blind outcome assessment was indicated in three trials (code C) which described the use of placebo. It may be noted that the study by Axelsson 1987 was performed double-blind and Axelsson 1987a single-blind (i.e. there were two relevant comparisons double-blind and one single-blind in this study which was treated as two studies, one double-blind and another single-blind).

LOSS TO FOLLOW UP
Seventy-four per cent (74%) of the participants originally enrolled in the studies were included in the final analysis (3386 analysed out of 4556 initially randomized). These data exclude five of the 12 included studies, which provided no information on the number of participants randomized to relevant groups. Drop-out rates were obtained from all but one study and ranged from 5% at 2 years to 40% at 2.5 years. The most common reason for attrition was that participants were not available for follow up examination at the end of the study.

OTHER METHODOLOGICAL FEATURES
Individuals were allocated to study arms in all trials, where each participant's caries incidence, over a period of time was used as the unit of analysis.

Type of randomization: stratified randomization was reported in five trials (but there was no mention of use of blocking).

Baseline comparisons and handling of any differences: one trial described as 'balanced' (for which randomization may have succeeded to produce nearly exact balance) did not report any of the actual values for the baseline characteristics (such as initial caries levels).

Objectivity/reliability of primary outcome measurement: diagnostic methods used (clinical or radiographic) were described in all studies, but thresholds/definitions used for caries and monitoring of diagnostic errors were not always reported (see 'Notes' in the 'Characteristics of included studies' table for methodological features assessed).

Results

EFFECT ON DENTAL CARIES INCREMENT
Pooled estimates of the relative effects of topical fluoride therapy (TFT) are presented for caries increment in the permanent dentition as Decayed, (Missing) and Filled Surfaces Prevented Fraction (D(M)FS PF). Estimates for caries increment in the deciduous dentition are presented as decayed, (missing/extraction indicated), and filled surfaces Prevented Fraction (d(m/e)fs PF).

Eleven studies contributed data suitable for meta-analysis. Standard deviations (SD) of mean caries increment data (new D(M)FS) were missing in three of the 11 studies (Arcieri 1988; Axelsson 1987; Axelsson 1987a). From the analysis of the 179 available treatment arms for the topical fluoride reviews with complete information (as of October 1999) we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries increment), (R-squared = 77%). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses. The single study reporting caries increment in deciduous tooth surfaces (Petersson 1985) did not provide standard deviations of mean caries increment (new dfs) either, and is not
The results are reported separately here for the following main comparisons:

(1) Adjuncts to toothpaste tested against toothpaste alone
[Any topical fluoride plus toothpaste versus toothpaste alone]
Subgroup 1: Fluoride mouthrinse plus toothpaste versus toothpaste alone
Subgroup 2: Fluoride gel plus toothpaste versus toothpaste alone
Subgroup 3: Fluoride varnish plus toothpaste versus toothpaste alone

(2) Other combinations of topical fluorides tested against any single modality
Subgroup 1: Fluoride mouthrinse plus gel versus mouthrinse alone
Subgroup 2: Fluoride mouthrinse plus gel versus gel alone
Subgroup 3: Fluoride mouthrinse plus toothpaste versus mouthrinse alone
Subgroup 4: Fluoride gel plus toothpaste versus gel alone
Subgroup 5: Fluoride mouthrinse plus gel versus gel alone
Subgroup 6: Fluoride varnish plus toothpaste versus varnish alone

Objective 1 is addressed in comparison (1), in the meta-analysis which pools data across all subgroups and includes nine trials, while each subgroup in comparison (1) in effect addresses Objective 2. It may be noted that there was one included study that had a common fluoride toothpaste group and tested two different relevant combinations of topical fluoride with toothpaste, mouthrinse plus toothpaste and varnish plus toothpaste. Due to the meta-analysis addressing Objective 1, this has been entered as two comparisons/studies (Axelsson 1987/Axelsson 1987a) in this review (dividing up the group of the fluoride toothpaste arm into approximately equally sized smaller groups to provide a pairwise comparison for each combination of the two modalities with fluoride toothpaste; means and standard deviations were unchanged).

In comparison (2), each subgroup addresses a relevant comparison for Objective 3.

As mentioned before, relatively few trial reports provided data able to contribute to meta-analysis and with the exception of three comparisons from three trials (Arcieri 1988; Axelsson 1987a, Marthaler 1970), all reported equivocal results for caries reductions, i.e. no demonstrated differential effect. Apart from the division of trials into the subsets comparing fluoride toothpaste in combination with gel, varnish or mouthrinse in comparison (1), no subgroup analyses were performed due to the lack of an appropriate volume of data. No metaregression and funnel plot analyses were performed either, on the grounds of insufficient data.

(1) Fluoride toothpaste plus any TFT versus toothpaste alone
For all nine trials combined (one comparing fluoride toothpaste with varnish plus toothpaste, three comparing toothpaste with gel plus toothpaste, and five comparing toothpaste with mouthrinse plus toothpaste; n = 4026), the D(M)FS prevented fraction pooled estimate from the random effects meta-analysis was 0.10 (95% CI, 0.02 to 0.17; p = 0.01), i.e., a significant difference was detected in favour of toothpaste used in combination with other topical fluorides. Heterogeneity in results was not detected statistically (chi squared = 11.75 on 8 degrees of freedom, p = 0.16), although some inconsistency in treatment effects can be observed graphically, and confirmed by the I-squared heterogeneity statistic (I squared = 32%). Nevertheless, the largest variation in D(M)FS PF (-0.15 and 0.48) accrues from the trials that carry the lowest weight in the meta-analysis.

Numbers of children needed to treat (NNT) to prevent one D(M)FS were calculated based on the pooled D(M)FS prevented fraction and on the caries increments in the single toothpaste groups of
the nine trials in the meta-analysis. The overall caries-inhibiting effect (% PF) derived from the pooled results of the trials was 10% (95% CI, 2% to 17%); the caries increments in the included trials ranged from 0.8 to 2.5 D(M)FS per year. In populations with a caries increment of 0.8 D(M)FS per year (at the lowest end of the results seen in the included studies), this implies an absolute caries reduction of 0.08 D(M)FS per year, equivalent to an NNT of 13 (95% CI, 8 to 63): i.e. 13 children need to use topical fluorides in combination to avoid one D(M)FS. In populations with a caries increment of 2.5 D(M)FS per year (at the highest range of the results seen in the included studies), this implies an absolute caries reduction of 0.25 D(M)FS per year, equivalent to an NNT of 4 (95% CI, 3 to 20): i.e. 4 children need to use combined TFT to avoid one D(M)FS.

Results for the separate subsets comparing fluoride toothpaste with this in combination with varnish, gel, or mouthrinse are as follows:

**Fluoride toothpaste plus mouthrinse versus toothpaste alone**

Five trials (Ashley 1977; Axelsson 1987; Blinkhorn 1983; Ringelberg 1979; Triol 1980) compared fluoride toothpaste in combination with mouthrinse versus toothpaste alone (n = 2738). The D(M)FS prevented fraction pooled estimate from the random effects meta-analysis of all five trials combined was 0.07 (95% CI, 0.00 to 0.13; p = 0.06), a just non-significant effect in favour of the combined regimen within a relatively narrow confidence interval for the pooled estimate of effect. Heterogeneity in the results could not be observed graphically nor statistically (chi squared = 1.42 on 4 degrees of freedom, p = 0.84; I squared = 0%).

**Fluoride toothpaste plus gel versus toothpaste alone**

Three trials (Mainwaring 1978; Marthaler 1970; Marthaler 1970a) compared fluoride toothpaste in combination with fluoride gel versus toothpaste alone (n = 1217). The D(M)FS prevented fraction pooled estimate from the random effects meta-analysis of the three trials combined was 0.14 (95% CI, -0.09 to 0.38; p = 0.23), a non-significant effect in favour of the combined regimen within a relatively large confidence interval. Although no significant heterogeneity was detected (chi squared = 5.12 on 2 degrees of freedom, p = 0.08), since the test would have minimal power to detect heterogeneity in this meta-analysis involving very few trials, the inconsistency in treatment effects is in fact large according to the I squared statistic (I squared = 61%).

**Fluoride toothpaste plus varnish versus toothpaste alone**

There was one small trial (Axelsson 1987a) for this comparison (n = 71), estimating the relative effects in the permanent dentition, which showed a large and highly significant effect in favour of fluoride varnish in combination with toothpaste, and very wide confidence interval for the estimate of effect. The D(M)FS prevented fraction for this trial was 0.48 (95% CI, 0.12 to 0.84; p = 0.009).

Numbers of children needed to treat (NNT) to prevent one D(M)FS were calculated based on the D(M)FS PF and on the caries increment in the toothpaste group of this trial. In populations with a caries increment of 0.8 D(M)FS per year (seen in this study), this implies an absolute caries reduction of 0.38 D(M)FS per year, equivalent to an NNT of 3 (95% CI, 2 to 11): i.e. 3 children need to use the combined regimen (rather than toothpaste alone) to avoid one D(M)FS.

Another trial (Petersson 1985) comparing fluoride varnish combined with toothpaste versus toothpaste alone (n = 173) assessed the relative effect in terms of caries increment in deciduous surfaces only and provided no standard deviations or data from which these could be derived. It reported a dfs PF of 0.15 in favour of the combined therapy (CI not obtainable).

(2) Other combinations of topical fluorides tested against any single modality
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus

Fluoride mouthrinse plus gel versus fluoride mouthrinse alone
Only one trial (DePaola 1980) compared fluoride gel in combination with mouthrinse versus mouthrinse alone (n = 252). It showed non-significant differences in effect. The D(M)FS prevented fraction was 0.02 (95% CI, -0.20 to 0.24; p = 0.86) suggesting that there is insufficient evidence from this trial to confirm or refute a differential effect in caries reduction.

Fluoride gel plus mouthrinse versus fluoride gel alone
Two trials (Arcieri 1988; DePaola 1980) compared fluoride gel in combination with mouthrinse versus mouthrinse alone (n = 497). The D(M)FS prevented fraction pooled estimate from the random effects meta-analysis of the two trials combined was 0.23 (95% CI, 0.04 to 0.43; p = 0.02), a significant effect in favour of the combined regimen. Although heterogeneity in the results could not be detected by the standard chi squared test (chi squared = 2.05 on 1 degree of freedom, p = 0.15), this was not due to homogeneity but to the smaller number of studies (I squared = 51%).

Numbers of children needed to treat (NNT) to prevent one D(M)FS were calculated based on the pooled D(M)FS PF and on the caries increments in the gel groups of the trials that contributed data to the meta-analysis. The caries increments were 1.56 and 5.09 D(M)FS per year. In populations with a caries increment of 1.56 D(M)FS per year, this implies an absolute caries reduction of 0.36 D(M)FS per year, equivalent to an NNT of 3 (95% CI, 2 to 56): i.e. 3 children need to use the combined regimen (rather than fluoride gel alone) to avoid one D(M)FS. In populations with a caries increment of 5.09 D(M)FS per year, this implies an absolute caries reduction of 1.17 D(M)FS per year, equivalent to an NNT of 1 (95% CI, 1 to 5): i.e. one child need to use the combined regimen to avoid one D(M)FS.

Fluoride mouthrinse plus toothpaste versus mouthrinse alone
Four trials (Ashley 1977; Axelsson 1987; Blinkhorn 1983; Ringeiberg 1979) compared fluoride toothpaste in combination with mouthrinse versus mouthrinse alone (n = 1678). The D(M)FS prevented fraction pooled estimate from the random effects meta-analysis of the four trials combined was 0.05 (95% CI, -0.05 to 0.15; p = 0.33), a non-significant effect in favour of the combined regimen. Heterogeneity in the results could not be observed graphically nor statistically (chi squared = 3.38 on 3 degrees of freedom, p = 0.34; I squared = 11%).

Fluoride gel plus toothpaste versus gel alone
Three trials (Mainwaring 1978; Marthaler 1970; Marthaler 1970a) compared fluoride toothpaste in combination with fluoride gel versus gel alone (n = 759). The D(M)FS prevented fraction pooled estimate from the random effects meta-analysis of the three trials combined was 0.10 (95% CI, -0.01 to 0.21; p = 0.06), a just non-significant effect in favour of the combined regimen. Heterogeneity in the results could not be observed graphically nor statistically (chi squared = 0.17 on 2 degrees of freedom, p = 0.92; I squared = 0%).

Fluoride varnish plus toothpaste versus varnish alone
The single trial (Petersson 1985) comparing fluoride varnish combined with fluoride toothpaste versus varnish alone (n = 186) assessed the relative effect in terms of caries increment in deciduous surfaces only and provided no standard deviations or data from which these could be derived. It reported a dfs PF of 0.19 in favour of the combined therapy (CI not obtainable).

EFFECT ON OTHER OUTCOMES
Data for unacceptability of treatment were reported in six trials that reported dropouts fully. Each
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus

of the six trials reported equivocal results for this outcome, i.e. no demonstrated differential effect. Meta-analysis results for these are described below.

(1) Fluoride toothpaste plus any TFT versus toothpaste alone
The pooled estimate (random effects meta-analysis) of the relative risk (RR) of dropping out from the fluoride toothpaste group as opposed to the group where other fluoride treatment is in combination with toothpaste in the five trials that reported dropouts was 1.06 (95% CI, 0.96 to 1.21), a non-significant effect (p = 0.37) slightly in favour of fluoride toothpaste. Heterogeneity was not detected in these results (chi squared = 2.66 on 4 degrees of freedom, p = 0.62; I squared = 0%). Using alternative measures of effect has given similar results (OR 1.09, CI 0.88 to 1.34; RD 0.00, CI -0.03 to 0.03).

Fluoride toothpaste plus mouthrinse versus toothpaste alone
The pooled estimate (random effects meta-analysis) of the relative risk (RR) of dropping out from the fluoride toothpaste group as opposed to the combined mouthrinse-toothpaste arm in the three trials (Axelsson 1987; Blinkhorn 1983; Ringelberg 1979) that reported dropouts was 1.03 (95% CI, 0.84 to 1.26). Heterogeneity was not detected in these results (chi squared = 2.15 on 2 degrees of freedom, p = 0.34), and the amount present was negligible (I squared = 8%). Using alternative measures of effect has given similar results (OR 1.02, CI 0.74 to 1.40; RD 0.00, CI -0.05 to 0.05).

Fluoride toothpaste plus varnish versus toothpaste alone
The pooled estimate (random effects meta-analysis) of the relative risk (RR) of dropping out from the fluoride toothpaste group as opposed to the combined varnish-toothpaste arm in the two trials (Axelsson 1987a; Petersson 1985) that reported dropouts was 1.29 (95% CI, 0.61 to 2.71). Heterogeneity was not detected in these results (chi squared = 0.24 on 1 degree of freedom, p = 0.62; I squared = 0%). Using alternative measures of effect has given similar results (OR 1.31, CI 0.57 to 3.05; RD 0.01, CI -0.05 to 0.06).

(2) Other combinations of topical fluorides tested against any single modality
Fluoride mouthrinse plus toothpaste versus mouthrinse alone
Pooled estimates of the relative risk (RR) of dropping out from the fluoride toothpaste group as opposed to the combined TFT arm could be obtained for the three trials comparing fluoride mouthrinse plus toothpaste versus mouthrinse alone. Results are again consistent with no difference in effect: 0.88 (95% CI, 0.67 to 1.17), and heterogeneity is low (I squared = 24%).

Discussion
Topical fluorides in the form of toothpastes, mouthrinses, varnishes and gels are effective caries preventive interventions. The effectiveness of each of these has been fully assessed in four previous systematic reviews in this series (Marinho 2002; Marinho 2002a; Marinho 2003; Marinho 2003a). In these and in a subsequent review which compiles the evidence from the previous four and exploits power with additional investigation of covariates across all TFTs, we found no evidence that the effect of topical fluorides was dependent on background exposure to fluoridated water (Marinho 2003b). The main question addressed by this review is how effective the simultaneous use of combined topical fluoride therapy (TFT) for the prevention of caries in children is compared to one topical fluoride treatment used alone. The 11 studies included in the seven meta-analyses (or in the nine comparisons) have not tested all combinations of possible practical value, and there is a
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus small number of trials in each relevant comparison/meta-analysis. However, the randomized evidence that we have brought together is, as far as we can ensure, the totality of the available randomized evidence comparing the combined use of any two topical fluoride modalities with one of them used alone. Although there is a suggestion of a modest caries inhibiting effect with the combined use of topical fluorides in the permanent dentition for most of the comparisons, a general lack of statistical significance is apparent. Further, in a few comparisons, the confidence intervals are relatively wide and the variation among the results of the studies can be substantial. This calls for a cautious interpretation of the data.

Thus, for the primary objective of the review, there is evidence showing that simultaneous use of a topical fluoride treatment with fluoride toothpaste results in an enhanced caries inhibiting effect compared with the use of toothpaste alone. Over 4000 children were included in the trials, and for the majority of children the combined topical fluoride regimen they used at the same time was toothpaste and mouthrinse, followed by toothpaste and gel, and toothpaste and varnish. The random effects meta-analysis of the nine studies assessing the effect of fluoride mouthrinses, gels or varnishes used in combination with fluoride toothpaste on the permanent dentition suggests that their combined use is associated on average with a 10% (95% CI, 2% to 17%) reduction in decayed, missing and filled tooth surfaces. It may be noted that whilst there is evidence that additional caries protection accrues from their combined use, the size of the estimated benefit, of the order of 10%, is not substantial. As to the practical value of the combined regimens tested against fluoride toothpaste alone, the caries reduction would correspond to a number needed to treat (NNT) of 4 to avoid one decayed, filled or missing tooth surface (DMFS) per year in a child population with a caries increment of 2.5 D(M)FS per year (at the highest range of toothpaste group rates for included studies), or an NNT of 13 for children from a population with a caries increment of 0.8 D(M)FS per year (at the lowest end of the observed range). There was only one trial assessing the effect of the combined use of topical fluorides with toothpaste on the deciduous dentition. This compared varnish plus toothpaste versus toothpaste alone only and suggests a 15% reduction in decayed and filled tooth surfaces in favour of the combined therapy, but it is unclear whether the effect was significant.

To what extent statistically significant caries reductions in the order of 10% should be considered important? Some authorities have advocated the use of arbitrary thresholds that indirectly define clinical significance for anticaries products. For example, the American Dental Association produced guidelines proposing that a toothpaste cannot be claimed to be superior to another unless it provides a 10% difference in effect (just the size of the difference for the simultaneous use of TFT and fluoride toothpaste in this review) (CDT-ADA 1988). The trials in a review may give a power calculation that specifies the size of effect the trialists considered to be important, which may be preferred to the use of arbitrary thresholds. In this review this was provided in the trial by Blinkhorn 1983, which had an 80% power to detect a 25% difference between the combined TFT group (toothpaste and mouthrinse in this trial) and the fluoride toothpaste group. Taking this as the clinically important difference indicates that the combined use of toothpaste with other TFTs had no greater effect than toothpaste used alone.

A secondary objective of this review was to examine whether there was a beneficial effect in terms of caries prevention from the addition of each TFT modality to toothpaste separately compared to toothpaste alone or from the combined use of any other two TFT modalities separately compared to one of them alone. We were unable to detect a clear differential effect from all but two of the seven available comparisons.

Thus, a differential treatment effect for each relevant subset in the main meta-analysis, which
assessed the effect of fluoride gel plus toothpaste and toothpaste alone and of fluoride mouthrinse plus toothpaste and toothpaste alone on the permanent dentition, could not be clearly detected, whereas the evidence from one single small trial, which was not carried out double-blind, of a significant differential effect in caries reduction favouring the combined use of fluoride varnish and toothpaste over fluoride toothpaste alone should be viewed with caution, as this is far from definite.

Turning to the combined use of gels or mouthrinses with toothpaste when compared with gels or mouthrinses used alone respectively the general observation is that there is indication of an increased benefit with the use of the combined topical fluoride regimens, although, again, results are not conclusive and the magnitude of any possible differential effect seems to be small.

Among the other relevant combined regimens analysed there is evidence of an increased benefit with the use of fluoride gel and mouthrinse compared to fluoride gel alone, and no suggestion of a significant beneficial effect with the use of fluoride mouthrinse and gel compared to mouthrinse alone. This finding may in fact indirectly suggest that larger caries reductions may be achieved with fluoride mouthrinse used singly, as opposed to the single use of fluoride gel.

As regards the acceptance of combinations of topical fluoride treatments, as measured by the proportion of children dropping out from the trials, there is no suggestion of significant differences in effect. We found little useful information about the effects of combined topical fluorides on other clinically important outcomes such as caries incidence in the deciduous dentition, and on outcomes such as the proportion of children remaining caries-free. We also found no useful information on adverse effects such as fluorosis, oral allergic reactions, or tooth staining. This lack of evidence about adverse effects makes it more difficult for clinicians and policy makers to weigh the benefits of using topical fluorides in different combinations that appeared to be effective for the prevention of caries in children against possible shortcomings of the combined procedures. In general, even with additional caries protection accruing from some of the combined preventive regimens, the additional cariostatic effect may be slight and not worth the extra effort with the use of a second intervention.
**Reviewers' conclusions**

**Implications for practice**
This review has found that compared with fluoride toothpaste used alone, topical fluorides (mouthrinses, gels, or varnishes) used in addition to fluoride toothpaste reduce caries by 10% on average. In terms of acceptability, there is no suggestion of differences in effect between topical fluorides used in combination and fluoride toothpaste used alone. Because the size of the effect is relatively small and as none of the trials consistently compared other important outcomes such as possible side effects from the combined use of topical fluorides and toothpaste, it is not possible to make a clear recommendation on superiority. As for all other combined regimens tested separately against one single topical fluoride, there is an indication that the additional cariostatic effects that may accrue from the combined topical fluorides are slight, and most results are not significant.

**Implications for research**
There is a general lack of randomized trial evidence evaluating the use of different combinations of topical fluorides for the prevention of dental caries in children, and, therefore, a modest treatment effect may have been missed for most relevant comparisons. However, the lack of a clear suggestion of significant benefits from the data analysed in the majority of the comparisons may not indicate priority for the performance of new studies.
### Characteristics of included studies

<table>
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<th>Study ID</th>
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<tr>
<td>Arcieri 1988</td>
<td>Stratified quasi-random allocation; blind caries assessment stated but unclear (C); non-placebo-controlled; 28.5% drop out after 2 years (study duration = 2 years). Reason(s) for attrition NR; no differential group losses.</td>
<td>246 children analysed at 2 years (available at final examination). Age range at start: 7-11 years. Surfaces affected at start: 4.5 DMFS. Exposure to other fluoride: water. Year study began: 1983. Location: Brazil.</td>
<td>FG vs FG+FR</td>
<td>2yDMFS increment. Reported at 1 and 2 years follow ups. Proportion of children remaining caries-free. Drop out. Side effects (incomplete data).</td>
<td>Participants randomized (N = C 344). Baseline characteristics (dental age, DMFS) 'balanced'. Clinical (VT) caries assessment by two examiners; diagnostic threshold NR; state of tooth eruption included NR; diagnostic errors NR.</td>
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<tr>
<td>Ashley 1977</td>
<td>Stratified random allocation; double-blind (A); placebo-controlled; 12% drop out (for all study groups combined) after 2 years (study duration = 2 years). Natural losses; any differential group losses not assessable.</td>
<td>514 children analysed at 2 years (available at final examination). Average age at start: 12 years. Surfaces affected at start: 9.1 DFS. Exposure to other fluoride: no. Year study began: 1973. Location: UK.</td>
<td>FR+PLT vs FR+FT vs FT+PLR</td>
<td>2yNetDFS increment - (E+U)(NCA)cl+(ER)xr. Reported at 2 years follow up. PF-DFS. MD-BL-DFS. MD-DFS. DFS (U).</td>
<td>Participants randomized (numbers for relevant groups NR). Baseline characteristics (age, DFS, DMFS, DMFT) 'balanced'. Clinical (V) caries assessment by one examiner (FOTI used); diagnostic threshold = NCA. Radiographic assessment (postBW) by one examiner; diagnostic threshold = ER. State of tooth eruption included = E/U. Intra-examiner reproducibility checks for</td>
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Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental

**Axelsson 1987**

Random allocation; double-blind (A); placebo-controlled; 16% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers by group; no differential group losses.

143 children analysed at 3 years (available at final examination).

Age range at start: 13-14 years.

Surfaces affected at start: relevant data NR.

Exposure to other fluoride: no.

Year study began: 1977.

Location: Sweden.

**FR+PLT vs FR+FT vs FT+PLR**

**FR = NaF 230 ppm F.**

School mouthrinsing/supervised, weekly.

**FT = NaF 1000 ppm F.**

Home toothbrushing/unsupervised, daily frequency assumed (instructed to brush twice a day).

Abrasive system: silica.

**Caries progression.**

**Drop out.**

Participants randomized (N = 170).

Baseline characteristics (DS) 'balanced'.

Radiographic assessment (4 postBW) by two examiners; diagnostic threshold = ER.

State of tooth eruption included NR. Examiner reproducibility checks for incremental caries data performed ('consistency of duplicate examination reached 94% for scores 1&2 combined').

**Axelsson 1987a**

Random allocation; single-blind (B); placebo-controlled; 15% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers by group; no differential group losses.

96 children analysed at 3 years (available at final examination).

Age range at start: 13-14 years.

Surfaces affected at start: relevant data NR.

Exposure to other fluoride: no.

**FT+PLR* vs FT+FV**

**FT = NaF 1000 ppm F.**

Home toothbrushing/unsupervised, daily frequency assumed (instructed to brush twice a day).

Abrasive system: silica.

**Caries progression.**

**Drop out.**

Participants randomized (N = 113).

Baseline characteristics (DS) 'balanced'.

Radiographic assessment (4 postBW) by two examiners; diagnostic threshold = ER.

State of tooth eruption included NR. Examiner
## Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental decay

### Blinkhorn 1983

| Year study began: 1977. | Location: Sweden. | FV (Fluor Protector®) = NaF 7000 ppm F. | Applied 4 times a year. | 567 children analysed at 3 years (available at final examination). | Age range at start: 11-12 years. | Surfaces affected at start: 8.4 DMFS. | Exposure to other fluoride: no. | Year study began: 1972. | Location: UK. | 3yNetDFS increment - (E+U)(CA)cl+(DR)xr. Reported at 3 years follow up. | Participants randomized (N = B 621). | Baseline characteristics (DMFS, DMFT, SAR) 'balanced' (DFS baseline data NR). | Clinical (V) caries assessment by one examiner, diagnostic threshold = CA. | Radiographic assessment (1 postBW) by one 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). |
|------------------------|-------------------|-----------------|-----------------|-----------------------------------------------------------------|-----------------|-----------------|-----------------|------------------------|-------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Stratified random allocation; double-blind (A); placebo-controlled; 9% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers; no differential group losses. | FR+PLT vs FR+FT vs FT+PLR | FR = NaF 230 ppm F. School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with appropriate toothpaste at school). | FT = SMFP 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by mouthrinsing with appropriate solution); appropriate toothpaste provided for home use. Abrasive system: IMP (main abrasive). | FR+PLT vs FR+FT vs FT+PLR | FR = NaF 230 ppm F. School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with appropriate toothpaste at school). | FT = SMFP 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by mouthrinsing with appropriate solution); appropriate toothpaste provided for home use. Abrasive system: IMP (main abrasive). | FR+PLT vs FR+FT vs FT+PLR | FR = NaF 230 ppm F. School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with appropriate toothpaste at school). | FT = SMFP 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by mouthrinsing with appropriate solution); appropriate toothpaste provided for home use. Abrasive system: IMP (main abrasive). | FR+PLT vs FR+FT vs FT+PLR | FR = NaF 230 ppm F. School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with appropriate toothpaste at school). | FT = SMFP 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by mouthrinsing with appropriate solution); appropriate toothpaste provided for home use. Abrasive system: IMP (main abrasive). | FR+PLT vs FR+FT vs FT+PLR | FR = NaF 230 ppm F. School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with appropriate toothpaste at school). | FT = SMFP 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by mouthrinsing with appropriate solution); appropriate toothpaste provided for home use. Abrasive system: IMP (main abrasive). | FR+PLT vs FR+FT vs FT+PLR | FR = NaF 230 ppm F. School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with appropriate toothpaste at school). | FT = SMFP 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by mouthrinsing with appropriate solution); appropriate toothpaste provided for home use. Abrasive system: IMP (main abrasive). | FR+PLT vs FR+FT vs FT+PLR | FR = NaF 230 ppm F. School mouthrinsing/supervised, daily, for 0.5 min (after toothbrushing with appropriate toothpaste at school). | FT = SMFP 1000 ppm F. School toothbrushing/supervised, daily, for 1 min (followed by mouthrinsing with appropriate solution); appropriate toothpaste provided for home use. Abrasive system: IMP (main abrasive). |

### DePaola 1980

| Year study began: 1972. | Location: UK. | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | 380 children analysed at 1* year (after exclusions, present for entire study period). | Age range at start: 12-14 | TyNetDFS increment - (CA)c1+cxr. Reported at 1 and 2 years follow ups (and 1 year post-treatment). | Participants randomized (numbers NR). | Baseline characteristics (age, dental age, DFS) described as 'balanced' (values NR). |
|------------------------|-------------------|-----------------|-----------------|-----------------------------------------------------------------|-----------------|-----------------|-----------------|------------------------|-------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Random allocation; double-blind (A); placebo-controlled; drop out rate NR nor obtainable (study duration = 2 years + 1 year) | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under | FG+PLR vs FG+FR vs FR+PLG | FG = APF 12,300 ppm F. Self-applied under |

*FT+PLR is the same group as in Axelsson 1987
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries.

Mainwaring 1978

Stratified random allocation; double-blind (A); placebo-controlled; 18% drop out (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable.

1402 children analysed at 3 years (available at final examination).

Age range at start: 11-12 years.

Surfaces affected at start: 8 DFS.

Exposure to other fluoride: no.

Year study began: in/before 1974.

Location: UK.

FG+PLT vs FG+FT vs FT+PLG (2 groups)

FG = APF 12,300 ppm F.
Operator-applied, with tray, twice a year, applied for 4 minutes (prior toothbrushing with non-fluoride toothpaste performed).

FT1&FT2 = SMFP 1000 ppm F (but of different flavours).
Home use/unsupervised, for 1 min, daily frequency assumed.
Abrasive system: Ca carbonate.

Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; state of tooth eruption included NR.

Radiographic assessment (2 postBW) by two examiners (diagnostic threshold NR); diagnostic errors NR.

*Intervention (gel) applied during 1st year of study only (thus, final 2 years results not considered).

Participants randomized (numbers for relevant groups NR).

Baseline characteristics (age, SAR, DFS) 'balanced'.

Clinical (VT) caries assessment by one examiner; diagnostic threshold = CA; state of tooth eruption included = E. Radiographic assessment (2 postBW) by one 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 4% of observed DFS increment in all groups.
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental

Marthaler 1970

Random allocation; indication of blind caries assessment (C); placebo-controlled; 18% drop out (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.

144 children analysed at 3 years (present for all examinations). Age range at start: 6-7 years. Surfaces affected: 1 DMFS. Exposure to other fluoride: salt. Year study began: 1966. Location: Switzerland.

FG+PLT vs FG+FT vs FT+PLG

FG = AmF/NaF 12,500 ppm F. Self-applied under supervision at school, with toothbrush, 20 times a year, 1g applied for 6 minutes.

FT = AmF 1250 ppm F. Home use/unsupervised, twice/three times a day/680 times a year estimated. Abrasive system: IMP.

3yNetDFS increment - (CA)cl+(DR)xr. Reported at 1 and 3 years follow ups.

1stmPF-DFS. 1stmMD-DFS.

Marthaler 1970a

Random allocation; indication of blind caries assessment (C); placebo-controlled; 30% drop out (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.

70 children analysed at 2&4* years (present for all examinations). Age range at start: 7-9 years. Surfaces affected: 1.9 DMFS. Exposure to other fluoride: salt. Year study began: 1966. Location: Switzerland.

FG+PLT vs FG+FT vs FT+PLG

FG = AmF/NaF 12,500 ppm F. Self-applied under supervision at school, with toothbrush, 22 times a year, 1g applied for 6 minutes.

FT = AmF 1250 ppm F. Home use/unsupervised, twice/three times a day/800 times a year estimated. Abrasive system: IMP.

2y*NetDFS increment - (CA)cl+(DR)xr. Reported at 2 and 4 years follow ups.

1stmPF-DFS (CA) cl. 1stmMD-DFS (DR) xr.
<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Control</th>
<th>Dropout</th>
<th>Reasons for Dropout</th>
<th>Number Analysed</th>
<th>Age at Start</th>
<th>Surfaces at Start</th>
<th>Exposure to Other Fluoride</th>
<th>Year Study Began</th>
<th>Location</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Baseline Characteristics</th>
<th>Clinical Assessment</th>
<th>Diagnostic Errors</th>
<th>Participants Randomized</th>
<th>N =</th>
<th>Baseline Characteristics</th>
<th>(DMFS, DMFT)</th>
<th>Balanced</th>
<th>Clinical Assessment</th>
<th>DMFS</th>
<th>DMFT</th>
<th>Stain Score</th>
<th>Drop out</th>
<th>Abrasive System</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petersson 1985</td>
<td>Quasi-random</td>
<td>Single-blind</td>
<td>Non-placebo-controlled</td>
<td>5% after 2 years</td>
<td>NR</td>
<td>No differential group losses</td>
<td>271</td>
<td>3</td>
<td>0.9</td>
<td>None assumed</td>
<td>1978</td>
<td>Sweden</td>
<td>FV+PLT vs FV+FT vs FT alone</td>
<td>2ydfs increment - (E) (CA)cl+(DR)xr</td>
<td>Reported at 2 years follow up</td>
<td>Participants randomized (N = C 285)</td>
<td>Baseline characteristics (dms) balanced</td>
<td>Clinical (VT) caries assessment by two examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) by two examiners; diagnostic threshold = DR. Diagnostic errors NR</td>
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</tr>
<tr>
<td>Ringelberg 1979</td>
<td>Stratified random</td>
<td>Double-blind</td>
<td>Placebo-controlled</td>
<td>40% after 2.5 years</td>
<td>NR</td>
<td>No differential group losses</td>
<td>1059</td>
<td>11</td>
<td>4.3</td>
<td>None assumed</td>
<td>1973</td>
<td>USA</td>
<td>FR+PLT (2 groups) vs FR+FT (2 groups) vs FT+PLR (2 groups)</td>
<td>2.5yNetDMFS increment - (CA)cl+(DR)xr</td>
<td>Reported at 2.5 years follow up</td>
<td>Participants randomized (N = B 1760)</td>
<td>Baseline characteristics (DMFS, DMFT) balanced</td>
<td>Clinical (VT) caries assessment by two examiners, diagnostic threshold = CA. Radiographic assessment (5 BW) by two examiners; diagnostic threshold = DR. State of tooth eruption included NR. Reversal rate between 4 and 9% of</td>
<td></td>
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</tr>
</tbody>
</table>
Triol 1980

Stratified random allocation; double-blind (A); placebo-controlled; 20% drop out after 2.5 years (study duration = 2.5 years). Natural losses; any differential group losses not assessable.

1054 children analysed at 2.5 years (available at all examinations). Age range at start: 10-13 years (average = 11.5). Surfaces affected at start: 9.9 DFS. Exposure to other fluoride: toothpaste assumed. Year study began: in/before 1977. Location: USA.

FT+PLR vs FR+FT (3 groups)

FT = SMFP 1000 ppm F (in all groups).
School toothbrushing/supervised, daily, 1g applied for 1 min (followed by water rinse and mouthrinsing with appropriate solution); Fluoride toothpaste provided to all for home use. Abrasive system: IMP (main abrasive).

FR1 = NaF 110 ppm F, FR2 = NaF 230 ppm F, FR3 = NaF 450 ppm F.
School mouthrinsing/supervised, daily, 7.5 ml applied for 0.5 min (after toothbrushing with fluoride toothpaste at school).

2.5yDMFS increment - cl+xr. Reported at 1.5 and 2.5 years follow ups.
MD-DMFS
DMFT
Drop out (no data by group).

Pyrophosphate in SnF2 toothpaste, NR for AmF toothpaste.

Participants randomized (N= 1320), numbers by group NR. Baseline characteristics (age, SAR, DFS, D, F, TAR, DFT) 'balanced' (DMFS baseline data NR). Clinical (VT) caries assessment; diagnostic threshold NR; state of tooth eruption included NR. Radiographic assessment (2 postBW); diagnostic threshold NR; diagnostic errors NR.
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental decay.

= bite-wing x-ray assessment; Ca = calcium; Ca carbonate = CaCO3; 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; d(e)ft/s = decayed, (extracted) and filled deciduous teeth or surface; dmft/s = decayed, missing (or extracted) and filled deciduous teeth or surface; D(M)FS/T = decayed, missing and filled permanent surfaces or teeth; DR = radiolucency into dentin; E = teeth erupted at baseline; ER = any radiolucency in enamel/enamel-dentin junction; F = fluoride; FG = fluoride gel; FR = fluoride mouthrinse; FT = fluoride toothpaste; FV = fluoride varnish; icc = intra-class correlation coefficient (for inter-rater reliability); IMP = insoluble Na metaphosphate; M = missing permanent teeth; MD = mesio and distal surfaces; N = numbers; Na = sodium; NaF = sodium fluoride; NCA = non-cavitated enamel lesions visible as white spots or discoloured fissures; NR = not reported; NS = not significant; NT = no treatment control; O = occlusal surfaces; PF = pit and fissure surfaces; PL = placebo; postBW = posterior bite-wing x-ray assessment; ppm F = parts per million of fluoride; ptc = prior tooth-cleaning performed with or without a non-fluoride paste; Silica = silicon dioxide (SiO2); SMFP = sodium monofluorophosphate; SnF2 = stannous fluoride; U = teeth unerupted at baseline; VT = visual-tactile assessment; xr = radiographic examination.
Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohannan 1985</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated. (FR plus FG vs FR)</td>
</tr>
<tr>
<td>Louw 1995</td>
<td>Random or quasi-random allocation not stated or indicated. Blind outcome assessment not stated or indicated. (FR plus FT vs FR)</td>
</tr>
<tr>
<td>Wilson 1978</td>
<td>Random or quasi-random allocation not stated. (FR plus FT vs FR; FT plus FR vs FT)</td>
</tr>
</tbody>
</table>

FG = fluoride gel; FR = fluoride mouthrinse; FT = fluoride toothpaste; FV = fluoride varnish
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes)

References to studies

Included studies

Arcieri 1988 {published data only}


Ashley 1977 {published data only}


Axelsson 1987 {published data only}


Axelsson 1987a {published data only}


Blinkhorn 1983 {published and unpublished data}


DePaola 1980 {unpublished data sought but not used}


Lu KH, Porter DR, Pickles TH. Separate and combined cariostatic effects of fluoride gel and rinse

Review Manager 4.2.2 26/09/2003
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes)


**Mainwaring 1978** (published data only)

**Marthaler 1970** (published data only)

**Marthaler 1970a** (published data only)

**Petersson 1985** (published data only)

**Ringelberg 1979** (published data only)


**Triol 1980** (unpublished data sought but not used)

**Excluded studies**

**Bohannan 1985** (published data only)
Bell RM, Klein SP, Bohannan HM, Disney JA, Graves RC, Madson R. Treatment effects in the
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes)


Louw 1995


Wilson 1978


Studies awaiting assessment

Torell 1969

Torell P. Bruk av fluortandkram i samband med fluorskoljning varannan vecka [The use of fluoride toothpaste combined with fluoride rinsing every two weeks]. Sver Tandlakarforb Tidningen 1969;61:873-5.

* indicates the primary reference for the study
Other references

Additional references

Burt 1998

CDT-ADA 1988

Chen 1995

Clarke 2000

Downer 1995

Dubey 1965

Egger 1997

Featherstone 1988

Glass 1982
Glass RL. The first international conference on the declining prevalence of dental caries. Journal of
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes)

Dental Research 1982;61:1301-83.

Horowitz 1980

Marinho 1997

Marinho 2002

Marinho 2002a

Marinho 2003

Marinho 2003a

Marinho 2003b

Marthaler 1971

Marthaler 1990
Marthaler TM. Cariostatic efficacy of the combined use of fluorides. Journal of Dental Research 1990;69 Spec No:797-800.

Marthaler 1994
Marthaler TM, Steiner M, Menghini G, Bandi A. Caries prevalence in Switzerland. International
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes)

Dental Journal 1994;44:393-401.

Marthaler 1996


Moynihan 1996


Murray 1991


Murray 1991a


O'Mullane 1995


Pitts 2001


Pitts 2002


Ripa 1991


Rolla 1991

Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes)

Seppa 1998

Sharp 1998

Thompson 1999

van Rijkom 1998
Table of comparisons

01 Fluoride toothpaste plus others (varnish, gel or rinse) versus toothpaste alone
   01 D(M)FS increment (PF) - nearest to 3 years (9 trials)
      01 Fluoride toothpaste plus mouthrinse versus Fluoride toothpaste
      02 Fluoride toothpaste plus gel versus Fluoride toothpaste
      03 Fluoride toothpaste plus varnish versus Fluoride toothpaste
   02 d(e)fs increment (PF) - nearest to 3 years (1 trial)
      01 Fluoride toothpaste plus varnish versus Fluoride toothpaste
   03 Unacceptability of treatment as measured by leaving study early (5 trials)
      01 Fluoride toothpaste plus mouthrinse versus Fluoride toothpaste
      02 Fluoride toothpaste plus varnish versus Fluoride toothpaste

02 Other combinations of topical fluoride versus one topical fluoride alone
   01 D(M)FS increment (PF) - nearest to 3 years
      01 Fluoride mouthrinse plus gel versus Fluoride mouthrinse (1 trial)
      02 Fluoride gel plus mouthrinse versus Fluoride gel (2 trials)
      03 Fluoride mouthrinse plus toothpaste versus Fluoride mouthrinse (4 trials)
      04 Fluoride gel plus toothpaste versus Fluoride gel (3 trials)
   02 d(e)fs increment (PF) - nearest to 3 years
      01 Fluoride varnish plus toothpaste versus Fluoride varnish (1 trial)
   03 Unacceptability of treatment as measured by leaving study early
      01 Fluoride gel plus mouthrinse versus Fluoride gel (1 trial)
      02 Fluoride mouthrinse plus toothpaste versus Fluoride mouthrinse (3 trials)
      03 Fluoride varnish plus toothpaste versus Fluoride varnish (1 trial)
Review: Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in

Total number of included studies: 12

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride toothpaste plus others (varnish, gel or rinse) versus toothpaste alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years (9 trials)</td>
<td>9</td>
<td>4026</td>
<td>Prevented Fraction (random),</td>
<td>0.10 [0.02, 0.17]</td>
</tr>
<tr>
<td>02 d(e)fs increment (PF) - nearest to 3 years (1 trial)</td>
<td>0</td>
<td>0</td>
<td>Prevented Fraction (random),</td>
<td>Not estimable</td>
</tr>
<tr>
<td>03 Unacceptability of treatment as measured by leaving study early (5 trials)</td>
<td>5</td>
<td>1998</td>
<td>RR (random), 95% CI</td>
<td>1.06 [0.93, 1.22]</td>
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<tr>
<td>02 Other combinations of topical fluoride versus one topical fluoride alone</td>
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<td></td>
</tr>
<tr>
<td>01 D(M)FS increment (PF) - nearest to 3 years</td>
<td></td>
<td></td>
<td>Prevented Fraction (random),</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>02 d(e)fs increment (PF) - nearest to 3 years</td>
<td></td>
<td></td>
<td>Prevented Fraction (random),</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>03 Unacceptability of treatment as measured by leaving study early</td>
<td></td>
<td></td>
<td>RR (random), 95% CI</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>
## Review
Combinations of topical fluoride toothpastes, mouthrinses, gels, varnishes versus single topical fluoride for preventing dental caries in children and adolescents (THESSIS CHAPTER 9)

## Comparison
01 Fluoride toothpaste plus others (varnish, gel or rinse) versus toothpaste alone

## Outcome
01 OAME: increment (PF) - nearest to 3 years (9 trials)

### Study

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Toothpaste and others</th>
<th>prevalence</th>
<th>prevented fraction (random)</th>
<th>Weight %</th>
<th>prevented fraction (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride toothpaste plus mouthrinse versus Fluoride toothpaste</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Axelsson 1987</td>
<td>50</td>
<td>25</td>
<td>0.0400 (0.2975)</td>
<td>1.09</td>
<td>0.06 (0.00, 0.14)</td>
<td>1987</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blender 1983</td>
<td>193</td>
<td>184</td>
<td>-0.0188 ( -0.0579)</td>
<td>1.00</td>
<td>-0.03 ( -0.13, 0.01)</td>
<td>1983</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Ringberg 1979</td>
<td>248</td>
<td>170</td>
<td>0.0587 (0.0629)</td>
<td>13.82</td>
<td>0.05 (0.11, 0.21)</td>
<td>1979</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Ashley 1977</td>
<td>249</td>
<td>246</td>
<td>0.0731 (0.0777)</td>
<td>15.00</td>
<td>0.07 (0.06, 0.22)</td>
<td>1977</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total 1980</td>
<td>789</td>
<td>634</td>
<td>0.0934 (0.0486)</td>
<td>15.00</td>
<td>0.09 (0.00, 0.15)</td>
<td>1980</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 1.42$, df = 4 ($P = 0.84$); I² = 0%
- Test for overall effect: $Z = 1.90$ ($P = 0.06$)

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Toothpaste and others</th>
<th>prevalence</th>
<th>prevented fraction (random)</th>
<th>Weight %</th>
<th>prevented fraction (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
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</thead>
<tbody>
<tr>
<td>02 Fluoride toothpaste plus gel versus Fluoride toothpaste</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mainwaring 1980</td>
<td>7</td>
<td>8</td>
<td>0.0000 (0.0000)</td>
<td>1.00</td>
<td>0.00 (0.00, 0.00)</td>
<td>1980</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 2.48$, df = 1 ($P = 0.12$); I² = 2%
- Test for overall effect: $Z = 1.19$ ($P = 0.23$)

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Toothpaste and others</th>
<th>prevalence</th>
<th>prevented fraction (random)</th>
<th>Weight %</th>
<th>prevented fraction (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>03 Fluoride toothpaste plus varnish versus Fluoride toothpaste</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axelsson 1987</td>
<td>46</td>
<td>25</td>
<td>0.1800 (0.1837)</td>
<td>1.40</td>
<td>0.43 (0.12, 0.84)</td>
<td>1987</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 3.12$, df = 2 ($P = 0.08$); I² = 31.9%
- Test for overall effect: $Z = 2.50$ ($P = 0.01$)

## Notes
- Non-prevented fraction (random)
- RR (random)
- Weight

## Outcome
02 data increment (PF) - nearest to 3 years (1 trial)

### Study

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Toothpaste and others</th>
<th>prevalence</th>
<th>prevented fraction (random)</th>
<th>Weight %</th>
<th>prevented fraction (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
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<tbody>
<tr>
<td>01 Fluoride toothpaste plus varnish versus Fluoride toothpaste</td>
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<tr>
<td>Peterson 1985</td>
<td>3</td>
<td>3</td>
<td>0.1000 (0.0000)</td>
<td>1.00</td>
<td>1.00 (0.37, 2.67)</td>
<td>1985</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 0$, df = 2 ($P = 0.84$); I² = 0%
- Test for overall effect: $Z = 2.61$ ($P = 0.000$)

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<th>Toothpaste and others</th>
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<th>Weight %</th>
<th>prevented fraction (random)</th>
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</tr>
<tr>
<td>Axelsson 1987</td>
<td>6</td>
<td>3</td>
<td>0.1800 (0.2015)</td>
<td>1.00</td>
<td>1.00 (0.40, 2.51)</td>
<td>1987</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 11.75$, df = 8 ($P = 0.16$); I² = 31.9%
- Test for overall effect: $Z = 2.50$ ($P = 0.01$)

## Notes
- Non-prevented fraction (random)
- RR (random)
- Weight

## Outcome
03 Non-compliance of treatment as measured by leaving study early (3 trials)

### Study

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Toothpaste and other</th>
<th>prevalence</th>
<th>prevented fraction (random)</th>
<th>Weight %</th>
<th>prevented fraction (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Fluoride toothpaste plus varnish versus Fluoride toothpaste</td>
<td></td>
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<td></td>
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<tr>
<td>Axelsson 1987</td>
<td>4</td>
<td>3</td>
<td>0.1800 (0.2015)</td>
<td>1.00</td>
<td>1.00 (0.40, 2.51)</td>
<td>1987</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 21.8$, df = 2 ($P = 0.34$); I² = 8.2%
- Test for overall effect: $Z = 2.26$ ($P = 0.07$)

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Toothpaste and other</th>
<th>prevalence</th>
<th>prevented fraction (random)</th>
<th>Weight %</th>
<th>prevented fraction (random)</th>
<th>Year</th>
<th>Quality</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Fluoride toothpaste plus varnish versus Fluoride toothpaste</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Peterson 1985</td>
<td>4</td>
<td>9</td>
<td>0.1000 (0.0000)</td>
<td>1.00</td>
<td>1.00 (0.37, 2.67)</td>
<td>1985</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 0$, df = 1 ($P = 0.01$); I² = 0%
- Test for overall effect: $Z = 2.61$ ($P = 0.01$)

<table>
<thead>
<tr>
<th>Sub-category</th>
<th>Toothpaste and other</th>
<th>prevalence</th>
<th>prevented fraction (random)</th>
<th>Weight %</th>
<th>prevented fraction (random)</th>
<th>Year</th>
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<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>03 Fluoride toothpaste plus varnish versus Fluoride toothpaste</td>
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<td>1.00 (0.37, 2.67)</td>
<td>1985</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Subtotal (95% Cl)

- Test for heterogeneity: $\chi^2 = 0$, df = 1 ($P = 0.01$); I² = 0%
- Test for overall effect: $Z = 2.61$ ($P = 0.01$)
### Study 1: Fluoride mouthwash plus gel versus Fluoride mouthwash (1 trial)

- **DePase 1980**: 123/123
- **Subtotal (95%)**: 105.00

**Test for heterogeneity**: Not applicable

**Test for overall effect**: Z = 0.02 (P = 0.98)

### Study 2: Fluoride gel plus mouthrinse versus Fluoride gel (2 trials)

- **DePase 1980**: 123/123
- **Anseri 1988**: 123/123

**Test for heterogeneity**: Chi² = 0.17, df = 2 (P = 0.92), I² = 0%

**Test for overall effect**: Z = 0.97 (P = 0.33)

### Study 3: Fluoride mouthwash plus toothpaste versus Fluoride mouthwash (4 trials)

- **Axelson 1987**: 50/50
- **Bishnoff 1983**: 193/193
- **Ringelberg 1979**: 246/246
- **Austen 1987**: 249/249

**Test for heterogeneity**: Chi² = 2.62, df = 2 (P = 0.27), I² = 23.6%

**Test for overall effect**: Z = 2.33 (P = 0.02)

### Study 4: Fluoride gel plus mouthrinse versus Fluoride gel (3 trials)

- **Mainwaring 1978**: 296/296
- **Marthaler 1970**: 26/26
- **Marthaler 1970a**: 38/38

**Test for heterogeneity**: Chi² = 0.02 (P = 0.99), I² = 0%

**Test for overall effect**: Z = 0.02 (P = 0.98)

### Study 5: Fluoride varnish plus toothpaste versus Fluoride varnish (1 trial)

- **Ringard 1979**: 348/348

**Test for heterogeneity**: Not applicable

**Test for overall effect**: Z = 0.85 (P = 0.39)

### Study 6: Fluoride mouthwash plus toothpaste versus Fluoride mouthwash (3 trials)

- **Axelson 1987**: 50/50
- **Mainwaring 1978**: 296/296
- **Marthaler 1970**: 26/26

**Test for heterogeneity**: Chi² = 0.17, df = 2 (P = 0.65), I² = 23.6%

**Test for overall effect**: Z = 0.45 (P = 0.65)