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# Xylitol for the prevention of acute otitis media episodes in children aged 1–5 years: a randomised controlled trial

Navindra Persaud ,[1,2,3] Amir Azarpazhooh,[4,5] Charles Keown-Stoneman,[3,5,6] Catherine S Birken,[5,7,8,9] Wanrudee Isaranuwatchai,[5] Jonathon L Maguire,[3,10] Muhammad Mamdani,[3,6,9,11] Christopher Allen ,[6] Dalah Mason,[8] Christine Kowal,[8] Mateenah Jaleel,[8] Farnaz Bazeghi,[8] Kevin E Thorpe,[5,6] Andreas Laupacis,[11] Patricia C Parkin[5,7,8,9]

For numbered affiliations see end of article.

**Correspondence to**
Dr Navindra Persaud, 80 Bond Street, St Michael's Hospital, Toronto M5B 1X2, Canada; nav.persaud@utoronto.ca

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## ABSTRACT

**Objective** To investigate the regular use of xylitol, compared with sorbitol, to prevent acute otitis media (AOM), upper respiratory tract infections (URTIs) and dental caries.

**Design** Blinded randomised controlled trial with a 6-month study period.

**Setting** Enrolment took place at 11 primary care practices in Ontario, Canada.

**Patients** Children aged 1–5 years who did not use xylitol or sorbitol at enrolment.

**Interventions** Children were randomly assigned to use a placebo syrup with sorbitol or xylitol syrup two times per day for 6 months.

**Main outcome measures** Primary outcome was the number of clinician-diagnosed AOM episodes over 6 months. Secondary outcomes were caregiver-reported URTIs and dental caries.

**Results** Among the 250 randomised children, the mean (SD) age was 38±14 months and there were 124 girls (50%). There were three clinician-diagnosed AOM episodes in the 125 placebo group participants and six in the 125 xylitol group participants (OR 2.04; 95% CI 0.43, 12.92; p=0.50). There was no difference in number of caregiver-reported URTI episodes (rate ratio (RR) 0.88; 95% CI 0.70, 1.11) between the placebo (4.2 per participant over 6 months; 95% CI 3.6, 5.0) and xylitol (3.7; 95% CI 3.2, 4.4) groups. Dental caries were reported for four participants in the placebo group and two in the xylitol group (OR 0.42; 95% CI 0.04, 3.05; p=0.42). In a post-hoc analysis of URTIs during the COVID-19 pandemic, the rate among the 59 participants receiving placebo was 2.3 per participant over 6 months (95% CI 1.8, 3.0) and for the 55 receiving xylitol, 1.3 over 6 months (95% CI 0.92, 1.82; RR 0.56; 95% CI 0.36, 0.87). The most common adverse event was diarrhoea (28% with placebo; 34% with xylitol).

**Conclusions** Regular use of xylitol did not prevent AOM, URTIs or dental caries in a trial with limited statistical power. A post-hoc analysis indicated that URTIs were less common with xylitol exposure during the COVID-19 pandemic, but this finding could be spurious.

**Trial registration number** NCT03055091.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies show that a variety of xylitol formulations may prevent acute otitis media (AOM), upper respiratory tract infections (URTIs) and dental caries in children.
⇒ Previous studies also suggest that xylitol must be administered frequently to confer benefits.
⇒ Xylito it is not currently recommended for routine use in young children.

### WHAT THIS STUDY ADDS

⇒ The purpose of this trial was to determine whether daily use of xylitol syrup reduces AOM episodes and other URTIs in children aged 1–5 years.
⇒ Findings showed no overall reduction in AOM, URTIs or dental caries.
⇒ A post-hoc analysis found a reduction in URTIs during the COVID-19 pandemic.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies are needed to determine whether xylitol prevents infections common during early childhood given the limited statistical power of this study.
⇒ The effects of xylitol for the prevention of COVID-19 could be addressed through a dedicated study.

## INTRODUCTION

Xylitol is a natural sweetener that can separate from nasopharyngeal cells the bacteria that cause common childhood infections such as acute otitis media (AOM), upper respiratory tract infections (URTIs) and dental caries including *Streptococcus pneumoniae* and *Haemophilus influenzae*.[1] Five clinical trials have found that a variety of xylitol formulations, including syrups, lozenges and chewing gum, may prevent AOM in children aged 12 years and younger, but the age ranges of included participants and the results vary.[2–6] The substantial burden of AOM is greatest in younger children who do not routinely use chewing gum, and trials have not established whether the use of

xylitol is effective in younger children who can consume syrup that may be less effective than chewing gum.[7]

AOM has similar symptoms as other URTIs, which are the most common reason for seeking healthcare during early childhood.[8 9] Xylitol has been postulated to prevent URTIs and also dental caries, another common condition during early childhood that is better prevented than treated.[10] Xylitol use has not been associated with any serious harms, but it may cause gastrointestinal side effects, and previous studies indicate that it needs to be administered frequently to confer benefits.[7] It is not currently recommended for routine use in young children.

The purpose of this trial was to determine whether daily use of xylitol syrup reduces AOM episodes in children aged 1–5 years. The two secondary outcomes were URTIs and dental caries.

## METHODS

### Trial design

This was a two-armed superiority, placebo-controlled randomised trial with 1:1 allocation, stratified by clinical site, where participants and caregivers, practitioners and analysts were blinded to the arm of allocation. Results are reported in accordance with Consolidated Standards of Reporting Trials guidance, and a full trial protocol was published and can be accessed online (https://bmjopen.bmj.com/content/8/8/e020941).[11 12]

### Participants

Children at primary care sites participating in The Applied Research Group for Kids (TARGet Kids!) primary care practice-based research network (https://www.targetkids.ca/) were approached by network staff.[13] Inclusion criteria were age 12–60 months, with a care provider who could provide informed consent in English. Children were excluded from the study if they had craniofacial malformations or structural middle ear abnormalities (as these could increase the risk of AOM), were currently using xylitol, had a sensitivity to xylitol or had a sibling living at the same address who was already enrolled in the trial. Participants were recruited year-round, but randomisation took place between September and January to ensure that the 6-month study period occurred during winter months.

### Interventions and blinding

The study statistician created a randomisation table with stratification for site and randomly permuted blocks of 2–4 using R (https://www.r-project.org/). Study personnel at clinical sites entered participant information into web-based electronic case report forms (REDCap) hosted at Unity Health Toronto.[14] The research pharmacy mailed investigational substances to participants. Participants were advised to use 5 mL of the investigational substance between 2 and 5 times per day. The syrup (that is sometimes referred to as a 'gel') could be used as toothpaste or simply applied in the mouth. The intervention was xylitol syrup (35% by weight, or 1.75 g per 5 mL dose). The control substance was sorbitol syrup (30% by weight, or 1.5 g per 5 mL dose) that appeared, smelled and tasted similar to xylitol but that, based on its lack of cariogenicity, has been used as a control substance in previous trials of xylitol.[15 16] Both substances were purchased from Xlear (USA) and packaged in tubes except for codes printed in tube crimps.

### Outcomes

The primary outcome was the total number of clinician-diagnosed AOM episodes based on clinical records that record both signs of AOM (eg, erythematous tympanic membrane) and a diagnosis of AOM. The secondary outcome of caregiver-reported URTI episodes was included because caregivers may not seek healthcare when young children have AOM symptoms and because the symptoms of URTIs and AOM overlap substantially. At monthly calls and emails, we asked caregivers if the child had nasal congestion, rhinorrhoea, cough, sore throat, wheezing or dyspnoea for at least 2 consecutive days based on the symptoms in the Canadian Acute Respiratory Illness and Flu Scale.[17] Caregivers were also asked if they were informed by a dentist or other healthcare providers that their child has had at least one dental caries. We asked about the average number of doses of study substances given. To assess safety, we asked about abdominal pain or discomfort, diarrhoea and other symptoms each month. All outcomes were assessed over the 6-month study period which started at the time of randomisation of each participant.

### Statistical analysis

To estimate the required sample size, we reviewed charts from the participating practices and found that the rate of clinician-diagnosed AOM was 0.14 AOM episodes per patient-month over the entire year, with events concentrated during winter months. We assumed a control event rate of 1.5 AOM episodes per participant over the 6-month study period that included winter months. We aimed to detect a relative risk of 0.8 (ie, relative risk reduction of 20%) with 80% power and alpha=0.05 (two-sided). Assuming a Poisson distribution for the number of AOM episodes and 10% loss to follow-up, the required sample size was 236 per group. Intention-to-treat populations were used for the analyses. Due to the low number of observed AOM episodes, Fisher's exact test was used for the primary outcome, defined as zero AOM or one AOM over the study period. Overdispersed Poisson regression models were used to analyse AOM, dental caries and URTI episodes. For the number of URTI episodes, an offset was included in the model to account for the number of months each participant had reported URTIs since there was varying follow-up duration due to incomplete follow-up data; such offsets are standard practice in count-based models used to estimate a rate ratio (RR).[18 19] For Fisher's exact tests, results are expressed as ORs, and for Poisson models, results are expressed as RRs. Post-hoc analysis was performed investigating differences in URTI RRs in relation to the COVID-19 pandemic that we defined as starting in March of 2020 given the dramatic shift in URTI epidemiology that occurred during the pandemic. All analyses were performed using R V.4.2.0 (https://www.R-project.org/).

### Protocol changes

After the trial started, we made two changes to the protocol to enhance the recruitment rate. We expanded the age range for eligibility from 2–4 years old to 1–5 years old, and we reduced the minimum frequency of investigational substance administration from 3 to 2 times per day to facilitate participation of children who were out of the home during the day. The trial was originally planned to take place over three winter seasons, but was extended by one winter season to allow further enrolment. Enrolment took place virtually during the COVID-19 pandemic and we added post-hoc analyses related to effects during and prior to the COVID-19 pandemic. Due to the low event rate, a Fisher's test was used for the analysis of AOM and dental caries rather than Poisson regression.

## RESULTS

Between 17 February 2017 and 31 January 2021, we approached 609 patients and 256 were enrolled (figure 1). After consenting,

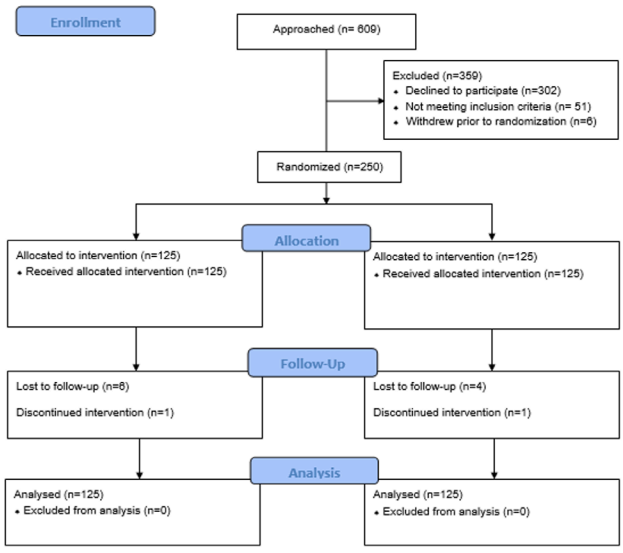


**Figure 1** Participant flow diagram.

six patients (2%) withdrew consent prior to randomisation. The characteristics of the 250 randomised participants are summarised in table 1.

There was a total three clinician-diagnosed episodes of AOM among the 125 placebo group participants and six in the 125 xylitol group participants (OR 2.04; 95% CI 0.43, 1.92; p=0.50) (see table 2). The rate of AOM was lower than anticipated, and none of the 169 (44%) participants enrolled during the COVID-19 pandemic had an AOM episode.

There was no difference in the number of caregiver-reported URTI episodes (RR 0.88; 95% CI 0.70, 1.11) with placebo (4.2 per participant; 95% CI 3.6, 5.0) or xylitol (3.7 per participant; 95% CI 3.2, 4.4) (see table 2). There was a total of 367 URTIs in the placebo group and 355 in the xylitol group over mean follow-up duration of 4.2±2.4 and 4.6±2.0 months, respectively. No URTI episodes were reported for 83 participants (44 or 35% with placebo and 39 or 31% with xylitol), between one and four episodes were reported for 102 (40%) participants (54 or 43% with placebo and 48 or 38% with xylitol) and five or more for 65 (26%) (33 or 26% with placebo and 32 or 26% with xylitol) over the 6-month trial period. A post-hoc analysis showed that during the COVID-19 pandemic, the 6-month rate of URTI episodes among 59 participants taking placebo was 2.3 per participant (95% CI 1.8, 3.0) and among 55 participants taking xylitol, 1.3 per participant (0.92 to 1.82; RR 0.56; 95% CI 0.36, 0.87).

**Table 1** Baseline characteristics

| | Placebo (sorbitol) n=125 | Xylitol n=125 |
|---|---|---|
| Female sex, n (%) | 63 (50.4) | 61 (48.8) |
| Age, months, mean (SD) | 38±14 | 37±14 |
| Household income | | |
| $0–$39 999 | 14 (11.2) | 13 (10.4) |
| $40 000–$79 999 | 17 (13.6) | 20 (16.0) |
| $80 000–$149 999 | 37 (29.6) | 32 (25.6) |
| $150 000 or more | 40 (32.0) | 43 (34.4) |
| Not reported | 17 (13.6) | 17 (13.6) |
| Ethnicity | | |
| White or European | 60 (48.0) | 52 (41.6) |
| South Asian | 12 (9.6) | 12 (9.6) |
| East Asian | 8 (6.4) | 12 (9.6) |
| Southeast Asian | 12 (9.6) | 12 (9.6) |
| African | 7 (5.6) | 10 (8.0) |
| Latin American | 5 (4.0) | 5 (4.0) |
| Middle Eastern | 1 (0.8) | 2 (1.6) |
| Not reported | 20 (16.0%) | 20 (16.0%) |

**Table 2** Effects of xylitol

| | Placebo (sorbitol) n=125 | Xylitol n=125 |
|---|---|---|
| Frequency of substance administration in doses per day (SD) | 2.0±1.2 | 2.1±1.2 |
| Primary | | |
| Acute otitis media episodes | 3 | 6 |
| Secondary | | |
| Upper respiratory tract infection episodes per 6 months | 4.2 (95% CI 3.6 to 5.0) | 3.7 (95% CI 3.2 to 4.4) |
| Participants with dental caries | 4 | 2 |

Dental caries were reported for four participants in the placebo group and two in the xylitol group (see table 2); the low event rate limited statistical comparisons between groups (OR 0.42; 95% CI 0.04, 3.05; p=0.42). In both groups, half of the events occurred during the COVID-19 pandemic.

Reported adherence to the placebo substance sorbitol (2.0±1.2 doses per day) was similar to that of xylitol (2.1±1.2 doses per day) (see table 2). A total of 164 adverse events were reported with placebo from 54 participants and 178 with xylitol from 66 participants. The most common adverse events reported in both groups were diarrhoea (35 or 28% with placebo and 42 or 34% with xylitol) and abdominal pain (32 or 26% with placebo and 37 or 30% with xylitol). No serious adverse events were reported. There were 24 (19%) early terminations in the placebo group and 14 (11%) in the xylitol group, and the most common reasons provided were palatability of the study substance and gastrointestinal symptoms.

## DISCUSSION

This randomised controlled trial of young children who regularly used xylitol syrup versus placebo for 6 months had similar low rates of AOM. There was also no overall reduction in URTIs or dental caries. A post-hoc analysis indicated that URTIs were less common with xylitol exposure during the COVID-19 pandemic, although this finding could be spurious. Future studies could determine whether this represents a real effect of xylitol and, if so, determine the pathogens affected.

### Comparisons with other studies

A systematic review of the safety and efficacy of xylitol in preventing AOM in children up to 12 years of age found that there is moderate certainty of evidence supporting the use of xylitol for the prevention of AOM (risk ratio, 0.75; 95% CI 0.65, 0.88) based on four randomised controlled trials of children in Finland attending daycare and one in the USA, but this review concluded that an adequately powered, well-designed trial is necessary and pointed to a lack of evidence in younger

children where the burden is highest.[12] Xylitol was ineffective in the one trial of children aged 6 months–5 years who were prone to recurrent AOM.[4] No trials of xylitol for the prevention of COVID-19 have been registered as far as we know, but one small (n=50) trial of xylitol for the treatment of COVID-19 in adults found no benefit.[20]

## Strengths and limitations

Sorbitol was chosen because it is difficult to distinguish from xylitol and its lack of antimicrobial properties, but it could cause or prevent caries although it has been used as a control substance in other trials.[15 16] The statistical power of this trial was limited due to lower than planned enrolment and a lower than anticipated rate of AOM including no AOM episodes recorded during the COVID-19 pandemic. The enrolment rate was hampered by the need to administer a study substance several times per day. Palatability of study substances and gastrointestinal adverse events led to a substantial dropout rate. The findings from the post-hoc analysis focusing on the COVID-19 pandemic could be explained by an unmeasured factor such as social distancing that could have varied between groups. Strengths of this study include its focus on early childhood when the burden of AOM is greatest and the use of a syrup, which is suitable in this age group, conveniently taken a minimum of two times per day. The trial intervention and outcomes were designed to be similar to previous trials in order to facilitate combination of results in meta-analyses.

## CONCLUSION

This trial of regular use of xylitol syrup in young children found no reduction in AOM or dental caries, although low event rate limits the conclusions that can be drawn. There was also no overall reduction in URTIs. A post-hoc analysis found a reduction in URTIs during the COVID-19 pandemic, and the effects of xylitol during the pandemic could be assessed in dedicated studies.

**Author affiliations**
[1]Department of Family and Community Medicine, St Michael's Hospital, Toronto, Ontario, Canada
[2]Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada
[3]Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada
[4]Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada
[5]University of Toronto Dalla Lana School of Public Health, Toronto, Ontario, Canada
[6]The Applied Health Research Centre of the Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada
[7]Division of Paediatric Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada
[8]SickKids Research Institute, Toronto, Ontario, Canada
[9]Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[10]Department of Pediatrics, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada
[11]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

**Contributors** NP and AA conceptualised and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript. CK-S, CSB, WI, JLM, MM, AL, PP, KET, CA, DM, CK, MJ and FB designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. NP is the guarantor.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by the Research Ethics Board at the Hospital for Sick Children and St Michael's Hospital in Unity Health Toronto (REB# 16-300). Caregivers of participants provided informed consent in writing or via email.

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**ORCID iDs**
Navindra Persaud http://orcid.org/0000-0003-3327-5580
Christopher Allen http://orcid.org/0000-0001-5430-8631

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