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Xylitol for preventing acute otitis media in children up to 12 years of age (Review)

Azarpazhooh A, Lawrence HP, Shah PS

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[Intervention Review]

Xylitol for preventing acute otitis media in children up to 12 years of age

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ABSTRACT

Background

Acute otitis media (AOM) is the most common bacterial infection among young children in the United States. There are limitations and concerns over its treatment with antibiotics and surgery and so effective preventative measures are attractive. A potential preventative measure is xylitol, a natural sugar substitute that reduces the risk of dental decay. Xylitol can reduce the adherence of *Streptococcus pneumoniae* (*S pneumoniae*) and *Haemophilus influenzae* (*H influenzae*) to nasopharyngeal cells in vitro. This is an update of a review first published in 2011.

Objectives

To assess the efficacy and safety of xylitol to prevent AOM in children aged up to 12 years.

Search methods

We searched CENTRAL (to Issue 12, 2015), MEDLINE (1950 to January 2016), Embase (1974 to January 2016), CINAHL (1981 to January 2016), LILACS (1982 to January 2016), Web of Science (2011 to January 2016) and International Pharmaceutical Abstracts (2000 to January 2016).

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs of children aged 12 years or younger where xylitol supplementation was compared with placebo or no treatment to prevent AOM.

Data collection and analysis

Two review authors independently selected trials from search results, assessed and rated study quality and extracted relevant data for inclusion in the review. We contacted trial authors to request missing data. We noted data on any adverse events of xylitol. We extracted data on relevant outcomes and estimated the effect size by calculating risk ratio (RR), risk difference (RD) and associated 95% confidence intervals (CI).

Main results

We identified five clinical trials that involved 3405 children for inclusion. For this 2016 update, we identified one new trial for inclusion. This trial was systematically reviewed but due to several sources of heterogeneity, was not included in the meta-analysis. The remaining four trials were of adequate methodological quality. In three RCTs that involved a total of 1826 healthy Finnish children attending daycare, there is moderate quality evidence that xylitol (in any form) can reduce the risk of AOM from 30% to around 22% compared with the control group (RR 0.75, 95% CI 0.65 to 0.88). Among the reasons for dropouts, there were no significant differences in abdominal discomfort and

rash between the xylitol and the control groups. Xylitol was not effective in reducing AOM among healthy children during a respiratory infection (RR 1.13, 95% CI 0.83 to 1.53; moderate quality evidence) or among otitis-prone healthy children (RR 0.90, 95% CI 0.67 to 1.21; low-quality evidence).

Authors' conclusions

There is moderate quality evidence showing that the prophylactic administration of xylitol among healthy children attending daycare centres can reduce the occurrence of AOM. There is inconclusive evidence with regard to the efficacy of xylitol in preventing AOM among children with respiratory infection, or among otitis-prone children. The meta-analysis was limited because data came from a small number of studies, and most were from the same research group.

PLAIN LANGUAGE SUMMARY

Xylitol sugar supplement for preventing middle ear infection in children up to 12 years of age

Review question
We reviewed the evidence about the effectiveness and safety of xylitol to prevent acute middle ear infection (acute otitis media; AOM) in children up to 12 years old.

Background
AOM is the most common bacterial infection among young children in the United States. Although serious complications are rare, this common childhood ailment imposes a huge impact on the healthcare system. In the United States, it accounted for almost 20 million office visits. Antibiotic treatment of AOM is costly and raises concerns about the development of antibiotic-resistant strains of bacteria. Surgery is invasive and costly, and because of these factors, effective measures for preventing AOM are sought. An alternative treatment is xylitol or birch sugar. Xylitol has been used for decades as a natural non-sugar sweetener principally in chewing gums, confectionery, toothpaste and medicines, and can reduce the risk of tooth decay.

Search date

We searched the literature up to January 2016. This is an update of a review that was last published in 2011.

Study characteristics
We identified five clinical trials that involved 3405 children, mostly from the same research group. Four trials were conducted in Finland and enrolled healthy children (three trials) or children with an acute respiratory infection (one trial). The fifth trial was conducted in the USA and enrolled otitis-prone children who were recruited from attendance at general medical practices.

Study funding sources

All five trials received governmental funding; and the Finnish study investigators have a US patent for the use of xylitol to treat respiratory infections.

Key results

Xylitol, administered in chewing gum, lozenges or syrup, can reduce the occurrence of AOM among healthy children with no acute upper respiratory infection from 30% to 22%. There is no difference in side effects (namely, abdominal discomfort and rash). Based on these results we would expect that out of 1000 children up to 12 years of age, 299 would experience an AOM compared with between 194 and 263 children who would experience an AOM if they are provided with xylitol chewing gum. The preventive effect among healthy children with respiratory infection or among otitis-prone children is inconclusive.

Quality of the evidence
The quality of evidence was moderate for healthy children and children with respiratory infections but low for otitis-prone children.

Summary of findings for the main comparison. Xylitol versus control for prevention of AOM in healthy children

Xylitol versus control for prevention of AOM in healthy children

Patient or population: preventing acute otitis media in children up to 12 years of age
Setting: daycare in Finland
Intervention: xylitol in any form (syrup, gum or lozenge)
Comparison: control in any form (gum, syrup)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk with control in any form (gum, syrup)	Corresponding risk with xylitol in any form (syrup, gum or lozenge)				
Final diagnosis of at least one episode of AOM	Study population		RR 0.75 (0.65 to 0.88)	1826 (3 RCTs)	⊕⊕⊕⊖ Moderate[1]	RR 0.74 (0.54, 1.01) with random-effects meta-analysis
	299 per 1000	224 per 1000 (194 to 263)				
	Moderate					
	296 per 1000	222 per 1000 (192 to 261)				
Gastrointestinal-related adverse events	Study population		RR 1.43 (0.74 to 2.75)	1826 (3 RCTs)	⊕⊕⊕⊖ Moderate[2]	RR 1.41 (0.60, 3.33) with random-effects meta-analysis
	17 per 1000	24 per 1000 (13 to 47)				
	Moderate					
	15 per 1000	21 per 1000 (11 to 40)				
Antibiotic administration	Study population		RR 0.64 (0.42 to 0.97)	306 (1 RCT)	⊕⊕⊕⊖ Moderate[3]	
	289 per 1000	185 per 1000 (121 to 280)				
	Moderate					

	289 per 1000	185 per 1000 (121 to 280)				
Hospitalisation - not reported	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Mortality - not reported	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Number of days missed at school or daycare - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Cost - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies

CI: Confidence interval; **RR:** Risk ratio

*The basis for the **assumed risk** for 'Study population' was the average risk in the control groups (i.e. total number of participants with events divided by total number of participants included in the meta-analysis). The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] There is inconsistency in th findings of the first two studies as compared to the third study of the same group
[2] 95% CIs are wide and imprecise. Moreover, there are few events and the CI includes appreciable benefit and harm[3] The evidence is based on 1 small trial of 306 patients

Summary of findings 2. Xylitol versus control for prevention of AOM in healthy children during a respiratory infection

Xylitol versus control for prevention of AOM in healthy children during a respiratory infection

Patient or population: preventing acute otitis media in children up to 12 years of age
Setting: daycare in Finland
Intervention: xylitol in any form (syrup, gum or lozenge)
Comparison: control in any form (gum, syrup)

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants	Quality of the evidence	Comments

	Risk with control in any form (gum, syrup)	Risk with xylitol in any form (syrup, gum or lozenge)		(studies)	(GRADE)	
Final diagnosis of at least one episode of AOM	Study population		RR 1.13 (0.83 to 1.53)	1253 (1 RCT)	⊕⊕⊕⊖ Moderate[1]	
	115 per 1000	130 per 1000 (95 to 176)				
	Moderate					
	115 per 1000	130 per 1000 (95 to 176)				
Gastrointestinal-related adverse events	Study population		RR 2.82 (0.61 to 13.00)	1277 (1 RCT)	⊕⊕⊕⊖ Moderate[1]	
	4 per 1000	11 per 1000 (2 to 53)				
	Moderate					
	4 per 1000	12 per 1000 (3 to 53)				
Antibiotic administration - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Hospitalisation - not reported	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Mortality - not reported	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Number of days missed at school or daycare - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Cost - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies

CI: Confidence interval; **RR:** Risk ratio

*The basis for the **assumed risk** for 'Study population' was the average risk in the control groups (i.e. total number of participants with events divided by total number of participants included in the meta-analysis). The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] 95% CIs are wide and imprecise. The evidence is based on one trial. Moreover, there are few events and the CI includes appreciable benefit and harm

Summary of findings 3. Xylitol versus control for prevention of AOM in otitis-prone children

Xylitol versus control for prevention of AOM in otitis-prone children

Patient or population: preventing acute otitis media in children up to 12 years of age
Setting: primary care in community
Intervention: xylitol in any form (syrup, gum or lozenge)
Comparison: control in any form (gum, syrup)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control in any form (gum, syrup)	Risk with xylitol in any form (syrup, gum or lozenge)				
Final diagnosis of at least one episode of AOM	Study population		RR 0.90 (0.67 to 1.21)	326 (1 RCT)	⊕⊕⊝⊝ Low[1 2]	
	367 per 1000	331 per 1000 (246 to 445)				
	Moderate					
	368 per 1000	331 per 1000 (246 to 445)				
Gastrointestinal-related adverse events	Study population		RR 1.04 (0.92 to 1.16)	326 (1 RCT)	⊕⊕⊕⊝ Moderate [1 3]	
	765 per 1000	796 per 1000 (704 to 887)				
	Moderate					
	765 per 1000	796 per 1000				

		(704 to 888)				
Antibiotic administration	Study population		RR 0.90 (0.69 to 1.16)	326 (1 RCT)	⊕⊕⊕⊖ Moderate [1] [3]	
	440 per 1000	396 per 1000 (303 to 510)				
	Moderate					
	440 per 1000	396 per 1000 (303 to 510)				
Hospitalisation - not reported	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Mortality - not reported	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Number of days missed at school or daycare - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies
Cost - not measured	See comment	See comment	Not estimable	(0 studies)	-	Not reported in included studies

CI: Confidence interval; **RR:** Risk ratio

*The basis for the **assumed risk** for 'Study population' was the average risk in the control groups (i.e. total number of participants with events divided by total number of participants included in the meta-analysis). The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk for attrition bias
[2] 95% CIs are wide and imprecise and includes appreciable benefit and harm
[3] 95% CIs are wide and imprecise

BACKGROUND

Description of the condition

AOM is the most common infection for which antibacterial agents are prescribed for children in the United States (AAP 2013). According to the evidence-based guidelines of the American Academy of Pediatrics and American Academy of Family Physicians, AOM is defined as the presence of middle ear effusion (thick or sticky fluid behind the eardrum in the middle ear) and a rapid onset of signs or symptoms of middle-ear inflammation, such as ear pain, otorrhoea (discharge from the ear) or fever (AAP 2013).

By the end of their first year of life, approximately 62% of children have experienced at least one episode of AOM, and by the age of three years, almost 83% of children have experienced at least one episode (Friedman 2006; Jansen 2009). The peak incidence occurs between six and 12 months of age (ACIP 2000). Although serious complications are rare, this common childhood ailment imposes a huge impact on healthcare systems. In the United States, AOM accounts for almost 20 million medical office visits annually (CDC 2015). Childhood AOM is a significant healthcare utilisation concern and accounts for approximately USD 2.88 billion in additional healthcare cost annually (Ahmed 2014)

The key step in the pathogenesis of AOM is colonisation of the upper airway with pathogenic bacteria which move from the nasopharynx to the middle ear by way of the eustachian tube (Murphy 2006). The aetiologic agents include bacteria, viruses and a combination of both (Guven 2006). *S pneumoniae* and *H influenzae* are the most common causes of bacterial otitis media (Murphy 2006). Studies using diagnostic tympanocentesis in children with AOM identified *S pneumoniae* in 28% to 55% of all middle ear aspirates (ACIP 2000).

Despite a large number of published RCTs, there is no consensus on therapy for AOM (Venekamp 2015). The rate of antibiotic use for AOM varies from 31% in the Netherlands (Akkerman 2005) to 95% in the USA and Canada (Froom 2001). AOM is the leading reason for antibiotic prescriptions in the United States (Venekamp 2015). This results in the widespread emergence of multidrug resistant pathogens (ACIP 2000; Friedman 2006). Treatment strategies for AOM include surgery, antibiotic prophylaxis and vaccination. Surgical procedures have limited and short-term efficacy on the occurrence of persistent or recurrent otitis media (McDonald 2008; Paradise 1999; Wallace 2014). The effectiveness of antibiotic therapy for AOM appears to be limited. When potential adverse events such as vomiting, diarrhoea or rash were considered, one in every 14 children treated with antibiotics experienced an adverse event that would not have occurred if antibiotics were withheld (Venekamp 2015). Moreover, in high-income countries most cases of AOM remit spontaneously with no complications (Venekamp 2015). Furthermore, pneumococcal vaccines make only a small difference (2% to 7% relative reduction) to numbers of AOM cases (Norhayati 2015).

Description of the intervention

Xylitol, or birch sugar, is chemically a pentitol or 5-carbon polyol sugar alcohol, naturally found in plums, strawberries, raspberries and rowan berries. It does not cause dental caries because, although a sugar alcohol, it cannot be fermented by cariogenic bacteria in the oral cavity. It has the same relative sweetness as sucrose, and is accordingly an ideal non-sugar sweetener approved in many countries, and principally used in chewing gums, confectionery, toothpaste and medicines (Maguire 2003; Uhari 2000). Xylitol consumption in the UK is about 1000 tonnes per year (Maguire 2003).

How the intervention might work

Xylitol inhibits the growth and acid production of certain strains of *Streptococcus mutans (S mutans)* (Uhari 2000). In an in vitro study, it was reported that 1% and 5% xylitol markedly reduced the growth of alpha-haemolytic streptococci including *S pneumoniae* and *Streptococcus mitis* (*S mitis*) during their logarithmic phase of growth (Kontiokari 1995). Clues to the mechanism are suggested by the finding that 5% xylitol reduced adherence of both *S pneumoniae* and *H influenzae* to nasopharyngeal cells (Kontiokari 1998). Xylitol is potentially clinically useful in preventing pneumococcal diseases, including AOM.

Why it is important to do this review

Antibiotic treatment of AOM is costly and raises concerns about the development of antibiotic-resistant strains of bacteria. Surgery is invasive and costly, and because of these factors, alternative, effective measures to prevent AOM are sought. An alternative treatment is xylitol. This review evaluated the efficacy of xylitol to prevent AOM in children.

OBJECTIVES

To assess the efficacy and safety of xylitol to prevent AOM in children aged up to 12 years.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs and one quasi-RCT of any type of xylitol intervention versus placebo or no intervention for the prevention of AOM in children aged up to 12 years. We did not include cluster trials due to potential differences in the ancillary treatments among centres. We included studies reporting on any primary or secondary outcomes.

Types of participants

Children up to 12 years of age without AOM.

Types of interventions

We included studies of xylitol in any form (e.g. syrup, chewing gum, lozenges or nasal spray) used to prevent AOM. We considered studies of any dose or duration of administration. Eligible control interventions included placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Number of children (healthy children, children with a respiratory infection, and otitis-prone children) with at least one AOM episode during the follow-up period.

Secondary outcomes

1. Safety and adverse events.

2. Antibiotic administration.
3. Hospitalisation (and its length) secondary to AOM or its complications in studies where at least one hospitalisation was reported.
4. Mortality secondary to complications of AOM in studies where at least one death was reported.
5. Number of days missed at school or daycare centre.
6. Cost (direct such as emergency room or general practitioners visits; hospitalisations; medication and indirect costs such as time taken from work for parents or care givers; the opportunity cost of leisure time; informal nursing care; and out-of-pocket expenses for transportation).

Search methods for identification of studies

Electronic searches

For this 2016 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2015, Issue 12 December) (accessed 27 January 2016), which includes the Cochrane Acute Respiratory Infections Specialised Register, MEDLINE (June 2011 to January 2016), Embase (June 2011 to January 2016), CINAHL (June 2011 to January 2016), LILACS (2011 to January 2016), International Pharmaceutical Abstracts (June 2011 to Jan 2016), and Web of Science (2011 to January 2016). We did not apply language or publication restrictions. We used the terms in Appendix 1 to search MEDLINE (OVID) and CENTRAL. We did not combine the search with a strategy for identifying randomised trials in MEDLINE as there were too few results. We adapted this search strategy to search Embase (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4) and Web of Science (Appendix 5). Previously we searched: CENTRAL 2011, Issue 3; MEDLINE (1950 to August week 1, 2011); Embase.com (1974 to August 2011); CINAHL (1981 to August 2011); Health and Psychosocial Instruments (1985 to August 2011); Healthstar (OVID) (1966 to August 2011); and the International Pharmaceutical Abstracts (2000 to August 2011).

Searching other resources

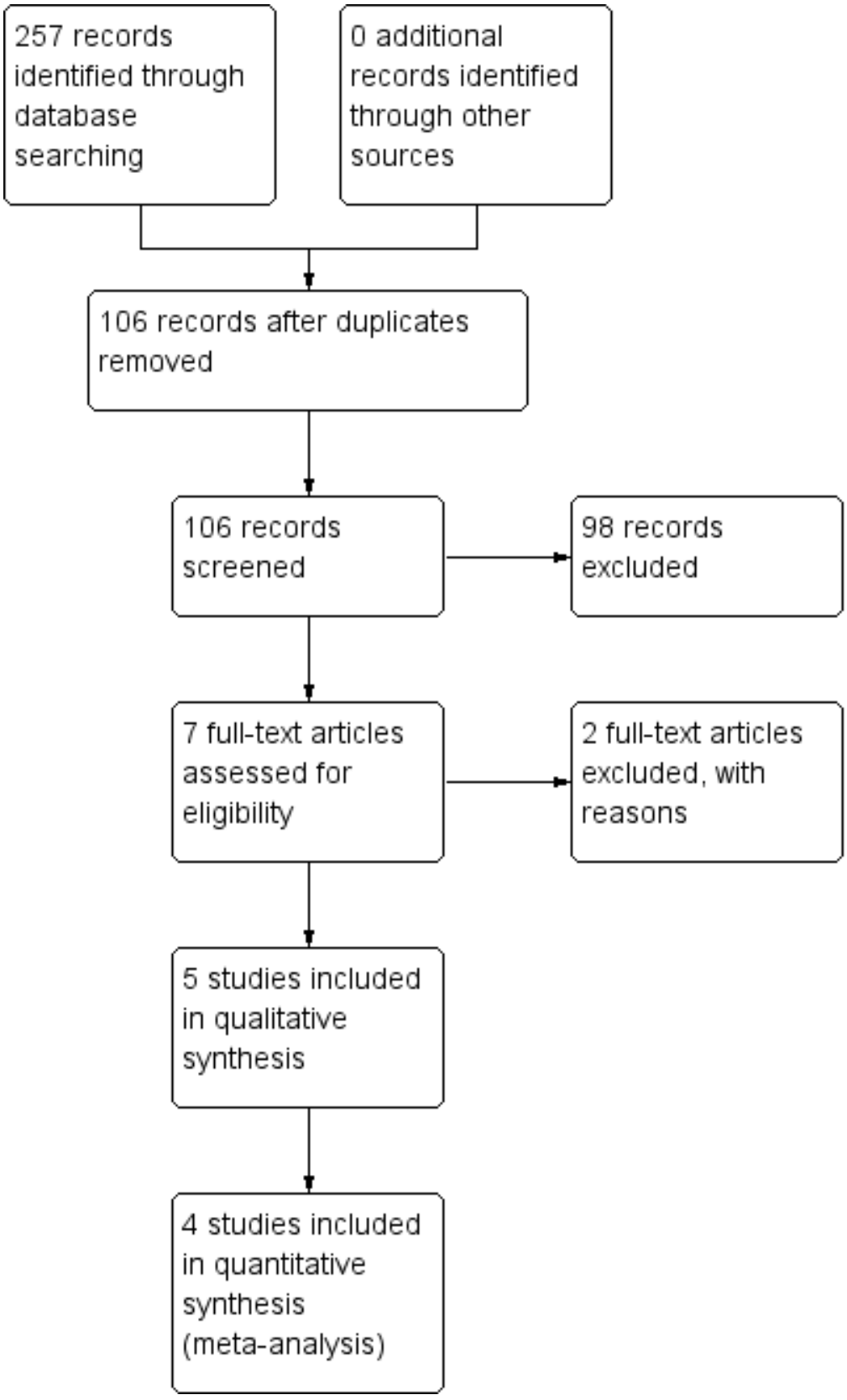
We searched the WHO ICTRP and ClinicalTrials.gov trials registries for completed and ongoing trials using the term 'xylitol' (latest search 27 January 2016). We attempted to search for unpublished studies (or grey literature) such as technical reports, dissertations, or studies published in languages other than English, which may not have been indexed to major databases, by contacting authors of identified trials. We also conducted Internet searches using Google Scholar™. We searched the first 100 hits that included xylitol and otitis media in the title. We searched dissertations and theses databases (from inception up to 2016) through ProQuest. We also searched in the Open Grey (System for Information on Grey Literature in Europe) database (from inception up to 2016) and the reference lists of identified articles. We also searched abstracts from the annual meetings of the American Association for Respiratory Care, European Respiratory Care Association, the Australian Asthma and Respiratory Educators Association, Society for Pediatric Research, American Pediatric Society and Pediatric Academic Societies published in Pediatric Research (2002 to 2016). There were no language or publication restrictions. We contacted trial authors if we needed to clarify or obtain relevant data on outcomes not reported in the study. We identified manufacturers and distributors of xylitol products based on information extracted mainly from included studies as well as an Internet search and contacted these agencies to locate unpublished trials. We contacted five xylitol distributors (Academy of Dental Resources, Xylarex, Oral Biotech, Xlear Inc. and Oxyfresh Worldwide, Inc.) and three researchers (October 2009) and requested information on any unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (AA, PS) independently screened titles and abstracts for inclusion of all the potential studies we identified as a result of the search. We retrieved the full text study reports/publication and the same review authors independently screened full text and identified studies for inclusion, and recorded reasons for exclusions. We resolved disagreements through discussion and consensus, or by consulting a third review author (HPL). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) (Moher 2009) and Characteristics of excluded studies.

Figure 1. Study flow diagram.



Data extraction and management

We extracted data using a standardised data collection form. Disagreements were resolved by discussion with a third author (HPL). We extracted the following information:

1. participant characteristics (age, sex, race, representative of, history of recurrent AOM, attendance at daycare or school);
2. study setting;
3. type of intervention and control and number studied in each group;
4. adverse effects;
5. method for diagnosing AOM;
6. occurrence of AOM and its complications during follow-up period;
7. percentages of children with at least one AOM episode during the follow-up period;
8. use of antibiotics to treat AOM or its complications;
9. time lost from daycare/school (for children) or from work (for parents or care givers) due to AOM;
10. costs of managing AOM;
11. randomisation method;
12. masking method (in randomisation, intervention, outcome assessment); and
13. whether analysis was by intention-to-treat (ITT).

Assessment of risk of bias in included studies

We assessed methodological quality using the information in the original publications. Two review authors (AA, PS) independently evaluated study quality using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We evaluated six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues) based on what was reported in the study and assigned judgements relating to the risk of bias for each domain. Possible judgments for these domains could be high, low or unclear risk of bias.

Measures of treatment effect

We analysed the primary outcome of interest (number of children with at least one AOM episode) using RevMan 5.3 for statistical analysis (RevMan 2014). We used RR and RD and planned to use mean difference (MD) if appropriate. We reported 95% CI for estimates of treatment effects. We used data from all intervention arms in the analyses for studies with more than two arms, where the same xylitol forms were compared in two or more experimental groups (for example, xylitol in chewing gum, syrup or lozenges were compared to a common control group). We analysed the secondary outcomes of interest (adverse events, hospitalisation, mortality, percentage of children needing antibiotic therapy) when the data were available, using RR or RD. We planned to summarise length of hospitalisations, number of days missed at school and cost differences as MD or with 95% CI if data were available.

Unit of analysis issues

We included data from a participant once only, even if the participant was recruited more than once.

Dealing with missing data

We contacted trial authors to request missing data or clarify methods whenever possible, but we received few responses.

Assessment of heterogeneity

We considered a conservative $P < 0.1$ as significant. We calculated I^2 statistic values to quantify heterogeneity (Higgins 2003). In addition, we inspected the graphical display of trials estimated treatment effects (along with their 95% CIs) for assessing heterogeneity.

Assessment of reporting biases

We assessed publication bias by checking trials registries and contacting the authors of identified studies to ask if they had other publications or were aware of any other unpublished studies we had missed.

Data synthesis

We used a fixed-effect model for meta-analyses.

GRADE and 'Summary of findings' tables

We created three 'Summary of findings' tables for three populations of healthy children, children with a respiratory infection, and otitis-prone children, in which the xylitol had been evaluated using the following outcomes: final diagnosis of at least one episode of AOM; adverse events; antibiotic administration; hospitalisation; mortality; number of days missed at school or daycare; and cost. We used the five GRADE (Atkins 2004) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (GRADEpro 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro GDT software (GRADEproGDT 2015). We justified all decisions to down- or up-grade the quality of studies using footnotes and we made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We performed four subgroup analyses based on the methodology of the identified studies:

1. younger children unable to chew gum;
2. older children who were able to chew;
3. for those whom xylitol was administered during respiratory infection; and
4. comparison between different types of xylitol vehicles.

Sensitivity analysis

We also looked at the results in subsets of trials with different methods of xylitol administration (syrup, chewing gum or lozenges). We applied Cochrane's Q test for between-study heterogeneity (Deeks 2011). We also performed random-effects meta-analysis to compare the pooled results to those of the fixed-effect meta-analyses.

RESULTS

Description of studies

Results of the search

This is an update of our previous review (Azarpazhooh 2011). For this 2016 update, we reviewed 33 potential citations. The study flow diagram is presented in Figure 1. We identified one new trial on ClinicalTrials.gov (www.clinicaltrials.gov/) completed and published (NCT01044030 as Vernacchio 2014) and a new trial that was not yet open for participant recruitment (NCT02592382). We saved this record for a future update (Characteristics of ongoing studies). Previously, our preliminary searches identified 84 potential citations. We read the titles and abstracts of these studies. We selected four studies for full text appraisal and these met the eligibility criteria for the first version of this review (Hautalahti 2007; Tapiainen 2002; Uhari 1996; Uhari 1998). This review included five clinical trials that involved 3405 children. Details of the participants enrolled in these studies are described in Characteristics of included studies.

Included studies

Vernacchio 2014 performed a pragmatic practice-based RCT. Ninety-seven practices of three paediatric practice–based networks (the Slone Center Office-based Research Network at Boston University, the Pediatric Physicians' Organization at Children's (Boston), and the North Carolina Child Health Research Network at the University of North Carolina) referred 778 children, aged six to 71 months, to the study for eligibility review. These children were all otitis-prone, that is, they had a history of at least three clinically diagnosed episodes of AOM in the previous 12 months with at least one in the previous six months and may have had middle ear effusions at the time of enrolment. Of these children, 326 were randomised to receive either a placebo syrup (n = 166, daily dose of 2.25 g sorbitol three times a day) or a viscous xylitol syrup (n = 160, daily dose of 5 g three times a day) for three months. All of the daily doses were administered by parents or other routine caregivers, not in a controlled daycare setting as in the previous trials. Compliance was monitored by asking parents, at each interview, how much of the recommended syrup the child had taken since the last interview. In total, about 28% of participants in the xylitol group and 24% of participants in the placebo group discontinued treatment before the end of the study period or the occurrence of the primary outcome. The most common reasons were gastrointestinal side effects (18 in the xylitol group and 11 in the placebo group), the participant refusing to take the solution (eight in each group), and the parent becoming too busy or finding the treatment too difficult to administer (eight xylitol, five placebo). At the end of the study, a blinded investigator reviewed medical records from each participant's primary care physician as well as any other healthcare provider whom the parent identified as having treated the participant during the study period. The clinical diagnoses of AOM was registered as reported in the medical records by a wide range of clinicians and were not otherwise verified. If medical records were not available, the diagnosis of AOM was registered as reported by the parents. By the end of the trial, two participants in the xylitol group and three in the placebo group declined further participation. Four participants in the xylitol group and three in the placebo group were lost to follow-up without any outcome information. The details of the participants enrolled in this study are described in Characteristics of included studies.

Hautalahti 2007 randomised 663 healthy children enrolled in daycare in the city of Oulu, Finland to four groups to receive either a control product (n = 331, daily dose of 0.5 g in the control chewing gum group or in a syrup three times a day, pulled together as one control group) or xylitol (n = 332, daily dose of 9.6 g in chewing gum or in a syrup three times a day, pulled together as one test group) for three months. The total daily amount of received xylitol in this study was equal to that used in earlier trials but the size of a piece of chewing gum and the amount of syrup needed per dose were bigger and dosing was less frequent (three versus five daily doses). In working days, two daily doses were given at the daycare centre and one dose at home. At weekends and holidays all three doses were given at home. Compliance and the consumption of additional xylitol products were monitored by asking parents to record the doses actually given and any other xylitol products on a daily report sheet and also by counting and measuring the unused returned products at the end of the trial. The occurrence of the first AOM diagnosed during any period of respiratory symptoms during the follow-up was the main outcome measure based on a finding of middle ear effusion in tympanometry (B, C or positive pressure curve) and confirmed with pneumatic otoscopy. Otorrhoea from a tympanostomy tube was counted as AOM. There was dropout of 96 participants (58 in the xylitol group and 38 in the control group). The baseline characteristics (demographic features, known AOM risk factors, or AOM history, earlier use of xylitol products) were similar in all four groups. By the end of trial, the dropouts range was statistically higher in the xylitol group (17%) versus the control group (11%). The reasons for dropouts and the related numbers per each group are as follows: child refused to take the product (control: 15 versus xylitol: 22); abdominal discomfort (control: seven versus xylitol: nine); chewing gum piece too big (control: one versus xylitol: five); duration of the trial too long (control: one versus xylitol: two); forgot to give the preparation when on holiday (control: three versus xylitol: three); illness (control: two versus xylitol: three); rash (control: three versus xylitol: three); parents tired of the trial (control: two versus xylitol: one); difficult to avoid additional xylitol products (control: zero versus xylitol: one); other (control: one versus xylitol: four) or unknown reasons (control: three versus xylitol: five). The details of the patients enrolled in this study are described in the Characteristics of included studies table.

Tapiainen 2002 randomised 1277 healthy children enrolled in daycare in the city of Oulu, Finland after screening with tympanometry to receive either the control mixture (n = 212), xylitol mixture (n = 212), control chewing gum (n = 280), xylitol chewing gum (n = 286) or xylitol lozenges (n = 287) during an acute respiratory infection. The parents began administering the products to their children at the onset of acute respiratory infection (ARI) symptoms, which was defined as the appearance of one or more of the following symptoms: clear or purulent discharge from the nose, congestive nose, cough, conjunctivitis, sore throat or earache. Compliance was monitored by asking the parents to list the doses actually given on the daily symptom sheets and by counting the unused pieces of chewing gum and lozenges returned at the last appointment and measuring the volume of the unused mixture. The follow-up lasted until resolution of the symptoms or up to three weeks. AOM was diagnosed based on a finding of middle ear effusion in tympanometry (B, C or positive pressure curve) and confirmed with pneumatic otoscopy. A total of 1253 of the 1277 randomised children were eligible for the analysis of the primary outcome. The children who dropped out (n = 24) were excluded from the statistical analysis but those who prematurely stopped

using the products but still visited the clinic (n = 35) were included. The reasons for dropouts and the related numbers per each group are as follows: parents got tired (only two in the xylitol syrup and four in the xylitol chewing gum); child disliked the product (two only in the xylitol lozenge); other antibiotics for ARI (only one in the xylitol syrup and one in the control chewing gum); left the area (only one in the control syrup, four in the xylitol chewing gum and two in the xylitol lozenge); and unknown (syrup: zero in the control versus two in the xylitol group; chewing gum: two in control versus one in xylitol; lozenge: two in xylitol). Moreover, the administration was discontinued due to abdominal discomfort (syrup: one in control versus three in xylitol; chewing gum: one in control versus one in xylitol; lozenge: five in xylitol); child disliked the product (one in xylitol chewing gum and 10 in xylitol lozenge); or unknown (syrup: two in control versus two in xylitol; chewing gum: three in control versus three in xylitol; five in xylitol lozenge). The details of the participants enrolled in this study are described in Characteristics of included studies.

Uhari 1996 randomised 306 children in the city of Oulu, Finland daycare (157 in the xylitol group and 149 children in the sucrose group). Each child was instructed to chew two pieces of gum five times a day after meals or snacks until there was no taste (or until five minutes), making a total dose of 8.4 g xylitol per day for two months. Compliance was assessed by asking the parents to report the actual number of pieces of chewing gum used at the end of each month of the trial and also by reporting on the use of additional xylitol products and possible medications. Nasopharyngeal samples were taken before the sugar challenge, at two weeks and at the end of the study. Pneumococci were identified by (alpha) haemolysis on sheep blood agar plates, colony morphology and optochin sensitivity. Parents completed symptom sheets, time and reasons for being absent from daycare, and the use of additional xylitol products and possible medications. At a physician appointment, clinical diagnosis and the drugs prescribed were registered. AOM was diagnosed based on symptoms and signs of ARI and simultaneous signs of middle ear effusion: a cloudy tympanic membrane or impaired tympanic membrane motility in pneumatic otoscopy. The baseline characteristics were similar in the two randomised groups. By the end of trial, there was a dropout of 30 participants; 10 in the xylitol group and 20 in the control group, representing a dropout rate of 6% and 13%, respectively. The reasons for dropouts and the related numbers per each group are as follows: child got tired of eating chewing gum (sucrose: eight versus xylitol one), dental caries (sucrose three versus xylitol four), moved from area (sucrose five versus xylitol one), parents got tired (sucrose two versus xylitol two), insufficient follow-up data (sucrose: two versus xylitol zero) and loose stools (sucrose zero versus xylitol two). There were no differences in the duration of cough or other symptoms of infections between the groups as reported by parents. There was also no difference in the pneumococcal carriage rates during the study and between the groups as well as the numbers of upper respiratory tract infections without AOM, acute bronchitis, sinusitis and conjunctivitis. The details of the participants enrolled in this study are described in Characteristics of included studies.

Uhari 1998 randomised 857 healthy children enrolled in the city of Oulu, Finland daycare to one of five treatment groups. Participants received control syrup (n = 165), xylitol syrup (n = 159), control chewing gum (n = 178), xylitol gum (n = 179) or xylitol lozenge (n = 176) for three months. Two pieces of chewing gum or lozenges were chewed for at least five minutes five times a day after meals (three doses given by the personnel at the childcare centres during the day and the rest given by the parents at home). Compliance was monitored by asking the parents to list the doses actually given on the daily symptom sheets and also by counting and measuring the unused returned products at the end of the trial. AOM was diagnosed based on a finding of middle ear effusion in tympanometry (B- or C-curve), verified otoscopically with signs of inflammation in the tympanic membrane and the presence of symptoms of ARI (rhinitis, cough, conjunctivitis, sore throat, earache). The baseline characteristics (demographic features, known AOM risk factors or AOM history) and the mean number of forgotten dosages were similar in all five groups. By the end of trial, the dropouts range from 4.5% to 18.9% and were statistically higher in the xylitol syrups (18.9%) and xylitol lozenges (14.8%) as compared to their control groups of respectively control syrups (10.3%) and control chewing gum (4.5%). The reasons for dropouts and the related numbers per each group are as follows: unwilling to continue taking the product (syrup: nine in control versus 14 in xylitol; chewing gum: seven in control versus eight in xylitol; lozenge: 14 in xylitol), left the area (syrup: zero in control versus two in xylitol; chewing gum: zero in control versus two in xylitol; lozenge: one in xylitol), abdominal discomfort (syrup: five in control versus eight in xylitol; chewing gum: zero in control versus one in xylitol; lozenge: seven in xylitol), and unknown reason (syrup: three in control versus six in xylitol; chewing gum: one in control versus one in xylitol; lozenge: four in xylitol). The details of the patients enrolled in this study are described in the Characteristics of included studies table. It should be noted that these trials were all conducted in similar populations in Finland. The methodology appears to be similar with the small change in the control group after the first study (change from sucrose to low-dose xylitol in the control group), the population in the 2002 study (from healthy children to children with ARI) and the dosing in the 2007 study (five times per day to three times per day).

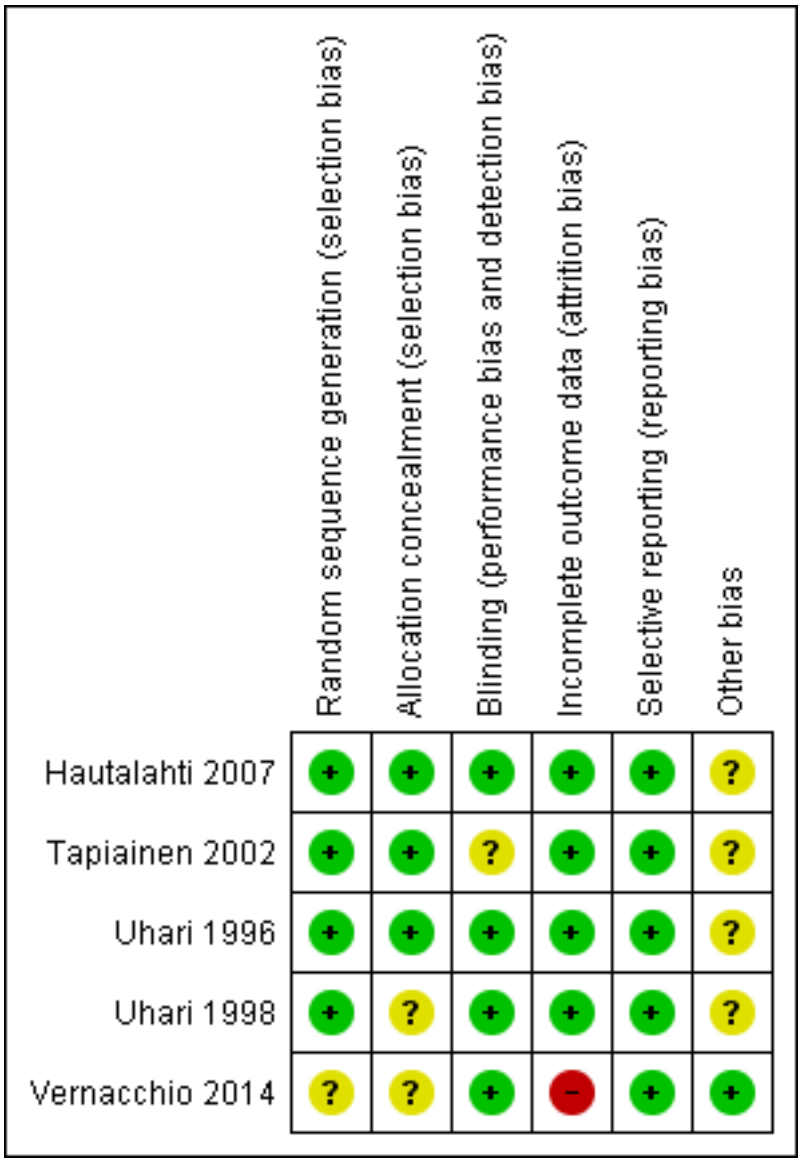
Excluded studies

We identified a recent trial that evaluated the effectiveness of xylitol paediatric topical oral syrup to reduce the incidence of dental caries among very young children (Milgrom 2009). In the published paper, it was mentioned that the effect of xylitol in reducing AOM will be published in a subsequent study. However, after contacting the primary investigator, it was understood that due to a lack of reliability of data regarding AOM, the plan to publish AOM results has been suspended.

Risk of bias in included studies

Figure 2 summarises the review authors' judgements about each risk of bias domain for each included study.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study



Allocation

With the exception of Vernacchio 2014 for which the sequence generation is unclear, the other four included trials had adequate sequence generation (low risk). For allocation concealment, three trials were considered to have low risk of bias (Hautalahti 2007; Tapiainen 2002; Uhari 1996) and the other two trials an unclear risk (Uhari 1998; Vernacchio 2014).

Blinding

Three out of five included studies had adequate blinding (Hautalahti 2007; Uhari 1996; Vernacchio 2014). The blinding procedure was not mentioned in one study (Uhari 1998) but it was judged to be 'probably done' as per the authors' earlier publication. Tapiainen 2002 was blinded as far as the mixture and chewing gum groups were concerned but open between the xylitol lozenge and control chewing gum groups.

Incomplete outcome data

In Vernacchio 2014, 62/160 allocated to xylitol (38.8%) declined participation, were lost to follow-up or discontinued intervention versus 58/166 allocated to placebo (34.9%). Intention-to-treat (ITT) analysis was performed. The other four trials clarified the number of and the reasons for dropouts, but did not perform an ITT analysis.

Selective reporting

No selective reporting was identified in the five included trials.

Other potential sources of bias

In four Finnish trials the test material was donated by industry (Hautalahti 2007; Tapiainen 2002; Uhari 1996; Uhari 1998). All five trials had governmental funding. No conflict of interest was declared in any of the included trials; however, it should be noted that the study authors in Finnish trials have a US patent for the use of xylitol in treating respiratory infections.

Effects of interventions

See: **Summary of findings for the main comparison** Xylitol versus control for prevention of AOM in healthy children; **Summary of findings 2** Xylitol versus control for prevention of AOM in healthy children during a respiratory infection; **Summary of findings 3** Xylitol versus control for prevention of AOM in otitis-prone children

See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3 for the main primary outcome 'Number of children (healthy children, children with a respiratory infection, and otitis-prone children, respectively) with at least one AOM episode during the follow-up period'. Overall, the quality of available evidence for this outcome was moderate for healthy children (due to inconsistency of the results) moderate for children with respiratory infections (due to imprecise estimates), and low for otitis-prone children (due to imprecise estimates and high attrition).

Primary outcome

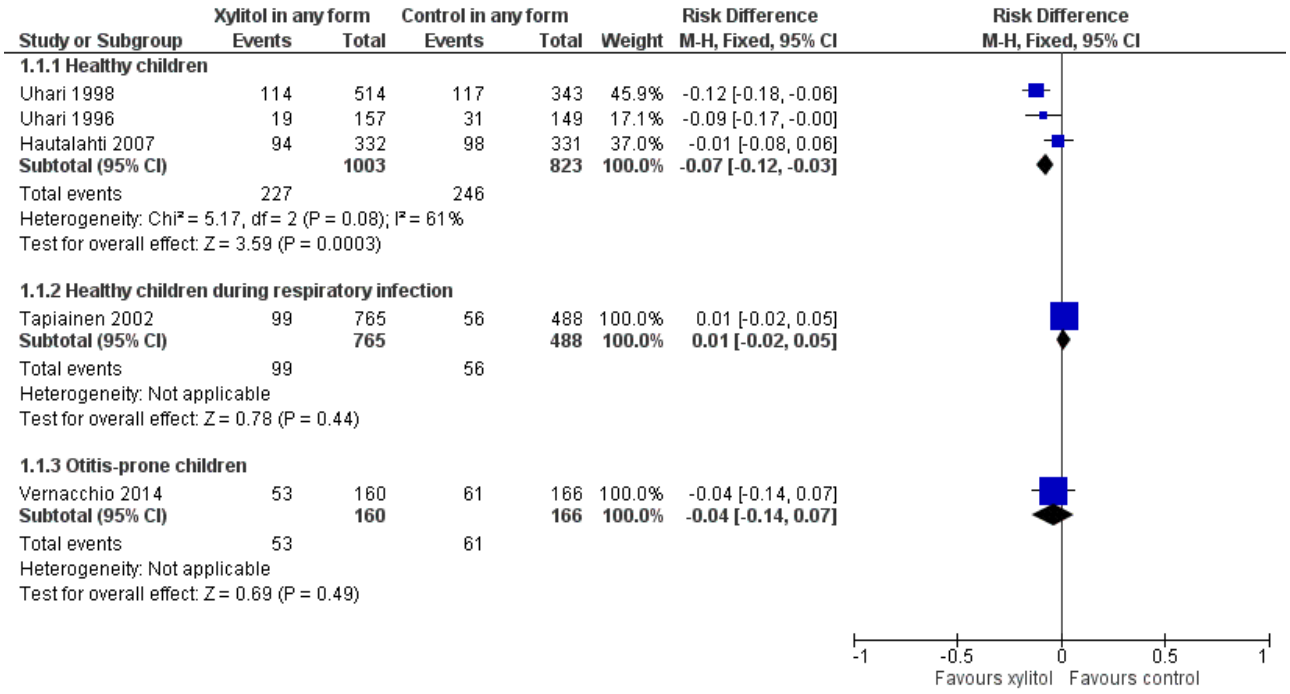
Number of children with at least one AOM episode during the follow-up period

The included trials reported on the primary outcome of number of children with at least one AOM episode during the follow-up period when xylitol was administered to healthy children (Hautalahti 2007; Uhari 1996; Uhari 1998), to healthy children with a respiratory infection (Tapiainen 2002), and to otitis-prone healthy children (Vernacchio 2014). In particular, for the latter, the population was not homogenous, the total dose was increased by 50% (15 g daily in the form of viscous xylitol solution) and the outcome was measured as what had been documented in the patients' medical charts. Due to the heterogeneity among these three groups, the results are presented separately for each outcome.

Xylitol in any form versus control in any form

Figure 3 summarises available data on our primary outcome. We combined the result of three trials among 1826 healthy children to compare the effect of xylitol in any form (syrup, chewing gum or lozenges) versus control of any kind (syrup or gum) (Hautalahti 2007; Uhari 1996; Uhari 1998). There was a statistically significant 25% reduction in the risk of occurrence of AOM among healthy children at daycare centres in the xylitol group compared to the control group (RR 0.75, 95% CI) 0.65 to 0.88 and RD -0.07, 95% CI -0.12 to -0.03; quality of evidence: moderate - downgraded for inconsistency). However, the effect of xylitol in reducing AOM among healthy children during a respiratory infection (Tapiainen 2002: 99 out of 765 children in the xylitol group versus 56 out of 488 children in the control group, RR 1.13, 95% CI 0.83 to 1.53; quality of evidence: moderate - downgraded for imprecision), or among otitis-prone healthy children (Vernacchio 2014: 53 out of 160 children in the xylitol group versus 61 out of 166 children in the control group, RR 0.90, 95% CI 0.67 to 1.21 and RD -0.07, 95% CI -0.14 to 0.07; quality of evidence: low - downgraded for imprecision and high attrition) was inconclusive.

Figure 3. Forest plot of comparison: 1 Xylitol in any form (syrup, gum or lozenge) versus control in any form (gum, syrup), outcome: 1.1 Final diagnosis of at least one episode of AOM.



Secondary outcomes

1. Safety and adverse events

There were no significant differences in the number of children with gastrointestinal-related adverse events during the follow-up period between xylitol and control group among 1826 healthy children (Hautalahti 2007; Uhari 1996; Uhari 1998 combined: RR 1.43, 95% CI 0.74 to 2.75), among 1277 healthy children with a respiratory infection (Tapiainen 2002: RR 2.82, 95% CI 0.61 to 13.00), and among 326 otitis-prone healthy children (Vernacchio 2014: RR 1.04, 95%

CI 0.92 to 1.16). Similarly, there was no significant differences in the occurrence of rash during the follow-up period between xylitol and control group (only reported in Hautalahti 2007: RR 1.00, 95% CI 0.20 to 4.90). The quality of evidence on this outcome was moderate, downgraded for imprecision.

2. Antibiotic administration

Among healthy children: Uhari 1996 and Uhari 1998 reported on antibiotic administration. However, the reported data could not be pooled.

- In Uhari 1996, the total number of antimicrobial drugs prescribed in the sucrose group was 60 compared with 34 in the xylitol group. There was a statistically significant 36% reduction in the risk of experiencing at least one exposure to antimicrobial drugs among children in the xylitol group than the children in the sucrose group (RR 0.64, 95% CI 0.42 to 0.97 and RD -0.10, 95% CI -0.20, -0.01; quality of evidence: moderate).
- In Uhari 1998, for children unable to chew, during the three-month follow-up period, the incidence rate of antimicrobial prescriptions per person years at risk (PYR) was significantly lower in the xylitol syrup group versus the control syrup group (respectively 3.20 versus 4.33, P = 0.012). Similarly, the number of days on antimicrobials/PYR was significantly lower in the xylitol syrup group versus the control syrup group (respectively 25.0 versus 31.7, P < 0.0001). For children able to chew, during the three-month follow-up period, the incidence rate of antimicrobial prescriptions/PYR was significantly lower in the xylitol chewing gum group versus the control chewing gum group (respectively 1.66 versus 2.26, P = 0.046), but there was no difference between the xylitol lozenges group and control chewing gum (respectively 1.86 versus 2.26, P = 0.211). The number of days on antimicrobials/PYR was significantly lower (P < 0.0001) in both the xylitol chewing gum group (11.8) and xylitol lozenges (13.8) versus control chewing gum (17.8).

Antibiotic administration was not measured among healthy children with a respiratory infection.

Among otitis-prone children, Vernacchio 2014 reported no significant differences in antibiotic administration between the xylitol and control groups (RR 0.90, 95% CI 0.69 to 1.16). The quality of evidence was moderate and was downgraded for imprecision and high attrition. Total antibiotic use was 6.8 days per 90 days in the xylitol group versus 6.4 in the placebo group (difference 0.4, 95% CI –1.8 to 2.7, P = 0.7). The incidence of AOM-related antibiotic use was 5.2 days per participant per 90 days in the xylitol group versus 5.1 in the placebo group (absolute difference 0.1 days, 95% CI for difference –1.9 to 2.2 days. P = 0.9).

3. Hospitalisation (and its length) secondary to AOM or its complications

No case of hospitalisation was reported in the included studies.

4. Mortality secondary to complications of AOM in studies where at least one death was reported

No case of mortality was reported in the included studies.

5. Number of days missed at school or daycare centre

Identified studies did not report on this outcome.

6. Cost

Information on cost was not reported in the included studies.

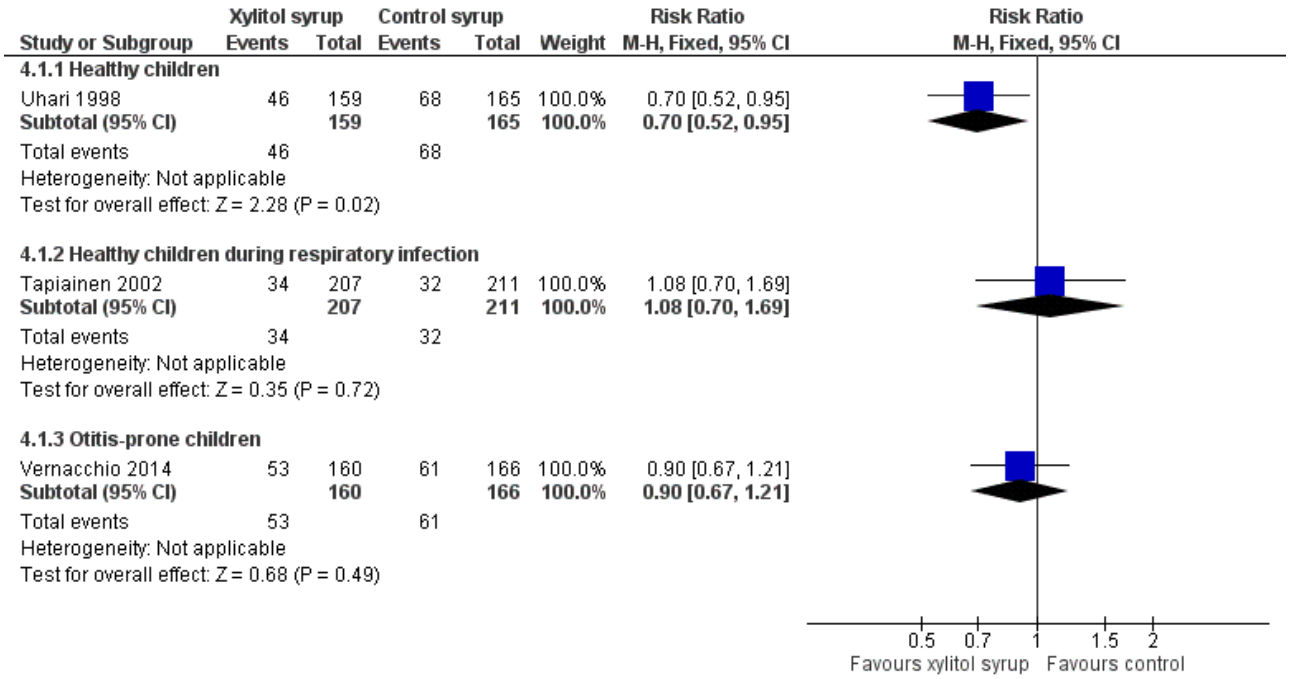
Subgroup analysis

Based on the methodology of the identified studies, we defined the subgroup analyses of a) younger children unable to chew gum; b) older children who were able to chew and c) comparison between different types of xylitol vehicles. The subgroup analyses were tested among the population of healthy children, healthy children during respiratory infection, as well as otitis-prone healthy children. It should be noted that although Hautalahti 2007 included the subgroups of chewing gum and syrup (for both xylitol group and control group), the data were presented collectively for control and xylitol group with no breakdown of the AOM in the subgroups. We contacted the trial authors several times but no further information was obtained and therefore the results of the subgroups of Hautalahti 2007 were not included in the subgroup analysis.

Younger children unable to chew gum

Figure 4 presents data from three trials that compared the effect of xylitol syrup versus control syrup in younger children unable to chew gum (Tapiainen 2002; Uhari 1998; Vernacchio 2014). Due to the heterogeneity in these studies, the results were not pooled. Among healthy children, Uhari 1998 showed that xylitol syrup resulted in a statistically significant 30% decrease in the occurrence of AOM among healthy younger children at daycare centres who were unable to chew gum (46 out of 159 children in the xylitol group versus 68 out of 165 children in the control group, RR 0.70, 95% CI 0.52 to 0.95; RD -0.12, 95% CI -0.23 to -0.02). However, the effect of xylitol syrup in reducing AOM among healthy children during a respiratory infection (Tapiainen 2002: 34 out of 207 children in xylitol group versus 32 out of 211 children in control group, RR 1.08, 95% CI 0.70 to 1.69), or among otitis-prone healthy children (Vernacchio 2014: 53 out of 160 children in the xylitol group versus 61 out of 166 children in the control group, RR 0.90, 95% CI 0.77 to 1.21; RD -0.04, 95% CI -0.14 to 0.07) was inconclusive.

Figure 4. Forest plot of comparison: 3 Xylitol syrup versus control for younger children unable to chew, outcome: 3.1 Final diagnosis of at least one episode of AOM.



Older children who were able to chew

The results of Uhari 1996 and Uhari 1998 were combined to compare the effect of xylitol chewing gum or lozenges versus control chewing gum among the subgroup of older healthy children able to chew gum. Based on the pooled result of these two studies, compared to control chewing gum, xylitol resulted in a statistically significant 34% decrease in the occurrence of AOM if it was administered in chewing gum or lozenges (Figure 5 RR 0.66, 95% CI 0.50 to 0.87; RD -0.09, 95% CI -0.14 to -0.03), and in a statistically significant 41% decrease in the occurrence of AOM if it was administered in chewing gum only (Figure 6 RR 0.59, 95% CI 0.42 to 0.81; RD -0.10, 95% CI -0.16 to -0.04). The effect of xylitol lozenge in reducing AOM was inconclusive (only reported in Uhari 1998, RR 0.80, 95% CI 0.56 to 1.16; RD -0.05, 95% CI -0.14 to 0.04). Among the healthy children during a respiratory infection (only reported in Tapiainen 2002), there was no difference in the outcome whether xylitol was administered in chewing gum or lozenges (Figure 5 RR 1.34, 95% CI 0.86 to 2.10), in chewing gum only (Figure 6 RR 1.29, 95% CI 0.78 to 2.14), or in lozenges only (RR 1.40, 95% CI 0.85 to 2.29). Vernacchio 2014 did not report this subgroup.

Figure 5. Forest plot of comparison: 4 Xylitol chewing gum/lozenges versus control chewing gum for older children able to chew, outcome: 4.1 Final diagnosis of at least one episode of AOM.

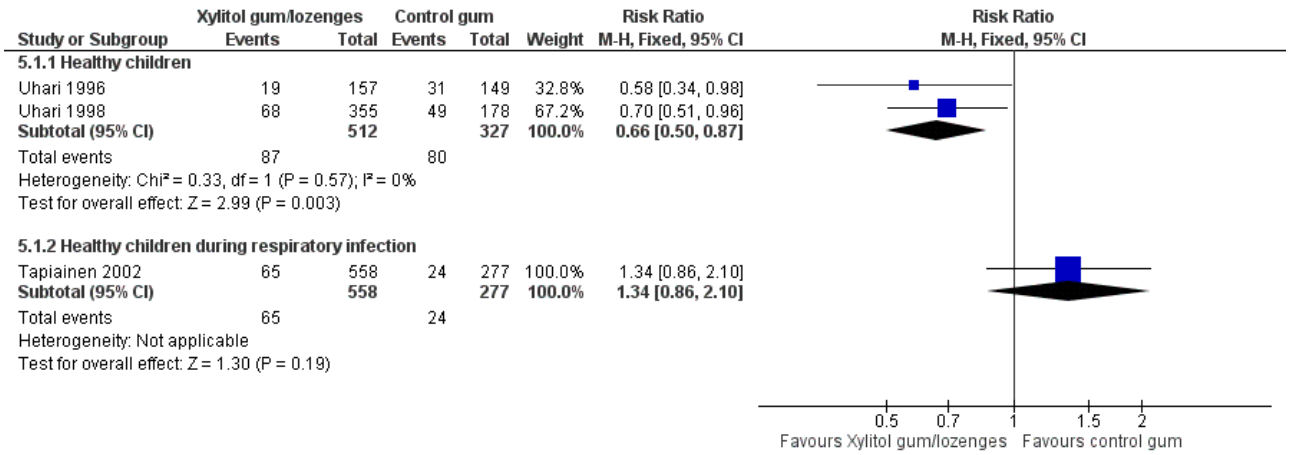
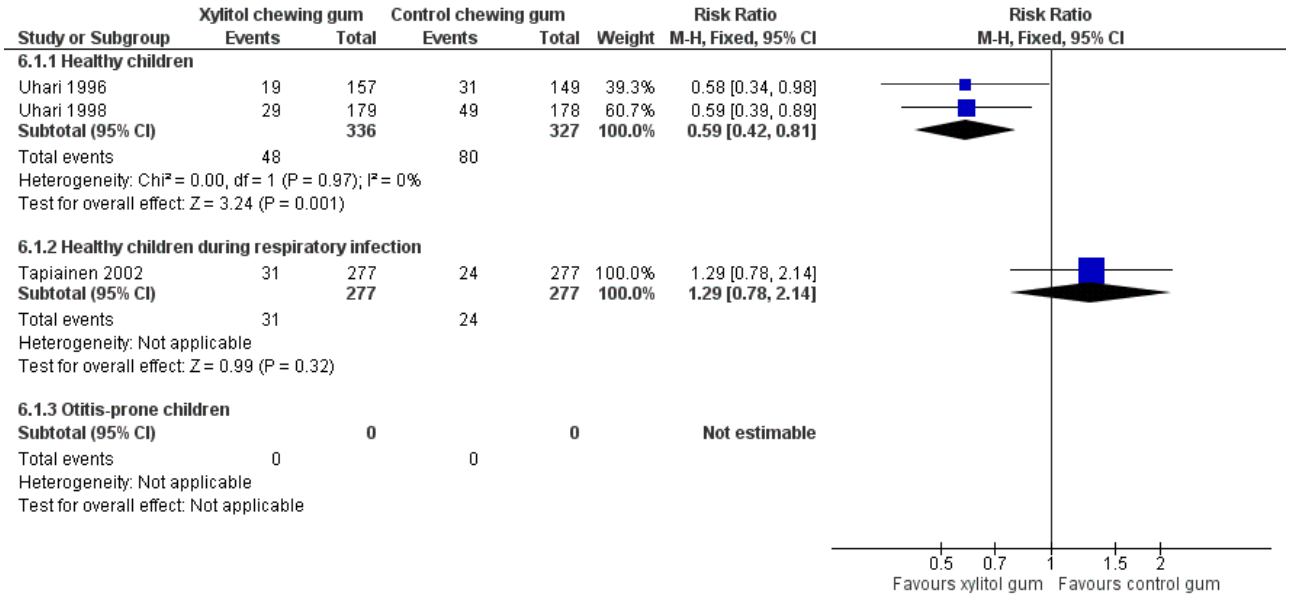


Figure 6. Forest plot of comparison: 5 Xylitol chewing gum versus control chewing gum for older children able to chew, outcome: 5.1 Final diagnosis of at least one episode of AOM.



Comparison of different types of xylitol vehicles

We also compared the outcome of the final diagnosis of at least one episode of AOM between the active ingredients groups to assess whether the mode of delivery for the ingredient makes any difference. We performed this analysis on healthy children (Uhari 1998), and also on children with a respiratory infection (Tapiainen 2002). It should be noted that this comparison is limited to one study in each population group: Uhari 1996 did not test different modes of delivery for xylitol (chewing gum only); and although Hautalahti 2007 used two modes of delivery for xylitol (chewing gum and syrup), the data were collectively presented as one test group. The analyses show that xylitol chewing gum is superior to xylitol syrup in preventing AOM among healthy children (RR 0.59, 95% CI 0.39 to 0.89), but not for children with a respiratory infection (RR 0.68, 95% CI 0.43 to 1.07). There was no difference between xylitol lozenges and xylitol syrup in preventing AOM among healthy children (RR 0.77, 95% CI 0.53 to 1.11), or among children with a respiratory infection (RR 0.74, 95% CI 0.47 to 1.14). Similarly, no difference was noted between xylitol chewing gum and xylitol lozenges in preventing AOM among healthy children (RR 0.73, 95% CI 0.47 to 1.13), or among children with a respiratory infection (RR 0.92, 95% CI 0.59 to 1.46). Vernacchio 2014 did not report this subgroup.

DISCUSSION

Summary of main results

This review has attempted to find evidence for a preventive effect of xylitol in reducing the occurrence of acute otitis media (AOM). Safety and adverse events were not statistically significantly different. This finding is similar to Vernacchio 2007a, where oral xylitol solution at dosages of 5 g three times per day and 7.5 g once daily were found to be well-tolerated by young children. However, the relative rarity of events and the few patients from whom data are available prevents us from arriving at firm conclusions on safety. Xylitol in connection with dental decay has been used for decades, since it has been shown to reduce mutans streptococci counts in plaque and saliva (Haresaku 2007) and reduce lactic acid production in dental plaque through interference with metabolic pathways (Twetman 2003). In a recent systematic review (Ly 2008) and meta-analysis (Deshpande 2008), it is claimed that xylitol could benefit people at high risk of caries and should be considered for routine use in clinical dentistry. However, the use of xylitol in dental decay suggests that it may also be useful for preventing AOM, which is the focus of this review.

Overall completeness and applicability of evidence

Considering the concerns over the treatment of AOM using antibiotics and surgery, we wanted to explore the literature for alternative preventive strategies. In the earlier version of this review (Azarpazhooh 2011), following an exhaustive search strategy, we found three clinical trials that investigated the efficacy of xylitol administered prophylactically to children in daycare centres (Hautalahti 2007; Uhari 1996; Uhari 1998). All these trials were double-blinded, randomised and placebo-controlled, with appropriate randomisation and masking procedures. While the trials stemmed from the same group of trial authors, the design of the trials was improved following the first one (Uhari 1996), which utilised sucrose in the control group. This study was later criticised due to the possibility of risking dental caries in the participants. Therefore, in the following studies, xylitol was used as a sweetener in the control groups as well, to avoid the increased risk for caries. While the chewing gums were similar in taste, the xylitol mixture tasted sweeter than the control syrup (Hautalahti 2007; Uhari 1998). These studies did not discuss why the low dose of xylitol (0.5 g/day) in the control group can be considered as equivalent to placebo. In this update, we identified a pragmatic practice-based RCT (Vernacchio 2014), which determined if viscous xylitol solution versus sorbitol solution could reduce the occurrence of clinically diagnosed AOM among otitis-prone children six months through to five years of age. We elected not to pool the result of this trial with those we identified in 2011 (Azarpazhooh 2011), because as

compared to trials included in our 2011 review, the population was not homogenous, the total dose was increased by 50% (15 g daily) and the outcome was measured as what had been documented in the patients' medical charts.

Based on the studies we reviewed, xylitol seems to be a promising alternative to conventional therapies to prevent AOM among healthy children. Even in one study (having controlled for parental education and smoking, breast feeding, use of pacifier, sibling prone to otitis, previous history of AOM, previous use of xylitol and nasopharyngeal carriage of pneumococci) children receiving xylitol had fewer AOM episodes (P = 0.045) (Uhari 1996). The overall results from combining the data from the preventive clinical trials among healthy children (comparing xylitol to a control group of sucrose or minimum non-therapeutic dose of xylitol plus sorbitol) are encouraging. The magnitude of the reduction in the occurrence of AOM was an overall 25% (1- RR 0.75) when the results of all types of administration are considered (i.e. syrup, lozenge or chewing gum) and was 30% (1- RR 0.70) if it is administered in a syrup for younger children unable to chew. Among those older children who were able to chew, xylitol in chewing gum form was effective in the prevention of AOM by 41% (1- RR 0.59); in contrast, xylitol lozenges were not preventive. Also, it was found that chewing gum is a better vehicle for xylitol administration with an extra 41% preventive effect when compared to xylitol syrup (1- RR of 0.59). That said, in this update, the result of the identified pragmatic practice-based RCT (Vernacchio 2014) showed that 15 g daily dose of a viscous xylitol solution was ineffective in reducing clinically diagnosed AOM among otitis-prone children. The observed effect in this trial could be the result of lack of adherence to treatment since almost 28% in the xylitol group and 24% in the placebo group discontinued treatment before the end of the study period or the occurrence of the primary outcome. Furthermore, xylitol in reducing AOM among healthy children during a respiratory infection (Tapiainen 2002) was ineffective. The trial authors speculated their findings to the increased bacterial adherence to pharyngeal cells during viral infection, and the increased incidence of otitis media pathogens in the nasopharynx at such times.

Through the literature search and as part of the peer refereeing process, we came across some important papers that can shed more light on the applicability of the results of this review and the potential limitations and obstacles to the applicability of these findings, in particular those of chewing gum. The first obstacle is the knowledge of medical practitioners about medical uses for xylitol. A recent national survey of paediatricians in the USA regarding their knowledge and opinions about xylitol use as a prophylaxis for AOM found that only about half of the participants knew about medical uses for xylitol; of those, most were aware of its use in chewing gum to prevent AOM but had not used it with patients (Danhauer 2010b). Perhaps the most encouraging result of this survey, and a follow-up focus group survey by the same research group on 10 US paediatricians known to have more experience with xylitol for AOM (Stockwell 2010), was that the majority of the US paediatricians would use xylitol if evidence supported it and wanted information about it via reprints or electronically.

It should also be noted that xylitol chewing gums are commercially available in Finland (the country where four out of five included studies took place) and their use is recommended by the dental organisations. However, in the USA, some school districts prohibit gum chewing altogether, while others leave it up to the discretion of individual teachers. For example, a recent survey of all the Kindergarten through 3rd Grade teachers in Santa Barbara, CA School Districts (Danhauer 2011a), regarding their knowledge about AOM and their willingness to participate in AOM prevention programmes, found that all of the schools and almost all of the teachers did not permit chewing gum on campus or in their classrooms. Other obstacles identified in this pilot survey were supervision, liability, school regulation, compliance issues, potential distractions to classes and risk of choking. These obstacles point to the importance of educational and informational outreach programmes to educate practitioners, parents and school teachers about the medical use of xylitol, in particular when added to chewing gum for both the reduction of dental caries and the occurrence of AOM.

Given the evidence that parental reporting of children's recent AOM history correlates well with medical records (Vernacchio 2007b), in our previous review, we proposed that considering the potential obstacles to AOM prevention programme in daycare and school settings, in-home use of xylitol needs to be investigated. Fortunately, one such study became available for this update (Vernacchio 2014); however, this study did not find a significant effect for a viscous xylitol solution at a dose of 5 g three times per day in reducing clinically diagnosed AOM among otitis-prone children. There is some evidence to show that mothers' chewing xylitol gum was a prophylaxis against bacteria and caries in their children. The use of such mother-child transmission model as a possible vehicle for preventing AOM would be worth further investigations (Danhauer 2011b).

Although the results of this present meta-analysis show that chewing gum is a better vehicle for xylitol administration, the present obstacles could preclude the use of xylitol chewing gum in school settings for small children who are unable to chew gum. This happens to be the group most susceptible to AOM and therefore, for such children, vehicles other than chewing gum need to be pursued (Danhauer 2011a). For example, we found unpublished evidence internal to Xlear Inc. Orem (Utah, USA) that a xylitol nasal wash three times daily during a three-month period lowered the recurrence of AOM and the frequency of antibiotic therapy and upper airways infections (Kalanin 2005). Moreover, in our 2016 updated search, we identified a randomised, double-blinded clinical trial registered with Clinicaltrial.gov that is not yet open for participant recruitment (NCT02592382). This trial, based in Rambam Health Care Campus, Haifa, Israel, is designed to enrol 50 children aged from one to five years who have had three episodes of recurrent otitis media in the last six months prior to entering the study. They will randomly receive isotonic saline nasal spray or 5% xylitol spray (three times daily for two months) and the occurrence of AOM will be measured for five months. We will monitor the progress of this trial for future updates of this review.

Xylitol syrup can also be administered with pacifiers that have reservoirs used to supply medicine to the infant at bed time. That said, a recent web-based survey of 136 parents of young children in preschool and kindergarten settings (Danhauer 2015), found that most parents were unaware of xylitol's use for AOM and would be unwilling to use xylitol products or comply with a required regimen to prevent AOM in their children. That said, those who knew about xylitol and had children with a history of AOM would be more likely to do so, most would prefer chewing gum for older children and pacifiers for younger children (Danhauer 2015). There

remain to be a need for more educational public campaign on the potential benefits of xylitol and the importance of parental and school compliance for successful AOM prevention regimens. Finally, in our protocol, we decided not to include cluster-design RCTs due to potential differences in ancillary treatments between centres. Although we did not find any cluster-RCTs in our search, we will look for them in the future updates to this review.

Quality of the evidence

The quality of evidence for the number of children with at least one AOM episode during the follow-up period was moderate for healthy children due to the inconsistency of the results among trials, moderate for children with respiratory infections due to imprecise estimates, and low for otitis-prone children due to imprecise estimates and high attrition. Hence, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Potential biases in the review process

In our previous review, we decided to use fixed-effect analysis as there was sufficient homogeneity among the three Finnish studies. These studies were all from the same group of researchers in Finland; the studied population was homogenous (healthy children attending daycare centres in Oulu, Finland); the total dose of xylitol was similar (8 to 10 g/day); the control groups include 0 to 0.5 g of xylitol per day plus other ineffective sweetener in preventing AOM; the outcome measurement was similar. Althoug we had calculated I^2 statistic values which ranged from 0% to 69% in different analyses, the number of trials included in meta-analyses remain low and test for statistical heterogeneity tend to be underpowered.

Agreements and disagreements with other studies or reviews

Since publication of the protocol of this review in 2008, two systematic reviews have been published (Danhauer 2010a; Danhauer 2011b). Our results are in agreement with these systematic reviews that also concluded that xylitol can be a prophylaxis for AOM, but warrants further study, especially of vehicles other than chewing gum for young children.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of the included trials, we conclude that there is moderate-quality evidence that the supervised prophylactic administration of xylitol among healthy children attending daycare centres can reduce the occurrence of AOM from 30% to around 22%. If the children are unable to chew (for example, in the first two years of life), the effect size of AOM prevention with xylitol syrup was 30%. If the children were able to chew, the effect size of AOM prevention with xylitol chewing gum was 41%. There is not enough evidence to prove the efficacy of xylitol lozenges for the older children who were able to chew. In comparable situations, chewing gum is a better vehicle for xylitol administration, with an extra 41% preventive effect when compared to xylitol syrup. There is insufficient evidence of low to moderate quality for the efficacy of xylitol administration to prevent AOM only during a respiratory infection, or to otitis-prone children.

For those young children for whom antibiotics are a major risk, xylitol is a potential alternative for preventing AOM. The benefit appears to be a moderate one but more studies need to be conducted. There were insufficient studies in a variety of groups of children to develop evidence-based treatment guidelines. It should be noted that the potential obstacles (school classrooms, supervision, liability, school regulation, compliance issues, potential distractions to classes and risk of choking) could preclude the use of xylitol chewing gum as a school-based prevention programme. For small children who are unable to chew gum, other vehicles (such as nasal wash, pacifier for children or chewing gum for mothers) need to be investigated further.

Implications for research

In applying these results, it should be appreciated that the thorough literature searches revealed only five randomised clinical trials, four of which are from the same research group. The quality of evidence was moderate for healthy children and for children with respiratory infections and low for otitis-prone children. Hence, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Hence, there is still a need for the highest level of evidence, i.e. well-designed, double-blind RCTs (preferably a multicentre trial) with adequate sample size, limited or no loss to follow-up and carefully standardised methods of measurement and analysis, to evaluate the possible use of xylitol for preventing AOM in children up to 12 years of age, in particular targeting 'at risk' groups. Future research may need to focus on a safe and identically tasting placebo rather than low-dose xylitol. It is still not known what range of xylitol would be most useful for the prevention of AOM. Studies need to be conducted to determine the optimum xylitol exposure for a child on a g/kg body weight/day basis, the best vehicle for toddlers, and whether the first year of life is an appropriate age group to test. Other important outcomes, such as hospitalisation (and length of stay in hospital) secondary to AOM or its complications, percentage of children needing antibiotic therapy, number of days missed at school or daycare centre, and direct and indirect costs, should also be considered. Once the efficacy of the product is established, the next requirement is for high quality studies to evaluate the relative cost-effectiveness of the prophylactic interventions. In any case, informational outreach programmes are necessary to educate practitioners about medical use of xylitol, in particular chewing gum.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hautalahti 2007

Methods	Double-blind, placebo-controlled randomised study
Participants	663 healthy daycare children with normal ear status and without current ARI (normal tympanograms, A-curve) recruited from 21 childcare centres in the city of Oulu, Finland between August 2001 and January 2002. Age: 7 months to 7 years Exclusion criteria: current antimicrobial prophylaxis, craniofacial malformations and structural middle ear abnormalities
Interventions	Test group, unable to chew gum n = 60: 8 mL of a syrup containing 400 g/L xylitol 3 times a day (daily doses of 9.6 g of xylitol) Test group, able to chew gum n = 272: xylitol chewing gum 3 times a day (daily dose 9.6 g of xylitol) Placebo group, unable to chew gum n = 57: control syrup containing 20 g/L xylitol diluted in water without any other sweeteners 3 times a day (daily doses of 0.5 g xylitol) Placebo group, able to chew gum n = 274: control chewing gum 3 times a day (daily dose 0.5 g of xylitol) also contained sucrose as a sweetener
Outcomes	AOM based on a finding of middle ear effusion by pneumatic otoscopy and symptoms of acute respiratory infection
Notes	The daily amount of xylitol was the same as other trials but it was administered only 3 times a day

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Hautalahti 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed using tables of random numbers and a block approach with a block size of four."
Allocation concealment (selection bias)	Low risk	A randomisation list was given to the product providers and the products were packed using this random allocation sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All study physicians, authors, and participating families were blinded to the group assignment until data entry and data checking were complete."
Incomplete outcome data (attrition bias) All outcomes	Low risk	By the end of trial, the dropout range was statistically higher in test group (17%) versus the control group (11%). The reasons for dropouts were: child refused to take the product; abdominal discomfort; chewing gum piece too big; duration of the trial too long; forgot to give the preparation when on holiday; illness; rash; parents tired of the trial; difficult to avoid additional xylitol products; other or unknown reasons
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Unclear risk	The material was donated by industry. Governmental source of funding. The study authors declared no conflict of interest but based on their previous paper, they have a US patent for the use of xylitol in treating respiratory infection

Tapiainen 2002

Methods	Double-blind, placebo-controlled randomised study
Participants	1277 healthy daycare children the city of Oulu, Finland after screening with tympanometry during an ARI
Interventions	Children unable to chew gum: Placebo group: n = 212: 5 mL of a syrup containing 20 g/L xylitol diluted in water without any other sweeteners (daily doses of 0.5 g of xylitol) Test group: n = 212: 5 mL of a syrup containing 400 g/L xylitol 5 times a day (daily doses of 10 g of xylitol) Syrups administered after meals with a syringe during a period of 5 minutes to maintain a high concentration of xylitol in the oral cavity for as long as practically possible Children able to chew gum: Placebo group: n = 280, control chewing gum with daily dose 0.5 g of xylitol Test group: n = 286: xylitol chewing gum with daily dose 8.4 g of xylitol Test group: n = 287: xylitol lozenges with daily dose 10 g of xylitol Two pieces of chewing gum or lozenges were chewed for at least 5 minutes 5 times a day after meals. 3 of the doses were given by the personnel at the childcare centres during the day and the rest were given by the parents at home.
Outcomes	AOM based on a finding of middle ear effusion in tympanometry (B, C or positive pressure curve) and confirmed with pneumatic otoscopy; A total of 1253 of the 1277 randomised children were eligible for the analysis of the primary outcome

Tapiainen 2002 *(Continued)*

Notes	The daily doses of control and xylitol products were equal to those used in earlier trials The parents began administering the products to their children at the onset of symptoms of ARI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed in blocks of 4 in the mixture groups and in blocks of 3 in chewing gum and lozenge groups, using a random number table to make the proportion of participants in each study group approximately the same at each child care centre."
Allocation concealment (selection bias)	Low risk	Each child was given a unique participation number at the time of the initial screening
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was blinded as far as the mixture and chewing gum groups were concerned but open as between the xylitol lozenge and control chewing gum groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	The children who dropped out (n = 24) were excluded from the statistical analysis, but those who prematurely stopped using the products but still visited the clinic (n = 35) were included. The children who dropped out contributed days at risk to the cumulative occurrence analysis for as long as they continued to participate
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Unclear risk	The material was donated by industry. Governmental source of funding. The study authors declared they have a US patent for the use of xylitol in treating respiratory infection

Uhari 1996

Methods	Double-blind, placebo-controlled randomised study
Participants	306 children from 11 ordinary daycare nurseries for healthy, normal children from the city of Oulu, Finland were enrolled in March 1995 after parental consent. 30 dropouts, which left 276 children Xylitol group (n = 157), mean (SD) age = 5.0 (1.4); mean (SD) duration of daycare (months) = 26.5 (16.9) Sucrose group (n = 149), mean (SD) age = 4.9 (1.5) years; mean (SD) duration of daycare (months) = 25.2 (19.0) Exclusion criteria: children with dental caries
Interventions	Xylitol chewing gum n = 157: 2 pieces five times (one box) a day after meals or snacks were chewed until there was no taste left or for at least 5 minutes, making a total dose of 8.4 g xylitol a day Sucrose (control) chewing gum n = 149
Outcomes	AOM based on symptoms and signs of ARI and simultaneous signs of middle ear effusion: a cloudy tympanic membrane or impaired tympanic membrane motility in pneumatic otoscopy Antimicrobial treatment received during the intervention and nasopharyngeal carriage of *S pneumoniae*

Uhari 1996 *(Continued)*

Notes	Use of sucrose as the control group has been criticised as possibly increasing the dental caries experience. However, of the children who underwent a dental examination, there was no difference in the rate of dental decay (23/114 in sucrose group versus 21/111 in the xylitol group) The study population age ranges from 2 to 5 years, which is older than the usual peak age for otitis media (6 to 18 months,*Journal of Pediatrics* 1988; 113:581-7) Xylitol was administered 5 times a day which may be difficult in a practical situation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was made by using random number tables which were also used to number the cartridges. Block randomisation with a block size of 4 in each daycare was used to ensure equal numbers of children in the 2 groups Quote: "A randomisation list was made by using random number tables." To ensure equal numbers of children in the 2 groups in each of the nurseries we used block randomisation with a block size of 4
Allocation concealment (selection bias)	Low risk	The list was sealed in an envelope. The observers were blinded to the randomisation scheme Quote: "The cartridges were numbered accordingly, and the list was sealed in an envelope"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The observers in the trial were unaware of the randomisation scheme"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a dropout of 30 participants, 10 in xylitol group and 20 in control group representing a dropout rate of 6% and 13%, respectively. The reasons for dropouts were: child got tired of eating chewing gum, dental caries, moved from area, parents got tired, insufficient follow-up data, loose stools
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Unclear risk	The material was donated by industry, no conflict of interest was reported. Governmental source of funding

Uhari 1998

Methods	Double-blind, placebo-controlled randomised study
Participants	857 children from 34 typical daycare centres for healthy children from the city of Oulu, Finland were recruited after parental consent between September and December 1996 Exclusion criteria: antimicrobial prophylactics, congenital craniofacial malformation or a structural middle ear abnormality
Interventions	Test group, unable to chew gum n = 159: 5 mL of a syrup containing 400 g/L xylitol 5 times a day (daily doses of 10 g of xylitol) Test group, able to chew gum n = 179: 2 pieces of xylitol chewing gum 5 times a day (3 x in daycare and 2 x in home) after a meal for at least 5 minutes or as long as it tasted sweet (daily dose 8.4 g of xylitol), or 3 xylitol/maltitol lozenges (n = 176) lozenges 5 times a day after a meal for at least 5 minutes or as long as it tasted sweet (daily dose 10 g of xylitol)

Uhari 1998 *(Continued)*

	Control group, unable to chew gum n = 165: control syrup containing 20 g/L xylitol diluted in water without any other sweeteners with the same protocol as xylitol syrup group (daily doses of 0.5 g of xylitol) Control group, able to chew gum n = 178: chewing gum sweetened with sucrose and xylitol (daily dose 0.5 g of xylitol) with the same protocol as xylitol gum group
Outcomes	AOM based on a finding of middle ear effusion in tympanometry (B- or C-curve), verified otoscopically with signs of inflammation in the tympanic membrane, and the presence of symptoms of acute respiratory infection (rhinitis, cough, conjunctivitis, sore throat, earache)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed using tables of random numbers and using a block randomisation with a block size of six."
Allocation concealment (selection bias)	Unclear risk	Not mentioned but probably done as per their earlier publication
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The study was double-blind in the syrup and chewing gum groups and open between the chewing gum and lozenge groups. The xylitol syrup was sweeter than the control syrup, but the taste of the chewing gums was quite similar regardless of the sweeteners used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	By the end of trial, the dropouts range from 4.5% to 18.9% and were statistically higher in the xylitol syrups (18.9%) and xylitol lozenges (14.8%) as compared to their control groups of, respectively, control syrups (10.3%) and control chewing gum (4.5%). The reasons for dropouts were: unwilling to continue taking the product, left the area, abdominal discomfort, unknown reason
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Unclear risk	The material was donated by industry, no conflict of interest was reported. Governmental source of funding

Vernacchio 2014

Methods	Double-blind, pragmatic practice-based RCT
Participants	326 otitis-prone children ages 6 to 71 months with history of at least 3 clinically diagnosed episodes of acute otitis media (with/without middle ear effusions) in the previous 12 months with at least 1 in the previous 6 months, in good general health (see criteria for 'good health' on page 290) and English or Spanish speaking All children were identified and referred by participating physicians from 3 paediatric practice-based networks (the Slone Center Office-based Research Network at Boston University, the Pediatric Physicians' Organization at Children's (Boston), and the North Carolina Child Health Research Network at the University of North Carolina)
Interventions	Active treatment: Xylitol oral solution (Xylarex; Arbor Pharmaceuticals, Atlanta, GA) consisting of a 66.7% aqueous xylitol solution with the addition of carboxymethylcellulose and potato starch as mu-

Vernacchio 2014 *(Continued)*

	cosal adherence agents and natural flavouring. The dose for the xylitol syrup was 7.5 mL 3 times daily for 12 weeks (i.e. 5 g xylitol per dose) Placebo medication: 30% sorbitol oral solution with the addition of carboxymethylcellulose and potato starch as mucosal adherence agents and natural flavouring at a dose of 2.25 g sorbitol 3 times per day
Outcomes	Primary outcome: comparison of time to first clinically diagnosed AOM episode in the two study groups, using proportional hazards model. Secondary outcomes: 1. Proportion of participants in each group with no AOM episodes and no antibiotic use during the study period 2. Reduction in the 3-month cumulative incidence of AOM episodes, as measured by the risk difference and the hazard rate for AOM (in Poisson regression) 3. Reduction in antibiotic use per 90 days, as measured by the risk difference and the hazard rate (in Poisson regression) Frequency of occurrence of adverse events in either group, as measured by the risk difference
Notes	Analyses were based on the intention-to-treat principle. For the comparison of incidence of AOM episodes and antibiotic use per 90 days between the two groups, "rates were calculated individually (events divided by days of enrolment), assuming a zero rate for the 12 participants with no follow-up." Higher amount of xylitol per dose and per day over previous studies and the addition of mucosal adherence agents to the xylitol solution as compared to other studies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No direct quote was found. There was an acknowledgement to Qiaoli (Lily) Chen who generated randomisation assignments
Allocation concealment (selection bias)	Unclear risk	No information is provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded study syrups. Sorbitol is similar in appearance and taste to xylitol. "After randomisation, study materials, including the blinded study syrup, appropriate oral syringes, and a study calendar, were shipped to the subject's home." The principal investigator reviewed medical records in a blinded fashion. Quote: "At the end of the study, medical records from each subject's primary care physician and from any other health care provider whom the parent identified as having treated the subject during the study period were obtained and reviewed by the principal investigator (LV) in a blinded fashion."
Incomplete outcome data (attrition bias) All outcomes	High risk	62/160 allocated to xylitol (38.8%) declined participation, were lost to follow-up or discontinued intervention versus 58/166 allocated to placebo (34.9%)
Selective reporting (reporting bias)	Low risk	As compared to protocol NCT01044030, 2 secondary outcomes were not reported, although they do not represent key outcomes: 1) To determine the effect of viscous-adherent xylitol on nasopharyngeal and oropharyngeal colonisation with *S pneumoniae* and non-typable *H influenzae* and 2) To compare the antimicrobial resistance patterns of isolates of *S pneumoniae* and non-typable *H influenzae* cultured from the oropharynx and/or nasopharynx of subjects treated with viscous-adherent xylitol compared to placebo

Vernacchio 2014 *(Continued)*

Other bias	Low risk	*Potential bias for outcome assessment*: The study did not have any protocol of assessment for healthcare providers. Quote: "For the primary outcome of clinical diagnoses of AOM, the medical record was considered the gold standard. For those cases in which the medical record was not available, the parent's report of AOM diagnoses was used" The researchers assumed that inaccurate diagnoses would be equal in both groups. Quote: "AOM diagnoses were made by a wide range of clinicians and were not otherwise verified." "… assuming that AOM diagnoses were equally inaccurate in both study groups, the overall effect would be to bias the study toward a null result." The trial was performed under FDA New Drug application number 107246 and was registered at www.clinicaltrials.gov (NCT01044030) No financial incentives paid to parents/subjects or to enrolling practices, except a nominal reimbursement for staff time involved in referring potentially eligible parents.

AOM: acute otitis media
ARI: acute respiratory infection
n: number
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Milgrom 2009	No data on AOM. In the published paper, it was mentioned that the effect of xylitol in reducing AOM will be published in a subsequent study. However, after contacting the primary investigator, it was understood that due to lack of reliability of data regarding AOM, the plan to publish AOM results has been suspended

AOM: acute otitis media

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kalanin 2005

Methods	Multicentre, randomised, double-blind, placebo-controlled study
Participants	82 male and 86 female outpatients from 1 to 15 years of age with recurrent AOM. Mean age was 6.14 years. The population is from Prague and Mid-Bohemia region, Czech Republic
Interventions	Intervention: 3 daily doses of nasal wash, each consisting of 2 squirts per nostril, at regular assigned times daily (after waking up; after lunch; before going to bed). Patients received one of the following treatments as predetermined by their randomisation number: a solution of nasal xylitol (11% pure xylitol; XLEAR®) or distilled water
Outcomes	AOM recurrence; frequency of antibiotic therapy; frequency of upper airways infections; adverse events
Notes	Xlear Inc. has been contacted for further information about this unpublished report

AOM: acute otitis media

Characteristics of ongoing studies *[ordered by study ID]*

NCT02592382

Trial name or title	Nasal xylitol in the prevention of otitis media
Methods	Double-blind, RCT
Participants	50 children at the age of 1 to 5 years who had 3 episodes of recurrent otitis media in the last 6 months prior to entering the study. Those with immune deficiency, craniofacial malformations, chronic otitis media, or those who received prophylactic antibiotic treatment prior to entering the study (3 months) will be excluded
Interventions	Control: isotonic saline nasal spray; test: 5% xylitol spray (3 times daily for 2 months)
Outcomes	Primary outcome measures: prevalence of otitis media and the number of events of acute otitis media during the study period of 5 months Secondary outcome measures: side effects of treatment during a time frame of 2 months
Starting date	January 2016
Contact information	Arie Gordin, M, a_gordin@rambam.health.gov.il and Shani Fischershani_fi@clalit.co.il Sponsors and Collaborators: Rambam Health Care Campus, HaEmek Medical Center, Israel, Carmel Medical Center
Notes	

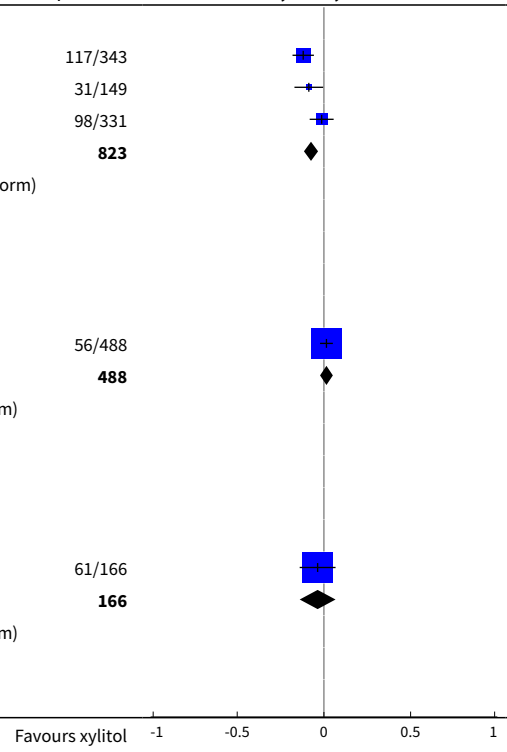
DATA AND ANALYSES

Comparison 1. Xylitol in any form (syrup, gum or lozenge) versus control in any form (gum, syrup)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	5		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	3	1826	Risk Difference (M-H, Fixed, 95% CI)	-0.07 [-0.12, -0.03]
1.2 Healthy children during respiratory infection	1	1253	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.02, 0.05]
1.3 Otitis-prone children	1	326	Risk Difference (M-H, Fixed, 95% CI)	-0.04 [-0.14, 0.07]

Analysis 1.1. Comparison 1 Xylitol in any form (syrup, gum or lozenge) versus control in any form (gum, syrup), Outcome 1 Final diagnosis of at least one episode of AOM.

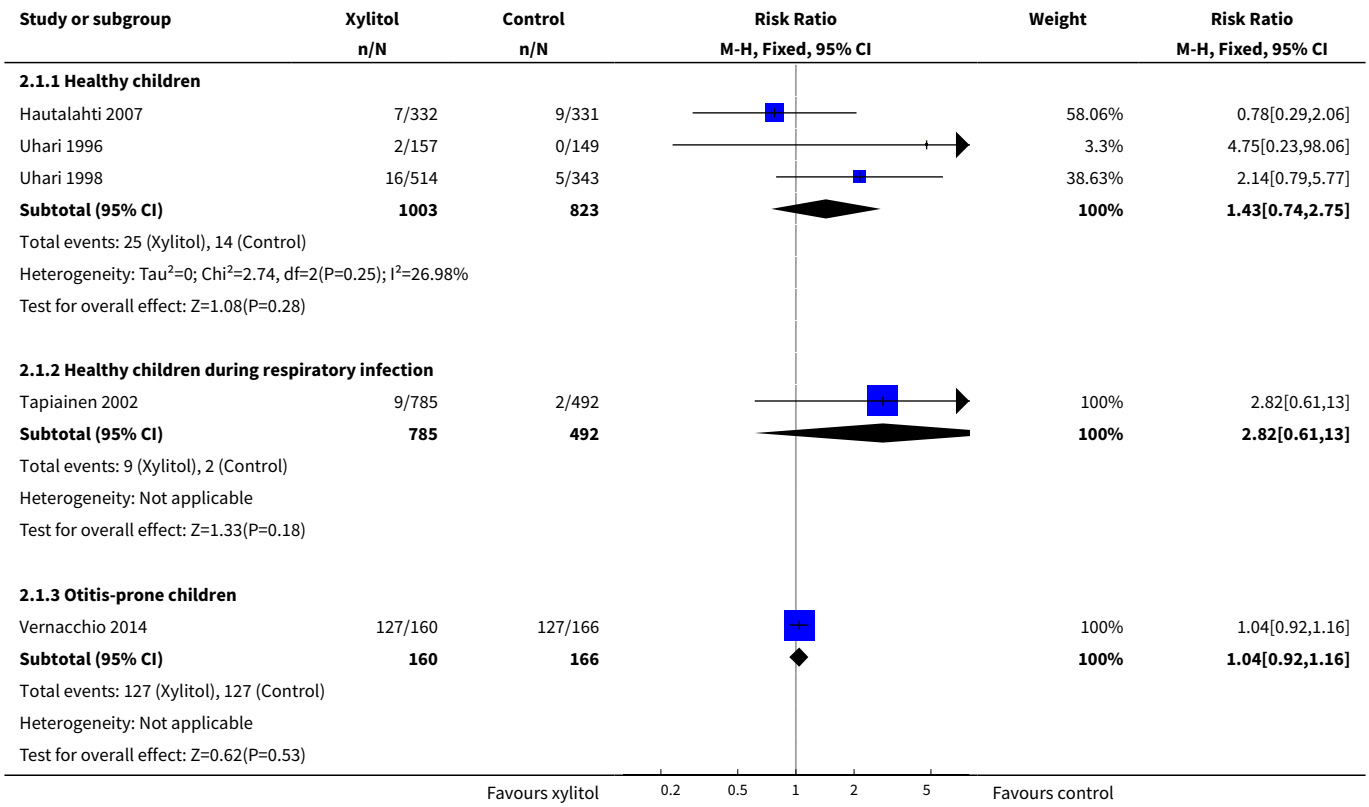
Study or subgroup	Xylitol in any form n/N	Control in any form n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.1.1 Healthy children					
Uhari 1998	114/514	117/343		45.93%	-0.12[-0.18,-0.06]
Uhari 1996	19/157	31/149		17.07%	-0.09[-0.17,-0]
Hautalahti 2007	94/332	98/331		37%	-0.01[-0.08,0.06]
Subtotal (95% CI)	**1003**	**823**		**100%**	**-0.07[-0.12,-0.03]**
Total events: 227 (Xylitol in any form), 246 (Control in any form)					
Heterogeneity: Tau^2=0; Chi^2=5.17, df=2(P=0.08); I^2=61.31%					
Test for overall effect: Z=3.59(P=0)					
1.1.2 Healthy children during respiratory infection					
Tapiainen 2002	99/765	56/488		100%	0.01[-0.02,0.05]
Subtotal (95% CI)	**765**	**488**		**100%**	**0.01[-0.02,0.05]**
Total events: 99 (Xylitol in any form), 56 (Control in any form)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.78(P=0.44)					
1.1.3 Otitis-prone children					
Vernacchio 2014	53/160	61/166		100%	-0.04[-0.14,0.07]
Subtotal (95% CI)	**160**	**166**		**100%**	**-0.04[-0.14,0.07]**
Total events: 53 (Xylitol in any form), 61 (Control in any form)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					



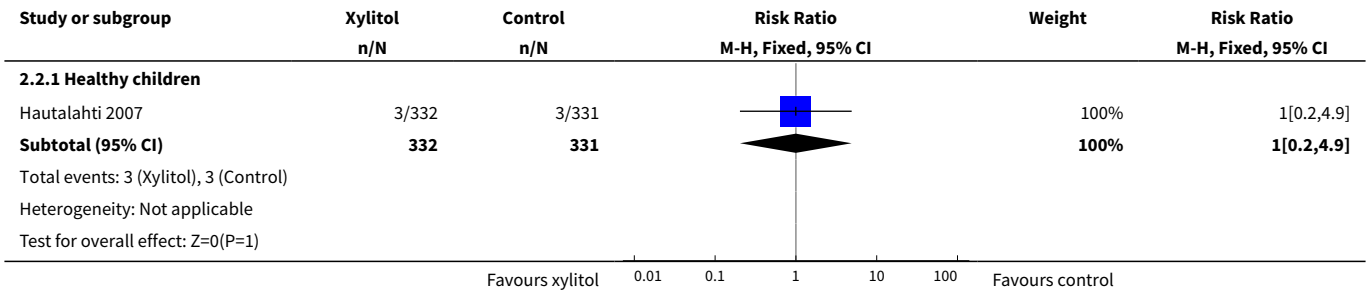
Comparison 2. Adverse effect: xylitol versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal-related adverse events	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	3	1826	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.74, 2.75]
1.2 Healthy children during respiratory infection	1	1277	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.61, 13.00]
1.3 Otitis-prone children	1	326	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.16]
2 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healthy children	1	663	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.20, 4.90]

Analysis 2.1. Comparison 2 Adverse effect: xylitol versus control, Outcome 1 Gastrointestinal-related adverse events.



Analysis 2.2. Comparison 2 Adverse effect: xylitol versus control, Outcome 2 Rash.

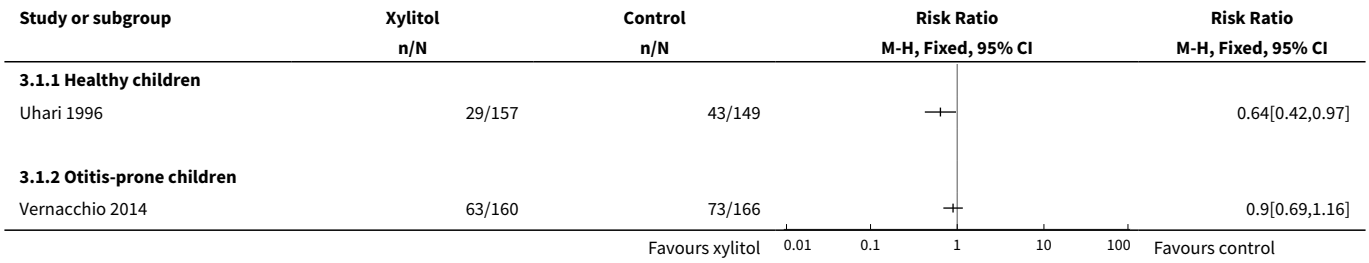


Comparison 3. Antibiotic administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least one exposure to antimicrobial drugs	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Healthy children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Otitis-prone children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

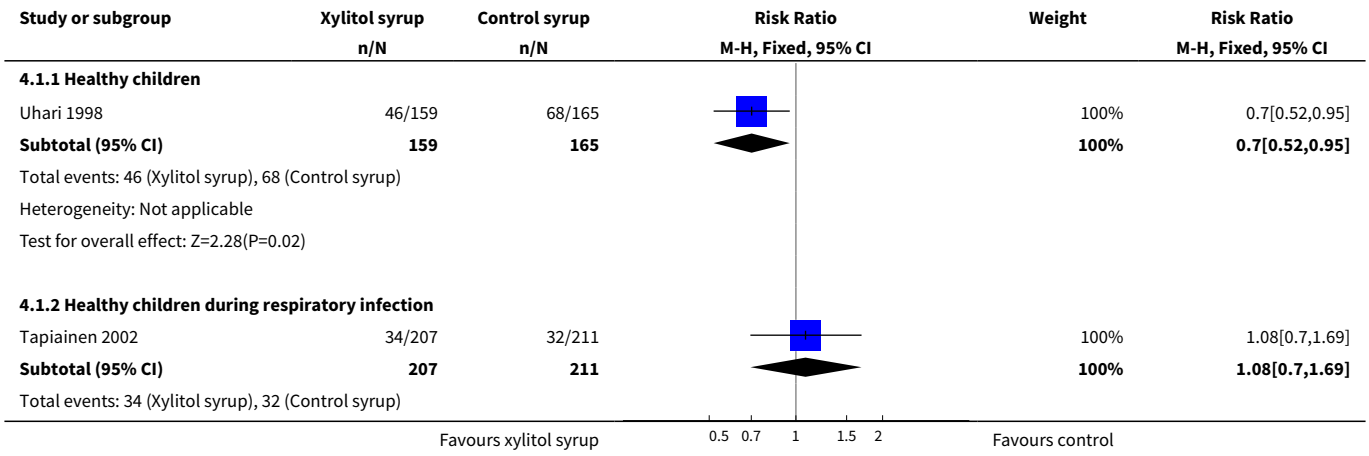
Analysis 3.1. Comparison 3 Antibiotic administration, Outcome 1 At least one exposure to antimicrobial drugs.

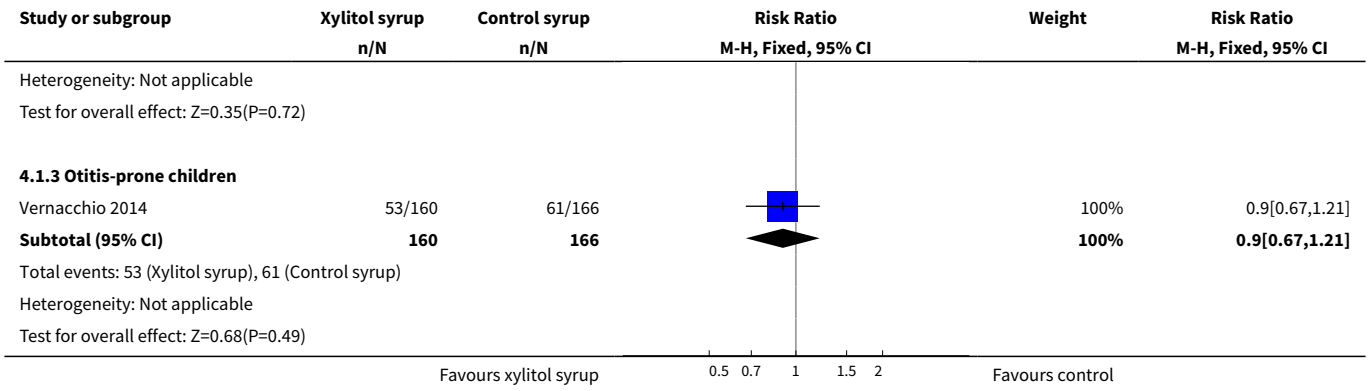


Comparison 4. Xylitol syrup versus control for younger children unable to chew

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	1	324	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.52, 0.95]
1.2 Healthy children during respiratory infection	1	418	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.70, 1.69]
1.3 Otitis-prone children	1	326	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.21]

Analysis 4.1. Comparison 4 Xylitol syrup versus control for younger children unable to chew, Outcome 1 Final diagnosis of at least one episode of AOM.

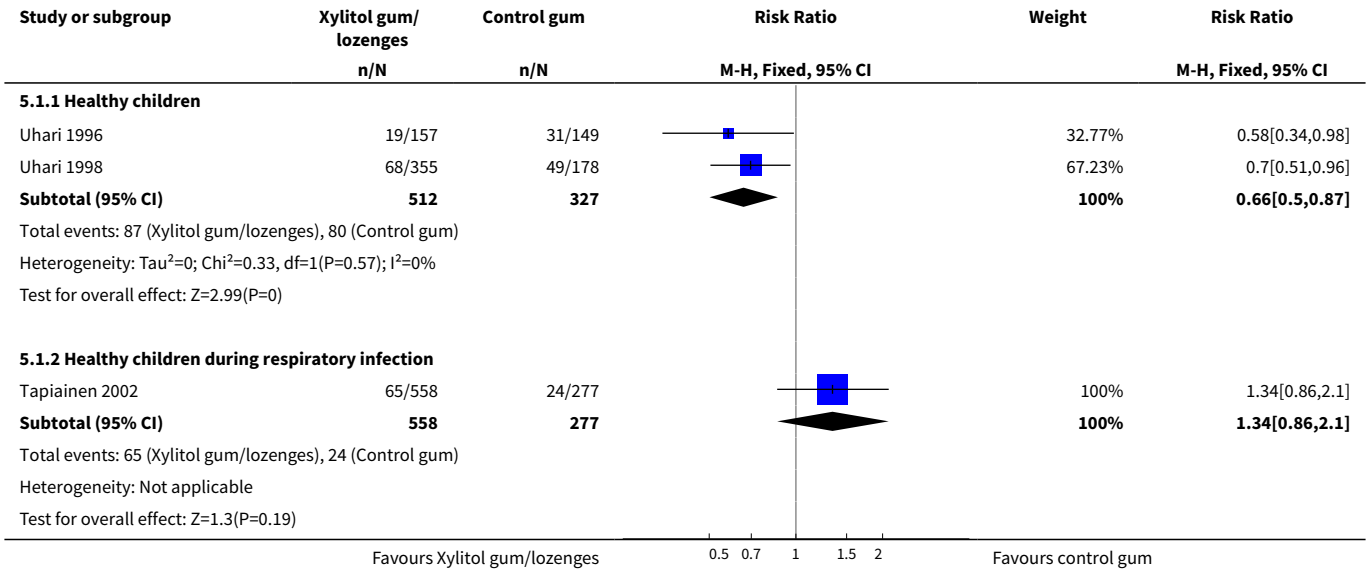




Comparison 5. Xylitol chewing gum/lozenges versus control chewing gum for older children able to chew

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	2	839	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.50, 0.87]
1.2 Healthy children during respiratory infection	1	835	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.86, 2.10]

Analysis 5.1. Comparison 5 Xylitol chewing gum/lozenges versus control chewing gum for older children able to chew, Outcome 1 Final diagnosis of at least one episode of AOM.

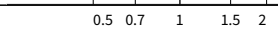


Comparison 6. Xylitol chewing gum versus control chewing gum for older children able to chew

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	2	663	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.81]
1.2 Healthy children during respiratory infection	1	554	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.78, 2.14]
1.3 Otitis-prone children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Xylitol chewing gum versus control chewing gum for older children able to chew, Outcome 1 Final diagnosis of at least one episode of AOM.

Study or subgroup	Xylitol chewing gum n/N	Control chewing gum n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 Healthy children					
Uhari 1996	19/157	31/149		39.3%	0.58[0.34,0.98]
Uhari 1998	29/179	49/178		60.7%	0.59[0.39,0.89]
Subtotal (95% CI)	**336**	**327**		**100%**	**0.59[0.42,0.81]**
Total events: 48 (Xylitol chewing gum), 80 (Control chewing gum)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=3.24(P=0)					
6.1.2 Healthy children during respiratory infection					
Tapiainen 2002	31/277	24/277		100%	1.29[0.78,2.14]
Subtotal (95% CI)	**277**	**277**		**100%**	**1.29[0.78,2.14]**
Total events: 31 (Xylitol chewing gum), 24 (Control chewing gum)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.99(P=0.32)					
6.1.3 Otitis-prone children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Xylitol chewing gum), 0 (Control chewing gum)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



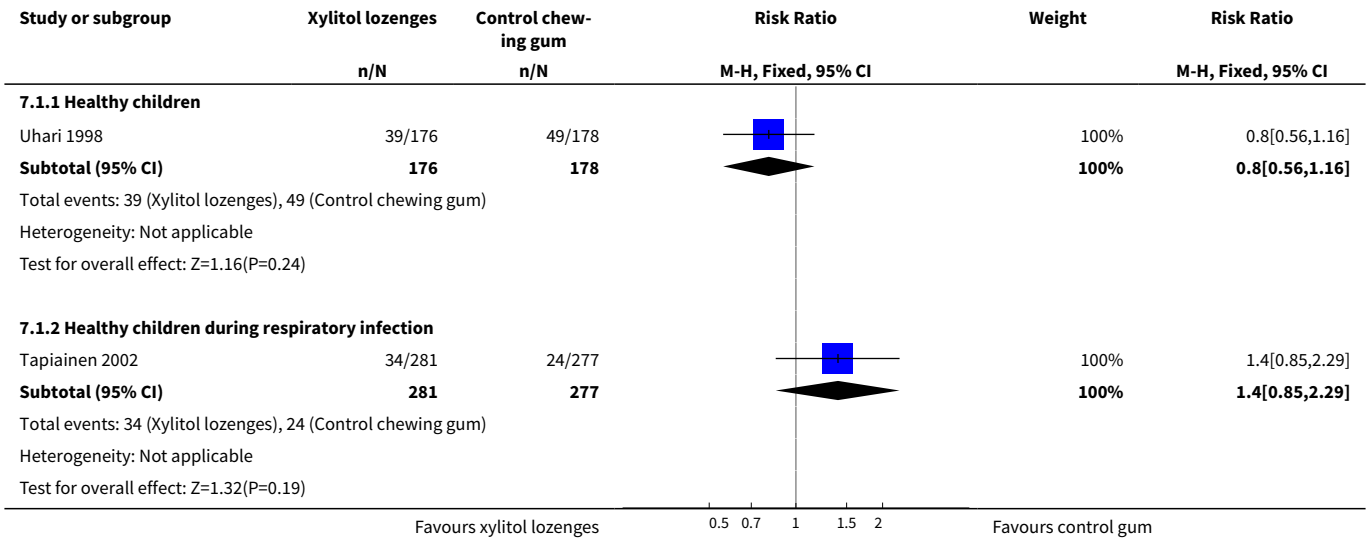
Favours xylitol gum — Favours control gum

Comparison 7. Xylitol lozenges versus control chewing gum for older children able to chew

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Healthy children	1	354	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.56, 1.16]
1.2 Healthy children during respiratory infection	1	558	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.85, 2.29]

Analysis 7.1. Comparison 7 Xylitol lozenges versus control chewing gum for older children able to chew, Outcome 1 Final diagnosis of at least one episode of AOM.



Comparison 8. Comparison between active ingredients groups: xylitol chewing gum versus xylitol syrup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	1	338	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.89]
1.2 Healthy children during respiratory infection	1	484	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.07]
1.3 Otitis-prone children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Comparison between active ingredients groups: xylitol chewing gum versus xylitol syrup, Outcome 1 Final diagnosis of at least one episode of AOM.

Study or subgroup	Xylitol gum n/N	Xylitol syrup n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 Healthy children					
Uhari 1998	29/179	44/159		100%	0.59[0.39,0.89]
Subtotal (95% CI)	**179**	**159**		**100%**	**0.59[0.39,0.89]**
Total events: 29 (Xylitol gum), 44 (Xylitol syrup)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.51(P=0.01)					
8.1.2 Healthy children during respiratory infection					
Tapiainen 2002	31/277	34/207		100%	0.68[0.43,1.07]
Subtotal (95% CI)	**277**	**207**		**100%**	**0.68[0.43,1.07]**
Total events: 31 (Xylitol gum), 34 (Xylitol syrup)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					
8.1.3 Otitis-prone children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Xylitol gum), 0 (Xylitol syrup)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours xylitol gum — Favours xylitol syrup

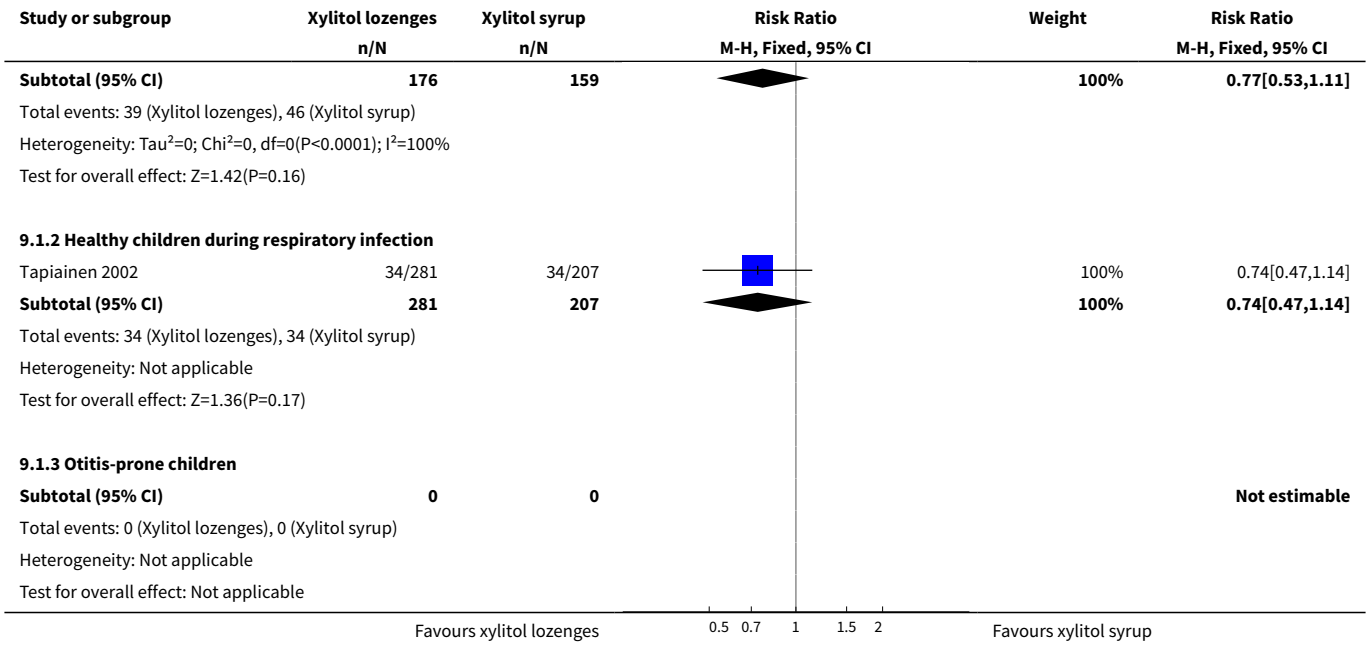
Comparison 9. Comparison between active ingredients groups: xylitol lozenges versus xylitol syrup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	1	335	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.53, 1.11]
1.2 Healthy children during respiratory infection	1	488	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.47, 1.14]
1.3 Otitis-prone children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Comparison between active ingredients groups: xylitol lozenges versus xylitol syrup, Outcome 1 Final diagnosis of at least one episode of AOM.

Study or subgroup	Xylitol lozenges n/N	Xylitol syrup n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 Healthy children					
Uhari 1998	39/176	46/159		100%	0.77[0.53,1.11]

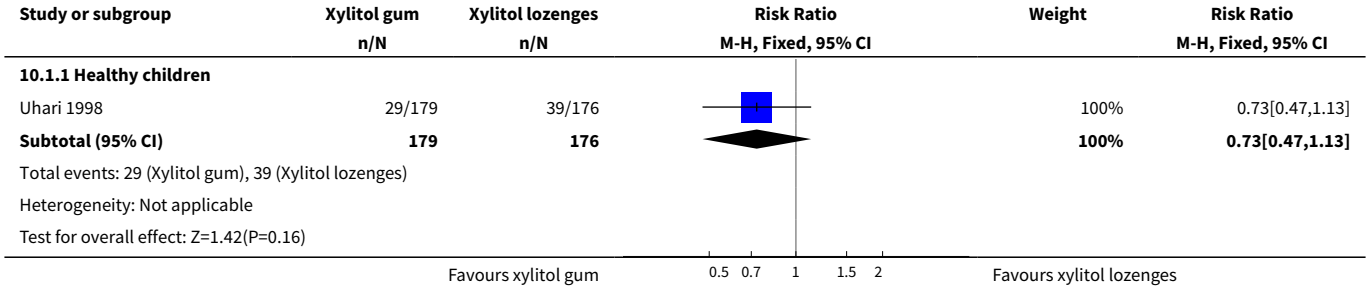
Favours xylitol lozenges — Favours xylitol syrup

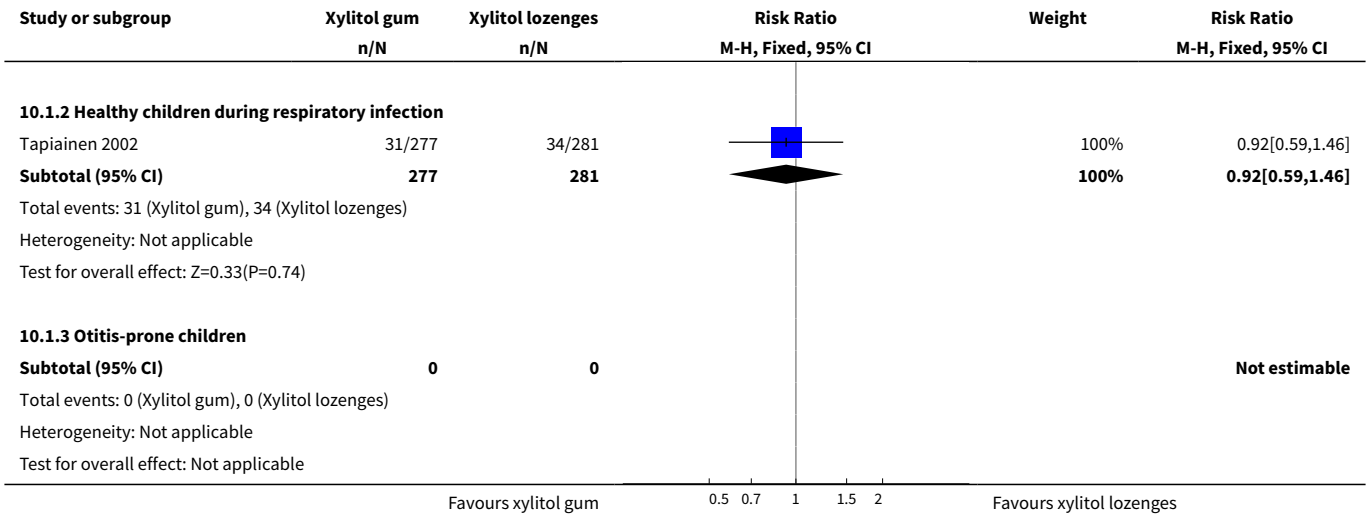


Comparison 10. Comparison between active ingredients groups: xylitol chewing gum versus xylitol lozenges

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final diagnosis of at least one episode of AOM	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Healthy children	1	355	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.13]
1.2 Healthy children during respiratory infection	1	558	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.59, 1.46]
1.3 Otitis-prone children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 10.1. Comparison 10 Comparison between active ingredients groups: xylitol chewing gum versus xylitol lozenges, Outcome 1 Final diagnosis of at least one episode of AOM.





APPENDICES

Appendix 1. OVID MEDLINE/CENTRAL search strategy

1 exp Otitis Media/
2 otitis media.tw.
3 (middle ear adj3 (infect* or inflam*)).tw.
4 (aom or ome).tw.
5 or/1-4
6 Xylitol/
7 xylitol.tw.
8 Chewing Gum/
9 chewing gum.tw.
10 birch sugar*.tw.
11 or/6-10
12 11 and 5

Appendix 2. Embase (Elsevier) search strategy

#10 #5 AND #9
#9 #6 OR #7 OR #8
#8 xylitol:ab,ti OR 'chewing gum':ab,ti OR 'birch sugar':ab,ti
#7 'chewing gum'/de
#6 'xylitol'/de
#5 #1 OR #2 OR #3 OR #4
#4 aom:ab,ti OR ome:ab,ti
#3 ('middle ear' NEAR/3 (infect* OR inflam*)):ab,ti
#2 'otitis media':ab,ti
#1 'otitis media'/exp

Appendix 3. CINAHL (Ebsco) search strategy

S14 S6 and S12
S13 S6 and S12
S12 S7 or S8 or S9 or S10 or S11
S11 TI birch sugar or AB birch sugar
S10 TI chewing gum or AB chewing gum
S9 (MH "Chewing Gum")
S8 TI xylitol or AB xylitol
S7 (MH "Xylitol")

S6 S1 or S2 or S3 or S4 or S5
S5 TI (aom or ome) or AB (aom or ome)
S4 TI middle ear N3 inflam* or AB middle ear N3 inflam*
S3 TI middle ear N3 infect* or AB middle ear N3 infect*
S2 TI otitis media or AB otitis media
S1 (MH "Otitis Media+")

Appendix 4. LILACS (BIREME) search strategy

(mh:"Otitis Media" OR mh:c09.218.705.663* OR "otitis media" OR "Otite Média" OR "middle ear infection" OR "middle ear infections" OR "middle ear inflammation") AND (mh:xylitol OR xylitol OR xilitol OR "chewing gum" OR "birch sugar") AND db:("LILACS")

Appendix 5. Web of Science (Thomson Reuters) search strategy

Topic=("otitis media" OR ("middle ear" NEAR/3 (infect* or inflam*))) AND Topic=(xylitol OR "chewing gum" OR "birch sugar")

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

Appendix 6. International Pharmaceutical Abstracts search strategy

1. 'otitis media'.tw.
2. 'aom'.tw.
3. 'ome'.tw.
4. (middle ear adj3 infect*).tw.
5. (middle ear adj3 inflamm*).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
6.1 or 2 or 3 or 4 or 5
7. 'xylitol'.tw.
8. 6 and 7

WHAT'S NEW

Date	Event	Description
28 January 2016	New citation required but conclusions have not changed	Searches updated. One trial registry was identified that is not yet open to recruit patients (NCT02592382); we saved this in the Ongoing studies section for a future update. We included one new trial which has several sources of heterogeneity (Vernacchio 2014). Conclusions were modified accordingly to highlight that xylitol was not effective in reducing acute otitis media among otitis-prone healthy children.
28 January 2016	New search has been performed	Hardy Limeback is not a co-author on this 2016 review update.

HISTORY

Protocol first published: Issue 2, 2008
Review first published: Issue 11, 2011

Date	Event	Description
1 December 2013	New search has been performed	This review updates the existing review of "Xylitol for preventing acute otitis media in children up to 12 years of age" published in the Cochrane Database of Systematic Reviews,November 2011 (Azarpazhooh 2011). An updated search September 02, 2013 identified no new eligible study. Conclusions have not changed.
2 September 2013	New search has been performed	Searches updated

CONTRIBUTIONS OF AUTHORS

Dr Amir Azarpazhooh (AA) conceptualised and designed the research, conducted and screened the results of search, assessed the quality of and abstracted data from included studies, performed the statistical analysis, interpreted data and drafted the review.
Dr Prakeshkumar S Shah (PS) critiqued and edited the review, assessed the quality of included studies, supervised the statistical analysis and data interpretation.
Dr Herenia P Lawrence (HPL) critiqued and edited the protocol and the review.

DECLARATIONS OF INTEREST

Amir Azarpazhooh: is an investigator on the Canadian Institue of Health Resarch's funded clinical trial related to this topic. The trial has not been initiated.
Herenia P Lawrence: none known
Prakeshkumar S Shah: none known

SOURCES OF SUPPORT

Internal sources

- Discipline of Dental Public Health, Faculty of Dentistry, University of Toronto, Canada.
- Department of Paediatrics, Mount Sinai Hospital, Canada.
- Department of Paediatrics, University of Toronto, Canada.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Based on the methodology of the identified studies, we defined the three subgroup analyses of younger children unable to chew gum, older children able to chew gum and xylitol administered during a respiratory infection. These subgroup analyses were not defined in the protocol.

In this 2016 update, we defined a new sensitivity analysis and performed random-effects meta-analysis to compare the pooled results to those of the fixed-effect meta-analyses. Furthermore, in this 2016 update, we changed the order and wording of the Secondary outcomes from:

Secondary outcomes

1. Any adverse events of xylitol (for example, gastrointestinal discomfort).
2. Hospitalisation secondary to AOM or its complications in studies where at least one hospitalisation was reported.
3. Mortality secondary to complications of AOM in studies where at least one death was reported.
4. Length of hospital stay.
5. Percentage of children needing antibiotic therapy.
6. Number of days missed at school or day care centre.
7. Cost (direct such as emergency room or general practitioners visits cost; hospitalisations cost; medication cost and indirect such as the time taken from work for parents or care givers; the opportunity cost of leisure time; informal nursing care; and out-of-pocket expenses for transportation).

To:

Secondary outcomes

1. Safety and adverse events.
2. Antibiotic administration.
3. Hospitalisation (and its length) secondary to AOM or its complications in studies where at least one hospitalisation was reported.
4. Mortality secondary to complications of AOM in studies where at least one death was reported.
5. Number of days missed at school or daycare centre.
6. Cost (direct such as emergency room or general practitioners visits cost; hospitalisations cost; medication cost and indirect such as the time taken from work for parents or care givers; the opportunity cost of leisure time; informal nursing care; and out-of-pocket expenses for transportation)

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Chewing Gum; Gels [therapeutic use]; Otitis Media [*prevention & control]; Randomized Controlled Trials as Topic; Sweetening Agents [adverse effects] [*therapeutic use]; Xylitol [adverse effects] [*therapeutic use]

MeSH check words

Child; Child, Preschool; Female; Humans; Infant; Infant, Newborn; Male