Evidence-Based Dentistry

Systematic Review of Controlled Trials on the Effectiveness of Fluoride Gels for the Prevention of Dental Caries in Children


Abstract: Fluoride gels have been widely used since the 1970s. The aim of this review was to assess the effectiveness and safety of fluoride gels in the prevention of dental caries in children and to examine factors potentially modifying their effectiveness. Relevant randomized or quasi-randomized trials were identified without language restrictions by searching multiple databases, reference lists of articles, and journals and by contacting selected authors and manufacturers. Trials with blind outcome assessment comparing fluoride gel with placebo or no treatment for at least one year and involving children under seventeen years of age were selected. Inclusion decisions, quality assessment, and data extraction were duplicated in a random sample of one third of studies, and consensus was achieved by discussion or a third party. Random effects meta-analyses were performed where data could be pooled. Potential sources of heterogeneity were examined in random effects meta-regression analyses. The main outcome was caries increment measured by the change in decayed, missing, and filled permanent tooth surfaces (D(M)FS). The primary measure of effect was the prevented fraction (PF) that is the difference in mean caries increment between the treatment and control groups expressed as a percentage of the mean increment in the control group. Potential adverse effects and unacceptability of treatment were also recorded. Twenty-five studies were included, involving 7,747 children. For the twenty-three that contributed data for meta-analysis, the D(M)FS pooled prevented fraction estimate was 28 percent (95 percent CI, 19 percent to 37 percent; 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 percent (95 percent CI, 5 percent to 33 percent; p<0.009) higher in non-placebo controlled trials. Only two trials reported on adverse events. There is clear evidence of a caries-inhibiting effect of fluoride gel. The best estimate of the magnitude of this effect, based on the fourteen placebo-controlled trials, is a 21 percent reduction (95 percent CI, 1 to 3) to avoid one D(M)FS in a population with a caries increment of 2.2 D(M)FS/year, or an NNT of twenty-four (95 percent CI, 18 to 36) based on an increment of 0.2 D(M)FS/year. However, further work is needed to identify and quantify potential harmful effects of fluoride gels.

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Topically applied fluoride gels have been widely used in dental surgeries and prevention programs in schools in many countries during recent decades. However, with the widespread use of fluoride, especially in the form of toothpaste, and the low caries severity and prevalence in many countries, questions have been raised about their cost-effectiveness and the possibility of overexposure to fluoride, particularly because of the high concentration of fluoride in some gels. The aim of this systematic review was to assess the effectiveness and safety of fluoride gels in the prevention of dental caries in children and to examine formally the main factors that may influence their effectiveness including initial level of caries severity, background exposure to other fluoride sources, methods of application, and fluoride concentration.

Fluoride gels can be professionally or self-applied under supervision, at a frequency from once to several times a year. Various fluoride compounds, concentrations, and methods of gel application have been used, with or without prior dental prophylaxis.
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. 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 fluoride toothpastes that are available in the form of gels. The “classic” 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.

The excessive ingestion of fluoride during topical application is not uncommon, and the greatest health hazard is associated with the use of 12,300 ppm F APF gels. The probable toxic dose (PTD) of 100 mg of fluoride for a 20 kg (five-to-six-year-old) child is contained in only 8 ml 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 a significant risk of overexposure, which can result in acute toxicity. Nausea, vomiting, headache, and abdominal pain are symptoms that have been reported in young people receiving fluoride gel applications. Because of the risk of overingestion, the use of gels in young children is not recommended.

Numerous clinical trials evaluating the caries preventive effect of fluoride gels have been reported; these have been the subject of narrative reviews and two meta-analyses. The most recent meta-analysis investigated the same question addressed in this systematic review, but it did not include a comprehensive search for individual studies or a formal assessment of the internal validity (methodological quality) of included studies. The review that is summarized in this paper is published in full in The Cochrane Library and is part of a series looking at topical fluoride interventions.

**Methods**

Studies were included if participants were allocated randomly or quasirandomly to fluoride gel or placebo (for any method of gel application) or no treatment (for tray or cotton tips methods but not for brushing or flossing) for at least one year/school year and in which blind assessment of outcome was used or indicated. Participants had to be children aged sixteen or less at the start of the study.

The types of intervention included in this review are professionally or self-applied fluoride gels, using any fluoride agent, at any concentration, amount, or duration of application, and with any technique of application, provided the frequency of gel application was at least once a year. Studies in which the intervention consisted of any other caries preventive agent/procedure in addition to fluoride gel were excluded. The main outcome is caries increment as measured by the change in decayed, missing, and filled tooth surfaces (DMFS) in the permanent dentition. Caries incidence in deciduous teeth and specific side effects including tooth staining or discoloration, oral allergic reactions, and adverse symptoms such as nausea and vomiting were other outcomes considered relevant.

We attempted to identify all relevant studies irrespective of language, from 1965 to 2000, by employing a comprehensive search strategy. We searched several databases from data of inception to 2000, including MEDLINE, EMBASE, BIOSIS, SCISEARCH, LILACS/BBO, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2000), and the Cochrane Oral Health Group’s Trials Register (May 2000). We also handsearched seven dental journals prospectively and the journal Community Dentistry and Oral Epidemiology from 1990 to January 2000, searched reference lists of articles, and contacted selected authors and manufacturers for unpublished studies. Full details of the search strategy can be found elsewhere.

All records electronically identified were scanned by title, abstract (when available) and/or keywords by one reviewer (VM). The full text of all reports identified from all sources searched and considered potentially relevant were obtained.

Based on pilot-tested inclusion criteria and data extraction forms, inclusion decisions, quality assessment, and data extraction were performed by one reviewer and duplicated independently by a second reviewer in a random sample of approximately one third of studies. Checking of interobserver reliability was limited to validity assessments. Consensus was achieved through discussion or a third party where necessary to resolve any disagreement. In addition, any study that could not be classified by the first reviewer or that posed doubts during quality assessment/data extraction was independently assessed by the second reviewer (again, a third reviewer was consulted where necessary to resolve uncertainty). Attempts were made to contact authors of trials that could not be classified in order to ascertain whether inclusion criteria were met and to obtain missing data. Trial reports thought to be poten-
entially relevant in languages not known by the reviewers were translated, and the reviewer completed the inclusion form and extracted the data, if the study was included, with reference to the translator.

Allocation concealment was recorded according to three categories (adequate concealment, indicated/unclear, inadequate concealment) as described in the Cochrane Reviewers’ Handbook. Blinding of main outcome assessment was also rated according to categories defined for the topical fluoride reviews: double-blind (blind outcome assessment and use of placebo described); single-blind (blind outcome assessment stated and no placebo used); blinding indicated (not stated but likely in any element/phase of outcome assessment); or reported but unclear.

A trial was excluded if random or quasi-random allocation was clearly not used or not stated and not indicated. A trial was also excluded if open outcome assessment was described or blind outcome assessment was 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).

Further quality assessment was carried out to assess completeness of follow-up and other methodological features, but these were not used as thresholds for inclusion.

Outcomes

We developed a set of a priori rules to choose the primary outcome data for analysis from each study: caries increment data on surface level would be chosen over data on tooth level, DFS data would be chosen over DMFS data and this 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. The primary choices described above were assumed 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 chosen measure of treatment effect was the prevented fraction (PF), which is defined as the mean increment in the controls minus mean increment in the treated group divided by mean increment in the controls.

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 gels to a placebo group, results (the numbers, mean caries increments, and standard deviations) from all relevant experimental groups were combined in order to obtain the measure of treatment effect. This strategy allowed us to include all relevant data in the primary meta-analysis. However, it may have slightly compromised the secondary investigations of dose response.

Missing standard deviations for caries increments that were not provided by contacting the original researchers were imputed through log linear regression of 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 to their standard deviations.

Analyses

The meta-analyses were conducted as inverse variance weighted averages. Variances were estimated using the formula presented in Dubey. 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 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.

Heterogeneity was assessed by inspection of a graphical display of the estimated treatment effects from the trials along with their 95 percent confidence intervals and by formal tests of homogeneity undertaken prior to each meta-analysis. The association of potential sources of heterogeneity 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.

To allow such investigation, relevant data were dealt with as follows: data on “baseline levels of car-
ies” were calculated from the study sample analysed 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 based on samples provided with nonfluoride toothpaste and from nonfluoridated areas (nonexposed), and another for studies based on samples using fluoride toothpaste or studies in fluoridated communities or both. When use or nonuse 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. This information was sought from authors or obtained from other sources when it was missing from studies carried out in other locations. When data on the year a study was started 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 by tray or by brush. Data on “frequency of application” and “fluoride concentration” have not been categorized, 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.

A funnel plot (plot of effect size versus standard error) was drawn. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger. For outcomes other than caries increment, data were analyzed by calculating risk ratios (RR) or risk differences (RD) in the Cochrane Review Manager software (RevMan 4.1/ Metaview).

Results

From over two thousand records produced by the searches and screened, eighty-eight reports were considered potentially eligible, sought, and assessed further. Thirty-one of these eighty-eight reports were considered immediately irrelevant for this review, and the remaining fifty-seven reports (related to thirty-nine studies) were considered further. These included reports published in German, Portuguese, Russian, Bulgarian, Hungarian, and Polish. There are thirty-four reports relating to twenty-five included studies, twenty reports relating to thirteen excluded studies, and three reports relating to two studies waiting assessment (in Polish) that require translation. However, only one (main) reference from each included and excluded study is cited here. The complete list of references related to individual studies is available elsewhere.

Thirteen studies were excluded for a variety of reasons. Four studies had other fluoride-based interventions in addition to fluoride gel. One study involved institutionalized children with specific health problems. Two studies were clearly not randomized or quasirandomized or did not imply randomization. Three studies did not mention or indicate random/quasirandom allocation nor blind outcome assessment. One study did not mention or indicate blind outcome assessment. Attempts to contact the author of this study were not successful, so it was assumed that blinding had not been done and the study was excluded. Two studies did not mention or indicate random or quasirandom allocation or blind outcome assessment. The authors of these studies were contacted, and the studies were excluded after we received a negative reply on blind assessment.

Summaries of the characteristics of individual studies and full details on findings are available elsewhere. Twenty-five trials were included, conducted between 1964 and 1996 (only five during the 1980s and one in the 1990s). Twelve trials were conducted in the United States, four in Europe, four in Brazil, and one in each of the following countries: UK, Canada, Israel, Hawaii, and Venezuela. The study conducted by Marthaler was treated as two independent trials because the results for the two age groups involved were reported separately as distinct studies.

Eight studies had more than one fluoride gel treatment group compared to a control. Sixteen trials used a placebo control group, four of which used an inactive treatment other than gel (placebo solution), and the remaining nine used a no treatment control group. Study duration ranged from one to four years, with twenty studies lasting two or three years. Studies were generally large, with only four allocating fewer than 200 children to relevant study groups, all recruited from school settings. There was substantial variation in the characteristics of participants and intervention in the trials included. All studies reported on exposure to water/salt fluoridation, and only five were conducted in
fluoridated communities. Exposure to fluoride toothpaste was clearly reported in only four studies. Caries prevalence at baseline was reported in all but three of the studies and ranged from 0.24 to 12.2 D(M)FS. Fourteen trials described gel applications carried out by professionals, and in the remaining eleven trials, gel was self-applied under supervision (by dental personnel in four trials, by trained nondental personnel in five trials, and by mothers and dental personnel in another; data were not available for one of the studies). Fluoride concentrations ranged from 2425 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 half of the included studies. The application frequency ranged from once a year (the most common frequency of application, reported in seven studies) to 140 times a year (unusually high frequency of application reported in the study of Englander 1967), but it varied greatly among the studies, with only five studies reporting twice a year application frequency.

Interrater reliability was excellent (89 percent) for both allocation concealment and blinding, and agreement was good for allocation (kappa = 0.61) and very good for blinding (kappa = 0.73). These calculations are based on twenty-eight studies included in the topical fluoride reviews and randomly selected for assessment of reproducibility and agreement between the two reviewers.

There was a considerable variation in the quality of the studies in this review (using the reported information and additional information obtained from investigators). Seventeen trials included in this review were described as randomized but provided no description on how the “random” allocation was done, and seven trials were considered to be quasi-randomized. One of the trials whose investigators provided further information in answer to our inquiry reported adequate allocation concealment. Double-blinding was described in fourteen trials, single-blinding (blind outcome assessment but no placebo used) was described in six trials, and blind outcome assessment was indicated in five trials.

Seventy-two percent (72 percent) of the participants originally enrolled in these studies were included in the final analysis (6,286 analyzed out of 8,739 initially randomized). These data exclude six of the twenty-five included studies that provided no information on the number of participants randomized to relevant groups. Dropout rates were obtained from all but two of the twenty-five included studies and ranged from 8 percent at one year to 55 percent at three years. The most common reason for attrition was that participants were not available for follow-up examination at the end of the study.

**Effect of Fluoride Gel on Caries Increment**

Standard deviations of mean caries increment data (new D(M)FS) were (partly) missing in four of the twenty-three studies that contributed data for the main meta-analysis. From the analysis of 179 available treatment arms for the topical fluoride reviews with complete information, we derived a regression equation log (SD caries increment) = 0.64 + 0.55 log (mean caries increment), (R-squared = 77 percent). This equation was used to estimate missing standard deviations from mean D(M)FS increments for the meta-analyses. 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), while the trial of Treide 1988 reported an effect (defs PF) of fluoride gel of 0.39 (CI not obtainable).

For all twenty-three trials combined, the D(M)FS prevented fraction pooled estimate was 0.28 (95 percent 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).

Univariate meta-regression did not reveal any statistically significant associations between estimates of D(M)FS prevented fractions and the prespecified 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 indication of greater benefit of fluoride gel with increasing frequency of application and with “total intensity of application” (frequency x concentration) with the prevented fraction, but statistical significance was lost in both analyses when the trial of Englander 1967, a study with high influence, was excluded.

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/quasirandom), blinding of outcome assessment (blind/blind likely), or dropout rate. However, the pooled estimated treatment effect was 19 percent (95 percent CI, 5 percent to 33 percent; p = 0.009) greater in trials with no treatment rather than placebo control groups. This association 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 percent CI, 0.24 to 0.53; p=0.0001), while that from the fourteen placebo-controlled trials was 0.21 (95 percent CI, 0.14 to 0.28; p<0.0001). Heterogeneity among the fourteen trials with placebo control groups was substantially less than that observed when all trials were included in the meta-analysis (Q = 22.52 on 13 degrees of freedom, p = 0.05). Although this was a post hoc analysis, we have decided to present the results of the main D(M)FS PF meta-analyses subgrouped by type of control group (see Figures 1 and 2).

We repeated the meta-regression analyses adjusting for type of control group; the results of these analyses are provided in Table 1. Statistically significant associations between prevented fraction and mode of gel delivery (operator- or self-applied) and application frequency were apparent in these analyses, but these disappeared if the Englander 1967 study was excluded. All meta-regression results should be interpreted with a degree of caution given the observational nature of the comparisons and the large number of comparisons made.

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 (percent PF) derived from the pooled results of the fourteen trials with placebo control groups was 21 percent (95 percent CI, 14 percent to 28 percent). 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 percent 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 3 (95 percent CI, 2 to 4).

A funnel plot of the twenty-three studies in the analysis (Figure 3) reporting D(M)FS PFs indicated a relationship between prevented fraction and precision (related to sample size). The Egger test for asymmetry was statistically significant (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.

**Adverse Symptoms (Nausea/Vomiting)**

Only two trials reported usable data on adverse events, but one of these had no events in either arm. The pooled estimate of the risk difference between the gel and placebo arms was 0.01 (95 percent CI, -0.01 to 0.02; chi-square for heterogeneity 0.8 on 1 degree of freedom, p = 0.37), that is, marginally favoring the placebo/no-treatment arm, although the results were consistent with no difference.

**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. The review as a whole contains information from more than 7,000 children and suggests that the application of fluoride gel is associated with a substantial reduction in caries increment. Basing the estimate on those trials with placebo rather than no-treatment controls provides a more conservative estimate of treatment effect of 21 percent (95 percent CI, 14 percent to 28 percent) reduction in decayed, missing, and filled tooth surfaces. This estimate is very similar to that reported in a previous meta-analysis on the caries preventive effect of fluoride gels, which found a pooled D(M)FS estimate of 22 percent (95 percent CI, 18 percent to 25 percent). There were, however, substantial differences in selection criteria and methods between the reviews. Of the nineteen studies included in the review by van Rijkom 1998, nine were also included in this review. The van Rijkom review included four trials in which 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 in this review were excluded for a variety of reasons. An additional ten studies were identified for this re-
Figure 1. Random effects meta-analysis of D(M)FS increments in fourteen placebo controlled trials (treatment effect measured as a prevented fraction).

Figure 2. Random effects meta-analysis of D(M)FS increments in nine no-treatment controlled trials (treatment effect measured as a prevented fraction). The difference between the subgroup results (38 percent and 21 percent) differs from 19 percent as a result of an assumption of similar heterogeneity among PFs made in the meta-regression analysis.
Table 1. Random effects meta-regression analyses of D(M)FS prevented fractions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of studies</th>
<th>Slope estimate</th>
<th>95 percent c.i.</th>
<th>Slope interpretation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>23</td>
<td>19 percent</td>
<td>(5 percent to 33 percent)</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 percent</td>
<td>(-2.0 percent to 2.5 percent)</td>
<td>Increase per unit increase in mean baseline caries</td>
<td>0.8</td>
</tr>
<tr>
<td>Background fluoride</td>
<td>22</td>
<td>-6.6 percent</td>
<td>(-22 percent to 9 percent)</td>
<td>Lower PF in presence of background fluorides</td>
<td>0.4</td>
</tr>
<tr>
<td>Fluoride toothpaste use</td>
<td>22</td>
<td>-7.4 percent</td>
<td>(-26 percent to 11 percent)</td>
<td>Lower PF in presence of fluoride toothpaste use</td>
<td>0.1</td>
</tr>
<tr>
<td>Fluoridated water</td>
<td>23</td>
<td>-1.9 percent</td>
<td>(-22 percent to 18 percent)</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 percent</td>
<td>(1 percent to 28 percent)</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 percent</td>
<td>(-41 percent to 32 percent)</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 percent</td>
<td>(0.8 percent to 4.2 percent)</td>
<td>Increase per 10 extra applications/year</td>
<td>0.003</td>
</tr>
<tr>
<td>Fluoride gel concentration</td>
<td>20</td>
<td>-2.1 percent</td>
<td>(-5 percent to 0 percent)</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 percent</td>
<td>(0.2 percent to 0.9 percent)</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 percent</td>
<td>(-8 percent to 14 percent)</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 percent</td>
<td>(-23 percent to 8 percent)</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 percent</td>
<td>(-18 percent to 18 percent)</td>
<td>Higher PF with blind outcome assessment indicated (but not stated)</td>
<td>0.98</td>
</tr>
<tr>
<td>Double-blinding</td>
<td>23</td>
<td>15 percent</td>
<td>(-14 percent to 44 percent)</td>
<td>Higher PF with lack of double-blinding</td>
<td>0.3</td>
</tr>
<tr>
<td>Dropout</td>
<td>21</td>
<td>0.1 percent</td>
<td>(-6 percent to 6 percent)</td>
<td>Increase per 10 dropouts</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Figure 3. Funnel plot of effect sizes according to precision (twenty-three trials in the meta-analysis)
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. This result should, however, be interpreted with caution. Even a meta-analysis including twenty-three 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 thirteen 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 of gel application. Although plausible, these relationships were dependent on the inclusion of one study with particularly powerful effects. 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 in which 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 in which fluoride gel was professionally applied—with the exception of one study 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. 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. The only factor that 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 percent 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.

The asymmetry in the funnel plot 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 that 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 in the trials about the effects of fluoride gels on a number of other clinically important outcomes, such as caries incidence in the deciduous dentition and acute side effects, and no information on potential adverse effects such as tooth staining or oral allergic reactions. This lack of evidence makes it more difficult for clinicians and policymakers to weigh the benefits of fluoride gels in preventing caries against possible side effects.

It can be concluded that the application of fluoride gels, either by professionals or self-applied, is associated with a clear reduction in caries increment. Although many reports lacked important methodological details, the findings are quite strong. Further randomized comparisons of fluoride gel and placebo alone would be hard to justify. Head-to-head
comparisons of fluoride gels and other caries preventive strategies may provide more useful information. We found no evidence that the effect of gels 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), but these relationships were dependent on the inclusion of one study with particularly powerful effect. The evaluation of possible differences in effect associated to fluoride gel application features should be based on trials that directly address the comparison of such features. Unfortunately, there was a general lack of evidence on side effects. Further work is needed to identify and quantify potential harmful effects of the gels.

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All authors contributed to the development of the protocol and execution of the review. VM wrote the protocol, designed and implemented the search strategies, contacted authors, selected studies, assessed validity, and extracted data. JH duplicated study selection, quality assessment, and data extraction in a sample of studies, and SL and AS were consulted where necessary. VM entered and analyzed the data in consultation with JH and prepared the full review. All authors contributed to its revision, interpretation of results, and approval.

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