

Non-fluoride caries preventive agents

Full report of a systematic review and evidence-based recommendations

A Report of the Council on Scientific Affairs

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Introduction

Dental caries is the most common dental disease. Data from the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2004,¹ revealed that 28 percent of children ranging from 2 to 5 years of age had one or more primary teeth affected by dental caries and 51 percent of children had one or more primary teeth affected by age 6 to 11. In the permanent dentition, 10 percent of children aged 6 to 8 had dental caries and 51 percent of children were affected by age 12 to 15.¹ Dental caries affected 96 percent of adults 50 to 64 years of age. Root caries affected about 8 percent of adults aged 20 to 34 years and 21 percent of adults aged 50 to 64 years. Because of its high prevalence, dental caries is the focus of many interventions targeted toward prevention and control. The use of fluoridated toothpastes,² other topically applied fluorides,³ fluoridated municipal water⁴ and pit and fissure sealants⁵⁻⁷ along with dietary improvement remain mainstays of caries management. These modalities, which are based on high quality evidence, are the first choice for prevention and control of dental caries.

Nonfluoride agents may serve as **adjunctive** therapeutics for preventing, arresting or even reversing dental caries. A recent survey regarding the use of caries preventive agents of 467 practices within, the Dental Practice-Based Research Network (DPBRN)⁸, found some use of adjuncts: 7.7 percent of children and 17.3 percent of adults were prescribed chlorhexidine rinse and 35.3 percent of children and 32.2 percent of adults were recommended xylitol gum.

The objective of this report is to present evidence-based clinical recommendations on non-fluoride caries preventive agents on the market in the U.S. The authors evaluated studies of sucrose-free polyol chewing gums, xylitol dentifrices, chlorhexidine, chlorhexidine in combination with thymol, calcium-containing agents, phosphate-containing agents, casein derivatives, sialogogues, iodine and triclosan. Vaccines, genetically modified *Streptococcus mutans*, probiotics, and lasers, ozone and other mechanical devices were not within the scope of the review. This report is intended to assist practitioners with decision-making about the use of non-fluoride caries preventive agents to arrest, prevent or reverse caries. *The recommendations in this document do not purport to define a standard of care and rather should be integrated with a practitioner's professional judgment and a patient's needs and preferences.*

Use of any adjunctive strategies does not eliminate or change the requirements for proven modalities for caries prevention including topical fluorides and sealants. The panelists did not address questions comparing fluoride with non-fluoride therapies because they strongly recommend using proven caries prevention modalities including dietary improvement, fluorides and sealants before attempting to use other strategies, including those that are the topic of this report.

Methods

The authors are a multidisciplinary panel of subject matter experts convened by the American Dental Association (ADA) Council on Scientific Affairs (CSA).

Clinical Questions: The authors addressed two clinical questions:

1. In the general population, does the use of a nonfluoride caries preventive agent reduce incidence, arrest or reverse caries?
2. In individuals at higher caries risk, does the use of a nonfluoride caries preventive agent reduce incidence, arrest or reverse caries? (Trials that specifically enrolled subjects with incipient or cavitated lesions, prior caries experience or those with high salivary or plaque *Streptococcus Mutans* scores levels categorized as providing evidence for “high-risk” patients).

Literature Search: One author (KA) used the following strategy to search MEDLINE through PubMed. She (KA) searched the Cochrane Library with a similar search strategy. She also searched references of selected articles in order to include studies that might have been missed through the electronic sources.

Dental Caries AND (prevention OR arrest OR reversal OR reduction OR incidence OR regression OR progression OR DMF Index[Mesh] OR ICDAS OR caries increment OR prevented fraction) AND ("casein phosphopeptide-amorphous calcium phosphate nanocomplex"[Substance Name] OR "amorphous calcium phosphate"[Substance Name] OR casein phosphopeptides OR calcium OR phosphate OR "Tooth Remineralization" OR "Tooth Demineralization" OR MI paste OR chewing gum OR "Sugar Alcohols"[Mesh] OR “artificial sweetener” OR chlorhexidine OR Thymol OR iodine OR triclosan OR cetylpyridinium chloride OR pilocarpine OR Salagen OR cevimeline) Limits: Humans

The search of MEDLINE and the Cochrane Library from 1966 through April 9, 2010 identified 2697 articles. One author (KA) identified six additional publications by manual search. Two authors (KA and JF) independently screened the articles using the inclusion and exclusion criteria presented in Table 1. Two members of the expert panel (JS and DZ) resolved disagreements between the reviewers.

While most of the inclusion and exclusion criteria were set *a priori*, the decision to exclude split-mouth studies and short-term (less than one years’ duration) studies that reported only on white-spot-lesions was made after screening had begun. Split-mouth studies were excluded because of concerns regarding site isolation and longitudinal crossover effects. Short-

term studies that only reported on white-spot lesions were excluded because short-term subtle outcome differences between test and control arms may provide misleading results when compared to long-term more clinically relevant outcomes.⁹ We did not contact the authors of the included studies for baseline caries data when it was not reported in the published paper. Such studies were excluded because the panel could not characterize the baseline caries status of the population. (For more information on Excluded Studies, see Appendix 2 of the supplemental material.)

Table 1: Inclusion and exclusion criteria and screening results

	Begin total	Identified for further consideration	Excluded
<p>Title/abstract review Inclusion criteria:</p> <ul style="list-style-type: none"> • Human clinical trials • Nonfluoride agents requiring professional application or prescription, or over-the-counter agents likely to be used upon the recommendation of a dentist • Studies that report caries incidence, arrest or reversal as outcomes • Prospective clinical studies including randomized and nonrandomized studies* <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • studies irrelevant to the topic • <i>in vitro</i> and animal studies • <i>in situ</i> studies using material surrogates (e.g. studies with removable appliances hosting enamel slabs) • studies that evaluated ONLY topical fluorides • studies where the only reported outcome was increased salivary flow or reduction in <i>Streptococcus mutans</i> • foreign language articles • split-mouth designs • studies in which the experimental arm had other co-interventions (fluorides/OH instruction etc.) in which the control arm did not. (e.g. Exp: CHX + F; Control: CHX) 	2697	149	(noted 45 on exclusion list)
<p>Full text review Exclusion criteria were:</p> <ul style="list-style-type: none"> • Baseline caries data not reported • Split-mouth studies • Studies without concurrent control group • Short-term (less than 1 year) studies that reported only on white spot lesions • Studies on Calcium Glycerophosphate/ sodium tri metaphosphate • Studies with sucrose as the control • Studies on triclosan that also included a copolymer (confounder) 	149 + 6 (from handsearch) = 155	68 + (Identified 3 more upon updating the search)	87

* Trials that used the word “random” to describe the allocation of subjects/groups were considered randomized controlled trials (RCT’s).

Search Update: Following the initial search on April 9, the search was periodically updated with the final update conducted on March 8, 2011. This update identified three¹⁰⁻¹² additional articles for inclusion.

Critical appraisal of included studies: Based on a published review of critical appraisal instruments for randomized and non-randomized interventions,¹³ one author (KA) identified an instrument¹⁴ suitable to appraise randomized and non-randomized trials for this systematic review. The questions in the instrument addressed five separate domains including reporting, external validity, bias, confounding and statistical power. All panel members participated in an orientation through a conference call to standardize the application of the critical appraisal instrument. Along with a copy of the instrument, each panel member received five to six studies to review. Independent from the panel member, one author (KA) duplicated the review and critical appraisal across all included studies. This ensured appraisal by two independent reviewers and standardized application of the instrument by all reviewers. **Following the critical appraisal, a composite score was developed for each study based on a standardized rating scale as follows.**

Reporting (range 1 - 10) >9 = Good; 8 - 7 = Fair; <6 = Poor; Internal validity including bias, confounding and power (range 1 - 14) >12 = Good; 11 -10 = Fair; <9 = Poor.

During the panel meeting, all panel members reviewed and extensively discussed results from each study.

Data synthesis and meta-analysis:

Choice of outcome measures. Caries increment was the outcome measure assessed for each study. Caries increment is the number of new decayed, missing or filled surfaces or teeth (DMF) experienced by each treatment group included in a study. The panel adapted a set of rules published in a recent Cochrane review of caries trials¹⁵ to select outcome data from each study for subsequent analysis. Specifically, the panel chose data on tooth surfaces level over data on tooth level; data for "all surface types combined" over data for "specific types" only; data for "all erupted and erupting teeth combined" over data for "erupted" only, and this over data for "erupting" only"; data from "clinical and radiological examinations combined" over data from "clinical" only, and this over "radiological" only; DMFS scores over DFS or DS; data for "dentinal/cavitated" caries lesions over data for "all stages" over data for "enamel/non-cavitated" lesions; net caries increment data over crude (observed) increment data; and follow up nearest to three years (often the one at the end of the treatment period) over all other lengths of follow up. Further, we chose DMFS data over defs data unless otherwise stated.

Combining relevant treatment arms. For studies that evaluated more than one relevant treatment arm, we combined the raw results (the numbers, mean DMF increments and standard deviations) from all parallel arms in order to obtain an estimate of treatment effect.¹⁵⁻¹⁷

Imputing variances. When possible, we imputed missing standard deviations that were not reported using linear regression of log (standard deviations) on log (mean caries) increments.¹⁵

Summary Estimate. When possible, meta-analysis was used to synthesize the results when multiple papers were included in the review. Meta-analyses use statistical methods to calculate a weighted average of the size of treatment effect when studies with the same outcome measure are combined. Similar to the summary estimate used in the Cochrane review of caries trials,¹⁵ the panel selected “prevented fraction” (PF) as the measure of treatment effect. PF is the difference in DMF increment scores between the groups that received the experimental treatment and those who received a comparison or no active treatment divided by the average number of DMF scores in people who received a comparison or no active treatment. Variances were estimated using a previously published formula.¹⁶

The summary estimate used for the meta-analysis was “prevented fraction” that gives the reader an understanding of the relative preventive effect found between treatments. **Since the “prevented fraction” is not based on standard epidemiological measures of risk and rate, it does not provide an estimate of the magnitude of treatment effect. Differences in outcome measures reported among studies precluded the panel from meaningfully combining the studies to estimate the magnitude of caries preventive effect.**

Generating forest-plots. Random-effects meta-analyses were conducted throughout to generate forest plots using RevMan 5 software.

Heterogeneity. The I^2 statistic generated by RevMan quantified the statistical heterogeneity. The panel did not consider any formal methods to further investigate heterogeneity. The panel used a random-effects model to overcome some of the limitations of heterogeneous data and graded the level of certainty based on these considerations.

Process for developing clinical recommendations: The panel developed evidence statements based on the body of evidence and graded the level of certainty of the evidence as high, moderate or low on the basis of a standardized grading system (Table 2). Then, the panel developed clinical recommendations. When the panel found evidence supporting efficacy, the panel members assessed adverse events reported in the trials and discussed any potential adverse events that could be associated with the intervention based on their knowledge of the existing literature. (Note

that the panel did not conduct a review of the data specifically for adverse effects). Based on the level of certainty and the magnitude of net benefit (Table 3) the panel graded the strength of each (Table 4). When the panel was unable to reach a consensus in interpreting evidence into clinically relevant recommendations or when it made recommendations based largely on expert consensus, it used a simple majority vote to make final determinations.

Table 2: Definitions for levels of certainty.*

Level of Certainty	Description
High	<p>Strongly established by the best available evidence.</p> <p>The body of evidence usually includes consistent results from well-designed, well-conducted studies in representative populations. This conclusion is unlikely to be strongly affected by the results of future studies.</p>
Moderate	<p>Based on preliminary determination from the current best available evidence.</p> <p>But confidence in the estimate is constrained by one or more factors such as:</p> <ul style="list-style-type: none"> the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited applicability due to the populations of interest; or lack of coherence in the chain of evidence. <p>As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.</p>
Low	<p>Available evidence is <i>insufficient</i> to support the statement or the statement is based on extrapolation from the best available evidence</p> <p>Evidence is insufficient or reliability of estimated effects is limited by factors such as:</p> <ul style="list-style-type: none"> the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies gaps in the chain of evidence; findings not applicable to the populations of interest; or a lack of information on important health outcomes. <p>More information may allow a reliable estimation of effects on health outcomes.</p>

*Adapted from the United States Preventive Services Task Force system

Table 3: Balancing Level of Certainty and Magnitude of Effect

Certainty of Effect	Magnitude of net benefit			
	Substantial	Moderate	Small	Zero/negative
High	Strong	In favor	Weak	Against
Moderate	In favor	In favor	Weak	Against
Low	Expert Opinion			

Table 4: Definitions for the strength of recommendation:*

Grade	Strength of Recommendation
Strong	Evidence strongly supports providing this intervention
In favor	Evidence favors providing this intervention
Weak	Evidence suggests implementing this intervention after alternatives have been considered.
Against	Evidence suggests not implementing this intervention or discontinuing ineffective procedures
Expert Opinion	Expert Opinion guides this recommendation

*Adapted from the USPSTF system

External Review and Approval: The panel sought comments to this report from other subject matter experts, methodologists, epidemiologists and end-users before finalizing the recommendations. The CSA approved the final report for publication.

Role of the Funding Source: The CSA commissioned this work and the Centers for Disease Control and Prevention partly funded this project.

Evidence Summary

Author	Age	Country	Intervention	Control	Other exposure for both groups	Follow-up duration	Outcome measure	Recruited high-risk patients?	Reporting	Internal Validity	Study Design*
Sucrose-free polyol gums											
Finn SB, 1978 ¹⁸	5 to 16	US	3 gm stick with 50 - 70% sorbitol and mannitol thrice daily	No gum	Non-F dentifrice	2.5 yr	DMFS (cavitated)	No	Poor	Fair	RCT
Richardson AS, 1972 ¹⁹	8 to 10	Canada	3 sticks sugar-less gum per day. Chew for 20 mins	No gum	Low water F and children given F free toothpaste	26 months	DMFS (cavitated)	No	Poor	Poor	RCT
Szöke J, 2001 ²⁰	8 to 13	Hungary	1 stick thrice daily with 65% sorbitol and mannitol	No gum	Non-fluoridated water; Used F toothpastes	2 yr	DMFS (all stages and cavitated)	No	Fair	Poor	GRCT
Beiswanger BB, 1998 ²¹	11 to 12	Puerto Rico	40 - 60 % sorbitol + 4-15% mannitol thrice daily for 20 min	No gum	Low water F, continue routine oral hygiene and dental care	3 yr	DMFS (cavitated)	No (but post-hoc analysis)	Fair	Poor	GRCT
Peng B, 2004 ²²	6 to 7	China	0.8g gum containing 55.5% sorbitol + 4.3% xylitol + 2.3% carbamide four time daily	No gum	Low fluoride area	2 yr	DMFS (cavitated)	No	Poor	Poor	GCCT
Glass RL 1983 ²³	7 to 11	USA	Sorbitol gum, 2 sticks per day	No gum	Non-fluoridated water	2 yr	DFS (cavitated)	No	Fair	Poor	RCT
Machiulskiene 2001 ²⁴	9 to 14	Lithuania	1. 589mg sorbitol gum; 2. 589mg xylitol gum; chew 5 pieces daily for 10 min	No gum	Low water F	3 yr	DMFS (all stages and cavitated)	No	Fair	Good	GRCT
Mäkinen KK, 1995 ²⁵	Ave 10.2	Belize	1. 65% sorbitol (9g/day) 2. 65% xylitol 3 times (4.3g/day) 3. 65%xylitol gum 5 times daily (8.5g/day)	No gum	Not fluoridated; Used F toothpastes, regular hygiene	40 month	DMFS (cavitated)	No	Fair	Fair	GCCT
Mäkinen KK, 1996 ²⁶	6	Belize	1. 65% sorbitol gum (10.67g/day) 2. 61% sorbitol gum (10.42 g/day) 3. 60.5%xylitol gum (10.42g/day) 4. 65% xylitol gum (10.67 g/day) - Chew 10 pieces per day	No gum	Not fluoridated	2 yr	Lesion onset per subject (primary teeth) (cavitated)	No	Fair	Fair	GCCT
Kandelman D, 1990 ²⁷	8 to 9	Canada	1. 15% w/w xylitol (0.8 g/day) + 50% w/w sorbitol (2.4g/day) 2. 65% xylitol (3.3g/day)	No gum	0.2% naF mouthrinse weekly, dental visits	2 yr	DMFS (all stages)	No	Poor	Poor	GCCT

Petersen PE, 1999 ²⁸	6 to 9	Madagascar	0.8g gum containing 55.5% sorbitol/4.5% xylitol and 2.3% carbamide	No gum	Low fluoride water supply; Used F toothpastes	3 yr	DMFS (cavitated)	No	Poor	Poor	GCCT
Alanen P, 2000 ²⁹	11	Finland	65% w/w xylitol - Chew for 10 mins six times daily – 5 g/ day	Sealants	F toothpastes and varnishes	5 yr (3 yr use)	DMFS (cavitated)	No	Fair	Good	GRCT
Kovari H, 2003 ³⁰	3 to 6	Finland	65% w/w xylitol gum - Chew for 5 - 10 min thrice daily 2.5 g/day	Fluoride toothpaste	Not Stated	Varied tx duration from 1 - 3. Examined at age 7 and 9	dmfs (cavitated)	No	Fair	Poor	GRCT
Isokangas P, 1988 ³¹	11 to 12	Finland	64%xylitol gum with 3.5g xylitol - Chew for 5 min thrice daily – 10g/day	No gum	Supplements, F toothpaste, biweekly F rinse, Low F water	2 yr	DMFS (all stages and cavitated)	No	Poor	Poor	GCCT
Alanen P/Isokangas, 2000 ³²	10	Estonia	65% w/w xylitol gum; Chew for 10 min thrice daily; 5g/day	No gum	Preventive measures	3 yr	DMFS (cavitated)	No	Poor	Fair	GRCT
Xylitol candy/lozenge/syrup											
Alanen P/Isokangas, 2000 ³²	10	Estonia	1. 49% Xylitol maltitol 2. 49% xylitol polydextrose; Chew for 10 min thrice daily; 5 g/day	No candy	Preventive measures	3 yr	DMFS (cavitated)	No	Poor	Fair	GRCT
Honkala E, 2006 ³³	10 to 27	Kuwait	49% Xylitol Candy; one candy three times a day for 5 – 10 mins (dose unclear)	No candy	Not Stated	1.5 yr	DMFS (cavitated)	No	Fair	Poor	CCT
Stecksén-Blicks 2008 ³⁴	10 to 12	Sweden	422 mg xylitol, 2 candies thrice daily; 544 mg/day	Conventional care including preventive varnish	Not Stated	2 yr	DMFS (approximal only) (all stages)	Yes	Fair	Poor	CCT
Oscarsen 2000 ³⁵	2 years	Sweden	0.48g xylitol tablet, one tablet for 6 months and then 2 tablets	No tablets	Fluoridated dentifrice and regular dental care	2 yr (6 months after stopping intervention)	dmfs (cavitated)	No	Fair	Good	RCT
Milgrom 2009 ³⁶	9 -15 months	Marshall islands	Xylitol Syrup - 8 g/day	Xylitol Syrup- 2.67g/day	Low fluoride area, no topical fluoride exposure	10 months	dmfs (cavitated)	No	Good	Good	RCT
Xylitol + fluoride dentifrice compared to fluoride dentifrice without xylitol											
Sintes 2002 ³⁷	7 to 12	Costa Rica	10% xylitol/DICAL/0.836%sodium monofluorophosphate	DICAL/0.836%sodium monofluorophosphate	Water F less than 0.1ppm. Fluoridated salt	2.5 yr	DFS (cavitated)	Yes	Good	Poor	RCT
Sintes 1995 ³⁸	8 to 10	Costa Rica	10%xylitol/0.243%NaF	0.243%NaF	Water F less than 0.1ppm. Fluoridated salt	3 yr	DFS (cavitated)	Yes	Fair	Fair	RCT

Calcium and/or phosphate agents with or without casein derivatives											
Acevedo 2005 ³⁹	10 to 11	Venezuela	Arginine bicarbonate/Calcium carbonate toothpaste (Cavistat) - 3 times daily brushing for 1 minute	Fluoride toothpaste	Salt fluoridation (Low water F community)	2 yr	DMFS (cavitated)	Yes	Poor	Poor	GCCT
Acevedo 2008 ⁴⁰	10.5 to 11	Venezuela	Sugar-less confection with arginine bicarbonate/Calcium carbonate (Cavistat) - 2 mints twice daily	Sugar-less mints	F toothpaste and Salt fluoridation	1 yr	DMFS, defs (cavitated)	Yes	Fair	Fair	RCT
Papas 2008 ⁴¹	32 to 83	US	CaP+ NaF (Enamelon) dentifrice - Twice daily for 60 seconds	1100 ppm NaF dentifrice	F varnish before treatment and F rinse for both groups during treatment and pilocarpine 5 mg q.i.d	1 yr	DMFS (all stages)	Yes	Good	Good	RCT
Silva 2001 ⁴²	6 to 10	Maceio, Alagoas, Brazil	DiCalciumphosphate dihydrate + NaF dentifrice - Brush twice daily	0.243% NaF dentifrice	Low water F,	2 yr	DMFS (cavitated)	Yes	Fair	Fair	RCT
Kolmakow 1991 ⁴³	8	Finland	2% remineralizing agent + 0.2% NaF - Biweekly mouthrinsing	Placebo mouthrinse + 0.2% NaF mouthrinse	F toothpaste	2 yr	DFS, EFD, SS (all stages and cavitated)	No	Poor	Fair	RCT
Morgan2008 ⁴⁴	11.5 - 13.5	Australia	162 mg/day (54 mg CPP-ACP in polyol gum chewed 3 times daily for 10 min)	Polyol gum	Fluoridated water + 1000 ppm NaF dentifrice for both groups	2 yr	Radiographic approximal only (all stages)	No	Fair	Fair	RCT
Hay 2002 ⁴⁵	> 25	New Zealand	CD-CP mouthrinse - Rinse thrice daily	0.05% NaF mouthrinse	Not reported	1 yr	DFS (cavitated)	Yes	Fair	Fair	RCT
Rao 2009 ⁴⁶	12 to 15	India	toothpaste with 2% w/w CPP - Brush twice daily for 5 min each for 12 months	1. toothpaste with 0.76 w/w SMFP 2. placebo without either active	Not reported	2 yr (1 yr after stopping interventions)	DS (cavitated)	Yes	Good	Good	RCT
Andersson 2007 ⁴⁷	12 - 16	Sweden	CPP-ACP cream for 3 months and F dentifrice for 3 months	0.05% NaF rinse and F dentifrice for 6 months	Low water F	1 yr	Post ortho WSL – laser fluorescence	Yes	Poor	Poor	RCT
Iodine											
Xu 2009 ⁴⁸	6 to 9	China	10% Iodine/fluoride foam - 4 min tray application. Once a week for 3 weeks	Fluoride foam	Low water F	1 yr	QLF	Yes	Good	Good	RCT
Zhan 2006 ⁴⁹	2 to 6	US	10% povidone iodine - After restorative treatment - single application	Saline	APF gel	1 yr	ds (cavitated)	Yes	Fair	Fair	RCT

Lopez 2002 ⁵⁰	12 - 19 months	Puerto Rico	10% povidone iodine - Applied Every 2 months	Placebo	Not Stated	1 yr	Treatment failure – WSL	Yes	Fair	Fair	RCT
Simratvir 2010 ¹²	Av. 4.2	India	10% povidone iodine - Applied Every 3 months	DI water	No specific fluoride treatment provided.	1 yr	Number of children with relapse (cavitated)	Yes	Good	Good	RCT
Chlorhexidine products - Chlorhexidine Varnish											
Du 2006 ⁵¹	4 to 5	China	40% w/w CHX varnish - Start and every six months for 2 years	Placebo varnish	Low water F	2 years	dmfs (cavitated)	No	Poor	Fair	GRCT
Forgie 2000. ⁵²	11 to 13	Scotland	10% CHX - 4 - 6 varnish applications in the first year, 1 - 3 applications in subsequent years.	Placebo varnish	Comprehensive caries care	3 years	DMFS (all stages and cavitated)	Yes	Fair	Good	RCT
Fennis-le 1998 ⁵³	5 to 12	Netherlands	40% w/w CHX Varnish - Applied every 6 months	Placebo varnish	Topical fluoride	3 years	DMFS/defs (all stages and cavitated)	No (reported on high-risk)	Poor	Poor	RCT
de Soet 2002, ⁵⁴	13 to 14	Surinam	CHX varnish 40% w/w - Once every 6 months	Placebo varnish	F toothpastes not used	30 months	DMFS (all stages)	No (reported on high-risk)	Good	Poor	RCT
Jenatschke 2001 ⁵⁵	11 to 18	Germany	40% CHX varnish - Every 8 weeks from banding to debanding	Placebo varnish	Naf rinse and F gel	median 21 months (8 weeks after debanding application)	Ortho - DMFS (cavitated)	Yes	Poor	Poor	RCT
Schaeken 1991 ⁵⁶	Ave 44.4 yrs	Netherlands	40% CHX - Applied every 3 months	1. F varnish 2. no varnish	Not Stated	1 year	DMFS (root caries)	Yes	Poor	Fair	RCT
Chlorhexidine products - Chlorhexidine Gels											
Lindquist 2006 ⁵⁷	12 to 14 years	Sweden	1% CHX gel - 1 ml of 1% Chx 5 min on consecutive days every three months	Duraphat	Bi-monthly F rinse; water F <0.1 mg/l	2 years	DFS (all stages)	Yes	Poor	Poor	RCT
Petti 2006 ⁵⁸	3 yrs	Rome	1% CHX gel - Applied for 3 consecutive days every 3 months	No gel	F toothpaste	18 months	dft (cavitated)	Yes	Poor	Poor	CCT
Lundström 1987 ⁵⁹	11 to 15	Sweden	1% CHX gel – Throughout ortho treatment	No gel	F varnish, F toothpaste and mouthrinse	1.8 years Ave	During ortho - DS - WSL	Yes	Poor	Poor	RCT
Gisselsson 1994 ⁶⁰	4	Sweden	Flossing with 1% CHX gel - 4 times per year	Flossing with Placebo gel	Low water F, use of F toothpastes and	3 years	Defs (WSL and cavitated)	No	Poor	Fair	RCT

					F tablets						
Gisselsson 1998 ⁶¹	12 to 15	Sweden	Flossing with 1% CHX - Gel application every third month	Flossing with Placebo gel	Low fluoride water, fluoride rinsing and fluoride toothpaste	3 years	DFS (WSL and cavitated)	No (reported on high-risk)	Fair	Fair	CCT
Emilson 1976 ⁶²	21 to 28	Sweden	Brushing with 0.5% CHX gel	Brushing with Placebo gel	Regular hygiene	1 year	DS (cavitated)	No	Fair	Fair	RCT
Keltjens 1990, ⁶³	34 - 75	Netherlands	Initial 5% chlorhexidine gel and after daily 1% Chlorhexidine gel + 0.1% NaF	0.1% NaF gel	Regular treatment	18 months	RCI	No	Poor	Poor	RCT
Chlorhexidine products - Mouthrinses											
Wyatt 2004 ⁶⁴	54 to 101	UK	0.12% CHX rinse - Daily use	1. Placebo rinse 2. Fluoride rinse	Some exposed to F toothpaste	2 years	DMFS, RCI (cavitated)	No	Good	Good	RCT
Wyatt 2007 ⁶⁵	60 to 75 years	U.S and Canada	0.12% Chlorhexidine rinse - Daily rinsing for 1 month and then weekly for 5 months. Cycle repeated every 6 months	Placebo rinse	Not Stated	5 years	Caries Rate (coronal and root) (cavitated)	No	Fair	Fair	RCT
Spets-Happonen 1991 ⁶⁶	11	Finland	0.05% CHX rinse - Rinse for 5 days every third week	No rinse	F varnishes, brushing	2 yr 9 months	DMFS (cavitated)	Yes	Fair	Fair	RCT
Luoma 1978 ⁶⁷	11 to 15	Serbia	CHX + F rinse - Use rinse for 2 min and brush at home twice a day with toothpaste having the same composition as rinse	F rinse. Use rinse for 2 min and brush at home twice a day with toothpaste having the same composition as rinse	F varnishes	2 years	DMFS (cavitated)	No	Poor	Fair	RCT
Chlorhexidine products– 1:1 mixture of Chlorhexidine/Thymol											
Petersson 2000 ⁶⁸	13 to 14	Sweden	Cervitec applied every three months	0.1% NaF varnish	Low water F, use of F toothpastes	3 years	DMFS (approximal) (all stages)	Yes	Fair	Poor	RCT
Petersson 1998 ⁶⁹	12	Sweden	1:1 mixture of 0.1% F varnish + Cervitec - Apply every 6 months	Fluoride varnish	Low water F	3 years	DFS (approximal) (all stages)	Yes	Poor	Poor	CCT
Splieth 2000 ⁷⁰	8 to 10	Germany	Cervitec + F gel - Once every three months	Fluoride gel	Not Stated	1 year	DMFS (all stages)	Yes	Fair	Good	RCT
Øgaard 2001, ⁷¹	12 to 15	Sweden	Cervitec + F varnish - First CHX or placebo varnish every 3 weeks. Then F varnish at	Placebo + Fluoride varnish	Fluoride toothpaste but no supplements	72 weeks	During ortho DS - WSL	No	Fair	Poor	RCT

			bonding and every 12 weeks thereafter									
Plotzitza 2005 ⁷²	1 to 2	Germany	Cervitec - 3 monthly applications for an year	No varnish	F salt, F toothpaste and supplements	1 year	Dmfs (all stages)	Yes	Good	Poor	CCT	
Baca 2002, 2004, ^{73, 74}	6 to 7	Spain	Cervitec - Varnish applied every 3 months for 2 years	No varnish	Low fluoride in water. No other preventive programs	2 years	DFS and dmfs (cavitated)	No (post-hoc high-risk for dmfs)	Fair	Poor	GRCT	
Twetman , 1999 ⁷⁵	8 to 10	Sweden	Cervitec - 3 times within a period of 2 weeks	No varnish but regular preventive treatment	Low water F	12 months	Progression score – approximal (all stages)	Yes	Poor	Poor	CCT	
Baca 2009 ⁷⁶	65 and older	Spain	Cervitec - At 1, 3, 6,9, 12 months	Placebo	Low water fluoride	1 year	RCI	No	Good	Good	RCT	
Brailsford 2002 ⁷⁷	77 - 87	London	Cervitec and fluoride - Applied at 1, 6, 13, 26 and 39 weeks	Placebo and fluoride	F toothpaste	52 weeks	Lesion characteristics	Yes	Poor	Fair	RCT	
Tan 2010 ¹⁰	78.8 +/- 6.2	Hong Kong	Cervitec and OHI every 3 months	OHI	Not Stated	3 years	RCI	No	Good	Good	RCT	
Caries prevention via administration of a nonfluoride agent to mother												
Isokangas P, 2000 ⁷⁸	0 - 5	Finland	1. 65% w/w xylitol gum (6 - 7 g per day) - Chew gum 4 times per day 3 months post p until 24 months post partum; 2. 40% CHX vanish at 6, 12, 18 months post partum	Fluoride varnish	Routine care	5 years	dmf	NA	Fair	Poor	RCT	
Köhler B, 1994 ⁷⁹	7	Sweden	1% Chlorhexidine gel + preventive program upto 3 years post partum	preventive program	Not Stated	7 years	defs	NA	Poor	Poor	CCT	
Dasanayake	4	USA	10 % CHX - Four weekly	Placebo	Not Stated	4 years	dfs	NA	Good	Fair	RCT	

AP 2002 ⁸⁰			applications at 6 months after delivery followed by single application every 6 months								
Bergel 2010 ¹¹	12	Argentina	2 g Calcium supplements per day	Placebo	Not stated	12 years	dmft/DMFT	NA	Fair	Fair	RCT

*RCT = randomized controlled trial; GRCT = group randomized controlled trial; CCT = trial without randomization; GCCT = allocation by groups trial without randomization/cohort studies

Review and recommendations

The panel included 71 published articles whose authors described 50 randomized controlled trials (RCTs) and 15 non-randomized studies to assess the efficacy of various nonfluoride caries preventive agents. Only six of these studies were conducted in the United States. Although most studies were conducted in communities with low levels of fluoride in the water supply, participants often used fluoridated toothpaste, received regular dental care that included in-office fluoride therapies or both.

Results of the critical appraisal and meta-analysis are presented below by agent.

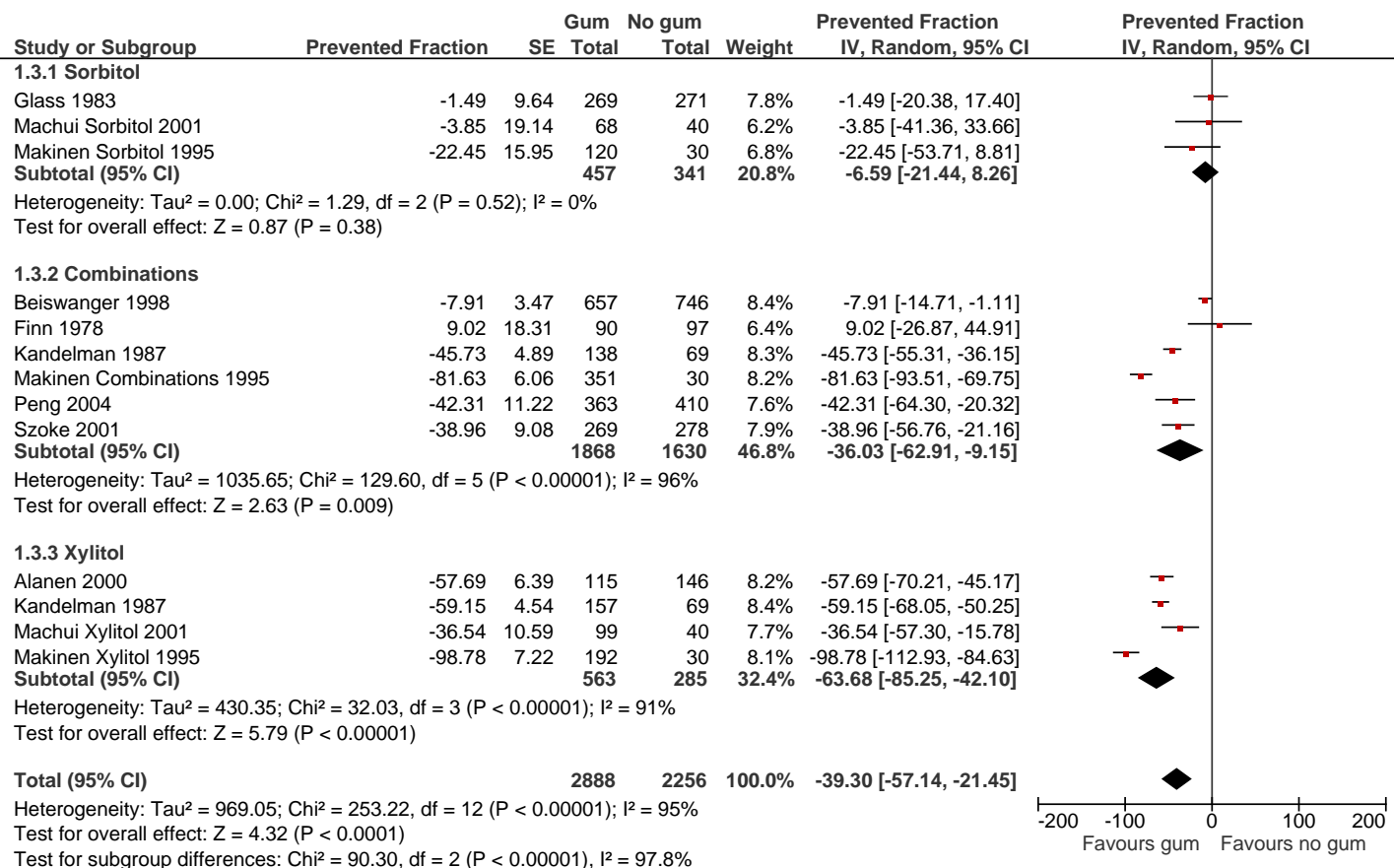
Sucrose-free polyol chewing gums versus no gum

The panel reviewed nine randomized trials^{18-21, 23, 24, 29, 30, 32} and six non-randomized clinical studies^{22, 25-28, 31} to assess the efficacy of sucrose-free polyol chewing gums. The studies compared subjects who chewed sucrose-free polyol gum (e.g. sorbitol only, xylitol only or polyol combinations) to subjects who were not provided any gum. All trials were conducted in school-age children between 5 – 13 years of age. In most trials and nonrandomized studies, gum chewing was conducted under supervised conditions. Frequency of gum chewing in the studies was between two and six times per day with duration of chewing ranging from 10 – 20 minutes. None of the 15 studies specifically enrolled children based on their individual caries-risk. One study²¹ performed post-hoc analysis on subjects to assess the impact of the intervention on children judged at high risk for caries. Although the panel believes that many of these studies were conducted in locations where the caries prevalence may be higher than the U.S., it is not possible to infer the caries risk status of individuals within these studies. Therefore, this body of evidence is derived from general populations across the world.

Of the 15 studies, the panel judged two studies^{24, 29} to be of good quality and four studies^{18, 25, 26, 32} to be of fair quality and the remaining studies were judged to be of poor quality.

The panel combined data from nine studies through a meta-analysis. Of the 15 studies, the panel excluded 6 from meta-analysis because of incomplete reporting of data,^{19, 28, 31} comparisons to sealants²⁹, toothpastes³⁰ or a non-comparable outcome measure²⁶. The panel also conducted additional analyses of the sub-group to determine if outcomes varied between different polyol sweeteners. One study²⁵ had more than one relevant intervention arm. To obtain a treatment effect for that study, we combined the raw results (the numbers, mean caries increments and standard deviations) from all parallel intervention arms.¹⁵

Sucrose-free polyol gum vs. no gum



Szoke: Used Radike values. Values adjusted for baseline caries

Beiswanger: ITT analysis not used. Covariance adjusted estimates used. Pooled RMSE values used for both groups.

Machiulskiene: Used the cavitated stages for three-year increments. Used adjusted mean values. Used CI for the unadjusted data because only that data were provided. Converted CI to SD using adjusted means.

Note that the studies classified under the “combinations” subgroup had varying concentrations and polyol combinations. [E.g. while the Peng et al study evaluated 0.8g gum containing 55.5% sorbitol + 4.3% xylitol, The Kandelman et al study evaluated 15% w.w xylitol (0.8 g/day) + 50% w/w sorbitol (2.4g/day) and the Makinen et al study had upto 60% xylitol in it's xylitol/sorbitol gums. The Szoke, Beiswanger and Finn studies evaluated sorbitol and mannitol combinations.] For more information. please refer to Table on Evidence Summary.

Makinen 1995: Sample size for control groups divided by 3

Makinen (combinations) 1995: Adjusted values used. Combined Group 4 -- -45% xylitol/30% sorbitol pellet gum 5 times per day (3:2 XS-p5) and Group 5 -- -15% xylitol/45% sorbitol pellet gum 5 times per day (1:3 XSp5) and Group 6 - -60% xylitol/9% Lycasin® stick gum 3 times per day (Xyl-s3); and Group 7 - -60% xylitol/9% Lycasin® stick gum 5 times per day (Xyl-s5)

Makinen (sorbitol) 1995: Adjusted values used. Only Group 3 -65% sorbitol pellet gum 5 times per day (Sorb-p5; "sorbitol gum")

Makinen (xylitol) 1995: groups 8 with -65% xylitol pellet gum 3 times per day (Xyl p3) and group 9 with 65% xylitol pellet gum 5 times per day (Xyl p5) Used adjusted values.

Kandelman; Sample size for control group divided by 2

Kandelman (combinations): Data for the 15% Xylitol group was used. SD not reported for 24 month data, hence the 12 month data reported in Kandelman and Gagnon 1987 J Dent Res 66(8):1407-1411,

Kandelman (xylitol): Data for the 65% Xylitol group was used. SD not reported for 24 month data, hence the 12 month data reported in Kandelman and Gagnon 1987 J Dent Res 66(8):1407-1411,

SENSITIVITY ANALYSIS: Including only studies that claimed to be randomized (exclude Peng, Makinen and Kandelman): -21.62 [-41.63, -1.62]

Including only studies of fair/good quality (include Alanen, Makinen, Machiulskiene): -45.58 [-70.18, -20.98]

Adjustment for cluster randomized trials.⁸¹

Note. The Szoke study did not provide information on cluster size. Hence the adjusted values have been reported excluding the Szoke data.

No adjustment and excluding Szoke -39.24 (-58.34, -20.13)

Assumed intracluster coefficient of 0.02 and excluding Szoke -39.44 (-59.78, -19.09)

Including only studies that claimed to be randomized AND adjusting for allocation/analysis errors

Note. The Szoke study did not provide information on cluster size. Hence the adjusted values have been reported excluding the Szoke data.

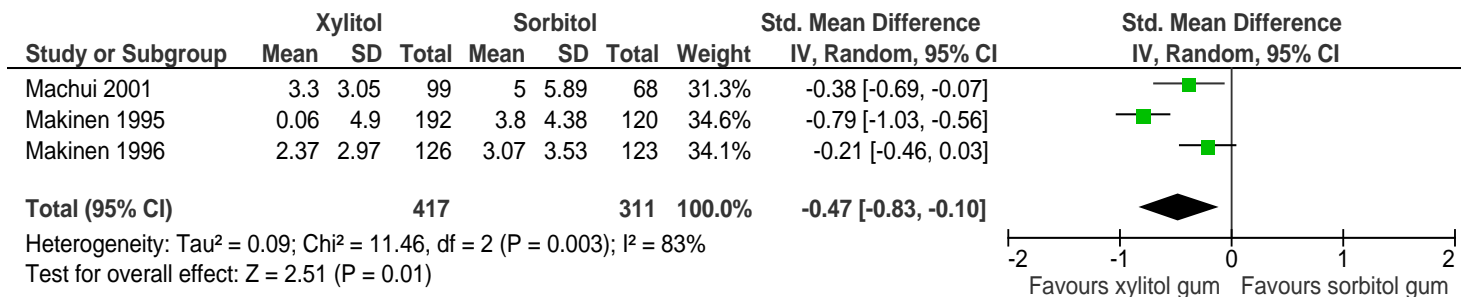
No adjustment and excluding Szoke - -18.33 [-41.19, 4.52]

Assumed intracluster coefficient of 0.02 and excluding Szoke -16.57 [-34.41, 1.27]

The results of meta-analysis of studies that recorded caries in permanent teeth indicate that there is a statistically significant reduction in caries with the use of sucrose-free polyol gums compared with no gum chewing. The preventive effect, however, was not the same for all types of polyols. Subgroup analyses show that xylitol gum has the highest caries reduction, followed by gums with a combination of polyols. The use of gum sweetened with sorbitol alone showed a nonsignificant difference in caries reduction compared with no gum chewing. Confidence in the summary estimate is limited because several of these trials were cluster or group-randomized typically by classroom or school followed by analyses that were based on the number of subjects included in the study (i.e. unit of analysis error). A statistically significant reduction with the use of sucrose-free polyol gums compared to no gum chewing was maintained after adjusting for these errors. However, when the non-randomized studies were excluded *and* adjustments were made within the subset of studies with unit of analysis errors⁸¹, the result in favor of sucrose-free polyol gum became statistically nonsignificant.

The panel performed a second analysis to directly compare the efficacy of xylitol gum with sorbitol gum. The panel reviewed evidence from three studies that compared xylitol and sorbitol gums²⁴⁻²⁶. Two studies^{24, 25} reported DMFS while the other study²⁶ reported “lesion onset per subject” in primary dentition. In order to combine data from all three studies, the panel chose to use standardized mean difference as the summary estimate for this analysis. Based on these three studies that provided data for such a direct comparison, xylitol gum was more efficacious in reducing incidence of caries compared to sorbitol gum.²⁴⁻²⁶

Xylitol gum Vs. Sorbitol gum



Overall, there was significant statistical heterogeneity ($I^2 = 95\%$) confirming clinical and or methodological differences amongst studies included in the metaanalysis. The low quality of most studies limited the panel's confidence in the observed results, however the number of studies showing a consistent preventive effect led the majority of the panel to conclude with **moderate certainty** that

In children aged 5 – 16 years, supervised consumption of chewing gum sweetened with sucrose-free polyol (xylitol only or polyol combinations) for 10 – 20 minutes after meals marginally reduces incidence of caries¹⁸⁻³²

It is biologically plausible that the act of chewing itself increases the rate of food clearance from the mouth, increases saliva production and more quickly neutralizes plaque acids, thereby potentially lowering the incidence and progression of caries. Unfortunately study participants in the control arms of these studies did not chew gum, making it impossible to distinguish between possible benefits associated with chewing itself versus those associated with the effects of the polyol. An ongoing clinical trial in adults is examining if increased salivary flow alone might account for differences in the caries development.⁸² In addition, a recent systematic review⁸³ noted a dose-response relationship between xylitol load (total grams of xylitol consumed per day) and caries reduction.

In making its recommendations, the panel weighed the benefits of caries prevention with the potential for adverse impacts of gum chewing. Chewing gum is considered a potential choking hazard and the American Academy of Pediatrics (AAP) recommends against gum chewing by children younger than 4 years old.⁸⁴ Children younger than four and children with chewing or swallowing disorders are at greater risk of food-related choking. Caregivers should pay special attention to choking prevention among children with neurologic impairments regardless of the age. Behavioral factors may also affect a child's risk for choking.⁸⁴ Therefore, chewing gum use should be reserved for neurologically healthy children 5 years and

older who are willing and able to chew for an extended period (the investigators in most of the studies included in this review reported that the participants chewed for at least 10 minutes). The metabolic and neurobehavioural effects of polyols such as sorbitol, xylitol, erythritol, or non-caloric sweeteners in chewing gum have remained largely unstudied with different monosaccharides thought to have different metabolic effects.⁸⁵⁻⁸⁷ Chewing gum has been associated with some adverse health effects.^{88, 89}

In balancing the benefits and the potential adverse effects of the use of these chewing gums, the majority of the panel believed that the benefits of supervised gum chewing added to a caries prevention regimen, especially in children at high risk of experiencing caries, could outweigh the potential adverse effects. Therefore, the panelists agreed with the recommendation that practitioners advise parents and caregivers of healthy children older than 5 years and at high risk of experiencing caries, that the children use sucrose-free polyol chewing gum (containing either xylitol only or polyol combinations) after meals. The panel extrapolated the evidence to adults who are at higher risk of developing caries and recommended chewing sucrose-free polyol gum (containing either xylitol only or polyol combinations) after meals.

In balancing the benefits and risks of a chewing gum regimen, some panel members thought that the evidence for efficacy was not strong enough to make a recommendation in favor of instituting gum chewing after meals.

Xylitol candy, lozenge, syrup

The panel reviewed four studies³²⁻³⁵ that evaluated caries reduction with the use of xylitol candy/lozenges/tablets. One trial³⁴ compared xylitol lozenge to conventional care including fluoride varnish and was therefore not used when combining the studies for the meta-analysis. This study specifically enrolled high-risk patients and reported nonsignificant difference between the groups.

In the remaining three trials^{32, 33, 35} the authors compared xylitol lozenge/tablets with no candy/tablets. One trial³⁵ evaluated caries reduction in primary teeth of children at 2 years of age reporting dmfs scores while the remaining studies evaluated caries reduction in the permanent dentition reporting DMFS scores. In terms of frequency, two studies reported that subjects sucked on tablets three times a day.^{32, 33} These studies^{32, 33} reported a sucking duration of 10 minutes. In all three studies, the authors did not specifically enroll children at high-risk for caries. Of the three studies, one was judged to be of good quality³⁵, one was fair³² and the third³³ was judged to be of poor quality.

The panel combined the results from the three studies.^{32, 33, 35} and found a statistically significant effect in favor of xylitol, lozenge/candy. Based on the limited number of studies the panel concluded with **low certainty** that:

In children reporting caries experience, consumption of xylitol containing lozenges or hard candy reduces incidence of coronal caries^{32, 33, 35}

Xylitol Lozenge vs. no lozenge

Study or Subgroup	Prevented Fraction		Xyl lozenge		No lozenge		Prevented Fraction		Prevented Fraction	
	SE	SE	Total	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	IV, Random, 95% CI	
Alanen 2000	-49.77	6.41	139	146	35.9%	-49.77 [-62.33, -37.21]				
Honkala 2006	-134.29	11.86	105	40	34.7%	-134.29 [-157.54, -111.04]				
Oscarson 2006	-52.5	26.3	55	63	29.3%	-52.50 [-104.05, -0.95]				
Total (95% CI)			299	249	100.0%	-79.93 [-142.96, -16.91]				

Heterogeneity: Tau² = 2835.98; Chi² = 39.68, df = 2 (P < 0.00001); I² = 95%
 Test for overall effect: Z = 2.49 (P = 0.01)

Alanen: Data from 2 groups combined. Candy 1, 3 years and Candy 2, 3 years. One was a xylitol-maltitol combination while the other was a xylitol-polydextrose combination.
 Oscarson: Values adjusted for baseline status used. Unadjusted values available.

SENSITIVITY ANALYSIS: Adjustment for unit of allocation/analysis errors
 Excluding Alanen 2000: -96.76 [-176.64, -16.88]

For children below age two, in addition to the study that evaluated xylitol tablets³⁵, the panel reviewed another study³⁶ that evaluated xylitol-containing syrup among children in the Marshall Islands and reported a statistically significant difference in favor of xylitol syrup. Although this study was judged to be of good quality, based only on this single study, the panel concluded that:

There is insufficient evidence that xylitol syrup prevents caries in children under 2 years of age.³⁶

A conclusion of “insufficient” evidence does not mean that the intervention is ineffective, rather that the panel did not find enough evidence to support a recommendation.

Of the three studies providing evidence regarding xylitol lozenges, one was a nonrandomized trial whose evidence was judged to be of poor quality.³³ Another study conducted in 2 year olds evaluated a xylitol dose of 0.96 g/day.³⁵ The results from these trials provided only weak evidence for caries preventive benefit from xylitol lozenges. However, the findings are consistent across the studies which together evaluated over 500 subjects. On the basis of results from these studies, **a majority of the panel** recommended the use of xylitol lozenges or hard candy after meals for children older than 5 years. The majority of the panel also suggested a dose of 5 to 8 grams/day divided into two or three doses to maximize clinical benefits. Practitioners should be aware that polyols in large doses have been linked to adverse gastrointestinal

effects in some individuals.⁹⁰ As discussed previously, hard candy also should be used under supervised conditions in neurologically healthy children to reduce the risk of choking.⁸⁴ The panel did not find sufficient evidence to support recommendations for use of xylitol by children younger than 5 years. Some members of the panel thought that the existing weak evidence was not sufficient to support a recommendation for the use of xylitol delivered through lozenges. An ongoing clinical trial may provide evidence for use of xylitol lozenges in adults.⁸²

Xylitol Dentifrice

The panel considered two large-scale studies that compared 10% xylitol in fluoride dentifrices with fluoride dentifrices without xylitol. Both were RCTs, of which one was judged to be of fair quality;³⁸ while the other was of poor quality.³⁷ Both trials were conducted in school-age high-risk children. The dentifrice evaluated in these studies had additional components, which are thought to have the ability to enhance the efficacy of other active agents. Based on these studies the panel was not able to make a determination for or against the effect of xylitol in caries reduction when added to a dentifrice. The panel concluded that:

There is insufficient evidence that xylitol in dentifrices prevents caries.^{37, 38}

Antimicrobial (or Antibacterial) Agents

Triclosan

The panel found no published literature evaluating the effects of triclosan alone on caries prevention. Although there are studies that evaluated triclosan in dentifrices,⁹¹⁻⁹⁵ the addition of other components to dentifrices (some of which may themselves have anti-caries effect) makes it difficult to evaluate the effects of triclosan alone. The panel concluded that:

There is insufficient evidence that triclosan lowers incidence of caries.

Iodine

The panel found four RCT's that evaluated 10% povidone-iodine on coronal caries^{12, 48-50} in pre-school and school-age children. All four studies were one year in length. Iodine, a topical antiseptic, reduces *S. mutans* concentrations in plaque biofilm and saliva. Three studies assessed caries using a visual examination. One study⁴⁸ used laser fluorescence for diagnosis and reported quantitative laser fluorescence (QLF) scores. Two studies were judged to be of fair quality^{49, 50} and two studies^{12, 48} were of good quality. However, all studies were relatively small and three of the four studies^{12, 49, 50}

included fewer than 20 subjects per group. Combining data was not possible because of differences in outcome measures reported in the studies. Although two studies^{48, 49} reported statistically nonsignificant results, one study⁵⁰ reported fewer treatment failures and another¹² reported lower caries progression with the use of iodine.

The panel concluded that:

There is insufficient evidence that use of iodine lowers incidence of caries.⁴⁸⁻⁵⁰

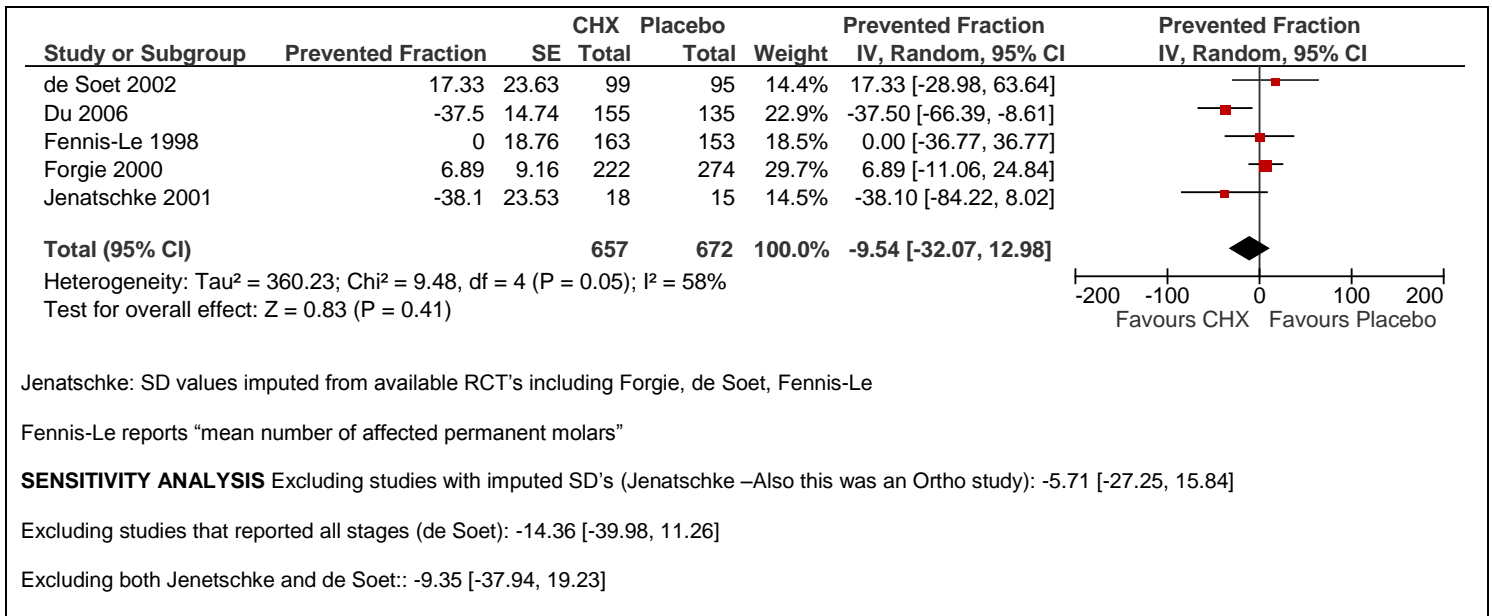
Topical chlorhexidine products

In the United States, chlorhexidine is marketed as a 1:1 mixture of chlorhexidine-thymol varnish (such as Cervitec Gel, Ivoclar Vivadent, Schaan, Liechtenstein ®) and a 0.12 percent chlorhexidine gluconate mouthrinse (such as Peridex Chlorhexidine Gluconate 0.12% Oral Rinse [3M ESPE, St. Paul, Minn.] and PerioGard [Colgate, New York City]). The U.S. Food and Drug Administration has not approved either of these agents for caries prevention. In Europe, 10 to 40 percent chlorhexidine varnishes (for example, EC40 [Biovent, Nijmegen, Netherlands], BioC® [Biovent] and Chlorzoin® [Knowell Therapeutic Technologies, Toronto]) are marketed. Chlorhexidine gels also are not available in the United States. The panel identified 24 studies relating to various chlorhexidine products including varnishes, gels and rinses.

Chlorhexidine varnish.

The panel found five RCTs⁵¹⁻⁵⁵ evaluating the efficacy of chlorhexidine varnish products, currently not available in the U.S., compared with placebo varnish. The studies evaluated varnish application in pre-school, school-age and adolescent children. Two studies^{52, 55} enrolled children at high risk for caries. Four studies^{51, 53-55} evaluated 40 percent chlorhexidine varnish; one study⁵² evaluated a 10 percent varnish. The panel rated the quality of two of these studies^{51, 56} as fair and one study as good⁵². The results from all five studies were combined for the meta-analysis that showed a nonsignificant difference between 10 – 40% chlorhexidine varnish and placebo varnish. This result did not change after excluding studies over 1 year that reported on white spot lesions. The result also remains nonsignificant if only the studies that included high-risk patients are considered.

Chlorhexidine varnish (10 – 40 percent) vs. placebo varnish for coronal caries



Because on a large number of subjects (over 1300) were evaluated in 5 RCT's and the metanalysis reveals a nonsignificant result, the panel interpreted this to be evidence for lack of effect. , Therefore, the panel had **moderate certainty** in concluding that:

In children aged 4 to 18 years, professionally applied 10 to 40 percent chlorhexidine varnish does not reduce the incidence of caries.⁵¹⁻⁵⁵

The panel included one RCT⁵⁶ that showed statistically significant root surface caries reduction with the use of 40 percent chlorhexidine varnish in adults with root caries. The panel judged this study to be of poor quality. Based on the single RCT on root caries, the panel concluded that:

In adults, there is insufficient evidence that use of 40 percent chlorhexidine varnish reduces the incidence of root caries.⁵⁶

An ongoing randomized clinical trial evaluating a 10 percent chlorhexidine varnish in adults may provide additional evidence.⁹⁶

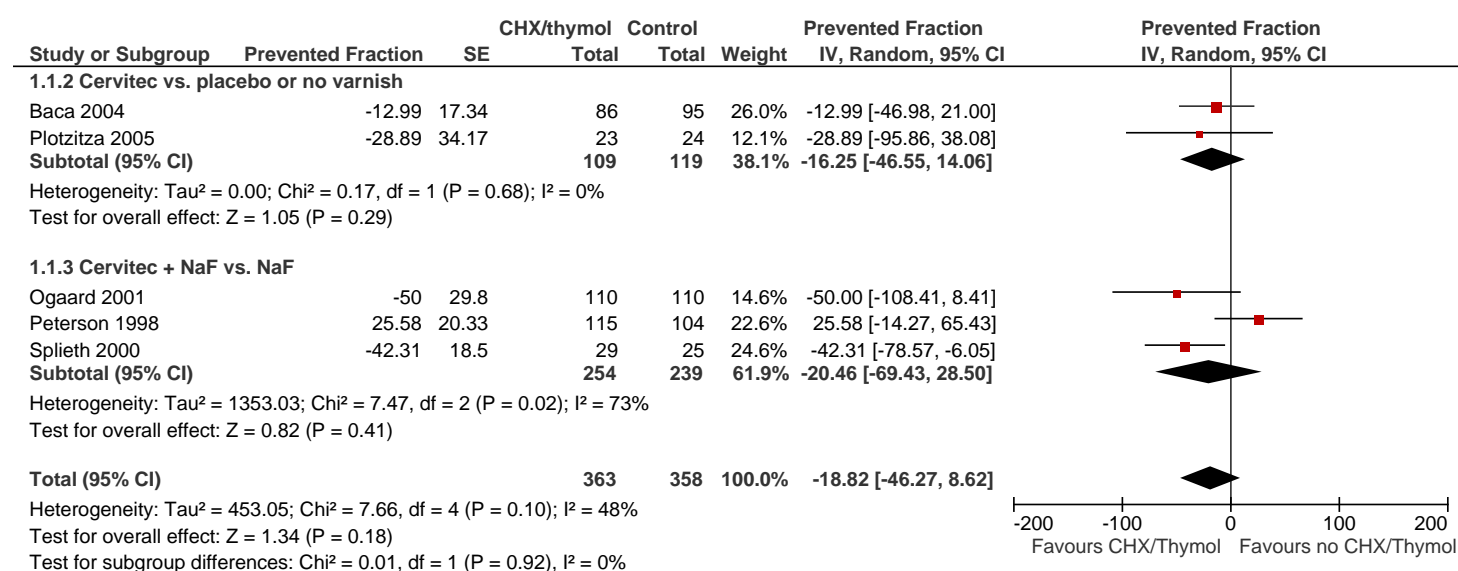
Chlorhexidine/Thymol Varnish

The panel found six studies^{69-73, 75} evaluating the efficacy of a 1:1 mixture of chlorhexidine/thymol varnish (1:1 mixture is 1 percent chlorhexidine and 1 percent thymol). Three studies^{72, 73, 75} compared a 1:1 mixture of chlorhexidine/thymol varnish

application to no varnish while three others⁶⁹⁻⁷¹ compared a 1:1 mixture of chlorhexidine/thymol varnish in combination with sodium fluoride to a sodium fluoride control. Five studies evaluated varnish application in school-age children; one study⁷² evaluated varnish application in children aged 1 – 2 years. The studies varied in design with three of them being RCT's.^{70, 71, 73} All studies except one⁷³ specifically enrolled subjects at high-risk for caries. Only one of the RCT's⁷⁰ was judged to be of good quality while the remaining studies were all judged to be of poor quality.

One study⁷⁵ reported progression score as the outcome and therefore could not be combined in the meta-analysis. The panel combined the results from the remaining five studies by a meta-analysis which showed a nonsignificant difference among the groups. A nonsignificant difference was observed. This result did not change after excluding studies over 1 year that reported on white spot lesions. The result also remains nonsignificant if only the studies that included high-risk patients are considered.

Chlorhexidine/Thymol varnish comparisons for coronal caries



Baca: Used the dmfs score reported in the 2004 papers instead of the DFS score reported in the 2002 paper since the Plotzitza was on primary teeth as well. Also Baca is subject to unit of analysis error.

SENSITIVITY ANALYSIS:

Excluding Ogaard (ortho study only reporting on WSL): -13.50 [-43.84, 16.84]

In addition, the panel found one study⁶⁸ comparing a 1:1 mixture of chlorhexidine/thymol varnish to fluoride varnish. This study reported a nonsignificant difference between the two types of varnish.

The metanalysis included over 700 subjects and showed a nonsignificant difference between the groups. The panel weighed the overall power of the metaanalysis against the nonsignificant result and chose to interpret this result as lack of clinical benefit. Based on the poor quality of most studies the panel had **low certainty** in concluding that:

In children up to 15 years, application of a 1:1 mixture of chlorhexidine/thymol varnish does not reduce the incidence of caries.^{69-73, 75}

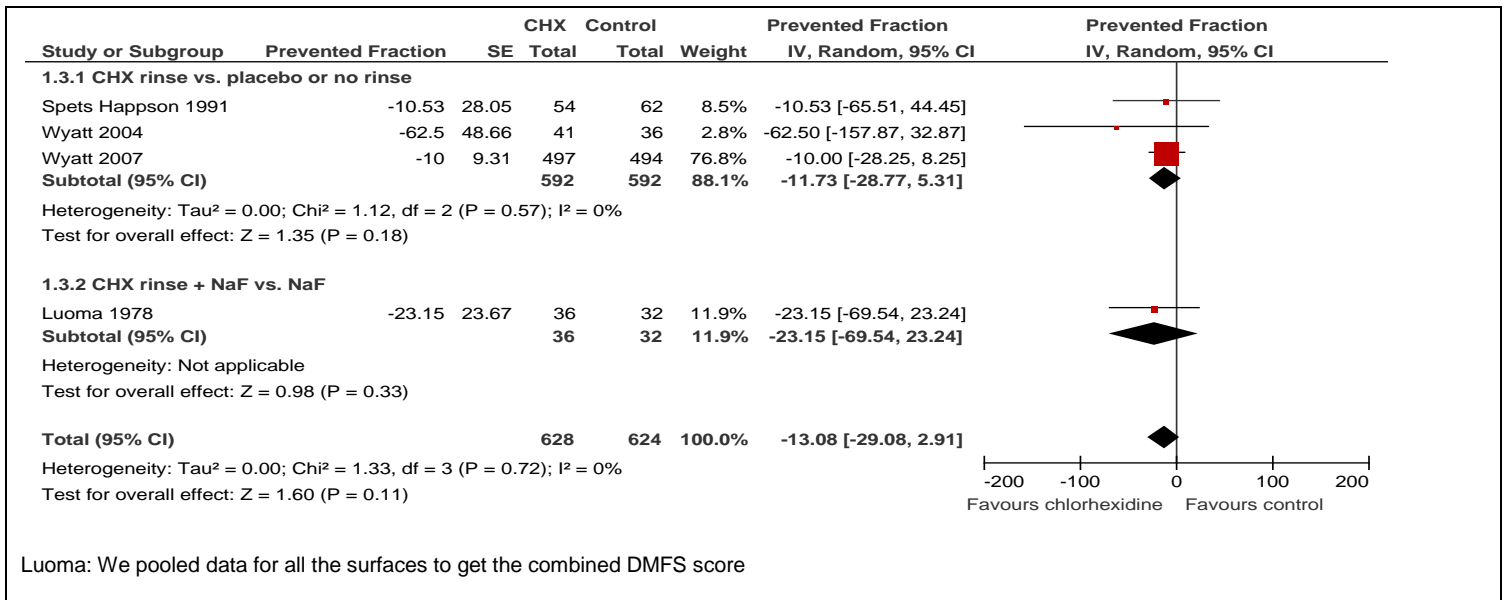
The panel found three RCT's^{10, 76, 77} evaluating the efficacy of 1:1 chlorhexidine/thymol varnish on root caries. They judged two^{10, 76} to be of good quality while the third⁷⁷ was fair in quality. Two studies^{10, 76} showed a statistically significant reduction in the incidence of caries with the use of chlorhexidine/thymol varnish compared to placebo or no varnish. In the third study conducted in high-risk patients⁷⁷, authors used a combination of chlorhexidine/thymol along with fluoride varnish comparing it to a fluoride varnish and demonstrated that lesion progression was reduced in the test group compared to the control group which received only the fluoride varnish. Based on these three RCT's on root caries, all of which showed a statistically significant improvement in caries status with the use of chlorhexidine/thymol varnish, the panel concluded with **moderate certainty** that:

In adults and elderly people, application of a 1:1 mixture of chlorhexidine/thymol varnish reduces the incidence of root caries.^{10, 76, 77}

Chlorhexidine mouthrinses

The panel found four⁶⁴⁻⁶⁷ RCT's evaluating the efficacy of 0.12 percent chlorhexidine mouthrinse. Three studies⁶⁴⁻⁶⁶ compared chlorhexidine rinse with placebo or no rinse; one study⁶⁷ compared rinse with chlorhexidine and fluoride to fluoride-only rinse. One study⁶⁴ was judged to be of good quality while all other studies were judged to be of fair quality. One study⁶⁶ specifically enrolled high-risk individuals. The panel combined the results from the studies through meta-analysis which showed a nonsignificant difference.

Chlorhexidine Rinse for coronal caries



Based on these four RCT's judged to be fair or good quality and the results of the metaanalysis that included over 1200 subjects and showed a nonsignificant difference , the panel concluded with **high certainty** that:

In children and adults, use of 0.05 to 0.12 percent chlorhexidine rinse does not reduce the incidence of coronal caries^{64-67, 97}

The two RCT's^{64, 65} also reported on the incidence of root caries in adults and elderly. Both trials conducted in the general population appeared adequately powered (with one trial including almost 1000 subjects) and found that use of chlorhexidine rinse does not result in a statistically significant decrease in root caries incidence among adults and elderly compared to placebo rinse. Based on these two trials the panel concluded with **moderate certainty** that:

In adults and elderly people, use of 0.12 percent chlorhexidine rinse does not reduce the incidence of root caries.

64, 65

Chlorhexidine gels

The panel found five studies⁵⁸⁻⁶² evaluating the efficacy of chlorhexidine gel. Two studies^{58, 59} conducted in high-risk patients compared a 1 percent chlorhexidine gel professionally applied using trays with no gel application. Two studies^{60, 61} conducted in the general population compared professional flossing with 1 percent chlorhexidine gel to flossing with placebo gel. One study⁶² also conducted in the general population compared brushing at home with 0.5 percent gel compared to brushing with a placebo gel. Only three studies⁶⁰⁻⁶² were judged to be of fair quality while the remaining

studies were judged to be of poor quality. Because of the different delivery methods used in the studies, the panel did not combine the results for meta-analysis. Three of the five studies^{58, 59, 62} reported a nonsignificant difference between the intervention arms. The remaining two studies^{60, 61} reported favorable results for approximal lesions, but included professional flossing in addition to gel applications. In addition, the panel found one study⁵⁷ comparing 1 percent chlorhexidine gel to fluoride varnish. This study, conducted in high-risk patients, was judged to be of poor quality and reported a nonsignificant difference.

Due to the differences among studies in terms of methods of gel application, limited number of studies^{59, 62} including less than 20 subjects per intervention arm and inconsistency in the results, the panel was unable to make a determination on the efficacy of 1 percent chlorhexidine gel for caries prevention and concluded that:

In children aged 3 – 15 years, there is insufficient evidence that professionally applied 1 percent chlorhexidine gel reduces the incidence of caries.⁵⁸⁻⁶²

The panel found one small RCT⁶³ that compared a self-applied chlorhexidine gel to self-applied sodium fluoride gel in overdenture patients and reported no statistically significant difference between the two agents. This study was judged to be of poor quality. The panel concluded that:

In adults and elderly, there is insufficient evidence that chlorhexidine gels reduce the incidence of root caries.⁶³

In summary, although chlorhexidine has been shown to reduce *Streptococcus mutans*⁹⁸ in the oral cavity temporarily, most of the clinical study investigators who evaluated coronal caries as the outcome did not show a statistically significant reduction in caries with the use of chlorhexidine in any vehicle. On the basis of the results of these studies the panel recommended against using chlorhexidine products for coronal caries prevention at this time. With respect to root caries, the panel concluded that application of chlorhexidine-thymol varnish may help reduce the incidence of root caries in adults and elderly people and reported insufficient evidence supporting the use of 10 to 40 percent chlorhexidine varnish.

Calcium and/or phosphate agents with and without casein derivatives

These agents are hypothesized to promote remineralization of tooth structure damaged by bacterial acids and are being added to toothpastes or other vehicles. The panel identified nine studies³⁹⁻⁴⁷ that evaluated various calcium and/or phosphate containing agents with and without casein derivatives. Two of these^{41, 46} were judged to be of good quality; five^{40, 42-45} was judged to be of fair quality and the others were poor in quality. All studies except one³⁹ were RCT's.

One study⁴², compared a sodium fluoride dentifrice containing dicalcium phosphate dihydrate with a sodium fluoride control dentifrice and concluded that the addition of dicalcium phosphate dihydrate improved anticaries efficacy. The second study⁴¹ evaluated a dicalcium phosphate dihydrate dentifrice in cancer radiation patients and demonstrated higher root caries reduction compared with a conventional fluoride dentifrice. This study did not find a reduction in the coronal caries.

One study⁴⁶ compared a dentifrice containing casein phosphopeptide to a fluoride-containing dentifrice and a placebo. This study concluded that the caries prevention efficacy of the dentifrice containing casein phosphopeptide was similar to that of the fluoride dentifrice and both were more efficacious than the placebo.

Of the two studies on arginine bicarbonate/calcium phosphate, one evaluated the agent in dentifrice³⁹ and the other evaluated the agent in mints⁴⁰. The dentifrice study³⁹ reported a statistically significant reduction in caries at the 12 month follow-up although the difference was less in magnitude at 24 months. The second study that evaluated mints reported a statistically significant reduction in caries at 12 months.⁴⁰

One study⁴³ evaluated a mouthrinse with a “remineralizing agent” and concluded that rinsing with the solution provided a caries preventive benefit in children with low initial caries prevalence when added to other prophylactic measures.

Three studies evaluated calcium phosphates in casein derivatives. One study⁴⁵ evaluated this agent in mouthrinses on patients with salivary gland dysfunction and reported a nonsignificant difference between the test rinse and fluoride rinse. The second study⁴⁴ evaluated a casein phosphopeptide complexed with amorphous calcium phosphate (CPP-ACP) in chewing gum and concluded, based on radiographic comparisons, that the CPP-ACP gum lowered the likelihood of caries progression. Although the authors of this study reported collecting caries data using visual and tactile methods on other tooth surfaces, these were not reported. The third study⁴⁷ evaluated a dental cream containing CPP-ACP complexes and fluoride products on regression of white spots and reported nonsignificant difference between the groups.

Although the panel found several studies on calcium and phosphate agents with and without casein derivatives, the differences in composition of the products, their varying delivery mechanisms, differing study designs and the varied results made it difficult to determine the efficacy of each agent or to group them into a meta-analysis. The panel concluded that:

There is insufficient evidence from clinical trials that use of agents containing calcium and/or phosphates with or without casein derivatives lowers incidence of either coronal or root caries.³⁹⁻⁴⁷

Sialogogues

The panel found no published reports that evaluated the use of sialogogues (for example, pilocarpine, cevimeline) for caries prevention.

Use of nonfluoride agents in mothers to prevent caries in children

The panel found four studies^{11, 78-80} that evaluated the use of caries preventive agents in mothers aimed at positively affecting the caries status of their children. One RCT⁷⁸ evaluated xylitol gum and 40 percent chlorhexidine varnish compared to fluoride varnish and reported that use of xylitol gum significantly lowered the incidence of caries in children. One RCT⁸⁰ evaluated 10 percent chlorhexidine varnish and reported nonsignificant difference in caries increment while the other controlled trial⁷⁹ evaluated 1 percent chlorhexidine gel and reported a statistically significant reduction in caries experience. The fourth study¹¹ evaluated calcium supplementation in mothers and its effect on children and reported a 27% reduction in risk of developing caries. Two studies^{11, 80} were judged to be of fair quality while the other two^{78, 79} were of poor quality. Based on these four trials which were conducted on different agents the panel concluded that

There is insufficient evidence that use of xylitol gum, chlorhexidine varnish or gel or calcium supplementation in mothers lowers incidence of caries in children.^{11, 78-80}

Clinical considerations and recommendations

A clinician must consider a patient's risk of experiencing disease and other factors such as readiness for change, oral health literacy and compliance when developing an optimal caries prevention plan. Patient education, dietary advice and periodic clinical examinations should be part of such a plan. Clinicians should encourage parents and caregivers to limit a child's consumption of sugar-containing foods and drinks and, when possible, to confine consumption to meal times.^{99, 100}

In light of good supportive evidence the panel reminds clinicians that professional and home fluoride products, including fluoridated toothpastes and dental sealants remain the primary interventions effective in preventing caries.^{2, 3, 5-7} and recommends that clinicians follow published evidence-based guidelines for these modalities.^{3, 6} In contrast, the modalities examined in this review had less evidentiary support, both for and against.

Regarding some studies in which the evidence was lacking, of poor quality, or contradictory and the in which the panelists could not reliably estimate the benefit versus the basis of the findings of published studies, the panelists concluded that there was insufficient evidence. In such cases, clinicians and patients alike should understand fully the uncertainty in the underlying evidence as well as any potential risks of using or not using a particular intervention. The patient's caries risk status, the practitioner's professional judgment, and a patient's needs and preferences should guide all decision-making. The panel made recommendations for specific nonfluoride agents in Table 5 based on the best available evidence and the balance between benefits and adverse events.

Table 5: Recommendations from the American Dental Association Council on Scientific Affairs Nonfluoride Caries-Preventive Agents Expert Panel.

<p>This panel acknowledges the oral and systemic benefits of lowering the quantity and frequency of sugar consumption and encourages practitioners to provide dietary counseling.^{99, 100} The panel also strongly recommends that practitioners first implement evidence-based recommendations^{3, 6} regarding topical fluorides and sealants before attempting to use any nonfluoride therapies. The following recommendations may be considered as adjuncts to dietary counseling and a regular caries preventive program* offered to patients at higher risk for caries.</p>	
Evidence-based recommendations	Strength <i>(refer to Table 2 for definitions)</i>
Advise parents and caregivers of children 5 years or older, that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 - 20 minutes after meals may reduce incidence of coronal caries	Weak
Apply 1:1 mixture of chlorhexidine/thymol varnish every three months to reduce the incidence of root caries.	In favor
Applying 10 – 40 percent chlorhexidine varnish alone or in combination with fluoride for prevention of coronal caries is not recommended.	Against
Using 0.12 percent chlorhexidine rinse alone or in combination with fluoride for prevention of coronal or root caries is not recommended.	Against
Advise adults, that use of sucrose-free polyol (xylitol only or polyol combinations) chewing gum for 10 – 20 minutes after meals may reduce incidence of coronal caries.	Expert Opinion
Advise parents and caregivers of children 5 years or older, that the daily use of xylitol-containing lozenges or hard candy that are dissolved slowly in the mouth after meals may reduce incidence of coronal caries. (5-8 grams/day divided into two to three doses)	Expert Opinion
Applying 0.5 to 1.0 percent chlorhexidine gel alone or in combination with fluoride for caries prevention of coronal or root caries is not recommended.	Expert Opinion
Applying 1:1 mixture of chlorhexidine/thymol varnish alone or in combination with fluoride for prevention of coronal caries is not recommended.	Expert Opinion
<p>*A regular caries preventive program includes routine and periodic examination by a dentist, patient education, dietary advice and appropriate use of professional and home fluoride products and dental sealants.</p>	

The panel noted the limited investment in prevention studies in the U.S. and made specific recommendations for research on nonfluoride caries preventive agents.

Specifically the panel recommended,

Multiple well-designed independent, appropriately powered, placebo-controlled RCT's following Consolidated Standards of Reporting Trials (CONSORT) guidelines conducted in the US with standardized reporting by age, dentition and caries risk status.

Studies that evaluate;

1. the optimal mode of delivery, dosage, frequency, duration of treatment and adverse systemic effects of xylitol when delivered via different vehicles such as gums, lozenge, hard candy or syrup on caries prevention in adults, elderly and special needs populations with varied backgrounds of fluoride exposures.
2. the efficacy and effectiveness of nonfluoride agents in combination with fluorides for caries prevention in elderly patients and populations with special needs.
3. the efficacy and effectiveness of nonfluoride agents that prevent tooth surface demineralization or promote remineralization in different delivery vehicles on caries prevention in children and adults.
4. the efficacy and effectiveness of iodine, triclosan or other antimicrobial agents on caries prevention in children and adults.
5. the efficacy and effectiveness of agents to reduce the incidence or promote the reversal of root surface lesions.

Other studies that;

1. evaluate the effectiveness of systemic pharmacological agents in caries prevention in high-risk populations.
2. identify reliable surrogate markers for caries outcomes for Phase I and II trials.
3. determine whether agents that prevent progression of, or reverse, white spots can be judged effective against caries
4. develop measures for caries risk to develop more standardized definitions or risk groups
5. identify reliable methodologies and technologies to assess the transition of the earlier manifestations of disease (i.e. white spot lesions) in order to test the power of preventive agents in stopping or reversing carious lesions

Also,

assess the relationship between *S. mutans* and caries outcomes through a systematic review of published literature to determine how *S. mutans* changes relate to caries changes.

After conducting a comprehensive review of the literature the panel concluded that certain non-fluoride agents may provide some benefit as adjunctive therapies in children and adults who are at higher risk of experiencing caries. The panel found at least 10 ongoing clinical trials that may in the future provide additional evidence for or against the effectiveness of many of these modalities. Therefore, on the basis of available evidence, the panel recommended sucrose-free chewing gum (containing either only or polyol combinations) or xylitol lozenges for caries prevention. In addition, the panel found that a 1:1 mixture of chlorhexidine/thymol varnish may be efficacious in the prevention of root caries. The panel will update its recommendations when information from ongoing clinical trials becomes available.

Strengths and Limitations

The panel noted numerous limitations to the evidence reviewed in this report.

-- Overall, the published literature on these topics lacks clinical trials that follow-the Consolidated Standards of Reporting Trials (CONSORT) guidelines¹⁰¹ especially with regard to appropriate methods of randomization, sample allocation concealment, accounting for losses to follow-up, and lack of intention-to-treat analyses.

-- Furthermore, the panel noted that most studies failed to report the use of independent data safety monitoring boards and failed to report funding sources and potential conflicts of interest;

- Most trials included in this systematic review involved assessment of the efficacy of nonfluoride agents. In efficacy trials (explanatory trials) researchers aim to determine whether an intervention produces the expected result under ideal circumstances. In effectiveness trials (pragmatic trials) researchers measure the degree of beneficial effect in real world clinical settings.¹⁰² The panel noted that effectiveness trials have greater clinical relevance.

-- The panel found that available study findings provided limited information about the caries risk status of participants.

-- The lack of uniformity in description of the background fluoride exposure of study samples, in part, led the panel to conclude that the nonfluoride preventive agents should be considered as “adjunctive” to a regular caries prevention program. The evidence does not indicate that these agents are effective in patients whose condition is refractory to proven methods of caries prevention.

-- The panel identified caries incidence, arrest and reversal as three outcomes worthy of assessment. Unfortunately, the caries outcomes reported in most trials were limited to composite DMFS/DMFT scores that did not permit the panel to determine the effects of these agents on arrest or reversal (remineralization) of caries.

-- Although conclusions were reported in the literature specific to various age groups, these groupings do not represent biologically or behaviorally distinct populations. Therefore, to make meaningful recommendations, the panel extrapolated the evidence to standardized age ranges.

- The competitive environment in which clinical trials are financed and conducted as well as the non-reporting of negative results by some investigators or publications, may foster publication bias.¹⁰³

The panel recommended that future trials be designed to overcome these limitations and be registered with clinicaltrials.gov or equivalent registries to avoid publication bias.

Further, this systematic review contains a number of potentially important limitations.

- The panel attempted to capture all available evidence from controlled studies listed in only two databases, namely PUBMED and Cochrane, and included only studies published in English.
- Notwithstanding that randomized controlled clinical trials are considered the gold standard for therapeutic interventions, in light of the paucity of literature the panel considered both randomized and non-randomized studies.
- In addition, the main tool used to evaluate study quality¹⁴ required considerable customization (for caries trials) and operator training to assure reliable application.
- The caries data were summarized using the methods from a previously published systematic review². This approach combines DMFS and DMFT values, ignores differences in caries transitions and differences in risk status and is not based on standard epidemiological measures of risk and rate. As a result, the “prevented fraction” reported in this review reflects an abstract caries measure useful only to appreciate the relative differences between groups.

Future Technologies

A variety of novel technologies are currently under development or evaluation as caries preventive agents. For example, the addition of the arginine to food or oral care products is reported to inhibit the initiation and progression of caries and to promote tooth remineralization.¹⁰⁴ Probiotics, consisting of naturally-occurring oral bacteria, food-grade microorganisms, or genetically-modified bacteria, are under investigation as means to promote healthier plaque ecologies.¹⁰⁵ Note that although probiotic bacteria for oral use are now available in the health food marketplace, safety and effectiveness have not been rigorously tested. Researchers have also developed biomolecules aimed at preferentially eradicating cariogenic species in oral biofilms. These technologies include smart molecules against specific bacteria, passive immunization with animal or plant derived antibodies against cariogenic bacteria, and peptide- and DNA-based vaccines aimed at pathogens' *colonization proteins*.^{106, 107} last, naturally-occurring compounds such as bioactive flavonoids, already shown to reduce caries in animal models, show promise in humans.¹⁰⁸ However, in light of their states of development and the lack of human research reports, none of these nascent technologies were reviewed by this panel.

Appendix 1: Critical Appraisal Worksheet

1. Study Citation

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2. Assessment of study quality for both randomized and nonrandomized studies

Criterion	Yes (1)	No (0)	Can't determine (0)
Reporting			
The following items attempt to assess if the authors have reported the study findings clearly in the publication			
1. <i>Is the hypothesis/aim/objective of the study clearly described?</i>			
2. <i>Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no</i>			
3. <i>Are the characteristics of the patients included in the study clearly described? In trials, inclusion and/or exclusion criteria should be given for the subjects.</i>			
4. <i>Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.</i>			
5. <i>Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided. Look at baseline characteristics for each group</i>			
Age			
Gender			
SES			
Fluoride			
Diet			
6. <i>Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).</i>			
7. <i>Does the study provide estimates of the random variability in the data for the main outcomes? In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. One of these estimates should be reported, however, if the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.</i>			
8. <i>Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).</i>			
9. <i>Have the characteristics of patients lost to follow-up been described? This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. Also mark yes if the number AND caries status of those lost to follow-up were described. This should be answered no where a study does not report the number of patients or caries status of those lost to follow-up.</i>			
10. <i>Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?</i>			
External validity			
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.			
11. <i>Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.</i>			
12. <i>Were those subjects who were prepared to participate representative of the entire</i>			

<p><i>population from which they were recruited?</i> The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.</p>			
<p>13. <i>Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?</i> For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a special care setting unrepresentative of the general population</p>			
Internal validity - bias			
<p>14. <i>Was an attempt made to blind study subjects to the intervention they have received?</i> For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.</p>			
<p>15. <i>Was an attempt made to blind those measuring the main outcomes of the intervention?</i></p>			
<p>16. <i>If any of the results of the study were based on “data dredging”, was this made clear?</i> Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.</p>			
<p>17. <i>In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?</i> Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for the answer should be yes. Studies where differences in follow-up are ignored should be answered no.</p>			
<p>18. <i>Were the statistical tests used to assess the main outcomes appropriate?</i> The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.</p>			
<p>19. <i>Was compliance with the intervention/s reliable?</i> Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.</p>			
<p>20. <i>Were the main outcome measures used accurate (valid and reliable)?</i> For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.</p>			
Internal validity - confounding (selection bias)			
<p>21. <i>Were the patients in different intervention groups recruited from the same population</i></p>			
<p>22. <i>Were study subjects in different intervention groups recruited over the same period of time?</i> For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.</p>			
<p>23. <i>Were study subjects/ groups randomised to intervention groups?</i> Studies which claim that randomization was performed should be answered yes.</p>			
	Subject Level		
	Group Level		
<p>24. <i>Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? (allocation concealment before intervention begins)</i> All non-randomised studies should be answered no. Mark yes, if sequence was concealed from both staff and patients or all recruitment was complete before randomization began. If assignment was concealed from patients but not from staff, it should be answered no.</p>			
<p>25. <i>Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?</i> For randomized trials - Mark no if the trial has a significant loss to follow-up and did not describe the effect of this on the caries status. For nonrandomized trials –Mark yes if the groups that completed the study were similar in terms of the principle confounders or, if the groups were similar at baseline and there was no significant loss to follow-up or, if the authors had adjusted for differences in their analysis. This question should be answered no for nonrandomized trials if: the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.</p>			
<p>26. <i>Were losses of patients to follow-up taken into account?</i> If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, or authors had imputed values to account for those lost to follow-up the question should be answered yes. Additionally mark yes, if those lost to follow-up had a caries status similar to those remaining in the study.</p>			

<i>Power</i>			
27. Did the authors of the study base their sample size on power calculations apriori? <i>Sample sizes have been calculated apriori to detect a difference of x% and y%.</i>			
<i>Conflict of Interest</i>			
28. Was the study free of any potential conflicts of interest? <i>For example an study funded by a company that makes the product should be answered no</i>			

Appendix 2: List of Excluded Studies

1. J Clin Dent. 2009;20(3):87-92. Long-term clinical observation of dental caries in salivary hypofunction patients using a supersaturated calcium-phosphate remineralizing rinse. Singh ML, Papas AS. **EXCLUDE -- NOT A CONTROLLED TRIAL**
2. Caries Res. 1998;32(1):10-6. Caries development from 11 to 22 years of age: a prospective radiographic study. Prevalence and distribution. Mejäre I, Källestål C, Stenlund H, Johansson H. **No CONTROL GROUP**
3. Int Dent J. 1995 Feb;45 (1 Suppl 1):93-107. Stabilisation of rampant caries: polyol gums and arrest of dentine caries in two long-term cohort studies in young subjects. Mäkinen KK, Mäkinen PL, Pape HR Jr, Allen P, Bennett CA, Isokangas PJ, Isotupa KP. **EXCLUDE – Main papers included**
4. 7. Community Dent Health. 1992 Mar;9(1):3-10. Caries-risk-reducing effects of xylitol-containing chewing gum and tablets in confectionery workers in Finland. Masalin K. **Exclude- Not a controlled study**
5. Int J Paediatr Dent. 2009 Jul;19(4):263-73. Epub 2009 Mar 23. Oral health programme for preschool children: a prospective, controlled study. Meurman P, Pienihäkkinen K, Eriksson AL, Alanen P. **EXCLUDE – OHP confounder**
6. Oral Health Prev Dent. 2003;1(1):53-7. Effect of maternal use of chewing gums containing xylitol, chlorhexidine or fluoride on mutans streptococci colonization in the mothers' infant children. Thorild I, Lindau B, Twetman S. **EXCLUDE No comparable groups**
7. Fogorv Sz. 1980 Nov;73(11):321-9. [3-year experience with clinical experiments on sorbitol used at the Fót children's town] [Article in Hungarian] Bánóczy J, Hadas E, Esztári I, Fözy I, Szántó S, Felsővályi A, Albi I. PMID: 6936264 [PubMed - indexed for MEDLINE]
8. Schweiz Med Wochenschr. 1980 Feb 16;110(7):269-73. [Sugar substitutes in caries prevention] [Article in German] Hefti A.
9. J Biol Buccale. 1983 Sep;11(3):255-63. [Prevention of dental caries in Thailand: 3 fluoridated products submitted for comparative tests] [Article in French] Khambanonda S, Chandravejjsarn R, Barmes DE, Sardo Infirri J, Möller I. Stomatologia (Mosk). 1987 Mar-Apr;66(2):80-3. [New method of treating caries at the white-spot stage] [Article in Russian] Suntsov VG, Leint'ev VK, Distel' VA.
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