BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020941
Article Type:	Protocol
Date Submitted by the Author:	04-Dec-2017
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Paediatrics
Keywords:	otitis media, upper respiratory tract infection, dental caries, xylitol, sorbitol

Xylitol for the prevention of acute otitis media episodes in children aged 2-4 years: Protocol for a pragmatic randomized controlled trial

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Key words: otitis media, upper respiratory tract infection, dental caries, xylitol, sorbitol

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Word count: 4596

ABSTRACT

Introduction

Xylitol (or "birch sugar") is a naturally occurring sugar with antibacterial properties that has been used as a natural non-sugar sweetener in chewing gums, confectionery, toothpaste and medicines. In this preventative randomized trial, Xylitol will be tested for the prevention of acute otitis media (AOM), a common and costly condition in young children. The primary outcome will be the incidence of AOM. Secondary outcomes will include upper respiratory tract infections (URTIs) and dental caries.

Methods and analysis

This study will be a pragmatic, blinded (participant and parents, practitioners and analyst), two-armed superiority; placebo randomized controlled trial (RCT) with 1:1 allocation, stratified by clinical site. The trial will be conducted in the eleven primary care group practices participating in the TARGet Kids! research network in Canada. Eligible participants between the ages of 2-4 years will be randomly assigned to the intervention arm of regular xylitol syrup use or the control arm of regular sorbitol use for 6 months. We expect to recruit 236 participants, per treatment arm, to detect a 20% relative risk reduction in AOM episodes. AOM will be identified through chart review. The secondary outcomes of URTIs and dental caries will be identified through monthly phone calls with specified questions.

Ethics and dissemination

Ethics approval has been obtained from St. Michael's Hospital, and The Hospital for Sick Children for the sites participating in the TARGet Kids! research network. Results will be submitted for publication to a peer-reviewed journal and will be discussed with decision makers.

Trial registration number: NCT03055091 (clinicaltrials.gov)

Strengths and limitations of this study

- This trial has the potential to determine whether a natural sweetener with antimicrobial properties prevents three common conditions during early childhood: otitis media, dental caries and upper respiratory tract infections
- The trial will be conducted through the TARGet Kids! primary care research network
- The six months of treatment and outcome assessment will allow the evaluation of the longer term effects of xylitol
- A challenge for trials with acute otitis media as an outcome is that parents may not distinguish AOM from other URTIs with similar symptoms and may not seek care; we will include both clinician-diagnosed AOM and parent-reported URTIs as separate outcomes.

INTRODUCTION

Acute otitis media (AOM) is a common and costly condition in young children.[1] The annual global incidence of AOM is 700 million per year and 50% of those affected are children under the age of 5 years.[2] By age 3 years, 84% of children have had at least one episode of AOM and

46% have had 3 or more episodes.[3] Antibiotic treatment has only a modest effect on AOM duration[4] and does not prevent serious complications such as mastoiditis or meningitis which can rarely be fatal.[5 6] Most (>80%) children with AOM presenting for care have spontaneous symptom resolution within 3 days and the number needed to treat for antibiotic treatment to reduce symptom duration is 20 days, which must be balanced by a number needed to harm (with adverse effects of antibiotics such as diarrhea) of 14 days.[4] The incidence of mastoiditis has not changed over time despite changes in antibiotic prescribing.[5 6 7] Rare sequelae of AOM include delayed cognitive development, impaired communication skills and permanent hearing loss.[3] Parents of children with otitis media report missing 2-3 days of work per episode.[1]

Another common and costly infectious disease amongst North American pre-school aged children is upper respiratory tract infections (URTIs).[8 9 10-12] URTIs are the most common reason for emergency department visits and unscheduled outpatient visits in Canada, accounting for 10% of emergency department visits for children under 10 years of age.[13 14 15] URTIs are also the most common reason for unscheduled visits to a care provider and Canadian children experience 3-8 URTIs per year at a cost to the healthcare system of several hundred million dollars per year.[16 17]

Nearly 30% of 2-5 year old children have dental caries.[18] Dental caries may lead to pain, difficulty eating and speaking, and can harm a child's self-esteem.[19] Treating dental caries in young children is challenging for practitioners, painful for the children and caries cost thousands of dollars to treat, with complicated caries requiring hospitalization costing several times more (and rarely resulting in death).[20 21 22 23 24 25]

In vitro studies have shown that xylitol can reduce the attachment of bacteria that cause AOM, URTIs, and dental caries such as *Streptococcus Pneumoniae* and *Haemophilus Influenzae* to nasopharyngeal cells. AOM occurs when the upper airway is colonized with bacteria, viruses or a combination of both that travel from the nasopharynx to the middle ear by way of the Eustachian tube.[26] A Cochrane systematic review of the safety and efficacy of xylitol in preventing AOM in children up to 12 years of age found that there is fair evidence supporting the use of xylitol for the prevention of AOM (risk ratio, 0.75; 95% CI, 0.65 to 0.88 based on 3 RCTs from the same research group, studying 1826 children in total), but concluded that an adequately-powered, well designed trial is necessary. [27] Previous trials have not established whether regular xylitol syrup use is effective at preventing AOM in young children (<4 years) who are most likely to have AOM. Several RCTs of xylitol for the prevention of dental caries indicate that the antimicrobial effect of xylitol (which is posited to account for its efficacy in preventing AOM) increases with duration of use.[28 29 30] Therefore, the effect of the same dose of xylitol may be more effective at preventing AOM over the 6 month study period in the proposed study than it was in the previous trials that lasted 2 or 3 months.[31] The longer trials of xylitol for the prevention of dental caries also demonstrate that daily xylitol administration is safe, feasible and well tolerated for the 6 month study period in the proposed trial.[28 29 30] A pilot study of higher concentrations of xylitol syrup in young children found good compliance and tolerability.[32] In summary, regular xylitol syrup used for the 6 month study period is safe and feasible, and there is clinical equipoise over its effectiveness at preventing AOM in young children. There is no recommendation for or against the use of xylitol in the United States or in Canada. The paucity of high quality randomized controlled trials has been cited as a reason for the lack of consistent recommendations regarding the use of xylitol in young children.[33]

The primary purpose of this study is to determine if regular use of xylitol syrup effectively prevents AOM in unselected 2-4 year old children. Such an intervention could

increase the productivity of parents and caregivers, reduce serious complications and reduce the suffering of young children - each episode of AOM involves several excess hours of crying for two to seven days.[34] This trial could change clinical practice if the results are positive. In several other countries xylitol is recommended for the prevention of dental caries. For example, the *American Academy of Pediatric Dentists* recommends regular xylitol use for the prevention of dental caries based on the results of eight clinical trials.[35] However, a survey of American pediatricians found that few physicians (12%) recommend xylitol to patients and that most would either definitely (68%) or possibly (29%) recommend xylitol if there was additional evidence that it prevented AOM.[36]

AIMS AND OBJECTIVES

Primary Question

Does regular xylitol syrup use for 6 months reduce the number of physician-diagnosed AOM episodes in children aged 2-4 years?

Secondary Questions

(1) Does regular xylitol syrup use reduce the number of parent-reported upper respiratory tract infection (URTI) episodes in children aged 2-4 years?
(2) Does regular xylitol syrup use reduce parent-reported dental caries in children aged 2-4 years?

METHODS AND ANALYSIS

Study Design

This will be a pragmatic, blinded (participant and parents, practitioners and analyst), two-armed superiority; placebo controlled randomized trial with 1:1 allocation, stratified by clinical site.

Setting

The trial will be conducted in the eleven primary care group practices currently participating in the TARGet Kids! research network (www.targetkids.ca) in Canada. There are no sites outside of Canada.

Eligibility Criteria

The patients in this study are healthy children aged 2-4 years who are participants of The Applied Research Group for Kids (TARGet Kids!), the largest pediatric primary care practice-based research network in Canada focused on child health (www.targetkids.ca).

***Inclusion criteria*:** age 24-48 months at start of intervention, and parent or care provider able to give consent for participation including being able to understand the information provided in English. All children recruited to this study will also be participants in the TARGet Kids! research network.

***Exclusion criteria*:** craniofacial malformations, structural middle ear abnormalities, sibling or any other child living at the same address already enrolled in the trial (in order to prevent

contamination), insertion of ventilation tubes prior to study period, current use of a xylitol product or reported xylitol sensitivity.

Intervention arm

Xylitol (or "birch sugar") is a naturally occurring sugar with antibacterial properties that has been used as a natural non-sugar sweetener in chewing gums, confectionery, toothpaste and medicines.[26 37 38]

The investigational agents will be provided by XLEAR, a producer of commercial xylitol products that are sold in Canada. The product specifications used for this agent is that of their syrup or "tooth gel" products sold in 60 mL tubes. The product is approved by Health Canada as a food additive. The product has a shelf life of 2 years based on stability studies. Each tube is labeled with a best before date and a lot number on the tube crimp.

The experimental intervention is the provision of xylitol syrup (35% Xylitol concentration per weight) and instructions to ingest is 3-5 times per day. Each dose will be 5 mL of 350 g/L, therefore the maximum possible daily dose will be 9 g of xylitol per day. This is the daily dose that may be effective from previous trials.[31]

Control Arm

The control intervention is the provision of sorbitol syrup (looks, smells and tastes like the xylitol syrup but is not an antimicrobial). Sorbitol is unlikely to have an effect on our primary outcome of AOM or the secondary outcomes of URTIs and dental caries; therefore it can be used as a placebo. The sorbitol syrup formulation is the same as the xylitol syrup except the concentration of sorbitol will be 30% by weight. The instructions for use are 3-5 times per day. Each dose will be 5 mL of 300 g/L of sorbitol; therefore the maximum daily dose will be 7.5 g of sorbitol.

XLEAR will produce the investigational agents through a dedicated production run and ship the products to the research pharmacy in a timely manner. This will allow preparation and shipment of the kits for each participant prior to the intervention period.

The data coordinating center will create master randomization tables and send these to the research pharmacy for dispensing. The study statistician will create the master randomization table using a computer-generated, site-stratified, block randomization design. The research pharmacy will use the randomization table for the dispensation of the investigational agents to each participant.

Intervention period

The treatment period will be 6 months for all participants. The intervention will be given during the winter season.

The follow-up period is identical to the treatment period, and so will also be 6 months for all participants.

Conducting the trial during winter months will maximize the efficiency of the trial because AOM and URTI incidences are highest during that time.[39] Since xylitol is not a treatment for infections, care will be provided as normal for any suspected infections.

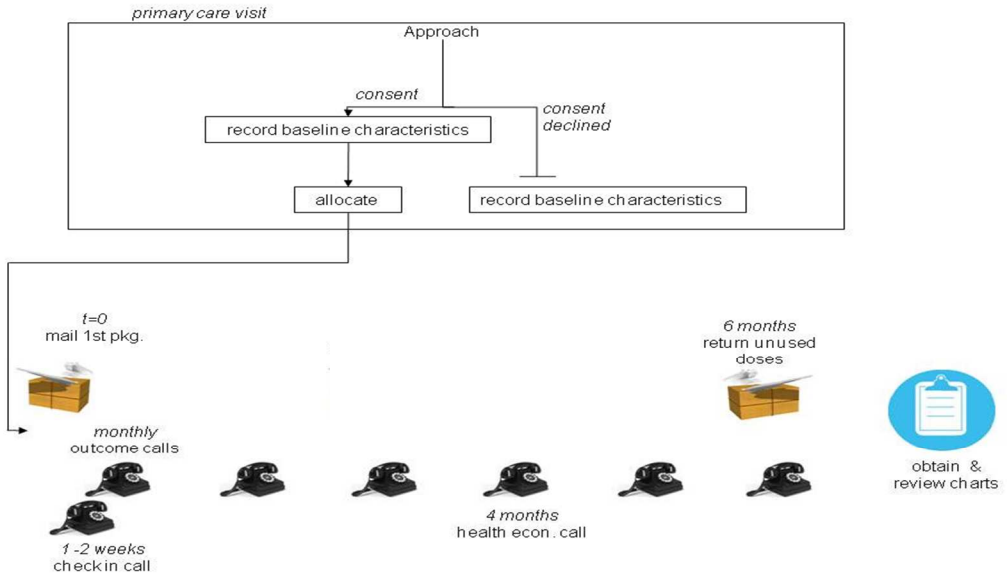

Figure 1. *Timeline for intervention and follow-up.*

Premature Withdrawal/Discontinuation Criteria

Xylitol is sweet and children generally enjoy consuming it.[32] The number of missed doses in previous trials with frequent daily dosing was around 10%.

Parents will be called two weeks after they have been given the package to discuss any challenges with compliance, as well as during monthly follow-up calls.

Based on data from previous trials conducted in the TARGet Kids! research network and the fact that the primary outcome will be determined using a chart review, we anticipate a low (< 5%) rate of being lost to follow-up in this trial where follow-up does not require any special visits for research purposes only. If a participant leaves the primary care practice, we will attempt to obtain the name of the current care provider and obtain the chart for review. If a participant has left the primary care practice and we are unable to contact the parents or caregivers, we will treat the data as censored. Despite this, the sample size calculation assumes 10% of participants will not complete follow-up.

Outcome Measures

Primary outcome

The primary outcome of the total number of physician-diagnosed AOM episodes will be assessed by reviewing charts of the primary care provider and any other care providers reported by parents or caregiver at monthly phone calls.

Three methods for determining the diagnosis of AOM have been used in trials: clinical signs (bulging and red tympanic membrane), clinical signs with tympanometry, and clinical signs with tympanocentesis.[40] In this trial, the number of AOM episodes will be assessed using both objective clinical signs of AOM recorded in the chart and a physician's diagnosis of AOM. In order to make a diagnosis of AOM for this trial, the chart must contain *both* the documentation of signs of AOM (e.g. erythematous tympanic membrane) plus the practitioners' diagnosis that the patient had AOM. The addition of tympanometry to clinical signs does not improve the accuracy of AOM diagnosis.[41]

Further, tympanometry is not employed in routine clinical practice at any of the TARGet Kids! sites. Tympanocentesis is therapeutic and can prevent subsequent AOM episodes[40] so it cannot be used in this trial of AOM prevention (and it requires instruments not present in primary care sites). Four of the five previous trials of xylitol for the prevention of AOM employed clinical signs with tympanometry, and one used clinical signs to determine the number of AOM episodes.[31]

Previous RCTs of AOM *management* in young children have relied on the diagnoses made by primary care providers (who are generally the clinicians who diagnose AOM for clinical purposes).[42 43] The studies, involving longer study periods, used chart reviews to determine the number of AOM episodes just as we will in this trial (*Appendix 1*).[43]
We have conducted a chart review of 1,637 patients in the TARGet Kids! research network using a method similar to those in completed RCTs of AOM that involves reviewing charts for physical examination findings consistent with AOM and a diagnosis or assessment of AOM.[44 42 43] In all of the episodes, the physical examination findings and the diagnosis were clearly documented in the chart (the term "AOM" was usually recorded in the assessment portion of the note), and there was perfect agreement between independent reviewers.

In addition to reviews of the patient's primary care provider medical record, the primary outcome will also include AOM episodes diagnosed by other care providers (e.g., at walk-in clinics or emergency rooms). Parental consent for release of this information will be obtained, and charts will be reviewed upon the end of follow-up period.
The primary analysis will be the total number of AOM episodes during the study period. We will also summarize the time to first AOM using survival curves.

A limitation of employing physician-diagnosed episodes of AOM is that parents may not seek care when their child has AOM symptoms. This limitation is addressed with the secondary outcome of parent reported URTIs (*see secondary outcomes below*). Another limitation of physician-diagnosed AOM is that there is variability in the diagnosis of AOM by clinicians, with one study of administrative data indicating that some clinicians diagnose AOM twice as often as others.[40 45] Since the clinicians will be blinded to the allocated group, differences in clinical assessment will not bias the results.

Note that our sample size calculation incorporates the incidence of AOM in the TARGet Kids! study population and so it takes into consideration the rate of AOM diagnosis by the same clinicians who will diagnose AOM in these study participants.

Secondary outcomes

The secondary outcome parent-reported URTI episodes will be assessed during monthly phone calls. A challenge in all trials that employ AOM as an outcome is the combined effect of two factors: (1) parents often decide not to seek care when a child has symptoms that may indicate AOM and (2) parents cannot distinguish between AOM and other URTIs because the symptoms are similar. We will address this challenge with our secondary outcome: parent-reported URTIs, a very common and costly (in aggregate) condition in early childhood.[17 46] The previous shorter (2 to 3 month) trials of xylitol found a non-significant trend towards fewer URTI episodes in children receiving xylitol.[31]

A cohort study of children aged 2 months to 12 years receiving care at Toronto primary care sites found that medical consultation was sought in only 56% of episodes of URTI symptoms.[47] This is not surprising given that guidelines recommend against antibiotics for AOM and other URTIs in many cases. As many parents are aware of this recommendation from

previous clinic visits, they may decide to treat children with analgesics and antipyretics without seeking care even if they believe the child has an AOM.[48] Thus, information about the total number of URTI episodes must be obtained directly from parents and caregivers as it will not be found in a patient's medical record even if it includes records from all institutions and clinics. Parents may not diagnose AOM accurately based on symptoms because they overlap substantially with symptoms of URTIs.[49] Irritability and crying are the most common symptoms in AOM and URTI episodes.[50] Forty percent of children *with* AOM do *not* have an earache and 31% do *not* have a fever, [49] while 72% of children *without* AOM exhibit symptoms of AOM (crying, fever or ear ache).[50]

Like previous studies, we will employ structured telephone interviews to assess the number of URTI episodes.[51 52 53] Parents or caregivers will be contacted every month and asked to report the number of URTIs the child has experienced since the last call (or since the beginning of the trial for the first call) using validated questions (*Appendix 1*).[53] We will employ the symptoms in the Canadian Acute Respiratory Illness and Flu (CARIF) scale that has been validated in this population.[54]

The secondary outcome, parent-reported dental caries, will also be assessed during the monthly phone calls. Parents or caregivers will be asked if they have been informed by a dentist or a physician that their child has or has had at least one or more dental caries (*Appendix 1*). This question has been used and validated in several epidemiological studies.[55 56 57 58] The dental caries secondary outcome will be binary (at least one versus none). Those with caries at baseline will be excluded from this analysis but included in all other analyses.

Other measures

Health economics measures will be collected for an economic evaluation. We will compare the cost and effect of the xylitol syrup against the control group using the net benefit regression framework from the perspective of the parents (who will be the payer for the syrup).[59] Costs will include costs incurred to the parents or caregivers such as their usual mode of transportation for attending medical appointments (collected during an extended phone call at the four month call).[59] The parent or caregiver hours of productivity (including employment) lost due to the child's AOM episodes (including, for example, the days the child could not attend daycare) will also be assessed during the monthly calls. The use of net benefit regression allows the economic evaluation to be conducted using regression methods (adjusting for potential confounders). The main outcome of the economic evaluation will be an incremental net benefit of xylitol syrup (in term of cost and number of physician-diagnosed AOM episodes) compared to control. In addition, we will estimate incremental cost-effectiveness ratios (e.g., an incremental cost per one physician-diagnosed AOM episode avoided and an incremental cost per one URTI episode avoided). Statistical uncertainty will be characterized using a 95% confidence interval and cost-effectiveness acceptability curves.[60]

Compliance (reported number of doses given per week) will be assessed during the monthly calls and by tallying the number of returned doses at the end of the study.

Sample size rationale

We used the results of three previous RCTs of xylitol for the prevention of AOM and data from participants in the TARGet Kids! research network to estimate the sample size.

In a chart review of TARGet Kids! research network participants, we found a comparable event rate as the control groups in the trials above: 670 episodes of AOM in 1637 patients (41%) over a three month period (0.14 AOM episodes per patient-month).

Since the data currently available suggest that the AOM rate is about 1.6 episodes per patient-year, we will somewhat conservatively assume a control event rate of 1.5. We will aim to detect a relative risk of 0.8 (i.e. relative risk reduction of 20%) with 80% power and alpha = 0.05 (two-sided). A 20% RRR was chosen based on previous surveys of reasons physicians do not currently recommend xylitol and the RRR used in previous trials. [31 36] The sample size calculations assumed a Poisson distribution for the number of AOM episodes and were based on the asymptotic distribution of the likelihood ratio test statistic. Calculations were performed in *R* (2.15.3) using the *asypow* package and power was confirmed via 10,000 simulations. The required sample size is 236 per group. (Note that while the number of participants is less than one of the previous trials [61], the mean treatment and follow-up period in our study will be longer.)The above calculations take into consideration non-compliance and a loss to follow-up of 10% of participants only completing 50% of the follow-up period. These calculations assume there will be no substantial contamination. While xylitol preparations are commercially available, the dose of xylitol is less than one-tenth the dose found in trials to be effective at preventing AOM. A survey of TARGet Kids! participants showed that xylitol use is rare (< 5%). Siblings of those already enrolled in the trial will be excluded since contamination would be likely if two members of the family are enrolled and allocated to different arms.

We expect to recruit 40 participants per month. Thus sufficient patients will be recruited during two calendar years for the intervention to take place over two winter seasons. A previous RCT in the TARGet Kids! research network with similar inclusion criteria, exclusion criteria and recruitment strategy successfully recruited more than 66 children each month for two years when the network was smaller. [62] Parents of children who are participating in the TARGet Kids! research network's longitudinal study will be approached by research assistants regarding this RCT during routine primary care visits throughout the year. Randomization will take place just before the intervention begins so the small number of patients who are recruited but leave the practice before the intervention period will not be randomized.

We will determine if xylitol is more effective in younger children (24-36 months old versus >36 months old at time of recruitment).

Statistical Analysis

The primary analysis will be performed based on the intention to treat population. The primary outcome will be analyzed with a Poisson regression model. To account for participants who do not complete the entire planned follow-up and slight variations in the observation time for completers, the logarithm of follow-up time will be added as an offset term to the model. The treatment effect, expressed as a rate ratio (relative risk), and 95% confidence interval will be obtained from the model. A secondary analysis will adjust for characteristics with an imbalance between groups at baseline. Patient demographics will be summarized descriptively (e.g., means and SD or median and IQR for continuous variables and frequency and percentages for categorical). Although randomization guarantees balance in the long-run, there is a chance of imbalances in any sample. The demographics will be reviewed for clinically important imbalances that may be adjusted for in a secondary analysis. The secondary outcomes, number of URTI episodes and dental caries, will be analyzed similarly to the primary outcome.

Safety Analysis

A data safety monitoring board is not necessary because xylitol has been demonstrated to be safe in previous trials for the prevention of AOM and dental caries, and the maximum possible efficacy can be estimated from previous trials. We therefore do not anticipate any reason to stop the trial early.

Xylitol can rarely cause osmotic diarrhea and abdominal discomfort. In previous trials, approximately 1% of children exposed to xylitol experienced diarrhea and slightly less than 1% of children exposed to control substances (e.g., sorbitol) experienced diarrhea (difference not statistically significant).[44] The vast majority of children, including 2-4 year olds, are able to tolerate total daily doses of 45g of xylitol without significant gastrointestinal side effects.[63] The maximum total daily dose of xylitol in this trial will be 10g per day.

In previous trials, a total of more than 1000 children were exposed to various formulations of xylitol or control substances and there were no reported episodes of choking or aspiration. The control intervention is the provision of sorbitol syrup which can cause diarrhea but at similar rates as xylitol.[64] Despite this, the consent form will alert parents to the potential of diarrhea.

Adverse events

All adverse events will be reported to the Hospital for Sick Children or St. Michael's Hospital Research Ethics Board according to their adverse event reporting requirements. All adverse drug reactions to the study medication will be reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. In the latter case, a follow-up report must be filed within 8 calendar days. Serious adverse events and serious unexpected adverse events will be reported to the Natural and Non-prescription Health Products Directorate (NNHPD) in an expedited manner.

To maintain the overall quality of the trial, unblinding will only be performed in exceptional circumstances when knowledge of the actual treatment is essential for management of the patient. If unblinding is deemed to be necessary by the investigator, the investigator will contact the coordinating center by telephone to ascertain the allocation group and communicate this to the participant's clinician and caregiver. The research staff will not be informed of the allocation group. Unblinding will not necessarily be a reason for discontinuation or exclusion from the analysis.

Management

The Applied Health Research Centre (AHRC) will be responsible for trial data coordination, database development, data management and statistical analysis. Study data and patient surveys will be entered and maintained on a secure password protected database developed using REDCap® (www.project-redcap.org) and will be accessible via the internet for data entry purposes. Quality and completeness of data entry will be reviewed as soon as possible after data entry, within 5 business days of data entry for the first 5 participants randomized at each site, and within 15 days of data entry thereafter. Corrections or changes in REDCap® are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel.

Ethics and dissemination

The *TARGet Kids!* research platform has been approved by the Research Ethics Board at the Hospital for Sick Children and St Michael's Hospital, as well as the other affiliated sites. Ethics approval for this study has been obtained for all participating sites. Results of the study will be submitted for publication to a peer-reviewed journal and will be discussed policy and decision makers.

SUMMARY

In summary, AOM, URTIs and dental caries are common and costly conditions in young children that might be prevented by regular xylitol use. Existing evidence indicates clinical equipoise on the efficacy of xylitol syrup in preventing AOM, URTIs and dental caries in preschool aged children. Evidence from previous long-term trials of xylitol for the prevention of dental caries has demonstrated that the intervention is well tolerated and feasible in this age group. The TARGet Kids! research network has a demonstrated record of conducting RCTs in young children and its existing research infrastructure will be mobilized to ensure that this trial will be completed efficiently and on schedule.

AOM and URTIs are commonly viewed as unavoidable during early childhood. This trial has the potential to transform the approach to these three common conditions.

Author Contributions

The following authors contributed substantially to conception and the design of the protocol: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
The following authors drafted the manuscript: NP and FB.
The following authors revised the manuscript critically for important intellectual content: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
The following authors approved the final manuscript: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, PP.
The following authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.

Funding

The study is funded by the Canadian Institutes of Health Research (CIHR). NP received salary support from a CIHR RCT training grant and from a PSI Graham Farquharson Knowledge Translation Fellowship.

Competing interests

There are no competing interests.

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Appendix 1. Outcome determinations

Primary outcome: number of episodes of physician diagnosed AOM

Information will be obtained from the chart review at the end of the study period.

(1) Does chart entry included diagnosis or assessment of "AOM" or "acute otitis media"? [Yes or No]
(2) Does a chart entry within 48 hours record physical examination findings of the tympanic membrane? [Yes or No]

If, and only if, answers to both question are "Yes", add one to total number of AOM episodes. Proceed to review the next chart entry until all chart entries during the study period have been reviewed.

Secondary outcome: number of parent reported URTIs

Information will be obtained via monthly telephone calls.

(1) Has the child had any of the symptoms for two consecutive days?

- stuffy nose or congestion or rhinorrhea
- cough
- sore throat
- wheeze
- shortness of breath

If the child has had any of the above symptoms for two consecutive days, add one to the total number of parent reported URTI episodes.

(2) Was the child well (symptom free) for two consecutive days during the illness?

If the child was well for two consecutive days, add another one to the total number of parent reported URTI episodes (as this is a separate URTI) and repeat step (2) if needed.

Secondary outcome: parent reported dental caries (binary)

Information will be obtained via monthly telephone calls.

Have the parents or caregivers ever been told by a dentist or a physician that the child has or has had:

- dental caries
- multiple dental caries
- early childhood caries or ECC

If the parents or caregivers have been told that the child has any of the above record the child as having dental caries (and in this case the parents and caregivers do not need to be asked about this on subsequent calls).

Note that this outcome will also be assessed at baseline so that children with dental caries at baseline can be excluded from the dental caries analysis. This is because the outcome is binary (caries or not). Based on information available about children in the TARGet Kids! network, we expect 5-8 % of children to have caries at baseline and to be excluded from the dental caries analysis. Of course, all children will be included in the primary AOM analysis (and in the URTI analysis) regardless of whether they have had dental caries.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5,10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-4
	6b	Explanation for choice of comparators	2-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	2,9,
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4-5,9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	2, 5, 9, 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10-11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10-11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6,10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10,11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Xylitol for the prevention of acute otitis media episodes in children aged 2-4 years: Protocol for a pragmatic randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020941.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Mar-2018
Complete List of Authors:	Persaud, Nav; St. Michael's Hospital, Li Ka Shing Knowledge Institute Laupacis, Andreas; St. Michael\'s Hospital, Li Ka Shing Knowledge Institute; University of Toronto, Department of Family and Community Medicine Azarpazhooh, Amir; Faculty of Dentistry, University of Toronto Birken , Catherine; University of Toronto Hoch, Jeffrey ; University of Davis, Center for Health Policy and Research Isaranuwatchai, Wanrudee; St. Michael's Hospital, Li Ka Shing Knowledge Institute, Knowledge Translation Maguire, Jonathan; Hospital for Sick Children, Department of Paediatrics Mamdani, Muhammad; St. Michael's Hospital, Applied Health Research Centre, Li Ka Shing Knowledge Institute Thorpe, Kevin; University of Toronto Dalla Lana School of Public Health Allen, Christopher; Li Ka Shing Knowledge Institute, The Applied Health Research Centre Mason, Dalah; Hospital for Sick Children, Child Health Evaluative Sciences Kowal, Christine; Hospital for Sick Children, Child Health Evaluative Sciences Bazeghi, Farnaz; St. Michael's Hospital, Li Ka Shing Knowledge Institue Parkin, Patricia; The Hospital for Sick Children, Pediatric Medicine TARGet Kids!, Collaboration; Hospital for Sick Children, ; St. Michael's Hospital,
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Paediatrics
Keywords:	otitis media, upper respiratory tract infection, dental caries, xylitol, sorbitol

Xylitol for the prevention of acute otitis media episodes in children aged 2-4 years: Protocol for a pragmatic randomized controlled trial

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Key words: otitis media, upper respiratory tract infection, dental caries, xylitol, sorbitol

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Word count: 4596

ABSTRACT

Introduction

Xylitol (or "birch sugar") is a naturally occurring sugar with antibacterial properties that has been used as a natural non-sugar sweetener in chewing gums, confectionery, toothpaste and medicines. In this preventative randomized trial, Xylitol will be tested for the prevention of acute otitis media (AOM), a common and costly condition in young children. The primary outcome will be the incidence of AOM. Secondary outcomes will include upper respiratory tract infections (URTIs) and dental caries.

Methods and analysis

This study will be a pragmatic, blinded (participant and parents, practitioners and analyst), two-armed superiority; placebo randomized controlled trial (RCT) with 1:1 allocation, stratified by clinical site. The trial will be conducted in the eleven primary care group practices participating in the TARGet Kids! research network in Canada. Eligible participants between the ages of 2-4 years will be randomly assigned to the intervention arm of regular xylitol syrup use or the control arm of regular sorbitol use for 6 months. We expect to recruit 236 participants, per treatment arm, to detect a 20% relative risk reduction in AOM episodes. AOM will be identified through chart review. The secondary outcomes of URTIs and dental caries will be identified through monthly phone calls with specified questions.

Ethics and dissemination

Ethics approval has been obtained from St. Michael's Hospital, and The Hospital for Sick Children for the sites participating in the TARGet Kids! research network. Results will be submitted for publication to a peer-reviewed journal and will be discussed with decision makers.

Trial registration number: NCT03055091 (clinicaltrials.gov)

Strengths and limitations of this study

- This trial has the potential to determine whether a natural sweetener with antimicrobial properties prevents three common conditions during early childhood: otitis media, dental caries and upper respiratory tract infections
- The trial will be conducted through the TARGet Kids! primary care research network
- The six months of treatment and outcome assessment will allow the evaluation of the longer term effects of xylitol
- A challenge for trials with acute otitis media as an outcome is that parents may not distinguish AOM from other URTIs with similar symptoms and may not seek care; we will include both clinician-diagnosed AOM and parent-reported URTIs as separate outcomes.

INTRODUCTION

Acute otitis media (AOM) is a common and costly condition in young children.[1] The annual global incidence of AOM is 700 million per year and 50% of those affected are children under the age of 5 years.[2] By age 3 years, 84% of children have had at least one episode of AOM and

46% have had 3 or more episodes.[3] Antibiotic treatment has only a modest effect on AOM duration[4] and does not prevent serious complications such as mastoiditis or meningitis which can rarely be fatal.[5 6] Most (>80%) children with AOM presenting for care have spontaneous symptom resolution within 3 days and the number needed to treat for antibiotic treatment to reduce symptom duration is 20 days, which must be balanced by a number needed to harm (with adverse effects of antibiotics such as diarrhea) of 14 days.[4] The incidence of mastoiditis has not changed over time despite changes in antibiotic prescribing.[5 6 7] Rare sequelae of AOM include delayed cognitive development, impaired communication skills and permanent hearing loss.[3] Parents of children with otitis media report missing 2-3 days of work per episode.[1]

Another common and costly infectious disease amongst North American pre-school aged children is upper respiratory tract infections (URTIs).[8 9 10-12] URTIs are the most common reason for emergency department visits and unscheduled outpatient visits in Canada, accounting for 10% of emergency department visits for children under 10 years of age.[13 14 15] URTIs are also the most common reason for unscheduled visits to a care provider and Canadian children experience 3-8 URTIs per year at a cost to the healthcare system of several hundred million dollars per year.[16 17 18]

Nearly 30% of 2-5 year old children have dental caries.[19] Dental caries may lead to pain, difficulty eating and speaking, and can harm a child's self-esteem.[20] Treating dental caries in young children is challenging for practitioners, painful for the children and caries cost thousands of dollars to treat, with complicated caries requiring hospitalization costing several times more (and rarely resulting in death).[21 22 23 24 25 26]

In vitro studies have shown that xylitol can reduce the attachment of bacteria that cause AOM, URTIs, and dental caries such as *Streptococcus Pneumoniae* and *Haemophilus Influenzae* to nasopharyngeal cells. AOM occurs when the upper airway is colonized with bacteria, viruses or a combination of both that travel from the nasopharynx to the middle ear by way of the Eustachian tube.[27] A Cochrane systematic review of the safety and efficacy of xylitol in preventing AOM in children up to 12 years of age found that there is fair evidence supporting the use of xylitol for the prevention of AOM (risk ratio, 0.75; 95% CI, 0.65 to 0.88 based on 3 RCTs from the same research group, studying 1826 children in total), but concluded that an adequately-powered, well designed trial is necessary. [28] Previous trials have not established whether regular xylitol syrup use is effective at preventing AOM in young children (<4 years) who are most likely to have AOM. Several RCTs of xylitol for the prevention of dental caries indicate that the antimicrobial effect of xylitol (which is posited to account for its efficacy in preventing AOM) increases with duration of use.[29 30 31] Therefore, the effect of the same dose of xylitol may be more effective at preventing AOM over the 6 month study period in the proposed study than it was in the previous trials that lasted 2 or 3 months.[32] The longer trials of xylitol for the prevention of dental caries also demonstrate that daily xylitol administration is safe, feasible and well tolerated for the 6 month study period in the proposed trial.[29 30 31] A pilot study of higher concentrations of xylitol syrup in young children found good compliance and tolerability.[33] In summary, regular xylitol syrup used for the 6 month study period is safe and feasible, and there is clinical equipoise over its effectiveness at preventing AOM in young children. There is no recommendation for or against the use of xylitol in the United States or in Canada. The paucity of high quality randomized controlled trials has been cited as a reason for the lack of consistent recommendations regarding the use of xylitol in young children.[34]

The primary purpose of this study is to determine if regular use of xylitol syrup effectively prevents AOM in unselected 2-4 year old children. Such an intervention could

increase the productivity of parents and caregivers, reduce serious complications and reduce the suffering of young children - each episode of AOM involves several excess hours of crying for two to seven days.[35] This trial could change clinical practice if the results are positive. In several other countries xylitol is recommended for the prevention of dental caries. For example, the *American Academy of Pediatric Dentists* recommends regular xylitol use for the prevention of dental caries based on the results of eight clinical trials.[36] However, a survey of American pediatricians found that few physicians (12%) recommend xylitol to patients and that most would either definitely (68%) or possibly (29%) recommend xylitol if there was additional evidence that it prevented AOM.[37]

AIMS AND OBJECTIVES

Primary Question

Does regular xylitol syrup use for 6 months reduce the number of physician-diagnosed AOM episodes in children aged 2-4 years?

Secondary Questions

(1) Does regular xylitol syrup use reduce the number of parent-reported upper respiratory tract infection (URTI) episodes in children aged 2-4 years?
(2) Does regular xylitol syrup use reduce parent-reported dental caries in children aged 2-4 years?

METHODS AND ANALYSIS

Study Design

This will be a pragmatic, blinded (participant and parents, practitioners and analyst), two-armed superiority; placebo controlled randomized trial with 1:1 allocation, stratified by clinical site.

Setting

The trial will be conducted in the eleven primary care group practices currently participating in the TARGet Kids! research network (www.targetkids.ca) in Canada. There are no sites outside of Canada.

Eligibility Criteria

The patients in this study are healthy children aged 2-4 years who are participants of The Applied Research Group for Kids (TARGet Kids!), the largest pediatric primary care practice-based research network in Canada focused on child health (www.targetkids.ca).

***Inclusion criteria*:** age 24-48 months at start of intervention, and parent or care provider able to give consent for participation including being able to understand the information provided in English. All children recruited to this study will also be participants in the TARGet Kids! research network.

***Exclusion criteria*:** craniofacial malformations, structural middle ear abnormalities, sibling or any other child living at the same address already enrolled in the trial (in order to prevent

contamination), insertion of ventilation tubes prior to study period, current use of a xylitol product or reported xylitol sensitivity.

Consent

Consent will be obtained by one of two methods:
1. For participants with an upcoming scheduled health visit: An invitation to participate will be mailed to participants along with the consent form two weeks prior to their scheduled health visit. At the visit a trained TARGet Kids! Research Assistant will review the eligibility criteria and the consent form with the parents/caregivers. Research Assistants will answer any questions in person.
2. For eligible TARGet Kids! participants without a scheduled visit: An invitation to participate will be mailed to participants along with the consent form. Parents/caregivers will have the opportunity to contact the Study Coordinator at any time (by email/phone) to answer questions. The consent form will be mailed back to the site.
Any participant that no longer wishes to participate in TARGet Kids! will not be approached.

Intervention arm

Xylitol (or "birch sugar") is a naturally occurring sugar with antibacterial properties that has been used as a natural non-sugar sweetener in chewing gums, confectionery, toothpaste and medicines.[27 38 39]

The investigational agents will be provided by XLEAR, a producer of commercial xylitol products that are sold in Canada. The product specifications used for this agent is that of their syrup or "tooth gel" products sold in 60 mL tubes. The product is approved by Health Canada as a food additive. The product has a shelf life of 2 years based on stability studies. Each tube is labeled with a best before date and a lot number on the tube crimp.
The experimental intervention is the provision of xylitol syrup (35% Xylitol concentration per weight) and instructions to ingest is 3-5 times per day. Each dose will be 5 mL of 350 g/L, therefore the maximum possible daily dose will be 9 g of xylitol per day. This is the daily dose that may be effective from previous trials.[32]

Control Arm

The control intervention is the provision of sorbitol syrup (looks, smells and tastes like the xylitol syrup but is not an antimicrobial). Sorbitol is unlikely to have an effect on our primary outcome of AOM or the secondary outcomes of URTIs and dental caries; therefore it can be used as a placebo. The sorbitol syrup formulation is the same as the xylitol syrup except the concentration of sorbitol will be 30% by weight. The instructions for use are 3-5 times per day. Each dose will be 5 mL of 300 g/L of sorbitol; therefore the maximum daily dose will be 7.5 g of sorbitol.

XLEAR will produce the investigational agents through a dedicated production run and ship the products to the research pharmacy in a timely manner. This will allow preparation and shipment of the kits for each participant prior to the intervention period.

The data coordinating center will create master randomization tables and send these to the research pharmacy for dispensing. The study statistician will create the master randomization table using a computer-generated, site-stratified, block randomization design. The research pharmacy will use the randomization table for the dispensation of the investigational agents to each participant.

Intervention period

The treatment period will be 6 months for all participants. The intervention will be given during the winter season.

The follow-up period is identical to the treatment period, and so will also be 6 months for all participants (see Figure 1).

Conducting the trial during winter months will maximize the efficiency of the trial because AOM and URTI incidences are highest during that time.[40] Since xylitol is not a treatment for infections, care will be provided as normal for any suspected infections.

Premature Withdrawal/Discontinuation Criteria

Xylitol is sweet and children generally enjoy consuming it.[33] The number of missed doses in previous trials with frequent daily dosing was around 10%.

Parents will be called two weeks after they have been given the package to discuss any challenges with compliance, as well as during monthly follow-up calls.

Based on data from previous trials conducted in the TARGet Kids! research network and the fact that the primary outcome will be determined using a chart review, we anticipate a low (< 5%) rate of being lost to follow-up in this trial where follow-up does not require any special visits for research purposes only. If a participant leaves the primary care practice, we will attempt to obtain the name of the current care provider and obtain the chart for review. If a participant has left the primary care practice and we are unable to contact the parents or caregivers, we will treat the data as missing. Despite this, the sample size calculation assumes 10% of participants will not complete follow-up.

Outcome Measures

Primary outcome

The primary outcome of the total number of physician-diagnosed AOM episodes will be assessed by reviewing charts of the primary care provider and any other care providers reported by parents or caregiver at monthly phone calls.

Three methods for determining the diagnosis of AOM have been used in trials: clinical signs (bulging and red tympanic membrane), clinical signs with tympanometry, and clinical signs with tympanocentesis.[41] In this trial, the number of AOM episodes will be assessed using both objective clinical signs of AOM recorded in the chart and a physician's diagnosis of AOM. In order to make a diagnosis of AOM for this trial, the chart must contain *both* the documentation of signs of AOM (e.g. erythematous tympanic membrane) plus the practitioners' diagnosis that the patient had AOM. The addition of tympanometry to clinical signs does not necessarily improve the accuracy of AOM diagnosis.[42]Although tympanometry is recommended by some guidelines, it is not employed in routine clinical practice at any of the TARGet Kids! sites. Tympanocentesis is therapeutic and can prevent subsequent AOM episodes[41] so it cannot be used in this trial of AOM prevention (and it requires instruments not present in primary care sites). Four of the five previous trials of xylitol for the prevention of AOM employed clinical signs with tympanometry, and one used clinical signs to determine the number of AOM episodes.[32]

Previous RCTs of AOM *management* in young children have relied on the diagnoses made by primary care providers (who are generally the clinicians who diagnose AOM for clinical purposes).[43 44] The studies, involving longer study periods, used chart reviews to determine the number of AOM episodes just as we will in this trial (*Appendix 1*).[44]

We have conducted a chart review of 1,637 patients in the TARGet Kids! research network using a method similar to those in completed RCTs of AOM that involves reviewing charts for physical examination findings consistent with AOM and a diagnosis or assessment of AOM.[45 43 44] In all of the episodes, the physical examination findings and the diagnosis were clearly documented in the chart (the term "AOM" was usually recorded in the assessment portion of the note), and there was perfect agreement between independent reviewers.

In addition to reviews of the patient's primary care provider medical record, the primary outcome will also include AOM episodes diagnosed by other care providers (e.g., at walk-in clinics or emergency rooms). Parental consent for release of this information will be obtained, and charts will be reviewed upon the end of follow-up period.

The primary analysis will be the total number of AOM episodes during the study period. We will also summarize the time to first AOM using survival curves.

A limitation of employing physician-diagnosed episodes of AOM is that parents may not seek care when their child has AOM symptoms. This limitation is addressed with the secondary outcome of parent reported URTIs (*see secondary outcomes below*). Another limitation of physician-diagnosed AOM is that there is variability in the diagnosis of AOM by clinicians, with one study of administrative data indicating that some clinicians diagnose AOM twice as often as others.[41 46 47] Since the clinicians will be blinded to the allocated group, differences in clinical assessment will not bias the results. If there is a substantial number of incorrect physician diagnosed episodes of AOM (false positives), there results will be biased against the efficacy of xylitol.

Note that our sample size calculation incorporates the incidence of AOM in the TARGet Kids! study population and so it takes into consideration the rate of AOM diagnosis by the same clinicians who will diagnose AOM in these study participants.

Secondary outcomes

The secondary outcome parent-reported URTI episodes will be assessed during monthly phone calls. A challenge in all trials that employ AOM as an outcome is the combined effect of two factors: (1) parents often decide not to seek care when a child has symptoms that may indicate AOM and (2) parents cannot distinguish between AOM and other URTIs because the symptoms are similar. We will address this challenge with our secondary outcome: parent-reported URTIs, a very common and costly (in aggregate) condition in early childhood.[17 48] The previous shorter (2 to 3 month) trials of xylitol found a non-significant trend towards fewer URTI episodes in children receiving xylitol.[32]

A cohort study of children aged 2 months to 12 years receiving care at Toronto primary care sites found that medical consultation was sought in only 56% of episodes of URTI symptoms.[49] This is not surprising given that guidelines recommend against antibiotics for AOM and other URTIs in many cases. As many parents are aware of this recommendation from previous clinic visits, they may decide to treat children with analgesics and antipyretics without seeking care even if they believe the child has an AOM.[50] Thus, information about the total number of URTI episodes must be obtained directly from parents and caregivers as it will not be found in a patient's medical record even if it includes records from all institutions and clinics. Parents may not diagnose AOM accurately based on symptoms because they overlap substantially with symptoms of URTIs.[51] Irritability and crying are the most common symptoms in AOM and URTI episodes.[52] Forty percent of children *with* AOM do *not* have an earache and

31% do *not* have a fever, [51] while 72% of children *without* AOM exhibit symptoms of AOM (crying, fever or ear ache).[52]

Like previous studies, we will employ structured telephone interviews to assess the number of URTI episodes.[53 54 55] Parents or caregivers will be contacted every month and asked to report the number of URTIs the child has experienced since the last call (or since the beginning of the trial for the first call) using validated questions (*Appendix 1*).[55] We will employ the symptoms in the Canadian Acute Respiratory Illness and Flu (CARIF) scale that has been validated in this population.[56]

The secondary outcome, parent-reported dental caries, will also be assessed during the monthly phone calls. Parents or caregivers will be asked if they have been informed by a dentist or a physician that their child has or has had at least one or more dental caries (*Appendix 1*). This question has been used and validated in several epidemiological studies.[57 58 59 60] The dental caries secondary outcome will be binary (at least one versus none). Those with caries at baseline will be excluded from this analysis but included in all other analyses.

Other measures

Health economics measures will be collected for an economic evaluation. We will compare the cost and effect of the xylitol syrup against the control group using the net benefit regression framework from the perspective of the parents (who will be the payer for the syrup).[61] Costs will include costs incurred to the parents or caregivers such as their usual mode of transportation for attending medical appointments (collected during an extended phone call at the four month call).[61] The parent or caregiver hours of productivity (including employment) lost due to the child's AOM episodes (including, for example, the days the child could not attend daycare) will also be assessed during the monthly calls. The use of net benefit regression allows the economic evaluation to be conducted using regression methods (adjusting for potential confounders). The main outcome of the economic evaluation will be an incremental net benefit of xylitol syrup (in term of cost and number of physician-diagnosed AOM episodes) compared to control. In addition, we will estimate incremental cost-effectiveness ratios (e.g., an incremental cost per one physician-diagnosed AOM episode avoided and an incremental cost per one URTI episode avoided). Statistical uncertainty will be characterized using a 95% confidence interval and cost-effectiveness acceptability curves.[62]

Compliance (reported number of doses given per week) will be assessed during the monthly calls and by tallying the number of returned doses at the end of the study.

Sample size rationale

We used the results of three previous RCTs of xylitol for the prevention of AOM and data from participants in the TARGet Kids! research network to estimate the sample size.

In a chart review of TARGet Kids! research network participants, we found a comparable event rate as the control groups in the trials above: 670 episodes of AOM in 1637 patients (41%) over a three month period (0.14 AOM episodes per patient-month).

Since the data currently available suggest that the AOM rate is about 1.6 episodes per patient-year, we will somewhat conservatively assume a control event rate of 1.5. We will aim to detect a relative risk of 0.8 (i.e. relative risk reduction of 20%) with 80% power and alpha = 0.05 (two-sided). A 20% RRR was chosen based on previous surveys of reasons physicians do not currently recommend xylitol and the RRR used in previous trials. [32 37] The sample size calculations assumed a Poisson distribution for the number of AOM episodes and were based on

the asymptotic distribution of the likelihood ratio test statistic. Calculations were performed in *R* (2.15.3) using the *asypow* package and power was confirmed via 10,000 simulations. The required sample size is 236 per group. (Note that while the number of participants is less than one of the previous trials [63], the mean treatment and follow-up period in our study will be longer.) The above calculations take into consideration non-compliance and a loss to follow-up of 10% of participants only completing 50% of the follow-up period. These calculations assume there will be no substantial contamination. While xylitol preparations are commercially available, the dose of xylitol is less than one-tenth the dose found in trials to be effective at preventing AOM. A survey of TARGet Kids! participants showed that xylitol use is rare (< 5%). Siblings of those already enrolled in the trial will be excluded since contamination would be likely if two members of the family are enrolled and allocated to different arms.

We expect to recruit 40 participants per month. Thus sufficient patients will be recruited during two calendar years for the intervention to take place over two winter seasons. A previous RCT in the TARGet Kids! research network with similar inclusion criteria, exclusion criteria and recruitment strategy successfully recruited more than 66 children each month for two years when the network was smaller. [64] Parents of children who are participating in the TARGet Kids! research network's longitudinal study will be approached by research assistants regarding this RCT during routine primary care visits throughout the year. Randomization will take place just before the intervention begins so the small number of patients who are recruited but leave the practice before the intervention period will not be randomized.

We will determine if xylitol is more effective in younger children (24-36 months old versus >36 months old at time of recruitment).

Statistical Analysis

The primary analysis will be performed based on the intention to treat population. The primary outcome will be analyzed with a Poisson regression model. To account for participants who do not complete the entire planned follow-up and slight variations in the observation time for completers, the logarithm of follow-up time will be added as an offset term to the model. The treatment effect, expressed as a rate ratio (relative risk), and 95% confidence interval will be obtained from the model. A secondary analysis will adjust for characteristics with an imbalance between groups at baseline. Patient demographics will be summarized descriptively (e.g., means and SD or median and IQR for continuous variables and frequency and percentages for categorical). Although randomization guarantees balance in the long-run, there is a chance of imbalances in any sample. The demographics will be reviewed for clinically important imbalances that may be adjusted for in a secondary analysis. The secondary outcomes, number of URTI episodes and dental caries, will be analyzed similarly to the primary outcome.

Safety Analysis

A data safety monitoring board is not necessary because xylitol has been demonstrated to be safe in previous trials for the prevention of AOM and dental caries, and the maximum possible efficacy can be estimated from previous trials. We therefore do not anticipate any reason to stop the trial early.

Xylitol can rarely cause osmotic diarrhea and abdominal discomfort. In previous trials, approximately 1% of children exposed to xylitol experienced diarrhea and slightly less than 1% of children exposed to control substances (e.g., sorbitol) experienced diarrhea (difference not statistically significant).[45] The vast majority of children, including 2-4 year olds, are able to

tolerate total daily doses of 45g of xylitol without significant gastrointestinal side effects.[32 35] The maximum total daily dose of xylitol in this trial will be 10g per day.

In previous trials, a total of more than 1000 children were exposed to various formulations of xylitol or control substances and there were no reported episodes of choking or aspiration. The control intervention is the provision of sorbitol syrup which can cause diarrhea but at similar rates as xylitol.[65] Despite this, the consent form will alert parents to the potential of diarrhea.

Adverse events

All adverse events will be reported to the Hospital for Sick Children or St. Michael's Hospital Research Ethics Board according to their adverse event reporting requirements. All adverse drug reactions to the study medication will be reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. In the latter case, a follow-up report must be filed within 8 calendar days. Serious adverse events and serious unexpected adverse events will be reported to the Natural and Non-prescription Health Products Directorate (NNHPD) in an expedited manner.

To maintain the overall quality of the trial, unblinding will only be performed in exceptional circumstances when knowledge of the actual treatment is essential for management of the patient. If unblinding is deemed to be necessary by the investigator, the investigator will contact the coordinating center by telephone to ascertain the allocation group and communicate this to the participant's clinician and caregiver. The research staff will not be informed of the allocation group. Unblinding will not necessarily be a reason for discontinuation or exclusion from the analysis.

Management

The Applied Health Research Centre (AHRC) will be responsible for trial data coordination, database development, data management and statistical analysis. Study data and patient surveys will be entered and maintained on a secure password protected database developed using REDCap® (www.project-redcap.org) and will be accessible via the internet for data entry purposes. Quality and completeness of data entry will be reviewed as soon as possible after data entry, within 5 business days of data entry for the first 5 participants randomized at each site, and within 15 days of data entry thereafter. Corrections or changes in REDCap® are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel.

Patient and Public Involvement

Patients were not directly involved in the development of the research question or the design of the study. A written summary of the study results will be sent to participants by email or by mail. The burden of the intervention on patients was not assessed prior to the start of the trial.

Ethics and dissemination

The *TARGet Kids!* research platform has been approved by the Research Ethics Board at the Hospital for Sick Children and St Michael's Hospital, as well as the other affiliated sites. Ethics approval for this study has been obtained for all participating sites. Results of the study will be submitted for publication to a peer-reviewed journal and will be discussed policy and decision makers.

SUMMARY

In summary, AOM, URTIs and dental caries are common and costly conditions in young children that might be prevented by regular xylitol use. Existing evidence indicates clinical equipoise on the efficacy of xylitol syrup in preventing AOM, URTIs and dental caries in preschool aged children. Evidence from previous long-term trials of xylitol for the prevention of dental caries has demonstrated that the intervention is well tolerated and feasible in this age group. The TARGet Kids! research network has a demonstrated record of conducting RCTs in young children and its existing research infrastructure will be mobilized to ensure that this trial will be completed efficiently and on schedule.

AOM and URTIs are commonly viewed as unavoidable during early childhood. This trial has the potential to transform the approach to these three common conditions.

Author Contributions

The following authors contributed substantially to conception and the design of the protocol: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
The following authors drafted the manuscript: NP and FB.
The following authors revised the manuscript critically for important intellectual content: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
The following authors approved the final manuscript: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, PP.
The following authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
Members of the TARGet Kids! Collaboration contribute to data collection and provide general input on research directions.

Funding

The study is funded by the Canadian Institutes of Health Research (CIHR). NP received salary support from a CIHR RCT training grant and from a PSI Graham Farquharson Knowledge Translation Fellowship.There was no role of the manufacturer in the concept, design, implementation, data collection and analysis and permission to publish. The products were purchased from the manufacturer using public research funding.

Competing interests

There are no competing interests.PP reports receiving the following grants unrelated to this study: a grant from Hospital for Sick Children Foundation during the conduct of the study; a grant from Canadian Institutes of Health Research (FRN # 115059) for an ongoing investigator-initiated trial of iron deficiency in young children, for which Mead Johnson Nutrition provides non-financial support (Fer-In-Sol® liquid iron supplement). These agencies had no role in the design, collection, analyses or interpretation of the results of this study or in the preparation, review, or approval of the manuscript.

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Figure Legend

Figure 1. Timeline for intervention and follow-up.

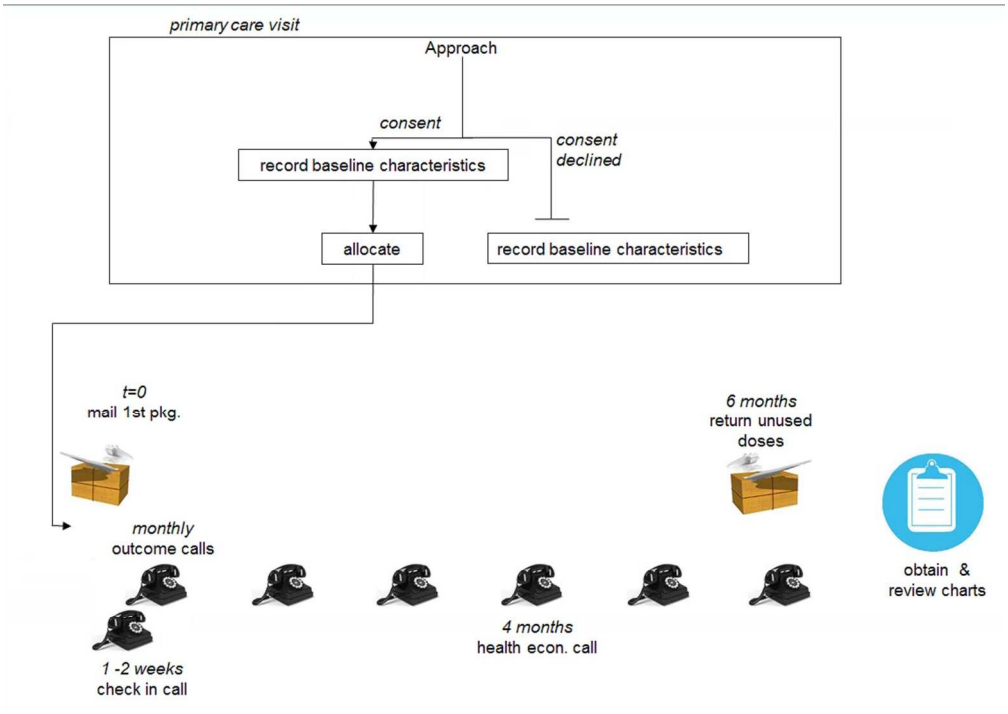

Figure 1. Timeline for intervention and follow up.

169x120mm (300 x 300 DPI)

Appendix 1. **Outcome determinations**

Primary outcome: number of episodes of physician diagnosed AOM

Information will be obtained from the chart review at the end of the study period.

(1) Does chart entry included diagnosis or assessment of "AOM" or "acute otitis media"? [Yes or No]
(2) Does a chart entry within 48 hours record physical examination findings of the tympanic membrane? [Yes or No]

If, and only if, answers to both question are "Yes", add one to total number of AOM episodes. Proceed to review the next chart entry until all chart entries during the study period have been reviewed.

Secondary outcome: number of parent reported URTIs

Information will be obtained via monthly telephone calls.

(1) Has the child had any of the symptoms for two consecutive days?

- stuffy nose or congestion or rhinorrhea
- cough
- sore throat
- wheeze
- shortness of breath

If the child has had any of the above symptoms for two consecutive days, add one to the total number of parent reported URTI episodes.

(2) Was the child well (symptom free) for two consecutive days during the illness?

If the child was well for two consecutive days, add another one to the total number of parent reported URTI episodes (as this is a separate URTI) and repeat step (2) if needed.

Secondary outcome: parent reported dental caries (binary)

Information will be obtained via monthly telephone calls.

Have the parents or caregivers ever been told by a dentist or a physician that the child has or has had:

- dental caries
- multiple dental caries
- early childhood caries or ECC

If the parents or caregivers have been told that the child has any of the above record the child as having dental caries (and in this case the parents and caregivers do not need to be asked about this on subsequent calls).

Note that this outcome will also be assessed at baseline so that children with dental caries at baseline can be excluded from the dental caries analysis. This is because the outcome is binary (caries or not). Based on information available about children in the TARGet Kids! network, we expect 5-8 % of children to have caries at baseline and to be excluded from the dental caries analysis. Of course, all children will be included in the primary AOM analysis (and in the URTI analysis) regardless of whether they have had dental caries.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5,10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-4
	6b	Explanation for choice of comparators	2-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	2,9,
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4-5,9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	2, 5, 9, 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10-11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10-11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6,10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10,11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Xylitol for the prevention of acute otitis media episodes in children aged 2-4 years: Protocol for a pragmatic randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020941.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Apr-2018
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Paediatrics
Keywords:	otitis media, upper respiratory tract infection, dental caries, xylitol, sorbitol

Xylitol for the prevention of acute otitis media episodes in children aged 2-4 years: Protocol for a pragmatic randomized controlled trial

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Key words: otitis media, upper respiratory tract infection, dental caries, xylitol, sorbitol

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Word count: 4596

ABSTRACT

Introduction

Xylitol (or "birch sugar") is a naturally occurring sugar with antibacterial properties that has been used as a natural non-sugar sweetener in chewing gums, confectionery, toothpaste and medicines. In this preventative randomized trial, Xylitol will be tested for the prevention of acute otitis media (AOM), a common and costly condition in young children. The primary outcome will be the incidence of AOM. Secondary outcomes will include upper respiratory tract infections (URTIs) and dental caries.

Methods and analysis

This study will be a pragmatic, blinded (participant and parents, practitioners and analyst), two-armed superiority; placebo randomized controlled trial (RCT) with 1:1 allocation, stratified by clinical site. The trial will be conducted in the eleven primary care group practices participating in the TARGet Kids! research network in Canada. Eligible participants between the ages of 2-4 years will be randomly assigned to the intervention arm of regular xylitol syrup use or the control arm of regular sorbitol use for 6 months. We expect to recruit 236 participants, per treatment arm, to detect a 20% relative risk reduction in AOM episodes. AOM will be identified through chart review. The secondary outcomes of URTIs and dental caries will be identified through monthly phone calls with specified questions.

Ethics and dissemination

Ethics approval from the Research Ethics Boards at the Hospital for Sick Children and St. Michael's Hospital has been obtained for this study and also for the TARGet Kids! research network. Results will be submitted for publication to a peer-reviewed journal and will be discussed with decision makers.

Trial registration number: NCT03055091 (clinicaltrials.gov)

Strengths and limitations of this study

- This is the first pragmatic trial in Canada determining whether regular xylitol syrup use is effective in preventing AOM in children under the age of 4 years (who are most likely to have AOM).
- The trial will be conducted through the TARGet Kids! primary care research network allowing for a multicenter study performed through routine primary care visits.
- The six months of treatment and outcome assessment will allow the evaluation of the longer term effects of xylitol.
- A challenge for trials with acute otitis media as an outcome is that parents may not distinguish AOM from other URTIs with similar symptoms and may not seek care; we will include both clinician-diagnosed AOM and parent-reported URTIs as separate outcomes.

INTRODUCTION

Acute otitis media (AOM) is a common and costly condition in young children.[1] The annual global incidence of AOM is 700 million per year and 50% of those affected are children under the age of 5 years.[2] By age 3 years, 84% of children have had at least one episode of AOM and 46% have had 3 or more episodes.[3] Antibiotic treatment has only a modest effect on AOM duration[4] and does not prevent serious complications such as mastoiditis or meningitis which can rarely be fatal.[5 6] Most (>80%) children with AOM presenting for care have spontaneous symptom resolution within 3 days and the number needed to treat for antibiotic treatment to reduce symptom duration is 20 days, which must be balanced by a number needed to harm (with adverse effects of antibiotics such as diarrhea) of 14 days.[4] The incidence of mastoiditis has not changed over time despite changes in antibiotic prescribing.[5 6 7] Rare sequelae of AOM include delayed cognitive development, impaired communication skills and permanent hearing loss.[3] Parents of children with otitis media report missing 2-3 days of work per episode.[1]

Another common and costly infectious disease amongst North American pre-school aged children is upper respiratory tract infections (URTIs).[8 9 10-12] URTIs are the most common reason for emergency department visits and unscheduled outpatient visits in Canada, accounting for 10% of emergency department visits for children under 10 years of age.[13 14 15] URTIs are also the most common reason for unscheduled visits to a care provider and Canadian children experience 3-8 URTIs per year at a cost to the healthcare system of several hundred million dollars per year.[16 17 18]

Nearly 30% of 2-5 year old children have dental caries.[19] Dental caries may lead to pain, difficulty eating and speaking, and can harm a child's self-esteem.[20] Treating dental caries in young children is challenging for practitioners, painful for the children and caries cost thousands of dollars to treat, with complicated caries requiring hospitalization costing several times more (and rarely resulting in death).[21 22 23 24 25 26]

In vitro studies have shown that xylitol can reduce the attachment of bacteria that cause AOM, URTIs, and dental caries such as *Streptococcus Pneumoniae* and *Haemophilus Influenzae* to nasopharyngeal cells. AOM occurs when the upper airway is colonized with bacteria, viruses or a combination of both that travel from the nasopharynx to the middle ear by way of the Eustachian tube.[27] A Cochrane systematic review of the safety and efficacy of xylitol in preventing AOM in children up to 12 years of age found that there is fair evidence supporting the use of xylitol for the prevention of AOM (risk ratio, 0.75; 95% CI, 0.65 to 0.88 based on 3 RCTs from the same research group, studying 1826 children in total), but concluded that an adequately-powered, well designed trial is necessary. [28] Previous trials have not established whether regular xylitol syrup use is effective at preventing AOM in young children (<4 years) who are most likely to have AOM. Several RCTs of xylitol for the prevention of dental caries indicate that the antimicrobial effect of xylitol (which is posited to account for its efficacy in preventing AOM) increases with duration of use.[29 30 31] Therefore, the effect of the same dose of xylitol may be more effective at preventing AOM over the 6 month study period in the proposed study than it was in the previous trials that lasted 2 or 3 months.[32] The longer trials of xylitol for the prevention of dental caries also demonstrate that daily xylitol administration is safe, feasible and well tolerated for the 6 month study period in the proposed trial.[29 30 31] A pilot study of higher concentrations of xylitol syrup in young children found good compliance and tolerability.[33] In summary, regular xylitol syrup used for the 6 month study period is safe and feasible, and there is clinical equipoise over its effectiveness at preventing AOM in young children. There is no recommendation for or against the use of xylitol in the United States or in Canada. The paucity

of high quality randomized controlled trials has been cited as a reason for the lack of consistent recommendations regarding the use of xylitol in young children.[34]

The primary purpose of this study is to determine if regular use of xylitol syrup effectively prevents AOM in unselected 2-4 year old children. Such an intervention could increase the productivity of parents and caregivers, reduce serious complications and reduce the suffering of young children - each episode of AOM involves several excess hours of crying for two to seven days.[35] This trial could change clinical practice if the results are positive. In several other countries xylitol is recommended for the prevention of dental caries. For example, the *American Academy of Pediatric Dentists* recommends regular xylitol use for the prevention of dental caries based on the results of eight clinical trials.[36] However, a survey of American pediatricians found that few physicians (12%) recommend xylitol to patients and that most would either definitely (68%) or possibly (29%) recommend xylitol if there was additional evidence that it prevented AOM.[37]

AIMS AND OBJECTIVES

Primary Question

Does regular xylitol syrup use for 6 months reduce the number of physician-diagnosed AOM episodes in children aged 2-4 years?

Secondary Questions

(1) Does regular xylitol syrup use reduce the number of parent-reported upper respiratory tract infection (URTI) episodes in children aged 2-4 years?
(2) Does regular xylitol syrup use reduce parent-reported dental caries in children aged 2-4 years?

METHODS AND ANALYSIS

Study Design

This will be a pragmatic, blinded (participant and parents, practitioners and analyst), two-armed superiority; placebo controlled randomized trial with 1:1 allocation, stratified by clinical site.

Setting

The trial will be conducted in the eleven primary care group practices currently participating in the TARGet Kids! research network (www.targetkids.ca) in Canada. There are no sites outside of Canada.

Eligibility Criteria

The patients in this study are healthy children aged 2-4 years who are participants of The Applied Research Group for Kids (TARGet Kids!), the largest pediatric primary care practice-based research network in Canada focused on child health (www.targetkids.ca).

***Inclusion criteria*:** age 24-48 months at start of intervention, and parent or care provider able to give consent for participation including being able to understand the information provided in

English. All children recruited to this study will also be participants in the TARGet Kids! research network.

***Exclusion criteria*:** craniofacial malformations, structural middle ear abnormalities, sibling or any other child living at the same address already enrolled in the trial (in order to prevent contamination), insertion of ventilation tubes prior to study period, current use of a xylitol product or reported xylitol sensitivity.

Consent

Consent will be obtained by one of two methods:
1. For participants with an upcoming scheduled health visit: An invitation to participate will be mailed to participants along with the consent form two weeks prior to their scheduled health visit. At the visit a trained TARGet Kids! Research Assistant will review the eligibility criteria and the consent form with the parents/caregivers. Research Assistants will answer any questions in person.
2. For eligible TARGet Kids! participants without a scheduled visit: An invitation to participate will be mailed to participants along with the consent form. Parents/caregivers will have the opportunity to contact the Study Coordinator at any time (by email/phone) to answer questions. The consent form will be mailed back to the site.
Any participant that no longer wishes to participate in TARGet Kids! will not be approached.

Intervention arm

Xylitol (or "birch sugar") is a naturally occurring sugar with antibacterial properties that has been used as a natural non-sugar sweetener in chewing gums, confectionery, toothpaste and medicines.[27 38 39]

The investigational agents will be provided by XLEAR, a producer of commercial xylitol products that are sold in Canada. The product specifications used for this agent is that of their syrup or "tooth gel" products sold in 60 mL tubes. The product is approved by Health Canada as a food additive. The product has a shelf life of 2 years based on stability studies. Each tube is labeled with a best before date and a lot number on the tube crimp.
The experimental intervention is the provision of xylitol syrup (35% Xylitol concentration per weight) and instructions to ingest is 3-5 times per day. Each dose will be 5 mL of 350 g/L, therefore the maximum possible daily dose will be 9 g of xylitol per day. This is the daily dose that may be effective from previous trials.[32]

Control Arm

The control intervention is the provision of sorbitol syrup (looks, smells and tastes like the xylitol syrup but is not an antimicrobial). Sorbitol is unlikely to have an effect on our primary outcome of AOM or the secondary outcomes of URTIs and dental caries; therefore it can be used as a placebo. The sorbitol syrup formulation is the same as the xylitol syrup except the concentration of sorbitol will be 30% by weight. The instructions for use are 3-5 times per day. Each dose will be 5 mL of 300 g/L of sorbitol; therefore the maximum daily dose will be 7.5 g of sorbitol.

XLEAR will produce the investigational agents through a dedicated production run and ship the products to the research pharmacy in a timely manner. This will allow preparation and shipment of the kits for each participant prior to the intervention period.

The data coordinating center will create master randomization tables and send these to the research pharmacy for dispensing. The study statistician will create the master randomization table using a computer-generated, site-stratified, block randomization design. The research pharmacy will use the randomization table for the dispensation of the investigational agents to each participant.

Intervention period

The treatment period will be 6 months for all participants. The intervention will be given during the winter season.

The follow-up period is identical to the treatment period, and so will also be 6 months for all participants (see Figure 1).

Conducting the trial during winter months will maximize the efficiency of the trial because AOM and URTI incidences are highest during that time.[40] Since xylitol is not a treatment for infections, care will be provided as normal for any suspected infections.

Premature Withdrawal/Discontinuation Criteria

Xylitol is sweet and children generally enjoy consuming it.[33] The number of missed doses in previous trials with frequent daily dosing was around 10%.

Parents will be called two weeks after they have been given the package to discuss any challenges with compliance, as well as during monthly follow-up calls.

Based on data from previous trials conducted in the TARGet Kids! research network and the fact that the primary outcome will be determined using a chart review, we anticipate a low (< 5%) rate of being lost to follow-up in this trial where follow-up does not require any special visits for research purposes only. If a participant leaves the primary care practice, we will attempt to obtain the name of the current care provider and obtain the chart for review. If a participant has left the primary care practice and we are unable to contact the parents or caregivers, we will treat the data as missing. Despite this, the sample size calculation assumes 10% of participants will not complete follow-up.

Outcome Measures

Primary outcome

The primary outcome of the total number of physician-diagnosed AOM episodes will be assessed by reviewing charts of the primary care provider and any other care providers reported by parents or caregiver at monthly phone calls.

Three methods for determining the diagnosis of AOM have been used in trials: clinical signs (bulging and red tympanic membrane), clinical signs with tympanometry, and clinical signs with tympanocentesis.[41] In this trial, the number of AOM episodes will be assessed using both objective clinical signs of AOM recorded in the chart and a physician's diagnosis of AOM. In order to make a diagnosis of AOM for this trial, the chart must contain *both* the documentation of signs of AOM (e.g. erythematous tympanic membrane) plus the practitioners' diagnosis that the patient had AOM. The addition of tympanometry to clinical signs does not necessarily improve the accuracy of AOM diagnosis.[42]Although tympanometry is recommended by some guidelines, it is not employed in routine clinical practice at any of the TARGet Kids! sites. Tympanocentesis is therapeutic and can prevent subsequent AOM episodes[41] so it cannot be used in this trial of AOM prevention (and it requires instruments not present in primary care sites).

Four of the five previous trials of xylitol for the prevention of AOM employed clinical signs with tympanometry, and one used clinical signs to determine the number of AOM episodes.[32]

Previous RCTs of AOM *management* in young children have relied on the diagnoses made by primary care providers (who are generally the clinicians who diagnose AOM for clinical purposes).[43 44] The studies, involving longer study periods, used chart reviews to determine the number of AOM episodes just as we will in this trial (*Appendix 1*).[44]

We have conducted a chart review of 1,637 patients in the TARGet Kids! research network using a method similar to those in completed RCTs of AOM that involves reviewing charts for physical examination findings consistent with AOM and a diagnosis or assessment of AOM.[45 43 44] In all of the episodes, the physical examination findings and the diagnosis were clearly documented in the chart (the term "AOM" was usually recorded in the assessment portion of the note), and there was perfect agreement between independent reviewers.

In addition to reviews of the patient's primary care provider medical record, the primary outcome will also include AOM episodes diagnosed by other care providers (e.g., at walk-in clinics or emergency rooms). Parental consent for release of this information will be obtained, and charts will be reviewed upon the end of follow-up period.

The primary analysis will be the total number of AOM episodes during the study period. We will also summarize the time to first AOM using survival curves.

A limitation of employing physician-diagnosed episodes of AOM is that parents may not seek care when their child has AOM symptoms. This limitation is addressed with the secondary outcome of parent reported URTIs (*see secondary outcomes below*). Another limitation of physician-diagnosed AOM is that there is variability in the diagnosis of AOM by clinicians, with one study of administrative data indicating that some clinicians diagnose AOM twice as often as others.[41 46 47] Since the clinicians will be blinded to the allocated group, differences in clinical assessment will not bias the results. If there is a substantial number of incorrect physician diagnosed episodes of AOM (false positives), there results will be biased against the efficacy of xylitol.

Note that our sample size calculation incorporates the incidence of AOM in the TARGet Kids! study population and so it takes into consideration the rate of AOM diagnosis by the same clinicians who will diagnose AOM in these study participants.

Secondary outcomes

The secondary outcome parent-reported URTI episodes will be assessed during monthly phone calls. A challenge in all trials that employ AOM as an outcome is the combined effect of two factors: (1) parents often decide not to seek care when a child has symptoms that may indicate AOM and (2) parents cannot distinguish between AOM and other URTIs because the symptoms are similar. We will address this challenge with our secondary outcome: parent-reported URTIs, a very common and costly (in aggregate) condition in early childhood.[17 48] The previous shorter (2 to 3 month) trials of xylitol found a non-significant trend towards fewer URTI episodes in children receiving xylitol.[32]

A cohort study of children aged 2 months to 12 years receiving care at Toronto primary care sites found that medical consultation was sought in only 56% of episodes of URTI symptoms.[49] This is not surprising given that guidelines recommend against antibiotics for AOM and other URTIs in many cases. As many parents are aware of this recommendation from previous clinic visits, they may decide to treat children with analgesics and antipyretics without seeking care even if they believe the child has an AOM.[50] Thus, information about the total

number of URTI episodes must be obtained directly from parents and caregivers as it will not be found in a patient's medical record even if it includes records from all institutions and clinics. Parents may not diagnose AOM accurately based on symptoms because they overlap substantially with symptoms of URTIs.[51] Irritability and crying are the most common symptoms in AOM and URTI episodes.[52] Forty percent of children *with* AOM do *not* have an earache and 31% do *not* have a fever, [51] while 72% of children *without* AOM exhibit symptoms of AOM (crying, fever or ear ache).[52]

Like previous studies, we will employ structured telephone interviews to assess the number of URTI episodes.[53 54 55] Parents or caregivers will be contacted every month and asked to report the number of URTIs the child has experienced since the last call (or since the beginning of the trial for the first call) using validated questions (*Appendix 1*).[55] We will employ the symptoms in the Canadian Acute Respiratory Illness and Flu (CARIF) scale that has been validated in this population.[56]

The secondary outcome, parent-reported dental caries, will also be assessed during the monthly phone calls. Parents or caregivers will be asked if they have been informed by a dentist or a physician that their child has or has had at least one or more dental caries (*Appendix 1*). This question has been used and validated in several epidemiological studies.[57 58 59 60] The dental caries secondary outcome will be binary (at least one versus none). Those with caries at baseline will be excluded from this analysis but included in all other analyses.

Other measures

Health economics measures will be collected for an economic evaluation. We will compare the cost-effectiveness of the xylitol syrup against the control group using the net benefit regression framework from the perspective of the parents (who will be the payer for the syrup).[61] Costs will include costs incurred to the parents or caregivers such as their usual mode of transportation for attending medical appointments (collected during an extended phone call at the four month call).[61] The parent or caregiver hours of productivity (including employment) lost due to the child's AOM episodes (including, for example, the days the child could not attend daycare) will also be assessed during the monthly calls. The use of net benefit regression allows the economic evaluation to be conducted using regression methods (adjusting for potential confounders). The main outcome of the economic evaluation will be an incremental net benefit of xylitol syrup (in term of cost and number of physician-diagnosed AOM episodes) compared to control. In addition, we will estimate incremental cost-effectiveness ratios (e.g., an incremental cost per one physician-diagnosed AOM episode avoided and an incremental cost per one URTI episode avoided). Statistical uncertainty will be characterized using a 95% confidence interval and cost-effectiveness acceptability curves.[62]

Compliance (reported number of doses given per week) will be assessed during the monthly calls and by tallying the number of returned doses at the end of the study.

Sample size rationale

We used the results of three previous RCTs of xylitol for the prevention of AOM and data from participants in the TARGet Kids! research network to estimate the sample size.

In a chart review of TARGet Kids! research network participants, we found a comparable event rate as the control groups in the trials above: 670 episodes of AOM in 1637 patients (41%) over a three month period (0.14 AOM episodes per patient-month).

Since the data currently available suggest that the AOM rate is about 1.6 episodes per patient-year, we will somewhat conservatively assume a control event rate of 1.5. We will aim to detect a relative risk of 0.8 (i.e. relative risk reduction of 20%) with 80% power and alpha = 0.05 (two-sided). A 20% RRR was chosen based on previous surveys of reasons physicians do not currently recommend xylitol and the RRR used in previous trials. [32 37] The sample size calculations assumed a Poisson distribution for the number of AOM episodes and were based on the asymptotic distribution of the likelihood ratio test statistic. Calculations were performed in *R* (2.15.3) using the *asypow* package and power was confirmed via 10,000 simulations. The required sample size is 236 per group. (Note that while the number of participants is less than one of the previous trials [63], the mean treatment and follow-up period in our study will be longer.) The above calculations take into consideration non-compliance and a loss to follow-up of 10% of participants only completing 50% of the follow-up period. These calculations assume there will be no substantial contamination. While xylitol preparations are commercially available, the dose of xylitol is less than one-tenth the dose found in trials to be effective at preventing AOM. A survey of TARGet Kids! participants showed that xylitol use is rare (< 5%). Siblings of those already enrolled in the trial will be excluded since contamination would be likely if two members of the family are enrolled and allocated to different arms.

We expect to recruit 40 participants per month. Thus sufficient patients will be recruited during two calendar years for the intervention to take place over two winter seasons. A previous RCT in the TARGet Kids! research network with similar inclusion criteria, exclusion criteria and recruitment strategy successfully recruited more than 66 children each month for two years when the network was smaller. [64] Parents of children who are participating in the TARGet Kids! research network's longitudinal study will be approached by research assistants regarding this RCT during routine primary care visits throughout the year. Randomization will take place just before the intervention begins so the small number of patients who are recruited but leave the practice before the intervention period will not be randomized.

We will determine if xylitol is more effective in younger children (24-36 months old versus >36 months old at time of recruitment).

Statistical Analysis

The primary analysis will be performed based on the intention to treat population. The primary outcome will be analyzed with a Poisson regression model. To account for participants who do not complete the entire planned follow-up and slight variations in the observation time for completers, the logarithm of follow-up time will be added as an offset term to the model. The treatment effect, expressed as a rate ratio (relative risk), and 95% confidence interval will be obtained from the model. A secondary analysis will adjust for characteristics with an imbalance between groups at baseline. Patient demographics will be summarized descriptively (e.g., means and SD or median and IQR for continuous variables and frequency and percentages for categorical). Although randomization guarantees balance in the long-run, there is a chance of imbalances in any sample. The demographics will be reviewed for clinically important imbalances that may be adjusted for in a secondary analysis. The secondary outcomes, number of URTI episodes and dental caries, will be analyzed similarly to the primary outcome.

Safety Analysis

A data safety monitoring board is not necessary because xylitol has been demonstrated to be safe in previous trials for the prevention of AOM and dental caries, and the maximum possible

efficacy can be estimated from previous trials. We therefore do not anticipate any reason to stop the trial early.

Xylitol can rarely cause osmotic diarrhea and abdominal discomfort. In previous trials, approximately 1% of children exposed to xylitol experienced diarrhea and slightly less than 1% of children exposed to control substances (e.g., sorbitol) experienced diarrhea (difference not statistically significant).[45] The vast majority of children, including 2-4 year olds, are able to tolerate total daily doses of 45g of xylitol without significant gastrointestinal side effects.[32 35] The maximum total daily dose of xylitol in this trial will be 10g per day.

In previous trials, a total of more than 1000 children were exposed to various formulations of xylitol or control substances and there were no reported episodes of choking or aspiration. The control intervention is the provision of sorbitol syrup which can cause diarrhea but at similar rates as xylitol.[65] Despite this, the consent form will alert parents to the potential of diarrhea.

Adverse events

All adverse events will be reported to the Hospital for Sick Children or St. Michael's Hospital Research Ethics Board according to their adverse event reporting requirements. All adverse drug reactions to the study medication will be reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. In the latter case, a follow-up report must be filed within 8 calendar days. Serious adverse events and serious unexpected adverse events will be reported to the Natural and Non-prescription Health Products Directorate (NNHPD) in an expedited manner.

To maintain the overall quality of the trial, unblinding will only be performed in exceptional circumstances when knowledge of the actual treatment is essential for management of the patient. If unblinding is deemed to be necessary by the investigator, the investigator will contact the coordinating center by telephone to ascertain the allocation group and communicate this to the participant's clinician and caregiver. The research staff will not be informed of the allocation group. Unblinding will not necessarily be a reason for discontinuation or exclusion from the analysis.

Management

The Applied Health Research Centre (AHRC) will be responsible for trial data coordination, database development, data management and statistical analysis. Study data and patient surveys will be entered and maintained on a secure password protected database developed using REDCap® (www.project-redcap.org) and will be accessible via the internet for data entry purposes. Quality and completeness of data entry will be reviewed as soon as possible after data entry, within 5 business days of data entry for the first 5 participants randomized at each site, and within 15 days of data entry thereafter. Corrections or changes in REDCap® are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel.

Patient and Public Involvement

Patients were not directly involved in the development of the research question or the design of the study. A written summary of the study results will be sent to participants by email or by mail. The burden of the intervention on patients was not assessed prior to the start of the trial.

Ethics and dissemination

The *TARGet Kids!* research platform has been approved by the Research Ethics Board at the Hospital for Sick Children and St Michael's Hospital, as well as the other affiliated sites. Ethics approval for this study has been obtained for all participating sites. Results of the study will be submitted for publication to a peer-reviewed journal and will be discussed policy and decision makers.

SUMMARY

In summary, AOM, URTIs and dental caries are common and costly conditions in young children that might be prevented by regular xylitol use. Existing evidence indicates clinical equipoise on the efficacy of xylitol syrup in preventing AOM, URTIs and dental caries in preschool aged children. Evidence from previous long-term trials of xylitol for the prevention of dental caries has demonstrated that the intervention is well tolerated and feasible in this age group. The TARGet Kids! research network has a demonstrated record of conducting RCTs in young children and its existing research infrastructure will be mobilized to ensure that this trial will be completed efficiently and on schedule.

AOM and URTIs are commonly viewed as unavoidable during early childhood. This trial has the potential to transform the approach to these three common conditions.

Author Contributions

The following authors contributed substantially to conception and the design of the protocol: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
The following authors drafted the manuscript: NP and FB.
The following authors revised the manuscript critically for important intellectual content: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
The following authors approved the final manuscript: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, PP.
The following authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: NP, AL, AA, CB, JH, WI, JM, MM, KT, CA, DM, CK, FB, and PP.
Members of the TARGet Kids! Collaboration contribute to data collection and provide general input on research directions.

Funding

The study is funded by the Canadian Institutes of Health Research (CIHR). NP received salary support from a CIHR RCT training grant and from a PSI Graham Farquharson Knowledge Translation Fellowship.There was no role of the manufacturer in the concept, design, implementation, data collection and analysis and permission to publish. The products were purchased from the manufacturer using public research funding.

Competing interests

There are no competing interests.PP reports receiving the following grants unrelated to this study: a grant from Hospital for Sick Children Foundation during the conduct of the study; a

grant from Canadian Institutes of Health Research (FRN # 115059) for an ongoing investigator-initiated trial of iron deficiency in young children, for which Mead Johnson Nutrition provides non-financial support (Fer-In-Sol® liquid iron supplement). These agencies had no role in the design, collection, analyses or interpretation of the results of this study or in the preparation, review, or approval of the manuscript.

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Figure Legend

Figure 1. Timeline for intervention and follow-up.

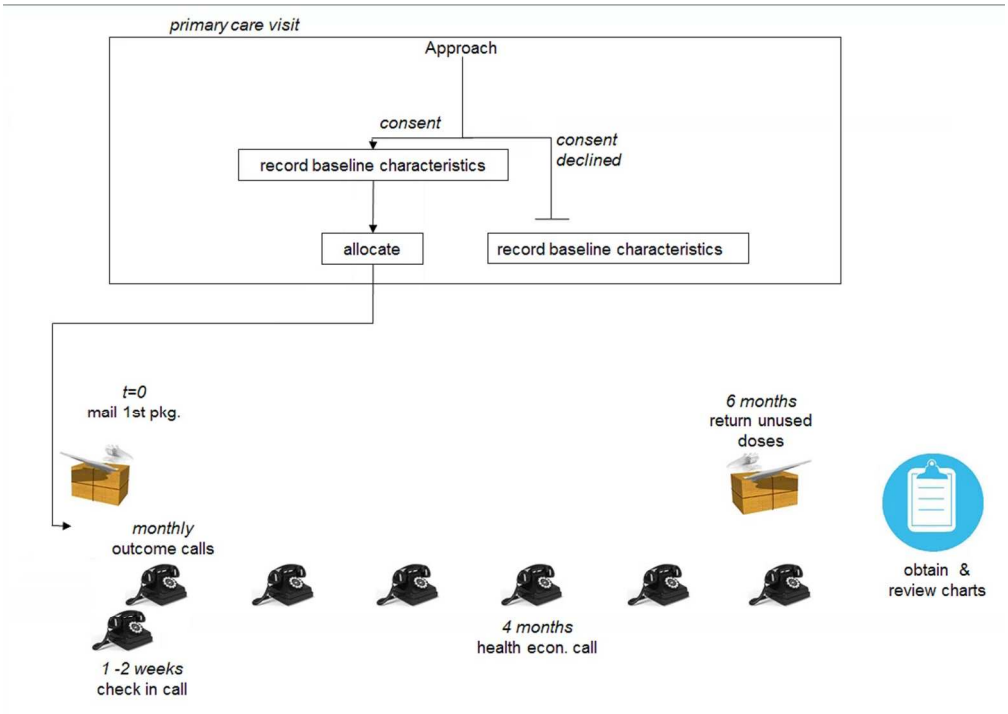

Figure 1. Timeline for intervention and follow up.

169x120mm (300 x 300 DPI)

Appendix 1. **Outcome determinations**

Primary outcome: number of episodes of physician diagnosed AOM

Information will be obtained from the chart review at the end of the study period.

(1) Does chart entry included diagnosis or assessment of "AOM" or "acute otitis media"? [Yes or No]
(2) Does a chart entry within 48 hours record physical examination findings of the tympanic membrane? [Yes or No]

If, and only if, answers to both question are "Yes", add one to total number of AOM episodes. Proceed to review the next chart entry until all chart entries during the study period have been reviewed.

Secondary outcome: number of parent reported URTIs

Information will be obtained via monthly telephone calls.

(1) Has the child had any of the symptoms for two consecutive days?

- stuffy nose or congestion or rhinorrhea
- cough
- sore throat
- wheeze
- shortness of breath

If the child has had any of the above symptoms for two consecutive days, add one to the total number of parent reported URTI episodes.

(2) Was the child well (symptom free) for two consecutive days during the illness?

If the child was well for two consecutive days, add another one to the total number of parent reported URTI episodes (as this is a separate URTI) and repeat step (2) if needed.

Secondary outcome: parent reported dental caries (binary)

Information will be obtained via monthly telephone calls.

Have the parents or caregivers ever been told by a dentist or a physician that the child has or has had:

- dental caries
- multiple dental caries
- early childhood caries or ECC

If the parents or caregivers have been told that the child has any of the above record the child as having dental caries (and in this case the parents and caregivers do not need to be asked about this on subsequent calls).

Note that this outcome will also be assessed at baseline so that children with dental caries at baseline can be excluded from the dental caries analysis. This is because the outcome is binary (caries or not). Based on information available about children in the TARGet Kids! network, we expect 5-8 % of children to have caries at baseline and to be excluded from the dental caries analysis. Of course, all children will be included in the primary AOM analysis (and in the URTI analysis) regardless of whether they have had dental caries.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5,10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-4
	6b	Explanation for choice of comparators	2-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5,10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	2,9,
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4-5,9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	2, 5, 9, 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10-11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10-11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6,10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10,11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.