

Xylitol Pediatric Topical Oral Syrup to Prevent Dental Caries

A Double-blind Randomized Clinical Trial of Efficacy

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Objectives: To evaluate the effectiveness of a xylitol pediatric topical oral syrup to reduce the incidence of dental caries among very young children and to evaluate the effect of xylitol in reducing acute otitis media in a subsequent study.

Design: Double-blind randomized controlled trial.

Setting: Communities in the Republic of the Marshall Islands.

Participants: One hundred eight children aged 9 to 15 months were screened, and 100 were enrolled.

Intervention: Children were randomized to receive xylitol topical oral syrup (administered by their parents) twice a day (2 xylitol [4.00-g] doses and 1 sorbitol dose) (Xyl-2× group) or thrice per day (3 xylitol [2.67-g] doses) (Xyl-3× group) vs a control syrup (1 xylitol [2.67-g] dose and 2 sorbitol doses) (control group).

Main Outcome Measures: The primary outcome end point of the study was the number of decayed primary teeth. A secondary outcome end point was the incidence of acute otitis media for reporting in a subsequent report.

Results: Ninety-four children (mean [SD] age, 15.0 [2.7] months at randomization) with at least 1 follow-up examination were included in the intent-to-treat analysis. The mean (SD) follow-up period was 10.5 (2.2) months. Fifteen of 29 of the children in the control group (51.7%) had tooth decay compared with 13 of 32 children in the Xyl-3× group (40.6%) and eight of 33 children in the Xyl-2× group (24.2%). The mean (SD) numbers of decayed teeth were 1.9 (2.4) in the control group, 1.0 (1.4) in the Xyl-3× group, and 0.6 (1.1) in the Xyl-2× group. Compared with the control group, there were significantly fewer decayed teeth in the Xyl-2× group (relative risk, 0.30; 95% confidence interval, 0.13-0.66; $P = .003$) and in the Xyl-3× group (0.50; 0.26-0.96; $P = .04$). No statistical difference was noted between the 2 xylitol treatment groups ($P = .22$).

Conclusion: Xylitol oral syrup administered topically 2 or 3 times daily at a total daily dose of 8 g was effective in preventing early childhood caries.

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EARLY CHILDHOOD CARIES (ECC) (baby bottle tooth decay or nursing caries) are characterized by severe tooth decay early in life. The Surgeon General's *Oral Health in America* report¹ sounded the alarm that tooth decay is the most prevalent childhood chronic disease and is 5 times more common than asthma. The *Healthy People 2010 Mid-course Review*² noted that the prevalence of ECC is rising. Poor children experience rates twice as high as those of their more affluent peers, and their disease is more likely to be untreated.¹ Native American,³ Alaskan Native,⁴ Hawaiian Native, and Pacific Island children⁵ have the highest rates of

ECC, and few have adequate access to dental care. Poor oral health affects diet and nutrition and significantly diminishes quality of life.¹ However, tooth decay is a disease that is largely preventable.⁶

*For editorial comment
see page 667*

Addressing childhood oral health has become a primary initiative for the American Academy of Pediatrics and the American Academy of Pediatric Dentistry. Similarly, the US Department of Health and Human Services' *National Call to Action to Promote Oral Health*⁷ urges interdisciplinary training of health professional personnel in pro-

SETTING

The study was conducted in the Delap and Laura districts of Majuro Atoll, Republic of the Marshall Islands. Early childhood caries is a serious health care problem in the Republic of the Marshall Islands. The caries rate is 2 to 3 times that of the typical US mainland community. The average child entering Head Start centers at age 5 years has 6.8 untreated cavities, and more than 90% of children have at least 1 decayed tooth.¹³ Fifty-one percent of 2-year-olds have at least 1 decayed tooth.¹⁴ Children drink water from rain catchments that do not contain appreciable fluoride, and supplemental fluoride or topical fluoride treatments have been unavailable for toddlers. Diets are full of cheap high-energy foods. Breastfeeding is encouraged to age 1 year, but it is common practice to give infants and toddlers bottles containing sugar water or canned fruit drinks.

EXPERIMENTAL DESIGN

We compared 2 active treatment groups, each receiving xylitol syrup (8 g/d) orally divided into 2 doses (4.00 g of xylitol per dose) (Xyl-2× group) or 3 doses (2.67 g of xylitol per dose) (Xyl-3× group) vs a control group (a single 2.67-g dose of xylitol). The internal review committee appointed by the Secretary of Health, Republic of the Marshall Islands, required that the control group receive a small amount of xylitol, although it was understood that a placebo control would be more ideal and that evidence does not suggest a single dose of xylitol (2.67 g/d) would have an effect.^{15,16}

The study was controlled for frequency of daily syrup use, whereby all groups received 3 syrup doses per day for 12 months. Groups taking xylitol syrup fewer than 3 times/d were given sorbitol syrup doses as follows: the control group received 1 xylitol (2.67-g) dose and 2 sorbitol (2.00-g) doses, the Xyl-2× group received 2 xylitol (4.00 g) doses and 1 sorbitol (2.00-g) dose, and the Xyl-3× group received 3 xylitol (2.67-g) doses (**Table 1**). Sorbitol is a polyol sweetener that is noncarcinogenic but has not been demonstrated to have active protective effects against caries.¹⁷ All families received oral health education and free health care during the study period. We tested the hypothesis that xylitol syrup (8 g/d) given in 2 or 3 divided doses would reduce the incidence of cavitated carious lesions during primary tooth eruption compared with a control group.

INTERVENTION

Each syrup dose contained 8 mL of syrup. **Table 2** gives the ingredients for each formulation. The syrups were matched for color, taste, and viscosity. The syrups were produced and packaged in a US Food and Drug Administration-compliant facility (Unicep, Sandpoint, Idaho) and were gamma sterilized at a dose of 30 to 50 kGy (Sterigenics, Hayward, California). The syrups were produced in 3 batches during the study period to minimize storage. Each batch was periodically tested to monitor for common food product microbial contamination.

HUMAN SUBJECTS

The internal review committee of the Ministry of Health and the Secretary of Health, Republic of the Marshall Islands approved the study. Approval was also obtained from the University of Washington Institutional Review Board, Seattle. Informed consent of the parents was obtained.

MEASURES

The primary outcome end point of the study was the number of decayed primary teeth, defined as cavitated carious lesions.

Table 1. Topical Oral Syrups Received by Study Group

| Topic Oral Syrup | Xyl-3× Group (n=32) | Xyl-2× Group (n=33) | Control Group (n=29) |
|------------------------|------------------------|------------------------|-------------------------|
| Xylitol (4.00 g/dose) | ... | 2 Doses | ... |
| Xylitol (2.67 g/dose) | 3 Doses | ... | 1 Dose |
| Sorbitol (2.00 g/dose) | ... | 1 Dose | 2 Doses |
| Total daily dose, g | | | |
| Xylitol | 8 | 8 | 2.67 |
| Polyol | 8 | 10 | 6.67 |

Abbreviation: Ellipsis, not applicable.

viding oral health education and preventive services to patients. Multimodality and interdisciplinary (eg, medical, dental, and behavioral) approaches to caries prevention in children are being aggressively sought. Administration of xylitol, a naturally occurring polyol sweetener, is among these modalities, as well as the use of dental sealant agents and topical fluorides and the promulgation of oral health education and dental risk assessment.

Several bacterial species have been implicated in the cause of tooth decay. Foremost are mutans streptococci, a group of gram-positive microorganisms that represent a small proportion of the oral flora but are damaging through their ability to colonize tooth surface and to produce lactic acid that demineralizes tooth enamel leading to cavitation.⁸ Mutans streptococci that are implicated in human tooth decay include *Streptococcus mutans* and *Streptococcus sobrinus*.

Approved by the US Food and Drug Administration for use in food since 1963, xylitol has been shown to be an effective tooth decay preventive agent.⁹ Xylitol exerts selective antibacterial-type actions against mutans streptococci by disrupting glucose cell-wall transport and intracellular glycolysis, inhibiting pathogen growth.¹⁰ It also reduces the adhesiveness of mutans streptococci to tooth biofilms.¹¹ However, the effectiveness of xylitol is dependent on consumption of a minimum daily frequency, an amount that is not found in foods or in most xylitol-containing products.¹²

Clinical investigations of xylitol have almost exclusively involved chewing gum or lozenges and have evaluated school-aged children and tooth decay in permanent teeth.¹² An effective xylitol vehicle that is acceptable and safe for toddlers has been elusive. To address this gap, we conducted a double-blind randomized controlled trial using a xylitol topical oral syrup during primary tooth eruption in toddlers.

METHODS

ENROLLMENT CRITERIA

Children aged 9 to 15 months were eligible. Children were excluded if they (1) were in the lower 10th percentile of US standard weight and height, (2) had a history of esophageal or digestive disease, (3) had congenital craniofacial malformation, or (4) had a history of adenoidectomy, tympanostomy tubes, or tympanic membrane perforations. Exclusion criterion 4 was included because a secondary aim of the study was to evaluate the effect of xylitol in reducing acute otitis media.

Table 2. Ingredients of Xylitol and Sorbitol Topical Oral Syrups

| Ingredient | Function | Syrup Formulation, % by Weight | | |
|--|---------------------|--------------------------------|--------------------------|---------------------------|
| | | Xylitol (4.00 g/Dose) | Xylitol (2.67 g/Dose) | Sorbitol (2.00 g/Dose) |
| Water, <i>US Pharmacopeia</i> purified | | 46.90 | 62.37 | 69.84 |
| Xylitol | Active sweetener | 50.00 | 33.00 | 0.00 |
| Sorbitol | Nonactive sweetener | 0.00 | 0.00 | 25.00 |
| Sodium carboxymethylcellulose | Thickening agent | 2.50 | 4.00 | 4.50 |
| Sucralose | Intense sweetener | 0.00 | 0.28 | 0.06 |
| Flavor, strawberry | Flavor | 0.40 | 0.40 | 0.40 |
| Color, carmine 50% | Color | 0.10 | 0.10 | 0.10 |
| Methylparaben | Preservative | 0.10 | 0.10 | 0.10 |

A secondary outcome end point was the incidence of acute otitis media for reporting in a subsequent report. A single dental examiner (O.K.T.) was trained according to the World Health Organization diagnostic protocol¹⁸ and examined the children's teeth visually using a disposable dental mirror and an artificial light. Compared with another examiner (P.M.), the study examiner demonstrated excellent reliability for caries diagnosis (interrater correlation coefficient, 1.00 at the prestudy dental examination and 0.96 at the midstudy examination). The examiner was always blinded to study group assignment.

PROCEDURES

The enrollment period extended from April 1, 2006, to August 31, 2006. After enrollment, children began a 5-week nontreatment observation period during which no syrup was given and children were visited by outreach workers at least twice a week to record loose stools or diarrhea symptoms (which are the most common adverse effects of consumption of polyol sweeteners such as xylitol and sorbitol). This was followed by a 3-week run-in period during which the children were given 1 dose per day of xylitol (2.67 g) for the first week. The dosage was increased by 1 dose each week to a maximum of 3 doses per day. This period was to allow the children's digestive systems to adjust to the polyol and to minimize unwanted adverse effects. A 4-week washout period followed to ensure that the xylitol was cleared from the body before initiation of the syrup randomization. The 12-month syrup randomization period began in August 2006, and the last participant completed follow-up in January 2008. Parents and outreach workers monitored children for adverse effects during all study periods. Loose stools and diarrhea episodes were recorded by the outreach workers during home visits.

Syrup doses were prepackaged for distribution in daily bags (3 doses per bag) labeled with identification numbers and the day of the week and were placed in larger bags labeled with the week number (range, 1-52). Workers who were not part of the study staff packaged the syrups according to a schematic.

Locally hired outreach workers completed training and certification to conduct study protocols. Outreach workers provided education about oral health and polyol adverse effects and trained and coached parents and caretakers in administering syrup topically to the teeth of children. A ratio of 1 outreach worker per 10 to 15 families was maintained throughout the study. The outreach workers visited participating families at least twice a week from enrollment through the early part of the syrup randomization period and then at least once a week thereafter to encourage adherence and to develop strategies with families to resolve challenges. Parents kept calendar logs to record administration of the syrup. Parents were also instructed to keep all used and unused syrup doses in their prepacked pack-

ages for collection, recording, and proper disposal by the outreach workers.

As incentives throughout the study, families received toys for their children and gift certificates that were good for use at local grocery stores. The incentives were chosen with advice from a local advisory committee. Mothers and children were also given T-shirts with the study logo, and families periodically received toothpaste and toothbrushes for other members of the family. Twice during the study, parents and children were invited to community parties, initially to receive a progress report on the study and then to hear the results.

RANDOMIZATION

At enrollment, subjects were given identification numbers that had been randomly assigned to study groups by a statistician using block randomization and the sample function of commercially available statistical software (S-PLUS; Insightful Corporation, Seattle, Washington). Block sizes of 30 and 15 were used for the Laura district, and block sizes of 36 and 18 were used for the Delap district. Except for the statistician, all study team members were blinded until study completion.

STATISTICAL ANALYSIS

We estimated that the rate of decayed cavitated lesions for children at 24 months of age was 60% in the control group and 30% in the xylitol-treated groups. Based on 80% power to detect a significant difference (2-sided $P = .05$) between the xylitol-treated and control groups, 32 children were required for each study group. To account for an expected 10% attrition, we planned to enroll 36 children per group.

Poisson regression analysis was used to compare the numbers of decayed teeth among the 3 study groups and included the natural logarithm of the follow-up time from the baseline dental examination following the syrup randomization protocol until the last recorded follow-up examination as an offset term. Generalized estimating equations with a robust variance estimator were used to fit the Poisson regression model to account for overdispersion owing to multiple teeth per subject.^{19,20} Additional Poisson regression analyses were performed that adjusted for study district, age at randomization, and number of teeth at the last follow-up examination. The prevented fraction (PF) (the proportion of disease occurrence in a population averted owing to a protective risk factor or a public health intervention [where ARR indicates absolute risk reduction]) and the number needed to treat (NNT) were calculated as follows: $ARR = \text{control event rate} - \text{experimental event rate}$. $NNT = 1/ARR + PF$, where PF equals $\{[(\text{incidence rate of test group} - \text{incidence rate of comparison group})]/\text{incidence rate}$

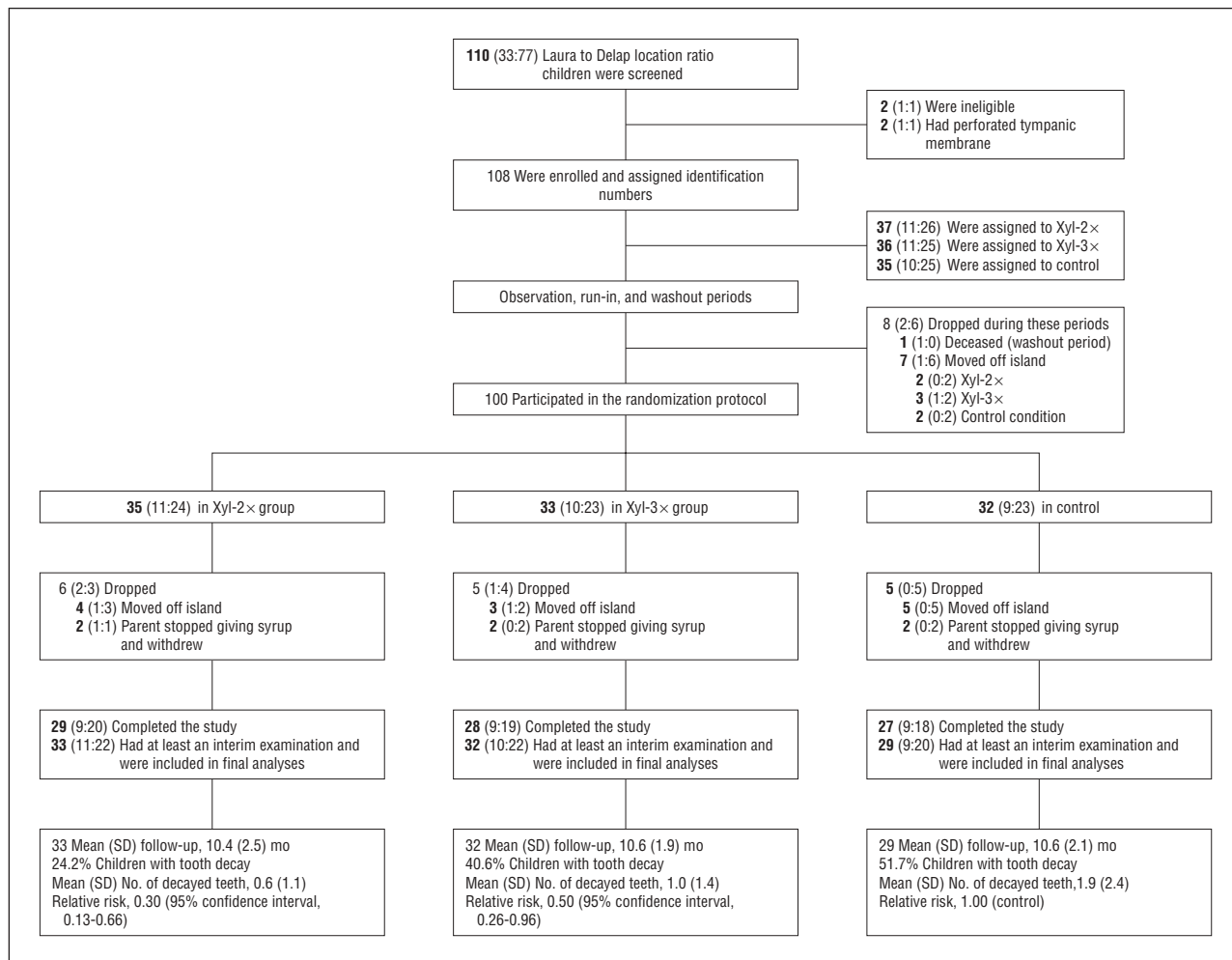


Figure. Enrollment, prerandomization and postrandomization protocols, follow-up, and outcomes in the xylitol pediatric topical oral syrup trial in the Republic of the Marshall Islands. For an explanation of the groups, see the “Experimental Design” subsection of the “Methods” section.

Table 3. Characteristics of 94 Children Included in the Final Analysis^a

| Characteristic | Xyl-2× Group (n=33) | Xyl-3× Group (n=32) | Control Group (n=29) | Overall (N=94) |
|--|---------------------|---------------------|----------------------|------------------|
| Ratio of Laura to Delap location | 11:22 | 10:22 | 9:20 | 30:64 |
| Female sex, No. (%) | 19 (57.6) | 18 (56.3) | 14 (48.3) | 51 (54.3) |
| Age at randomization, mean (SD), mo | 15.9 (2.6) | 13.7 (2.4) | 15.6 (2.7) | 15.0 (2.7) |
| Follow-up time, mean (SD), mo ^b | 10.4 (2.5) | 10.6 (1.9) | 10.6 (2.1) | 10.5 (2.2) |

^aNinety-four children had at least 1 follow-up examination during the study period and were included in the intent-to-treat analysis. Of these, 84 completed all follow-up examinations, and 10 dropped out after their interim examination. For an explanation of the groups, see the “Experimental Design” subsection of the “Methods” section.

^bThe syrup randomization follow-up period was 12 months. The mean follow-up time was reduced because 10 children dropped out after their interim examination.

of test group × 100}. Data were analyzed using statistical software (SAS version 9.1.3; SAS Institute, Cary, North Carolina).

RESULTS

Of 108 children enrolled (32 in Laura and 76 in Delap), 8 children dropped out during the observation, run-in, or washout periods, leaving 100 children who participated in the syrup randomization protocol.

Of these, 94 had at least 1 follow-up caries assessment (interim or final examination) and were included in the final analysis; 84 completed the study (**Figure**). **Table 3** gives the characteristics of 94 children included in the final analysis by study group. Subjects in the Xyl-3× group were about 2 months younger than subjects in the Xyl-2× and control groups at initiation of the randomization protocol ($P=.002$, analysis of variance). The mean syrup exposure time was

Table 4. Percentage With Tooth Decay and Number of Decayed Teeth Among 94 Children Included in the Final Analysis

| Group ^a | % With Decayed Teeth | No. of Teeth at the Last Examination, Mean (SD) | No. of Decayed Teeth, Mean (SD) [Maximum] | Relative Risk (95% Confidence Interval) ^b |
|--------------------|----------------------|---|---|--|
| Control (n=29) | 51.7 | 17.2 (2.5) | 1.9 (2.4) [8] | 1 [Reference] |
| Xyl-2× (n=33) | 24.2 | 17.2 (2.9) | 0.6 (1.1) [4] | 0.30 (0.13-0.66) |
| Xyl-3× (n=32) | 40.6 | 16.6 (3.2) | 1.0 (1.4) [6] | 0.50 (0.26-0.96) |

^aFor an explanation of the groups, see the “Experimental Design” subsection of the “Methods” section.

^bNonadjusted analysis. Generalized estimating equations with a robust variance estimator were used to fit the Poisson regression analysis to account for overdispersion owing to multiple teeth per subject.

similar among the groups ($P=.94$, analysis of variance). The syrup compliance rate during the study exceeded 90% for each group based on actual counts of daily consumed and unconsumed syrup doses. Results of periodic syrup microbial testing showed no changes compared with those of initial production testing.

CARIES HYPOTHESIS TEST

Table 4 gives the caries outcomes after exposure to the intervention for a mean of 10.5 months: 15 of 29 in the control group (51.7%) vs 13 of 32 children in the Xyl-3× group (40.6%) and 8 of 33 in the Xyl-2× group (24.2%) had tooth decay. No teeth were missing or lost to tooth decay. Compared with the control group, there were significantly fewer decayed teeth in the Xyl-2× group (relative risk, 0.30; 95% confidence interval, 0.13-0.66; $P=.003$) and in the Xyl-3× group (relative risk, 0.50; 95% confidence interval, 0.26-0.96; $P=.04$). No significant difference was noted between the 2 xylitol treatment groups ($P=.22$). The results after controlling for study site, age at entry, and the total number of teeth a child had at the last follow-up examination were similar.

PREVENTED FRACTION AND NNT

The incidence rates (unadjusted model) for decayed primary teeth were as follows: 2.20 decayed primary teeth per year for the control group, 0.66 for the Xyl-2× group, and 1.10 for the Xyl-3× group.

The prevented fraction ranged from 50% ($100\%[2.20 - 1.10]/2.20$) for the Xyl-3× group vs the control group to 70% ($100\%[2.20 - 0.66]/2.20$) for the Xyl-2× group vs the control group. The NNT ranged from 10 ($1/(51.7\% - 40.6\%)$) for the Xyl-3× group vs the control group to 4 ($1/(51.7\% - 24.2\%)$) for the Xyl-2× group vs the control group.

ADVERSE EFFECTS

The proportions of children who experienced loose stools or diarrhea during the run-in (10.0%) and washout (8.7%) periods were less than the proportion during the observation period (18.5%) immediately after enrollment. Adverse effects such as loose stools or diarrhea during the syrup randomization period (11.3% overall) occurred at similar rates across the 3 groups (10.6% for the Xyl-3× group, 11.7% for the Xyl-2× group, and 11.4% for the control group) and were similar to those before syrup ran-

domization. The children experienced no serious adverse events during the syrup randomization protocol.

COMMENT

Children with ECC are 3 times more likely than children without ECC to develop tooth decay in their permanent teeth.²¹ Childhood tooth decay has a negative effect on oral health-related quality of life,²² which improves after dental treatment.^{23,24} Minority group and poor children in the United States and in US-associated states and territories in the Pacific region have high rates of ECC, and access to care is limited and has not improved with enhanced Medicaid coverage under the Early and Periodic Screening, Diagnostic, and Treatment program.²⁵ In this study, 51.7% of the control group children experienced tooth decay before their third birthday. This rate is extraordinary but is consistent with a previous rate reported by Tut and Milgrom.¹⁴

Our results suggest that exposure to xylitol (8 g/d) in a twice-daily topical oral syrup during primary tooth eruption could prevent up to 70% of decayed teeth. Dividing the 8 g into 3 doses did not increase the effectiveness of the treatment. These results provide evidence for the first time (to our knowledge) that xylitol is effective for the prevention of decay in primary teeth of toddlers.

Some authors recommend that xylitol exposure of 5 to 10 g divided into at least 3 daily periods of consumption is needed for a therapeutic effect.^{9,11} A previous study²⁶ evaluated the response of mutans streptococci in plaque (a surrogate marker for tooth decay) to varying frequencies of xylitol chewing gum consumption for 5 weeks at a standard daily dose (10.3 g/d) among adults. The study found a linear reduction in mutans streptococci with increasing frequency (range, 0-5 times per day) of xylitol chewing gum consumption, but the reduction with twice-daily chewing did not reach statistical significance.²⁶ Because of inherent weaknesses, a short follow-up period, and the use of a surrogate marker for tooth decay, the findings of the study may not withstand comparison with those of a more rigorous, long, randomized controlled trial using tooth decay as the end point. Moreover, the acts of chewing and sucking are potent stimulators of salivary flow, which enhances the clearance of food debris, oral bacteria, and acid-buffering capacity, benefiting the remineralization of enamel and protecting it from tooth decay.¹⁷ Chewing gum and lozenges studies in which control subjects also used gum or lozenges may underestimate the re-

duction of mutans streptococci and tooth decay by xylitol. Given the absence of potential effects attributable to chewing or sucking that are inherent in xylitol chewing gum and lozenges studies, the results herein more accurately reflect the effects of xylitol use. Finally, xylitol administered during tooth eruption and colonization is suggested to have maximal protective effects.²⁰

The greater reduction in dental caries seen in the Xyl-2× group compared with the Xyl-3× group begs the question of synergistic effects between xylitol and sorbitol. However, the observed difference between the 2 study groups was not statistically significant. Furthermore, a 40-month chewing gum study²⁷ in Belize did not demonstrate support for synergistic effects between xylitol and sorbitol. At similar total daily doses of polyol, a xylitol-only regimen was most effective in caries reduction, followed by xylitol plus sorbitol and then by sorbitol alone, compared with a control group receiving no chewing gum.

The study had a low dropout rate (16 of 100 [16%]), and parents demonstrated high compliance to the study protocol and syrup administration. Children tolerated the polyols daily dose of 6 to 10 g and experienced few and minor adverse effects of laxation. Adverse effect rates were comparable between experimental and control groups and between the run-in and randomized periods. This is in agreement with a recent study²⁸ finding that xylitol solutions at daily doses of 5 to 7.5 g were well tolerated by toddlers aged 6 to 36 months.

Concern has been expressed about using sweet substances for the prevention of ECC. The literature on infant and toddler foods and on taste preference is sparse but suggests that infants have an innate predilection for sweet taste.²⁹ However, various experiential factors influence flavor preferences during childhood.³⁰⁻³² Consumption of sweet products has been associated with urbanization and with lower socioeconomic status.^{32,33} Nevertheless, there is no published evidence (to our knowledge) that long-term consumption of specific sweet foods during early childhood increases predilection for sweets in general as a juvenile or as an adult. Similarly, we are aware of no published literature about long-term xylitol exposure and future preference for sweet foods. Xylitol-based products have been widely available and consumed in Finland and northern Europe for several decades, without reports of undesirable effects in later years.²⁶

Young and colleagues³⁴ argued that a multimodality approach that includes antimicrobial therapy, professionally administered topical fluoride agents, and fluoridated water should be used wherever possible for the prevention of tooth decay. The prevented fraction in this study ranged from 50% to 70% for the xylitol treatment groups. The NNT ranged from 10 to 4 to prevent a child from developing tooth decay. These findings provide support for the use of xylitol syrup along with fluoride drugs, particularly for high-risk populations. The results also support the position of the American Academy of Pediatric Dentistry³⁵ and of a National Institutes of Health consensus statement³⁶ that xylitol is an important tool for the prevention of dental caries. More work is needed to develop vehicles and strategies for the public health application of xylitol. In populations with high rates of tooth decay, xylitol interventions are likely to be cost-effective.

In conclusion, this study is the first (to our knowledge) to demonstrate that xylitol topical oral syrup (8 g/d) divided into 2 or 3 doses given during primary tooth eruption in children aged 15 to 25 months reduces tooth decay. Furthermore, up to 70% of decayed teeth could be prevented by xylitol treatment in this setting.

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Additional Information: This was a special study setting, and the circumstances deserve to be recorded herein. The Republic of the Marshall Islands was previously a protectorate of the United States following World War II. Before independence, the United States conducted nuclear testing in the islands, causing adverse effects on the population³⁷ and resulting in distrust of any research performed by mainlanders.³⁸ This study was the first controlled trial that has been permitted among children. Special conditions were placed on the Ministry of Health and on the investigators regarding ethical conduct. Extensive debate went on before approval of the study, and community involvement and openness were stressed throughout. The study results were reported back to the communities and to the Ministry of Health, and considerable technical assistance was provided to the Republic of the Marshall Islands Dental Department to assist in meeting the excessive burdens of tooth decay, periodontal or gum disease, and oral cancer. As a result, efforts are under way to reduce the levels of oral disease in this population, including cooperative studies addressing tooth decay and periodontal disease in residents with uncontrolled diabetes mellitus, which is also common. This study may inspire collaborative research among other racially/ethnically diverse communities in the United States and elsewhere in which distrust regarding studies performed by outsiders continues to be high.

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Call for Papers

The *Archives* will publish a "rolling theme issue" this year on palliative care, dying, and bereavement. We are interested in original articles, narrative and systematic reviews, and commentaries that will add to the scientific knowledge about these topics. Such articles might include observational longitudinal studies such as the effects of loss of a family member on children and adolescents; clinical trials examining specific interventions or evaluating different systems of delivering palliative, hospice, or bereavement care; and ethical analyses regarding how we decide on and enact the goals and limits of medical therapy.

Our intent is to bring these issues to the forefront of pediatrics and adolescent medicine, just as they are in the minds of those children and families who are confronted with such loss. We hope the attention of the *Archives* will advance science and provide help to the physicians dealing with these issues on behalf of their patients and families.

This call for papers will be an ongoing one, and we intend to publish articles on this topic throughout the year as the manuscripts are submitted and accepted. For specific guidelines on manuscript preparation and submission, please consult the author instructions on our Web site at www.archpediatrics.com. Authors should indicate in their cover letter that the manuscript is to be considered for this theme.