UNIVERSITY OF WASHINGTON

Dental Public Health Sciences
School of Dentistry

January 15, 2009

Ms. Jackie Whitaker (Telephone 301-443-3893)
Lead Grants Management Specialist
Division of Grants Management Operations
5600 Fishers Lane, Room 11A-16
Rockville, MD 20857

RE: MCH Research Program
Grant No. R40MC03622

Dear Ms. Whitaker:

Appended is the final report of the above referenced grant. An electronic copy has been sent to the project officer.

Sincerely,

Peter Milgrom, DDS
Professor of Dental Public Health Sciences
Director, Northwest Center to Reduce Oral Health Disparities

Health Sciences Center Suite B509, Box 357475 Seattle, Washington 98195-7475 (206) 543-2034 FAX: (206) 685-4258

FINAL COMPREHENSIVE REPORT
THE MATERNAL AND CHILD HEALTH RESEARCH PROGRAM

Project title: " Xylitol for Acute Otitis Media (AOM) and Early Childhood Caries (ECC)"
PI: Peter Milgrom, DDS and Project Director: Kiet A. Ly, MD, MPH, University of Washington; Local Project Director: Ohnmar K. Tut, BDS, Preventive Dental Services, Ministry of Health, Republic of the Marshall Islands.

I. INTRODUCTION

IA. Nature of the Research Problem

Acute Otitis Media (AOM) and Early Childhood Caries (ECC) are two of the most common diseases in children and disproportionately affect the poor and ethnic minorities. Billions of dollars in direct and indirect costs are spent each year providing treatment and dealing with the consequences of these two highly prevalent but preventable diseases. A large part of these expenditures are by the Federal and State governments through Medicaid. Reductions in both diseases are primary objectives of Healthy People 2010.

Xylitol is a safe, naturally occurring sugar that is approved for use in the U.S. and many other countries. There is evidence that adding xylitol to the diet reduces the incidence of both AOM and ECC. However, research is needed to enhance current knowledge with the aim of developing and instituting preventive health programs using xylitol to improve child health.

IB. Purpose and Scope of the Investigation

The Primary Objective was to establish the feasibility of using orally administered xylitol syrup to reduce the incidence of AOM and ECC in toddlers among minority children in poor communities. **The Specific Aim** was to conduct a randomized control clinical trial to verify the protective effect of orally administered xylitol syrup on AOM and ECC in children in the first two years of life. Additionally, the study sought to determine if a xylitol syrup regimen of five applications per day, as shown to be effective in preventing AOM (Uhari, Kontiokari et al. 1998), could be reduced to a more manageable and practical use by parents for their children. The ultimate goal is to design an intervention that is feasible as part of a public health prevention program to reduce AOM and ECC in toddlers.

IC. Nature of the Findings

This was the first study to evaluate the effectiveness of xylitol in reducing ECC at first primary tooth eruption and reducing AOM among children two years of age and younger. Positive findings and demonstration of feasibility can lead to the development of community based public health program using xylitol syrup for the prevention of ECC and AOM among poor and ethnic minority children, the populations of interest to HRSA/MCHB.

II. REVIEW OF THE LITERATURE

Early Childhood Caries is a transmissible bacterial disease resulting in the destruction of the primary teeth beginning immediately after the eruption of the teeth around 12 months of age (Milgrom, Riedy et al. 2000). It occurs worldwide, especially among disadvantaged children. The prevalence of EEC in the mainland U.S. ranges from 11% to 72% with the higher rate more commonly found among minority and disadvantaged children (Berkowitz 2003). The Surgeon General's Oral Health in America report states, "dental caries (tooth decay) is the single most common chronic childhood disease…there are striking disparities in dental disease by income. Poor children suffer twice as much dental caries as their more affluent peers…" (DHHS 2000).

AOM is a disease of children with peak incidences at about two and five years of age. More than 90% of children suffer at least one episode by their second birthday (Block, Harrison et al. 2001). It is one of the most common infectious diseases of infancy and childhood and is a leading cause of physician visits and antibiotic prescriptions for this population at an annually overall expenditure of approximately $5.3 billion (Dagan and McCracken 2002). More than 800 antibiotic prescriptions are given per 1000 office visits (McCaig, Besser et al. 2002).

Xylitol is a naturally occurring 5-carbon sugar polyol found naturally in various trees, fruits and vegetables and approved for use in foods, pharmaceuticals and oral health products in more than 35 countries. It has been FDA approved as a dietary food additive since 1963 and has been used widely since the mid 1970s. Xylitol is safe for consumption by children and can be found in supermarket products such as gums, mints, candies, lozenges, toothpastes, and dietary foods. Transient gastrointestinal discomfort, laxation and diarrhea are the predominant side effects of excessive consumption (Forster, Quadbeck et al. 1982). Children can tolerate daily dose of 45 g without developing loose stools (Uhari, Kontiokari et al. 1998). These symptoms disappear after soon after the removal of xylitol from the diet (Akerblom, Koivukangas et al. 1982).

Xylitol has been shown to be an effective tooth decay preventive agent (Milgrom, Ly et al. 2008). Xylitol exerts selective antibacterial-like actions against mutans streptococci by disrupting glucose cell-wall transport and intracellular glycolysis thus inhibiting pathogen growth (Miyasawa-Hori, Aizawa et al. 2006). It also reduces the adhesiveness of mutans streptococci to tooth biofilms (Soderling 2008). However, xylitol's effectiveness in decreasing mutans streptococci and reducing tooth decay is dependent on consumption of a minimum daily frequency and amount that is not generally found in foods or most xylitol containing products (Ly, Milgrom et al. 2006).

Xylitol may play a role in reducing AOM in the pediatric population. In-vitro studies demonstrate that xylitol blocks the growth of *Streptococus pneumoniae* (Kontiokari, Uhari et al. 1995). In a double blinded randomized trial, children averaging five years old in Oulu, Finland were given either xylitol or sucrose (control) administered in chewing gum, two pieces, five times per day for a total of 8.4 g. During the two-month study period, 31/149 (20.8%) children who received sucrose experienced at least one event of AOM compared with 19/157 (12.1%) of those receiving xylitol (Uhari, Kontiokari et al. 1996). In a follow-up three months RCT among toddlers and older children, preschool children received five times per day xylitol chewing gum or xylitol lozenges (8.4 g per day), or xylitol solution (2 mg each dose in a 5ml xylitol/water solution, 10 g per day) or controls (xylitol at 0.5g per day). Children in the xylitol syrup group that had at least one event of AOM after any symptoms of respiratory infection was 30% lower relative to controls (68/165, 41% versus 46/159, 29%) (Uhari, Kontiokari et al. 1998).

III. STUDY DESIGN AND METHODS

IIIA. Study Design

This was a 12-month randomized controlled clinical trial to assess the feasibility of using xylitol syrup to prevent AOM and ECC among children age 9-15 months at recruitment. The planned sample size was one hundred children randomized into one of three groups, xylitol syrup twice/day (8 g xylitol total), thrice/day (8 g xylitol total), or controls (once/day at 2.3 g xylitol total). A positive control was used at the direction of the local Institutional Review Committee and the Ministry of Health. Each group received a total of three syrup unit-doses per day consisting of placebo (2 g sorbitol) and/or xylitol unit-doses.

IIIB. Population Studied

One hundred and eight children permanently living on Majuro Atoll aged 9-15 months were enrolled in the study. We elected to recruit 9-15 month olds because of the eruption pattern of the primary teeth and xylitol is considered to be most effective when present during tooth eruption. In addition, this age group was selected to ensure that the 12 months follow-up period was during peak incidence of AOM and allow for ascertaining the maximum cases. The setting was two districts (Delap and Laura) on Majuro Atoll, Republic of the Marshall Islands (RMI). RMI is located in eastern Micronesia and Majuro Atoll is a major urban center with a population of nearly 30,000 of the total 55,000 citizens of the RMI. RMI is an independent island state in free association with the U.S. and uses U.S. currency. The per capita income is estimaded at $3000US while supermarket product costs are similar to if not more expensive than the same products in the US. ECC is a serious health care problem in RMI with caries rate two to three times that of the typical U.S. mainland community. Fifty-one percent of two year olds have at least one decayed tooth (Tut and Milgrom 2002). The average child entering Head Start at age five has 6.8 untreated cavities and over 90% of children have at least one decayed tooth (Tut, Greer et al. 2005). Nearly all U.S. health programs, such as MCH Block Grants and HeadStart, are in place in the RMI. Thus, this population is included under the permissible sites for Title V projects under the Social Security Act.

IIIC. Sample selection

All children ages 9 to 15 months of age living in Majuro or Laura districts were eligible to participate. Recruitment occurred through community announcements and community health workers. Children with a history of adenoidectomy, the placement of tympanostomy tubes, or tympanic membrane perforations were excluded as were children with congenital craniofacial malformation or a structural middle ear abnormality. Children who were in the lower 10% of height and weight (by standard U.S. growth chart) or have a history of esophageal diseases or digestive diseases were also excluded.

IIID. Instruments used

There were two primary outcome measures: (1) incidence of AOM and (2) incidence of ECC. Children were examined for AOM and ECC at baseline. For ECC, children were again examined at mid-study and end of the study. Dental caries were assessed using standard WHO criteria for dental caries (World Health 1987) and a case of ECC is defined as a tooth with a cavitated lesion. Assessments were conducted at the Laura Clinic or Majuro Hospital Dental Clinic using artificial light and a disposable mouth mirror. For AOM, Outreach workers were trained in ascertaining signs and symptoms of AOM. Mothers were taught and instructed to post laminated information sheets on signs and symptoms of AOM in their home. At any time during the 12-month follow-up period, any child with signs or symptoms of AOM, as determined by the mother or outreach worker, an “AOM case inquiry questionnaire” was completed and the child examined by a physician (Majuro) or Medex (Laura Health Clinic Clinician) for AOM. AOM were assessed and treatment provided using the diagnostic criteria, treatment plan and follow up as outlined in the American Academy of Pediatrics “Practice Guideline – Diagnosis and Management of Acute Otitis Media” published in March 2004. These criteria were assessed by the history and physical examination using wall mounted or pocket otoscope. Tympanograms were also completed using the Grason-Stader 38 Auto Tympanometer to verify for the presence of fluid and assist in the diagnosis. Examinations were carried out at Majuro Hospital Clinic or Laura Health Clinic. Transportation (taxi fee) to the clinics was provided.

IIIE. Statistical techniques employed

Subjects were assigned to ID numbers serially at enrollment where ID numbers had been randomly assigned to conditions by a statistician generated by using a block randomization and the sample function of the S-PLUS® statistical software (Insightful Corporation, Seattle, WA). Block sizes of 30 and 15 were used for the Laura district and 36 and 18 were used for the Delap district. All study team members were blinded until study completion except for the statistician who generated the randomization and different from the statistician who completed the analysis. Poisson regression analysis was used to compare the number of decayed teeth between the three study conditions, which included the natural logarithm of the follow-up time from the baseline dental exam following the syrup randomization protocol until the last follow-up (recorded) exam as an offset term. Generalized estimating equations with a robust variance estimator were used to fit the Poisson regression model in order to account for overdispersion due to multiple teeth per subject (Hujoel, Makinen et al. 1999; Hardin and Hilbe 2003). Additional Poisson regression analyses adjusted for age at randomization, number of teeth at last follow-up, and study district were done. The prevented fraction and number needed to treat (NNT) were also calculated. NNT = 1/ARR (absolute risk reduction) and ARR = Control Event Rate – Experimental Event Rate. The data were analyzed using SAS (version 9.1.3) software package (SAS Institute, Inc., Carey, NC, USA, 2003). Poisson regression analysis and similar adjustment were also used to compare the number of AOM episodes between the three study conditions.

IV. Detailed Findings

Of the 108 children enrolled (Laura, N=32 and Delap, N=76), eight children dropped out during the observation, run-in, or wash-out period leaving 100 children who participated in the syrup randomization protocol. For ECC analysis, 94 of 100 children with at least one follow-up dental exam were included in the intent-to-treat analysis; 84 children completed the final dental exam. Table 1 shows the characteristics of the 94 children included in the final analysis. Subjects in the group given xylitol syrup three times/day (8 g per day) were about two months younger than subjects in the xylitol syrup two times/day (8 g per day) and the Control group (xylitol syrup one time/day at 2.3 g per day) at initiation of the randomization protocol (ANOVA, P=0.002). The mean follow-up period was 10.5$\pm$2.2 months and was similar between the conditions (ANOVA, p=0.94). The syrup compliance rate during the study was high, over 90% for each condition, based on actual counts of daily consumed and un-consumed syrup unit-doses. Results of periodic syrup microbial testing showed no changes compared to immediately after production testing.

Table 1. Characteristics of the 94 children included in the final analysis* for each condition in the xylitol pediatric topical oral syrup trial in the Marshall Islands.

	Xylitol 2X/day	Xylitol 3X/day	Control	Total
N (Laura/Delap)	33 (11/22)	32 (10/22)	29 (9/20)	94 (30/64)
Female sex – no. (%)	19 (57.8%)	18 (56.2%)	14 (48.3%)	51 (54.3%)
Age at randomization – months ± SD†	15.9 ± 2.6	13.7 ± 2.4	15.6 ± 2.7	15.0 ± 2.7
Follow-up time‡ – months ± SD	10.4 ± 2.5	10.6 ± 1.9	10.6 ± 2.1	10.5 ± 2.2

*****94 children had at least one exam follow-up exam during the study period and were included in this intent-to-treat analysis. Of these, 84 completed all follow-up exams and 10 who dropped out after having an interim exam.
†SD= Standard Deviation
‡Syrup randomization follow-up period was 12 months. However, some of the 94 children included in the analysis dropped out after their interim exam and thus reduced the mean follow-up time.

Table 2 shows that nearly 52% of children in the control group had tooth decay compared to 40.6% among xylitol three doses (8 g)/day group and 24% among xylitol two doses (8 g)/day group. The mean±SD number of decayed teeth was 1.9±2.4 for control, 1.0±1.4 for xylitol three doses/day, and 0.6±1.1 for xylitol two doses/day. Compared to controls, there was significantly fewer decayed teeth in the xylitol two doses/day (relative risk [RR], 0.30; 95% confidence interval [CI] 0.13, 0.66; P=.003) and xylitol three doses/day (RR, 0.50; 95% CI 0.26, 0.96; P=0.037) groups. There was no statistical difference between the two xylitol 8 g/day treatment groups (P=0.22).

Table 2. Percent of children with tooth decay and number of decayed teeth for the 94 children included in the final analysis.

Condition	Percent with Decayed teeth	No. teeth at last exam, Mean ± SD*	No. decayed teeth Mean ± SD [Max]†	Relative Risk‡ (95% CI)
Control (N=29)	51.7	17.2 ± 2.5	1.9 ± 2.4 [8]	1.00
Xylitol 2X/day (N=33)	24.2	17.2 ± 2.9	0.6 ± 1.1 [4]	0.30 (0.13, 0.66)
Xylitol 3X/day (N=32)	40.6	16.6 ± 3.2	1.0 ± 1.4 [6]	0.50 (0.26, 0.96)

94 children had at least one exam during the study period and were included in this intent-to-treat analysis. Of these, 84 completed all follow-up exams and 10 dropped out after having an interim exam.

*****SD = Standard Deviation.

†Max = maximum range.

‡Non-adjusted analysis. Generalized estimating equations with a robust variance estimator were used to fit the Poisson regression in order to account for overdispersion due to multiple teeth per subject.

§Wald test for comparison with control condition. Score test for overall condition effect (X_2=7.26; P-value = 0.027).

The incidence rates (unadjusted model) for decayed primary teeth were:

- Control group: 2.20 decayed primary teeth per year
- Xylitol 2X/day group: 0.66 decayed primary teeth per year
- Xylitol 3X/day group: 1.10 decayed primary teeth per year

The Prevented Fraction ranged from 50% (Xylitol 3X/day vs. Control: 100 x (2.2 – 1.1)/2.2) to 70% (Xylitol 2X/day vs. Control: 100 x (2.2 – 0.66)/2.2) and the Number Needed to Treat (NNT) ranged from 10 with Xyl-3X to 4 with Xyl-2X (Xyl-3X vs. Control: 1/(51.7% - 41.6%); Xyl-2X vs. Control: 1/(51.7% - 24.2%)).

For AOM, 93 children were included in the final analysis. Overall, 84% of the children had at least one clinic visit for Upper Respiratory Tract (URI) problems from referral by the parents/family or Outreach Workers during the 12 months follow-up when syrups were given. However, only 38% had one or more diagnosed case of AOM (Table 3). Interestingly, many more AOM cases were diagnosed in Laura (76%) by the Medex than in Delap (24%) by the Pediatricians. There were small differences in rates of AOM between the control group compared to the xylitol 8 g per day groups but the differences were not statistically significant.

Many of the children, particularly in Laura, had a lot of ear wax when they had their ears examined for AOM such that a thorough exam was commonly not possible. Frequently, cases where exams can not be completely well, Medex appeared to assume the worse case scenario – give the diagnosis of AOM – and treat the child while physicians tended to prescribe otic solutions, medicine for symptomatic relief, and scheduled for follow-up visit in a week. This may explain the higher rates of acute ear infection diagnosed in Laura.

Table 3. Percent of Children with AOM diagnosis by group and study district.

		Children	AOM Diagnosis	
		N	N	%
All (children)		93	35	37.6
Control		29	9	31.0
Xylitol Twice/day		32	13	40.6
Xylitol Thrice/day		32	13	40.6
1=Laura		29	22	75.9
2=Delap		64	13	24.1
1=Laura	**Control**	9	6	66.7
	Xylitol Twice/day	10	8	80.0
	Xylitol Thrice/day	10	8	80.0
2=Delap	**Control**	20	3	15.0
	Xylitol Twice/day	22	5	22.7
	Xylitol Thrice/day	22	5	22.7

V. DISCUSSION AND INTERPRETATION OF FINDINGS

VA. Conclusions

Oral xylitol syrup administered topically two or three times each day at a total dose of 8 g was effective in preventing Early Childhood Caries. More than half of the Control group (xylitol one a day at 2.3 g) developed tooth decay with an decayed teeth (cavitated lesions) incidence rate of 2.2 per year compared to 24% and 0.66 per year and 41% and 1.1 per year for children in groups given xylitol 8 g/day divided into two or three evenly divided doses respectively. The relative risk for the xylitol two times and three times per day groups were 0.30 and 0.50 respectively; the preventive fractions were 70% and 50% respectively; and the number needed to treat to prevent a child from developing tooth decay were 4 and 10 respectively. Although it appeared that the group given xylitol two times per day (8 g total) had better results for ECC than the group given xylitol three times per day (8 g total), the differences between them were not statistically significant. These results provided evidence for the first time that xylitol is effective for the prevention of ECC in toddlers.

Oral xylitol syrup administered topically two or three times each day at a total dose of 8 g was not effective in preventing Acute Otitis Media. The children in the control group had a slightly lower rate of AOM compared to the xylitol 8 g per day groups but the differences were not statistically significant.

VB. Study Limitations

The study had several limitations. The study cohort was relative small though provided adequate power to assess the differences between groups. This was in part because of the uniformity of the study cohort in terms of ethnic background and cultural practices. However, the population selection (Marshallese) and setting (Micronesia) may limit the extrapolation of the findings for ECC to other populations. The latter needs confirmation studies. Although the AOM diagnostic protocol was rigorous and the clinicians were trained and received refresher training during the study, it proved to be too difficult to carry out and maintain good quality control and compliance in this study setting where there was a shortage of pediatricians and the use of Medex as the primary clinician at community Health Clinics such as in Laura district. Medex tended to be less compliant in applying the AOM diagnostic protocol particularly in the use of tympanometry or in deferring diagnosis until wax has been cleared from the ear canal. Medex were more aggressive in positive diagnoses and treatment of AOM while the Pediatricians at Majuro Hospital Clinic were much more conservative in their diagnoses. Another limitation was the high reliance on Outreach Workers to motivate and maintain participant-families adherence to the syrup consumption protocol. Outreach workers visited families at least once a week. This intensity may not be feasible in a community-based public health program.

VC. Compare Findings with Other Studies

There is some consensus among researchers that a habitual xylitol exposure of five to 10 g divided into at least three daily periods of consumption is needed for a therapeutic effect. However, we previously evaluated the response of mutans streptococci in plaque--a surrogate marker for tooth decay--to varying frequencies of xylitol chewing gum consumption for five weeks at a standard daily dose (10.3 g/day) among adults. The study found a linear reduction in mutans streptococci with increasing frequency (zero to five) of xylitol chewing gum consumption but the reduction with twice daily chewing did not reach statistical significance.[32] That study had inherent weaknesses, a short follow-up and a surrogate marker, which may not withstand comparison to a more rigorous long RCT with tooth decay as the endpoint. Moreover, the act of chewing and suckling 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 from tooth decay.[17] Chewing gum and lozenges studies where controls also used gum or lozenges may under estimate the reduction of mutans streptococci and tooth decay by xylitol. Given the absence of potential effects attributable to chewing or suckling which are inherent in xylitol chewing gum and lozenges studies, the results found in this study more accurately reflect the effects of xylitol. Finally, xylitol given during tooth eruption and colonization is suggested to have maximal protective effects.[19]

The greater reduction seen with xylitol 2X/day (8 g xylitol + 2 g sorbitol/day) compared to xylitol 3X/day (8 g xylitol/day) begs the question of xylitol and sorbitol synergistic effects. However, it is important to appreciate that the difference observed between the experimental groups was not statistically significant. Furthermore, a 40 months chewing gum study in Belize did not find support for xylitol/sorbitol synergism. The study found that at similar total daily polyol doses, the xylitol only groups were most effective in caries reduction followed by the xylitol+sorbitol groups then sorbitol alone compared to no-gum control group.[25]

Both studies by Uhari et al. that reported positive effects of xylitol in reducing AOM used a 5 times/day frequency of consumption. We felt that this frequency was not feasible in public health programs and tested the reduced frequency of consumption, two and three times/day. At

these frequencies of consumption our results showed no protective effect for AOM. However, there were a number of weaknesses associated with the AOM diagnosis process as discussed above that may render our AOM results non-interpretable. Further study is needed in better controlled environment with highly qualified pediatricians to confirm or dismiss the positive findings by Uhari et al.

VD. Possible application of findings to actual MCH health care delivery situations

The ECC preventive effects of xylitol syrup found in this study provide support for the use of xylitol syrup along with fluorides, particularly for high risk population. The results also support the position of the AAPD and the NIH Consensus Statement: *Diagnosis and Management of Dental Caries Throughout Life* that xylitol is an important tool for the prevention of dental caries. In populations with high rates of tooth decay, xylitol interventions are likely to be cost-effective. A xylitol syrup intervention could be developed for use with WIC programs, Early HeadStart, perhaps even with HeadStart, and with young Children with Special Health Care Needs such as Autism, ADHD or other behavioral disorders. However, larger clinical trials with multi-ethnic populations or in the above mentioned populations are needed to confirm the ECC findings in this study. Furthermore, more work is needed to develop other xylitol vehicles and strategies for the public health application of xylitol across the life span and unique populations.

VE. Policy Implications

The ECC preventive effects of xylitol found in this study further solidify the position on xylitol held by the AAPD and the NIH and may influence the ADA to take similar position and encourage more dental providers to consider using xylitol products as part of their preventive care strategy particularly among high risk populations.

VF. Suggestions for Further Research

Larger clinical trials with multi-ethnic populations or in the above mentioned populations are needed to confirm the ECC findings in this study. Furthermore, more work is needed to develop other xylitol vehicles and strategies for the public health application of xylitol across the life span and for unique populations.

VI. LIST OF PRODUCTS

Peer-Reviewed Publication:

1. Milgrom P, Ly KA, Tut OK, Mancl L, Roberts M, Briand M, Gancio MJ. Xylitol pediatric topical oral syrup to prevent dental caries: a double-blind, randomized clinical trial of efficacy. Arch Pediatr Adolesc Med. (in press)
2. Milgrom P, Ly KA, Rothen M. Xylitol and Its Vehicles for Public Health Needs. Advances in Dental Research. Special supplement to appear in 2009 (in press)
3. Riedy CA, Milgrom P, Ly KA, Rothen M, Mueller G, Hagstrom MK, Tolentino E, Zhou L, Roberts MC: A surrogate method for comparison analysis of salivary concentrations of Xylitol-containing products. BMC Oral Health 2008, 8(1):5.
4. Ly KA, Rothen M, Milgrom P. Xylitol, Sweeteners and Dental Caries: A Practical Overview for Clinicians. *Pediatr Dent*, 2006; 28:154-163.

Book Chapter:

1. Food constituents and oral health: current status and future prospects. Michael Wilson, Chief Editor. Kiet A. Ly, Peter Milgrom: Chapter 8. Sugar alcohols and oral health. (in press)

Abstracts:

1. Xylitol Topical Oral Syrup Prevents Early Childhood Caries: A RCT. P. Milgrom, O.K. Tut K.A. Ly, M.J. Gancio, M. Roberts, L. Mancl, J.R. Langidrik, and K. Briand. (Presented at IADR 2008 meeting).
2. Bioavailability of Xylitol-Containing Products in Saliva. C.A. Riedy, K.A. Ly, M. Rothen, G. Mueller, M.K. Hagstrom, E. Tolentino, L. Zhou, M.C. Roberts, P. Milgrom P. (oral presentation, IADR meeting 2007)

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