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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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 are not intended to define a standard of care and rather should be integrated with a practitioner's professional judgment and a patient's needs and preferences.

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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 to11. 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 water [4] and pit and fissure sealants [5-7] 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 *apriori*, 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
Title/abstract review Inclusion criteria: • *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* Exclusion criteria: • studies irrelevant to the topic • *in vitro* and animal studies • *in situ* 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 *Streptococcus mutans* • 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)
Full text review Exclusion criteria were: • 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 three [10-12] 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 instrument [14] 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 trials [15] 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	Strongly established by the best available evidence. 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.
Moderate	Based on preliminary determination from the current best available evidence. But confidence in the estimate is constrained by one or more factors such as: 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. 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.
Low	Available evidence is *insufficient* to support the statement or the statement is based on extrapolation from the best available evidence Evidence is insufficient or reliability of estimated effects is limited by factors such as: 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. More information may allow a reliable estimation of effects on health outcomes.

*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.

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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 = trail 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, particpants 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.

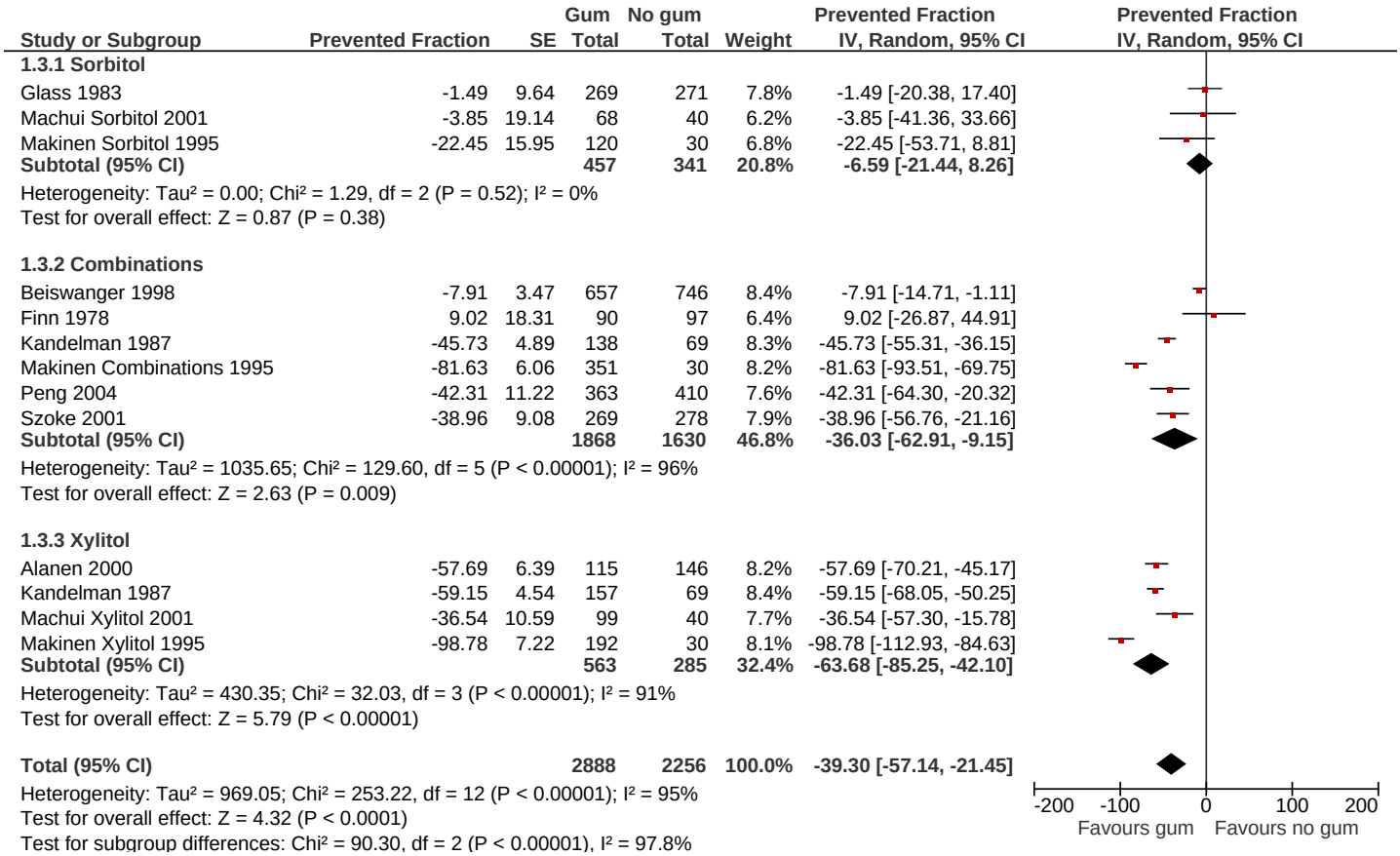
Sucrose-free polyol chewing gums versus no gum

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 study [21] 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 sealants[29], toothpastes[30] or a non-comparable outcome measure[26]. The panel also conducted additional analyses of the sub-group to determine if outcomes varied between different polyol sweetners. One study[25] 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** XS**p5) 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 randoomized 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]

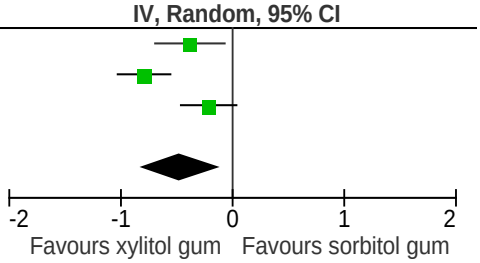
The results of meta-analysis of studies that recorded caries in permanent teeth indicate that there is a statistically significant reduction in caries with the use of sucrose-free polyol gums compared with no gum chewing. The preventive effect, however, was not the same for all types of polyols. Subgroup 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 errors[81], 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 gums[24-26]. Two studies [24, 25] reported DMFS while the other study[26] 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

Study or Subgroup	Xylitol Mean	Xylitol SD	Xylitol Total	Sorbitol Mean	Sorbitol SD	Sorbitol Total	Weight	Std. Mean Difference IV, Random, 95% CI
Machui 2001	3.3	3.05	99	5	5.89	68	31.3%	-0.38 [-0.69, -0.07]
Makinen 1995	0.06	4.9	192	3.8	4.38	120	34.6%	-0.79 [-1.03, -0.56]
Makinen 1996	2.37	2.97	126	3.07	3.53	123	34.1%	-0.21 [-0.46, 0.03]
Total (95% CI)			**417**			**311**	**100.0%**	**-0.47 [-0.83, -0.10]**

Heterogeneity: Tau² = 0.09; Chi² = 11.46, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 2.51 (P = 0.01)



Overall, there was significant statistical heterogeneity (I^2 = 95%) confirming clinical and or methodological differences amongst studies included in the metanalysis. 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 caries [18-32]

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 review [83] 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 develpoing 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 studies [32-35] that evaluated caries reduction with the use of xylitol candy/lozenges/tablets. One trial [34] 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 trial [35] 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 quality [35], one was fair [32] and the third [33] was judged to be of poor quality.

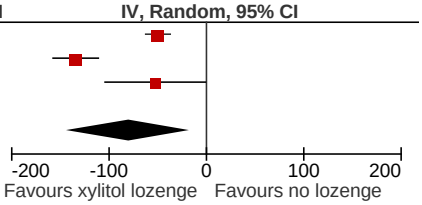
The panel combined the results from the three studies.[32, 33, 35] and found a statistically significant effect in favor of xylitol, lozenge/candy. Based on the limited number of studies the panel concluded with **low certainty** that:

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	SE	Xyl lozenge Total	No lozenge Total	Weight	Prevented Fraction 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-maltilol 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 tablets [35], the panel reviewed another study [36] 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 study[48] 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 study [50] reported fewer treatment failures and another[12] 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.

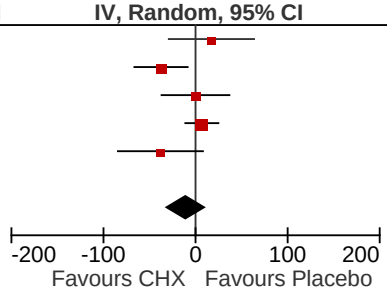
Chlorhexidine varnish.

The panel found five RCTs[51-55] 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 study[52] evaluated a 10 percent varnish. The panel rated the quality of two of these studies[51, 56] as fair and one study as good [52]. 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

Study or Subgroup	Prevented Fraction	SE	CHX Total	Placebo Total	Weight	Prevented Fraction IV, Random, 95% CI
de Soet 2002	17.33	23.63	99	95	14.4%	17.33 [-28.98, 63.64]
Du 2006	-37.5	14.74	155	135	22.9%	-37.50 [-66.39, -8.61]
Fennis-Le 1998	0	18.76	163	153	18.5%	0.00 [-36.77, 36.77]
Forgie 2000	6.89	9.16	222	274	29.7%	6.89 [-11.06, 24.84]
Jenatschke 2001	-38.1	23.53	18	15	14.5%	-38.10 [-84.22, 8.02]
Total (95% CI)			**657**	**672**	**100.0%**	**-9.54 [-32.07, 12.98]**

Heterogeneity: Tau² = 360.23; Chi² = 9.48, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 0.83 (P = 0.41)



Jenatschke: SD values imputed from available RCT's including Forgie, de Soet, Fennis-Le

Fennis-Le reports "mean number of affected permanent molars"

SENSITIVITY ANALYSIS Excluding studies with imputed SD's (Jenatschke –Also this was an Ortho study): -5.71 [-27.25, 15.84]

Excluding studies that reported all stages (de Soet): -14.36 [-39.98, 11.26]

Excluding both Jenetschke and de Soet:: -9.35 [-37.94, 19.23]

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 RCT[56] 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

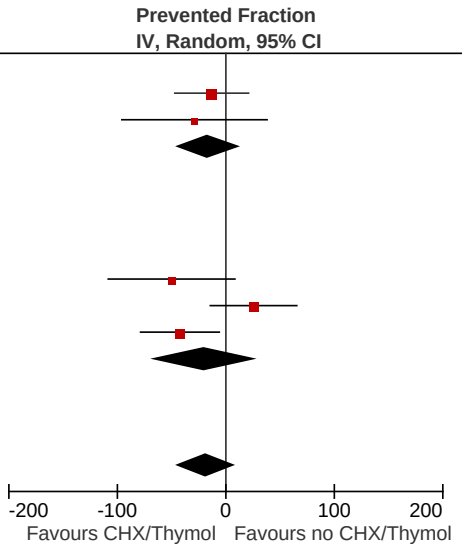
The panel found six studies[69-73, 75] evaluating the efficacy of a 1:1 mixture of chlorhexidine/thymol varnish (1:1 mixture is 1 percent chlorhexidine and 1 percent thymol). Three studies[72, 73, 75] compared a 1:1 mixture of chlorhexidine/thymol varnish

application to no varnish while three others[69-71] 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 study[72] evaluated vanish 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 one[73] specifically enrolled subjects at high-risk for caries. Only one of the RCT's[70] was judged to be of good quality while the remaining studies were all judged to be of poor quality.

One study [75] 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

Study or Subgroup	Prevented Fraction	SE	CHX/thymol Total	Control Total	Weight	Prevented Fraction IV, Random, 95% CI
1.1.2 Cervitec vs. placebo or no varnish						
Baca 2004	-12.99	17.34	86	95	26.0%	-12.99 [-46.98, 21.00]
Plotzitza 2005	-28.89	34.17	23	24	12.1%	-28.89 [-95.86, 38.08]
Subtotal (95% CI)			**109**	**119**	**38.1%**	**-16.25 [-46.55, 14.06]**
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
1.1.3 Cervitec + NaF vs. NaF						
Ogaard 2001	-50	29.8	110	110	14.6%	-50.00 [-108.41, 8.41]
Peterson 1998	25.58	20.33	115	104	22.6%	25.58 [-14.27, 65.43]
Splieth 2000	-42.31	18.5	29	25	24.6%	-42.31 [-78.57, -6.05]
Subtotal (95% CI)			**254**	**239**	**61.9%**	**-20.46 [-69.43, 28.50]**
Heterogeneity: Tau² = 1353.03; Chi² = 7.47, df = 2 (P = 0.02); I² = 73%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)			**363**	**358**	**100.0%**	**-18.82 [-46.27, 8.62]**
Heterogeneity: Tau² = 453.05; Chi² = 7.66, df = 4 (P = 0.10); I² = 48%						
Test for overall effect: Z = 1.34 (P = 0.18)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



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 study[68] 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]

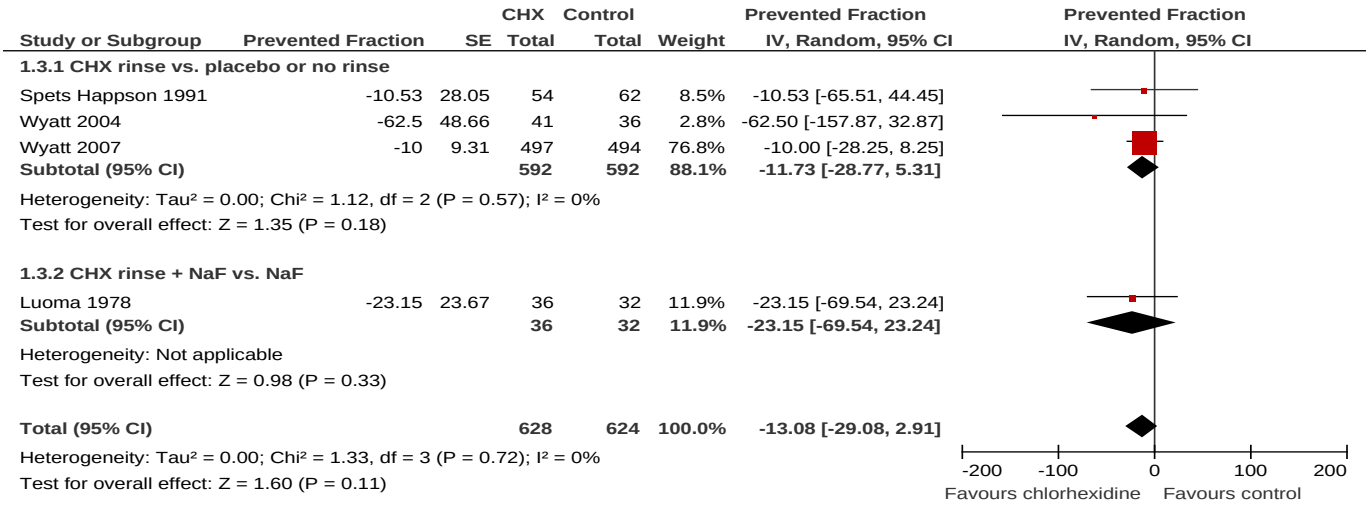
The panel found three RCT's[10, 76, 77] evaluating the efficacy of 1:1 chlorhexidine/thymol varnish on root caries. They judged two[10, 76] to be of good quality while the third[77] was fair in quality. Two studies[10, 76] showed a statistically significant reduction in the incidence of caries with the use of chlorhexidine/thymol varnish compared to placebo or no varnish. In the third study conducted in high-risk patients[77], 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 four [64-67] RCT's evaluating the efficacy of 0.12 percent chlorhexidine mouthrinse. Three studies[64-66] compared chlorhexidine rinse with placebo or no rinse; one study [67] compared rinse with chlorhexidine and fluoride to fluoride-only rinse. One study [64] was judged to be of good quality while all other studies were judged to be of fair quality. One study [66] 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



Luoma: We pooled data for all the surfaces to get the combined DMFS score

Based on these four RCT's judged to be fair or good quality and the results of the metanalysis 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 studies[58-62] 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 study[62] also conducted in the general population compared brushing at home with 0.5 percent gel compared to brushing with a placebo gel. Only three studies[60-62] 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 study[57] 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 RCT[63] 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 *Steptococcus 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 studies[39-47] 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 one[39] were RCT's.

One study[42], 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 study[41] 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 study[46] 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 dentifrice[39] and the other evaluated the agent in mints[40]. The dentifrice study[39] 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 study[43] 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 study[45] 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 study[44] 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 study[47] 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 RCT[78] 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 RCT[80] evaluated 10 percent chlorhexidine varnish and reported nonsignificant difference in caries increment while the other controlled trial[79] evaluated 1 percent chlorhexidine gel and reported a statistically significant reduction in caries experience. The fourth study[11] 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.

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.	
Evidence-based recommendations	***Strength*** *(refer to Table 2 for definitions)*
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
*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.	

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 re-mineralization 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) guidelines[101] 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 quality[14] 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 review [2]. 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

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. *Is the hypothesis/aim/objective of the study clearly described?*			
2. *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			
3. *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.			
4. *Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.			
5. *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			
Age			
Gender			
SES			
Fluoride			
Diet			
6. *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).			
7. *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.			
8. *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).			
9. *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.			
10. *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?*			
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. *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.			
12. *Were those subjects who were prepared to participate representative of the entire*			

population from which they were recruited? 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.			
13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?* 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			
Internal validity - bias			
14. *Was an **attempt made** to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.			
15. *Was an **attempt made** to blind those measuring the main outcomes of the intervention?*			
16. *If any of the results of the study were based on "data dredging", was this made clear?* 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.			
17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?* 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.			
18. *Were the statistical tests used to assess the main outcomes appropriate?* 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.			
19. *Was compliance with the intervention/s reliable?* 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.			
20. *Were the main outcome measures used accurate (valid and reliable)?* 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.			
Internal validity - confounding (selection bias)			
21. *Were the patients in different intervention groups recruited from the same population*			
22. *Were study subjects in different intervention groups recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.			
23. *Were study subjects/ groups randomised to intervention groups?* Studies which claim that randomization was performed should be answered yes.			
Subject Level			
Group Level			
24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? (allocation concealment before intervention begins)* 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.			
25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* 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.			
26. *Were losses of patients to follow-up taken into account?* 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.			

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

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. Mejàre 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, Felsövályi 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, Chandravejjsmarn R, Barmes DE, Sardo Infirri J, Möller I. Stomatologiia (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.
10. Orv Hetil. 1985 Oct 6;126(40):2447-51. [Caries-preventing action of xylitol-containing sweets, studied in children's institutions] [Article in Hungarian] Bánóczy J, Scheinin A, Esztári I, Szöke J, Hadas E, Zimmermann P.
11. Chir Dent Fr. 1985 Apr 25;55(292):41-8. [The effect of sugars and sugar alcohols on dental caries] [Article in French] Blot B. Int Dent J. 1976 Mar;26(1):4-13. Caries control through the use of sugar substitutes. Scheinin A. Exclude - We have the primary studies
12. Int Dent J. 1996 Feb;46(1):22-34. Conclusion and review of the Michigan Xylitol Programme (1986-1995) for the prevention of dental caries. Mäkinen KK, Mäkinen PL, Pape HR Jr, Peldyak J, Hujoel P, Isotupa KP, Soderling E, Isokangas PJ, Allen P, Bennett C. Exclude- Look for primary studies
13. Acta Odontol Scand. 1996 Aug;54(4):211-6. Timing of first restorations before, during, and after a preventive xylitol trial. Virtanen JI, Bloigu RS, Larmas MA. EXCLUDE – No relevant outcome Find the primary study
14. Oral Health Prev Dent. 2003;1(3):195-9. Effect of xylitol-containing chewing gums on lactic acid production in dental plaque from caries active pre-school children. Twetman S, Stecksén-Blicks C. EXCLUDE Prospective cross-over design
15. Proc Finn Dent Soc. 1989;85(1):21-4. Correlation between caries incidence and frequency of chewing gum sweetened with sucrose or xylitol. Rekola M. Exclude this one primary study included
16. Caries Res. 1991;25(1):74-9. Caries-preventive effect of dentifrices containing various types and concentrations of fluorides and sugar alcohols. Petersson LG, Birkhed D, Gleerup A, Johansson M, Jönsson G. EXCLUDE – FLUORIDE AS A CONFOUNDER since different F use between arms
17. Caries Res. 1991;25(6):444-8. Dental caries and mutans streptococci in the proximal areas of molars affected by the habitual use of xylitol chewing gum. Isokangas P, Tenovuo J, Söderling E, Männistö H, Mäkinen KK. EXCLUDE but make sure to look for the original study
18. Acta Odontol Scand. 2000 Dec;58(6):285-92. Efficacy of a slow-release device containing fluoride, xylitol and sorbitol in preventing infant caries. Aaltonen AS, Suhonen JT, Tenovuo J, Inkilä-Saari I. EXCLUDE – Not evaluating the agent
19. 25. Acta Odontol Latinoam. 2008;21(2):181-7. Comprehensive attention to oral health in early childhood: a longitudinal evaluation of the Infant Clinic Program of the Federal University of Rio Grande do Sul, Brazil. Figueiredo MC, Guarienti CA, Michel JA, Sampaio MS.EXCLUDE – NOT A CONTROLLED TRIAL
20. J Ir Dent Assoc. 2002;48(3):103. Study shows chewing sugarfree gum after meals and snacks helps reduce tooth decay by up to 40 per cent. [No authors listed] PMID: 12483793 EXCLUDE – Not the primary paper
21. Eur Arch Paediatr Dent. 2006 Dec;7(4):241-5. Caries in 4-year-old children after maternal chewing of gums containing combinations of xylitol, sorbitol, chlorhexidine and fluoride. Thorild I, Lindau B, Twetman S. EXCLUDE_ Groups not comparable
22. Acta Odontol Scand. 2004 Oct;62(5):245-50. Salivary mutans streptococci and dental caries in three-year-old children after maternal exposure to chewing gums containing combinations of xylitol, sorbitol, chlorhexidine, and fluoride. Thorild I, Lindau B, Twetman S. EXCLUDE – groups not comparable
23. Tandlaegebladet. 1974 Jan;78(1):1-11. [Effect of sorbitol-containing chewing gum on the occurrence of dental caries, plaque, and gingivitis] [Article in Danish] Moller IJ, Poulsen S. PMID: 4156097 [PubMed - indexed for MEDLINE] Duplicate
24. Rev Asoc Odontol Argent. 1981 Jun;69(4):199-206. [The use of fluoride and chlorhexidine for the prevention of radiation caries] [Article in Spanish] Katz S. PMID: 6947321 [PubMed - indexed for MEDLINE]
25. Bol Inf Dent (Madr). 1980 Mar-Apr;40(305):27-4. [Use of chlorhexidine and fluorides for the prevention of radiation caries] [Article in Spanish]
26. Community Dent Oral Epidemiol. 1976 Nov;4(6):232-9. The effect of various plaque control measures on gingivitis and caries in schoolchildren. Axelsson P, Lindhe J, Wäseby J. EXCLUDE – Does not evaluate the agent
27. Clin Oral Investig. 1998 Sep;2(3):137-42. Effect on caries experience of a long-term preventive program for mothers and children starting during pregnancy. Günay H, Dmoch-Bockhorn K, Günay Y, Geurtsen W. EXCLUDE - FLUORIDE AS A CONFOUNDER
28. J Clin Periodontol. 1993 Feb;20(2):130-8. A 6-month home usage trial of a 1% chlorhexidine toothpaste (1). Effects on plaque, gingivitis, calculus and toothstaining. Yates R, Jenkins S, Newcombe R, Wade W, Moran J, Addy M. EXCLUDE – But consider as background for local adverse effect

29. Acta Odontol Scand. 2004 Dec;62(6):339-42. Effect of topical applications of a chlorhexidine/thymol-containing varnish on fissure caries assessed by laser fluorescence. Sköld-Larsson K, Fornell AC, Lussi A, Twetman S. EXCLUDE – Split mouth
30. Stomatologija. 2007;9(4):129-36. Dynamics of pregnant women's oral health status during preventive programme. Vasiliauskiene I, Milciuviene S, Bendoraitiene E, Narbutaite J, Slabsinskiene E, Andruskeviciene V. EXCLUDE – FLUORIDE CONFOUNDER since no positive control
31. Caries Res. 2007;41(5):384-91. Noninvasive control of dental caries in children with active initial lesions. A randomized clinical trial. Hausen H, Seppa L, Poutanen R, Niinimaa A, Lahti S, Kärkkäinen S, Pietilä I. EXCLUDE – Fluoride COUNFOUNDER
32. J Clin Dent. 2000;11(2):42-6. Effect of chlorhexidine varnish on bacterial levels in plaque and saliva during orthodontic treatment. Madléna M, Vitalyos G, Márton S, Nagy G. Exclude Split mouth
33. Caries Res1992 26 (4) 275 – 280 Effects of chlorhexidine-fluoride gel treatments in mothers on the establishment of mutans streptococci in primary teeth and the development of dental caries in children Tenovuo J, Hakkinen P, Paunio P, Emilson CG EXCLUDE – Fluoride confounder
34. Caries Res. 1992;26(5):384-90. Caries incidence, mutans streptococci and lactobacilli in irradiated patients during a 12-month preventive programme using chlorhexidine and fluoride. Joyston-Bechal S, Hayes K, Davenport ES, Hardie JM. EXCLUDE Not a controlled trial
35. Int Dent J. 1995 Aug;45(4):245-54. A study into the prevention of fissure caries using an antimicrobial varnish. Bratthall D, Serinirach R, Rapisuwon S, Kuratana M, Luangjarmekorn V, Luksila K, Chaipanich P. EXCLUDE- Short follow-up with split mouth
36. J Periodontal Res. 1982 Jan;17(1):101-11. Effects of supervised chlorhexidine mouthrinses in children. A longitudinal clinical trial. Lang NP, Hotz P, Graf H, Geering AH, Saxer UP, Sturzenberger OP, Meckel AH. EXCLUDE – Short follow-up and perio
37. J Dent. 2001 May;29(4):247-54. Prevention of pit and fissure caries using an antimicrobial varnish: 9 month clinical evaluation. Joharji RM, Adenubi JO. EXCLUDE – Short follow-up and split mouth
38. Quintessence Int. 2009 Apr;40(4):279-85. Effect of xylitol and sorbitol on plaque acidogenesis. Splieth CH, Alkilzy M, Schmitt J, Berndt C, Welk A. Exclude –Short follow-up and no caries outcome
39. J Clin Periodontol. 1993 Jan;20(1):20-5. Evaluation of a mouthrinse containing chlorhexidine and fluoride as an adjunct to oral hygiene. Jenkins S, Addy M, Newcombe R. Chlorhexidine and fluoride have valuable preventive roles in dental and oral diseases. EXCLUDE – Short follow-up and perio
40. Braz Dent J. 2003;14(2):75-81. Epub 2003 Oct 3. Effect of caries preventive measures directed to expectant mothers on caries experience in their children. Zanata RL, Navarro MF, Pereira JC, Franco EB, Lauris JR, Barbosa SH. EXCLUDE – FLUORIDE CONFOUNDER
41. Community Dent Oral Epidemiol. 2000 Feb;28(1):26-34. Application of the high-risk strategy to control dental caries. Hausen H, Kärkkäinen S, Seppä L. EXCLUDE – FLUORIDE CONFOUNDER
42. 46. Medical Journal of Australia 2005; 182(2): 85-86. Does chewing sucrose-free chewing gum after meals reduce the development of carious lesions? EXCLUDE – Summary of study. Primary study included
43. Rev Chir Oncol Radiol O R L Oftalmol Stomatol Ser Stomatol. 1988 Jan-Mar;35(1):65-8. [Evaluation of the efficiency of the cariopreventive chewing gum produced in Romania] [Article in Romanian] Grivu O, Pop OA, Pop M, Grivu M, Barbu D, Pop E, Halawi M, Mihălceanu I, Veină M. PMID: 2978344 [PubMed - indexed for MEDLINE] EXCLUDE Non ENGLISH
44. Gerodontology. 1999 Jul;16(1):2-10. Double blind clinical trial of a remineralizing dentifrice in the prevention of caries in a radiation therapy population. Papas A, Russell D, Singh M, Stack K, Kent R, Triol C, Winston A. EXCLUDE INTERIM RESULTS MAIN PAPER INCLUDED
45. J Periodontol. 2007 Aug;78(8):1505-14. Comparative efficacy of stabilized stannous fluoride/sodium hexametaphosphate dentifrice and sodium fluoride/triclosan/copolymer dentifrice for the prevention of periodontitis in xerostomic patients: a 2-year randomized clinical trial. Papas A, He T, Martuscelli G, Singh M, Bartizek RD, Biesbrock AR.EXCLUDE PERIO
46. Caries Res. 1998;32(2):107-12. A descriptive report of the effects of a 16-month xylitol chewing-gum programme subsequent to a 40-month sucrose gum programme. Mäkinen KK, Hujoel PP, Bennett CA, Isokangas P, Isotupa K, Pape HR Jr, Mäkinen PL. EXCLUDE – No data for the control group
47. Gerodontics. 1987 Feb;3(1):47-50. Remineralization of carious lesions in elderly patients. Johansen E, Papas A, Fong W, Olsen TO. EXCLUDE NOT controlled trial
48. Caries Res. 1987;21(1):87-94. Approximal caries development during 2-year total substitution of dietary sucrose with xylitol. Rekola M. EXCLUDE ANALYSIS OF TURKU DATASET
49. Proc Finn Dent Soc. 1986;82(4):213-8. A planimetric evaluation of approximal caries progression during one year of consuming sucrose and xylitol chewing gums. Rekola M. EXCLUDE ANALYSIS OF TURKU DATASET
50. Dtsch Zahnarztl Z. 1977;32(5 Suppl 1):S66-70. Sorbitol containing chewing gum and its significance for caries prevention. Moller IJ. PMID: 266470 [PubMed - indexed for MEDLINE] EXCLUDE. Same as 1973 paper by authors
51. Caries Res. 1990;24(3):220-3. Cariological studies of individuals with long-term sorbitol consumption. Birkhed D, Svensäter G, Edwardsson S. EXCLUDE NOT CONTROLLED TRIAL
52. J Can Dent Assoc. 1988 Aug;54(8):595-8. Effect of a daily 0.2% chlorhexidine rinse on the oral health of an institutionalized elderly population. Yanover L, Banting D, Grainger R, Sandhu H. PMID: 3048596 [PubMed - indexed for MEDLINE] EXCLUDE NOT on caries
53. International journal of paediatric dentistry 2003 13 (Suppl 1) 60 Antimicrobial effect of povidone iodine solution on children with caries Montalvo M, Perez O, Ortega J, Velasco C EXCLUDE FULL TEXT Not available
54. Caries-Res 2003 37(4) 272; Povidone-iodine as an oral antiseptic in children with early childhood caries. Zhan L, Den Besten PK, Gansky SA, Hoover CI, et alEXCLUDE – Full Text not available
55. SADJ. 2005 Jul;60(6):248-51. Effect of after-meal sucrose-free gum-chewing on clinical caries. Szöke J, Bánóczy J.. EXCLUDE REPRINT
56. Community Dent Oral Epidemiol. 1989 Aug;17(4):200-3. Long-term effect of xylitol chewing gum on dental caries. Isokangas P, Tiekso J, Alanen P, Mäkinen KK. Isolated high-risk group and then made them chew one more year to find effect. No baseline numbers for the first study or in this one.
57. Proc Finn Dent Soc. 1987;83 Suppl 1:1-117. Xylitol chewing gum in caries prevention. A longitudinal study on Finnish school children. Isokangas P. THESIS. Author has several publications that are included
58. J Clin Dent. 2008;19(1):18-21. Effect of chlorhexidine-thymol varnish on caries lesion development in first permanent molars. Rodrigues CR, Marquezan M, Barroso LP, Grande RH, Myaki SI, Kabakura V, Miyamura A. EXCLUDE Split mouth design
59. Dent Res. 1987 Mar;66(3):761-5. A 30-month longitudinal study of the effects of some oral hygiene measures on Streptococcus mutans and approximal dental caries. Axelsson P, Kristoffersson K, Karlsson R, Bratthall D. EXCLUDE – Fluoride as a confounder

60. Caries Res. 2003 May-Jun;37(3):185-9. Effect of a varnish containing chlorhexidine and thymol (Cervitec) on approximal caries in 13- to 16-year-old schoolchildren in a low caries area. Haukali G, Poulsen S. Split mouth design. No baseline scores
61. Caries Res. 2002 Sep-Oct;36(5):373-6. Effect of Cervitec on mutans streptococci in plaque and on caries formation on occlusal fissures of erupting permanent molars. Araujo AM, Naspitz GM, Chelotti A, Cai S. No baseline results. Split mouth design
62. Chlorhexidine in cleft lip and palate patients with multibracket appliances. Results of a prospective study on the effectiveness of two different chlorhexidine preparations in cleft lip and palate patients with multibracket appliances. [Article in English, German] Weiss M, Weiss J, Müller-Hartwich R, Meier B, Jost-Brinkmann PG EXCLUDE – No concurrent control group
63. Oral Health. 1995 Sep;85(9):29-30. Effect of a chlorhexidine varnish on caries lesions. Bretz WA, Djahjah CA, Almeida RS, Villar do Valle E, Fonseca C, Valente I, Seabra G, Chiesa C. PMID: 8779742 [PubMed - indexed for MEDLINE] NO DATA reported
64. Pediatr Dent. 2004 Jan-Feb;26(1):5-10. Effect of povidone-iodine on Streptococcus mutans in children with extensive dental caries. Amin MS, Harrison RL, Benton TS, Roberts M, Weinstein P. Caries not an outcome. Only Strep scores
65. Pediatr Dent. 1999 Jan-Feb;21(1):9-11. Topical antimicrobial therapy in the prevention of early childhood caries. Lopez L, Berkowitz R, Zlotnik H, Moss M, Weinstein P. EXCLUDE Baseline scores not reported
66. Gerodontology. 2003 Jul;20(1):9-14. Non-invasive management of superficial root caries lesions in disabled and infirm patients. Johnson G, Almqvist H.EXCLUDED. No baseline data
67. ASDC Journal of Dentistry for Children 1992 59(4) 313-8 Caries preventive effect of high fluoride and xylitol containing dentifrices. Cutress T, Howell PT, Finidori C, Abdullah F Data not reported for the xylitol groups
68. J Public Health Dent. 2009 Summer;69(3):201-3. Evaluation of Pacific Islands Early Childhood Caries Prevention Project: Republic of the Marshall Islands. Milgrom P, Tut OK. EXCLUDE – Data from groups 2 and 3 combined for this paper
69. Spec Care Dentist. 1996 May-Jun;16(3):104-15. Polyol-combinant saliva stimulants and oral health in Veterans Affairs patients--an exploratory study. Mäkinen KK, Pemberton D, Mäkinen PL, Chen CY, Cole J, Hujoel PP, Lopatin D, Lambert P. EXCLUDE – Compares xylitol versus sorbitol
70. Quintessence Int. 2008 Feb;39(2):e45-51. Effectiveness of 2-year application of school-based chlorhexidine varnish, sodium fluoride gel, and dental health education programs in high-risk adolescents. Ersin NK, Eden E, Eronat N, Totu FI, Ates M. No Baseline data
71. Gerodontology. 2000 Dec;17(2):67-76. The effectiveness of 10% chlorhexidine varnish treatment on dental caries incidence in adults with dry mouth. Banting DW, Papas A, Clark DC, Proskin HM, Schultz M, Perry R. No Baseline Data
72. Caries Res. 1999 Sep-Oct;33(5):333-9. Caries prevention in a community-dwelling older population. Powell LV, Persson RE, Kiyak HA, Hujoel PP. No Baseline data
73. J Dent Res. 2006 May;85(5):469-72. Caries-inhibiting effect of chlorhexidine varnish in pits and fissures. Zhang Q, van 't Hof MA, Truin GJ, Bronkhorst EM, van Palenstein Helderman WH. No baseline Data and split mouth
74. J Nihon Univ Sch Dent. 1980 Sep;22(2):65-9. A study on the preventive effect of dental caries by chlorhexidine mouthwash. Okada K. PMID: 6934272 [PubMed - indexed for MEDLINE]No baseline Data
75. Scand J Dent Res. 1975 Sep;83(5):288-92. Effect of 2-years' use of chlorhexidine-containing dentifrices on plaque, gingivitis, and caries. Johansen JR, Gjermo P, Eriksen HM. NO Baseline Data
76. Scand J Dent Res. 1980 Feb;88(1):22-7.Caries increment and gingival status during 2 years' use of chlorhexidine- and fluoride-containing dentifrices. Dolles OK, Gjermo P. NO Baseline Data
77. J Dent Res. 1997 Apr;76(4):867-74. The effects of simple interventions on tooth mortality: findings in one trial and implications for future studies. Hujoel PP, Powell LV, Kiyak HA. EXCLUDE – No baseline or caries specific data
78. The effectiveness of three different strengths of chlorhexidine mouthrinse. Clark DC, Guest JL 1994 EXCLUDE No relevant outcomes
79. The effect of medicated chewing gums on oral health in frail older people: a 1-year clinical trial. Simons D, Brailsford SR, Kidd EA, Beighton D 2002 EXCLUDE No relevant outcomes
80. Comparative three-year caries protection from an aluminum-containing and a fluoride-containing toothpaste. Heidmann J, Poulsen S 1997 EXCLUDE Not evaluating agent
81. Clinical evaluation of an aged stannous fluoride-calcium pyrophosphate dentifrice Zacherl WA 1972 EXCLUDE Evaluating Fluoride
82. Fluoride and casein phosphopeptide-amorphous calcium phosphate. Reynolds EC, Cai F, Cochrane NJ, Shen P, Walker GD, Morgan MV, Reynolds C 2008 EXCLUDE- in situ
83. Anticaries efficacy of a triclosan.copolymer/NaF dentifric in vivo. (Orlando Congress Abstracts1996) Zhang Y, Sullivan R, Din C, Miller S, Schmid R, et al 1996 EXCLUDE
84. Pharmacol Ther Dent. 1980;5(1-2):11-6. Effect on dental caries of a stannous fluoride-calcium pyrophosphate dentrifice in an adult population: one-year results. Lu KH, Hanna JD, Peterson JK. EXCLUDE – FLUORIDE STUDY
85. J Prev Dent. 1977 Mar-Apr;4(2):8-14. Evaluation of sugar substitutes in preventive cariology. Imfeld T, Mühlemann HR. Could not find
86. J Can Dent Assoc (Tor). 1972 Apr;38(4):155-7. Clinical evaluation of an aged stannous fluoride-calcium pyrophosphate dentifrice. Zacherl WA. EXCLUDE_ FLUORIDE STUDY
87. J Am Dent Assoc. 1970 Jul;81(1):118-24. Effect of a combination of two cariostatic agents in children: two-year clinical study of supervised brushing in children's homes. Thomas AE, Jamison HC. EXCLUDE- SODIUM LAURL SACROCINATE
88. J Can Dent Assoc (Tor). 1970 Jun-Jul;36(7):262-4. Final report on the efficacy of a stannous fluoride-calcium pyrophosphate dentifrice. Zacherl WA, McPhail CW. EXCLUDE_ FLUORIDE STUDY
89. J Am Dent Assoc. 1966 Oct;73(4):853-5. Effectiveness of a SnF2-Ca2P2O7 dentifrice on dental caries in children whose teeth calcified in a natural fluoride area. II. Results at the end of 24 months. Gish CW, Muhler JC. EXCLUDE_ FLUORIDE STUDY
90. Xylitol based caries prevention without professionals suggests cost-effectiveness Alanen P, Isokangas P, Gutmann K 1998 EXCLUDE – Not relevant
91. Effect on dental caries of a stannous fluoride-calcium pyrophosphate dentrifice in an adult population: one-year results. Lu KH, Hanna JD, Peterson JK 1980 EXCLUDE Fluoride Study
92. A clinical trial of a calcium carbonate base dentifrice containing 0.76% sodium monofluorophosphate Glass RL,Shiere FR 1978 EXCLUDE Fluoride Study
93. Caries control through the use of sugar substitutes. Scheinin A 1976 EXCLUDE Summary of Turku Study

94. Xylitol in relation to the incidence of dental caries. Scheinin A 1976 EXCLUDE TURKU STUDY
95. The effect of a preventive programme on dental plaque, gingivitis and caries in schoolchildren Results after one and two years Axelsson P, Lindhe J 1974 EXCLUDE FLUORIDE STUDY
96. Caries-inhibiting action of three different topically-applied agents on incipient lesions in newly erupted teeth: results after 24 months. Hyde EJ 1973 EXCLUDE Fluoride Study
97. Effects of chlorhexidine-containing dentifrices. Gjermo P, Eriksen H 1972 EXCLUDE Abstract only
98. J Dent Res. 1997 Nov;76(11):1776-81. A three-year clinical trial of a combination of trimetaphosphate and sodium fluoride in silica toothpastes. O'Mullane DM, Kavanagh D, Ellwood RP, Chesters RK, Schafer F, Huntington E, Jones PR. Evaluates STMP
99. Caries Res. 1996;30(6):418-22. The effect of sodium trimetaphosphate on caries: a 3-year clinical toothpaste trial. Städtler P, Müller-Bruckschwaiger K, Schäfer F, Huntington E. Evaluates STMP
100. Community Dent Oral Epidemiol. 1983 Jun;11(3):143-7. Caries preventive effects of toothpastes containing monofluorophosphate and trimetaphosphate: a 3-year clinical trial. Andlaw RJ, Palmer JD, King J, Kneebone SB. Evaluates STMP
101. Caries Res. 1983;17(3):267-76. A four-year clinical study to determine the caries-inhibiting effect of calcium glycerophosphate and sodium fluoride in calcium carbonate base dentifrices containing sodium monofluorophosphate. Mainwaring PJ, Naylor MN.Evaluates Calcium glycerophosphate
102. Caries Res. 1979;13(1):39-46. A 3-year clinical trial of calcium carbonate dentifrice containing calcium glycerophosphate and sodium monofluorophosphate. Naylor MN, Glass RL. Evaluates Calcium glycerophosphate
103. A 3-year clinical trial of calcium carbonate dentifrice containing calcium glycerophosphate and sodium monofluorophosphate Naylor MN,Glass RL 1979 Evaluates Calcium glycerophosphate
104. Int J Paediatr Dent. 2008 Nov;18(6):446-51. Epub 2008 May 16. Association of chlorhexidine and fluoride for plaque control and white spot lesion remineralization in primary dentition. de Amorim RG, Leal SC, Bezerra AC, de Amorim FP, de Toledo OA. EXCLUDE – Short follow-up and WSL
105. J Dent Res. 2009 Dec;88(12):1148-53. Epub 2009 Nov 3. Regression of post-orthodontic lesions by a remineralizing cream. Bailey DL, Adams GG, Tsao CE, Hyslop A, Escobar K, Manton DJ, Reynolds EC, Morgan MV. EXCLUDE- Short follow-up and WSL
106. Inhibition of experimental caries by plaque prevention. The effect of chlorhexidine mouthrinses Loe H, Von der Fehr FR, Schiott CR 1972 No caries outcome
107. J Am Dent Assoc. 1967 Apr;74(5):987-95. The effect of a dicalcium phosphate chewing gum on caries incidence in children: 30-month results. Finn SB, Jamison HC. EXCLUDE They had one arm that compared a sugarless gum. But the other two has sugar i.e. sugar gum and sugar gum with phosphate
108. J Int Assoc Dent Child. 1981 Dec;12(2):59-63. Three-year results with sorbitol in clinical longitudinal experiments. Bánóczy J, Hadas E, Esztáry I, Marosi I, Nemes J. PMID: 7042853 [PubMed - indexed for MEDLINE] EXCLUDE SUCROSE is the control
109. Acta Odontol Scand. 1975;33(5):269-78. Turku sugar studies XVIII. Incidence of dental caries in relation to 1-year consumption of xylitol chewing gum. Scheinin A, Mäkinen KK, Tammisalo E, Rekola M. EXCLUDE Sucrose is the control group
110. Acta Odontol Scand. 1976;34(4):179-216. Turku sugar studies. V. Final report on the effect of sucrose, fructose and xylitol diets on the caries incidence in man. Scheinin A, Mäkinen KK, Ylitalo K. EXCLUDE – Sucrose is the control group
111. Quintessence Int. 2005 Mar;36(3):183-9. Use of laser fluorescence in monitoring the durability and cariostatic effects of fluoride and chlorhexidine varnishes on occlusal caries: a clinical study. Gokalp S, Başeren M. EXCLUDE-Short follow-up using diagnodent. No caries outcome
112. Effects of chlorhexidine-containing gel and varnish on abutment teeth in patients with overdentures. Keltjens HM, Creugers TJ, Schaeken MJ, Van der Hoeven JS 1992 Inconsistent intervention
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