Non-fluoride caries preventive agents: full report of a systematic review and evidence-based recommendations


CRD summary
This review concluded that certain non-fluoride agents may provide some benefit as additional therapy for children and adults at high risk of developing caries. Despite some limitations to the review, the authors seemed to make suitable judgments about when to pool studies and when there was sufficient evidence to produce recommendations, so their conclusions are likely to be reliable.

Authors' objectives
To assess whether non-fluoride caries preventive agents reduced the incidence, stopped, or reversed caries, in the general population, and in individuals at high risk of caries.

Searching
PubMed and The Cochrane Library were searched for English-language studies, from 1966 to March 2011; search strategies were reported. References of selected articles were searched.

Study selection
Prospective randomised and non-randomised studies that evaluated non-fluoride agents and reported caries incidence, arrest, or reversal, were eligible for inclusion. Agents that had to be professionally applied or required prescription, and over-the-counter agents likely to be recommended by a dentist, were eligible. Studies that evaluated only topical fluorides, or calcium glycerophosphate or sodium trimetaphosphate, those that reported only increased salivary flow or reduction in Streptococcus mutans, those where the co-interventions differed between study groups, those where sucrose was the control, and those where triclosan included a co-polymer, were excluded. A decision to exclude split-mouth studies, and studies lasting less than one year, was made after initial assessment.

Most included studies were conducted in communities with low levels of fluoride in the water supply. The vast majority assessed children. A significant proportion was conducted in high-risk groups. A wide range of interventions was considered, with considerable variation in regimens across the studies. Most controls were no intervention, placebo, or a co-intervention with treatment that was given on its own.

Two reviewers independently selected studies for the review; disagreements were resolved by discussion with two other members of the review team.

Assessment of study quality
Two reviewers independently assessed study quality for five domains: reporting, external validity, bias, confounding and statistical power. A composite score was produced, for each domain, for each study. The maximum score for reporting was 10; over 9 was good; 7 to 8 was fair; and under 6 was poor. For bias, confounding and power, the maximum was 14; over 12 was good; 10 to 11 was fair; and under 9 was poor. The classification for external validity was not reported. The level of certainty in the recommendations made was estimated using the definitions of the US Preventive Services Task Force (details reported). Disagreements were resolved by team discussion.

Data extraction
Data were extracted on the prevented fraction of caries (the difference in decayed, missing or filled surfaces – or teeth increment scores – between the treatment and control groups). The reviewers made a range of judgements on the priority of different types of data to be extracted, based on a Cochrane review (details reported). In studies that had more than one relevant treatment, data from the treatment groups were combined to calculate a mean treatment effect.

Methods of synthesis
Summary estimates of the prevented fraction of caries, with 95% confidence intervals, were produced using a random-
effects model. Heterogeneity was assessed using $I^2$.

**Results of the review**
Fifty randomised controlled trials (RCTs) and 15 non-randomised studies met the inclusion criteria.

**Sucrose-free polyol chewing gums**: There were nine RCTs, and six non-randomised studies in children. Two studies were considered to be good quality, four were fair, and the others were poor. Chewing gum significantly reduced caries, compared with no gum (prevented fraction -39.30, 95% CI -57.14 to -21.45; nine studies; $I^2=95$%). Significant benefits were identified for xylitol and combination interventions, but not sorbitol.

**Xylitol candy, lozenge, and syrup**: Three RCTs and two non-randomised studies in children were found. Three studies used no candy or tablets as the control; one was good, one fair, and one poor quality. These studies showed a statistically significant benefit of xylitol, lozenge or candy (prevented fraction -79.93, 95% CI -142.96 to -16.91; $I^2=95$%). A fourth study showed no significant difference between xylitol lozenge and conventional care plus fluoride varnish, in a high-risk group. The fifth study reported a statistically significant benefit of xylitol syrup in children under two years of age.

**Chlorhexidine**: None of the meta-analyses of chlorhexidine products showed a significant benefit of chlorhexidine: chlorhexidine varnish (five RCTs in children; two fair quality, one good and two poor); chlorhexidine or thymol varnish (three RCTs and two non-randomised studies in children; one good and four poor quality); 0.12% chlorhexidine mouth rinse (four RCTs in children and adults; one good and three fair quality).

The panel decided that there was insufficient evidence to assess the benefits of xylitol dentifrice (two RCTs in children; one fair and one poor quality); 10% povidone-iodine (four RCTs in children; two fair and two good quality); chlorhexidine gels (five studies in adults and children; three fair quality and two poor); calcium or phosphate agents or both, with or without casein derivatives (eight RCTs and one non-randomised study; two good, five fair, and two poor quality). No studies that evaluated triclosan or sialogogues met the inclusion criteria.

The results from studies where agents were used in mothers to prevent caries in children were reported.

**Authors’ conclusions**
Some non-fluoride agents may provide some benefit as additional therapy for children and adults at a high risk of developing caries. Sucrose-free chewing gum and xylitol lozenges were recommended.

**CRD commentary**
The review addressed a clear research question, supported by reproducible inclusion criteria. Relevant sources were searched, but only two of them, and only studies published in English were selected; non-English or unpublished studies could have been missed. Appropriate criteria were used to assess study quality, and the results were used to weight the reliability of the evidence.

The decision to pool certain studies seems to have been appropriate, but the results of studies with more than one treatment group were combined to produce an average treatment effect that was compared with the control. As it was demonstrated that there was a differential effect between some treatments, it is unclear how generalisable the pooled results will be for the individual treatments. Some recommendations were extrapolated to adults, from data in children, where data for adults were not available; it is unclear whether the effects would be the same in adults and children, and therefore whether this was appropriate.

Despite some limitations to the review, the authors seemed to make suitable judgments on to when to pool studies and where there was sufficient evidence to produce recommendations, so their conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice**: The authors stated that a clinician must consider a patient’s risk of disease and factors, such as readiness for change, oral health literacy and compliance, when developing their caries prevention plan. This plan should include patient education, dietary advice and periodic clinical examinations. On sufficient evidence, they recommended: gum chewing should not be used for children younger than four years; sucrose-free chewing gum after meals for healthy children older than five years, at a high risk of caries; and xylitol lozenges or hard candy after meals for children older than five years, with five to eight grams per day, in two or three doses, to maximise the clinical benefits. They stated
that professional and home-use fluoride products, including fluoridated toothpastes and dental sealants, were the primary interventions for preventing caries.

**Research:** The authors recommended well-designed independent, appropriately powered, placebo-controlled, randomised trials, reported according to the CONSORT statement, to evaluate: the best mode of delivery, dosage, frequency, duration of treatment, and adverse systemic effects of xylitol; non-fluoride agents in combination with fluorides in the elderly and people with special needs; iodine, triclosan or other antimicrobial agents in children and adults; agents to reduce the incidence or promote the reversal of root surface lesions; pharmacological agents in caries prevention in high-risk populations; and whether agents that prevent progression of, or reverse, white spots could be effective against caries. They recommended the development of standardised definitions and risk groups for caries, and highlighted the need to identify reliable methods and technologies to assess the transition of early manifestations of disease, to test the power of preventive agents in stopping or reversing carious lesions. They recommended a systematic review of the relationship between *Streptococcus mutans* and caries outcomes.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.