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Effectiveness of Xylitol Wipes On Caries in High Risk Infants

by

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THESIS

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Effectiveness of Xylitol Wipes on Caries in High-Risk Infants

Pearline Ying-Fong Chang

ABSTRACT

Purpose: To evaluate the effectiveness of xylitol wipes on caries prevention in high-risk infants.

Methods: In a double-blinded randomized controlled clinical trial, 44 mother-infant pairs were randomized into xylitol-wipe or placebo-wipe groups (n=22 per group). Guardians were instructed to use wipes on their infants 3-4 times daily and to brush the infants teeth with fluoride toothpaste twice daily. Saliva samples for mutans streptococci (**MS**) and lactobacilli (**LB**) enumeration (CFU/ml) and DMFS/dmfs scores were collected from mother-infant pairs at baseline and 1 year.

Results: Eighteen (xylitol-wipe group) and 11 (placebo-wipe group) pairs completed the study. Five dropout subjects from the placebo group returned at 1 year. The mean±SE logMS counts in infants at 1 year were 2.7±0.6 for the xylitol-wipe group, 2.8±0.8 for the placebo-wipe group, and 5.0±1.2 for the dropout group with logLB levels as 0.1±0.1, 0.1±0.1, and 1.4±0.9 respectively. Only the dropout group had significantly higher logLB at 1 year compared to the 2 wipe groups (ANOVA, $p < 0.05$). Children in the xylitol-wipe group had significantly fewer new decayed surfaces at 1 year (mean new ds±SE=0.06±0.06, $p < 0.05$) than the placebo-wipe (mean new ds±SE=0.45±0.20) and the dropout group (mean new ds±SE=0.75±0.47).

Conclusions: Although xylitol-wipe use did not significantly reduce MS and LB levels in infants, the development of new caries was significantly reduced by the use of xylitol wipes in infants daily. Wipe-use alone may help reduce cariogenic bacteria in infants. The daily use of xylitol wipes in infants in conjunction with brushing with fluoride toothpaste may be a very successful caries preventive regimen for infants.

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1. Introduction

Tooth decay is the most common infectious disease and the leading cause of oral pain and tooth loss in children[1]. While the collective oral health of children has improved over the past several decades, between 1988-1994 and 1999-2004, prevalence of caries in primary teeth increased for children aged 2 to 11 years from 24% to 28%[2].

Mutans streptococci (MS) and the lactobacilli (LB) species are the main cariogenic bacteria[3]. Early colonization and high levels of MS have been associated with increased risk for early child hood caries (ECC)[4, 5]. Children with ECC have a much greater probability of subsequent caries in both primary and permanent dentitions[6]. Thus, understanding the mechanism of MS transmission and prevention of MS colonization and reduction of MS levels may be advantageous for the prevention and management of ECC.

2. Literature Review

2.1 Early Childhood Caries (ECC)

ECC, a rampant form of caries that develop soon after dental eruption, is a significant public health concern that affects millions of families with young children[7]. The American Academy of Pediatric Dentistry (AAPD) defines ECC as "the presence of 1 or more decayed (non-cavitated or cavitated), missing (due to caries), or filled tooth surfaces" in any primary tooth in a child 71 months of age or younger[8]. ECC is microbiologically characterized by dense dental infection of MS[9]. As stately earlier, MS and LB species, either separately or together, are the major cariogenic bacteria in ECC; MS include *Streptococcus mutans* and *S. sobriunus*; the LB species, as MS, are prolific producers of lactic acid[3]. These reside in dental plaque, a sticky matrix of bacteria, food debris, dead mucosal cells, and salivary components that adheres to the tooth surfaces. If not removed, the plaque will harbor increasing numbers of cariogenic bacteria and the acid by-products of these bacteria will cause demineralization of the enamel, involving

the loss of calcium, phosphate, and carbonate followed by eventual cavitation if the process is not arrested or reversed[10].

The major pathological factors in ECC include, as previously mentioned, early cariogenic bacteria colonization and frequent fermentable carbohydrates intake[11]. The AAPD notes that frequent consumption of liquids containing fermentable carbohydrates such as juice or formula increases the risk of caries due to prolonged contact between sugars in the liquid and cariogenic bacteria on the teeth[11]. Improper feeding practices such as frequent bottle feedings at night, prolonged and repetitive use of a no-spill cup are also associated with ECC[12]. In addition, it has been found that infants whose mothers have high levels of MS are at a greater risk of acquiring the bacteria than infants whose mothers have low levels[13].

ECC is an infectious disease. MS are the most commonly cultured cariogenic bacteria from the mouths of infants[14]. Studies have shown that children whose teeth are colonized by MS at an early age tend to have a higher caries experience with increased risk of ECC than those colonized later or not at all[15]. Recent studies reported that over 30% of infants are already infected with MS before 6 months of age[16]. While many studies have found that most infants appear to acquire the microorganisms from their mothers[11, 12, 17], other studies have shown that infants acquire MS from other sources as well, such as their fathers or playmates[18-23]. LB is the other major cariogenic bacteria. The initiation of caries tended to be preceded by increased levels of both MS and LB; caries frequently occurred in the absence of LB, but not in the absence of MS[24].

There are many adverse consequences of ECC. Infants with ECC are 3 times more likely to develop tooth decay in their permanent teeth than those without[25]. Infants with severe ECC may have more hospitalization visits, insufficient growth development, accumulated loss of school days, diminished ability to learn, and more[26]. Thus, prevention of ECC may be beneficial in improving oral health-related quality of life. Some infants with severe ECC require full mouth

rehabilitation under general anesthesia. The cost for facilities and general anesthesia imposes an extensive financial burden to the society and the families.

2.2 Prevention

It is important to remember that dental caries is an infectious and transmissible disease. As clinical studies have consistently shown that caries risk is correlated with age at which initial MS colonization occurred, preventive strategies for development of ECC should encompass timely control of oral MS colonization and transmission in infants. Prevention of dental caries, in addition to good oral hygiene care and diet modification, includes application of fluoride and the use of chemotherapeutics agent such as xylitol, povidone iodine, and chlorhexidine.

2.2.1 Fluoride

The near universal use of fluoride, in the forms of dentifrice, mouth-rinse, and professionally applied topical gels, foams, or vanishes, along with improvement in oral hygiene and school-based prevention programs, have played a major role in the decline of tooth decay in the United States and other developed countries[16]. These fluoride products have been shown to decrease caries development between 30 and 70% compared with no fluoride use[27]. Fluoride, which is retained by dental plaque, inhibits bacterial metabolism and demineralization and enhances remineralization through its topical action[3]. As pH is lowered with production of acids by cariogenic bacteria, fluoride present in dental plaque is converted to HF and diffuses into the bacterial cell, releasing fluoride ions that then interfere with enzymes necessary for carbohydrate metabolism[3]. In addition, fluoride present among the enamel or dentin crystals adsorbs to these crystal structures and help reduce dissolution of tooth minerals by acid[3]. Also, in response to a lower pH due to bacteria metabolism, fluoride is released from the plaque and taken up with calcium and phosphate to form a more acid-resistant tooth structure, a veneer of "fluorapatitelike" mineral of low solubility[28]. Clinical studies conclude that there is a major anti-caries effect if 0.1ppm of fluoride in saliva can be achieved consistently. However, the goal of developing a

commercially effective device that could sustain such levels continually has yet to be met and studies with fluoride varnish have not consistently shown positive results. In a study by Soderling *et al*., it was found that biannual fluoride varnish applications in mothers did not significantly reduce MS transmission from mother to infant, whereas xylitol consumption did show a significant reduction[16]. Despite the many benefits of fluoride, dental caries remains a major issue in infants[2]. It is also important to point out that dental fluorosis is a risk associated with duration of cumulative exposure to high levels of fluoride intake[29]. In the face of high bacterial challenge faced by infants with high caries risk factors and the potential risk of fluorosis with excessive fluoride use, development of supplemental therapies in addition to fluoride use is a logical step to take in combating ECC.

2.2.2 Chlorhexidine

Fluoride alone, as mentioned earlier, is insufficient for high caries risk individuals. Therefore, in cases of high bacterial challenge, one must deal with the fundamental problem, namely, bacterial infection. One such antibacterial agent to consider is chlorhexidine. Chlorhexidine is currently viewed as one of the most successful chemotherapeutic agents against MS[30]. Studies have shown that chlorhexidine varnish can provide a sustained release and thus suppress MS in plaque for 6 months after its use[30]. In a 2004 review, it was found that the use of chlorhexidine varnish for dental caries prevention was inconclusive[31]. In a 24-month clinical study, the use of chlorhexidine varnish at 3-month intervals resulted in a lower incidence of caries in children aged 6-7 who were caries-free at the beginning[32]. Current U.S. products are limited to 0.12 percent chlorhexidine gluconate rinse[33]. While this is appropriate for most high-risk and highly compliant adults, it is not a suitable delivery method for infants. The up-to-date consensus is that chlorhexidine is able to reduce MS levels, and when used with fluoride therapy, can significantly lower future caries risk. However, it is not as effective against LB and compliance with the use of chlorhexidine, with its unpleasant taste and extrinsic tooth-staining characteristics,

is a major issue that needs to be solved in order for its use to be widely accepted in the fight against ECC. The utilization of a good tasting agent, in an appropriate form of delivery vehicle, would be advantageous, particularly in infants.

2.2.3 Xylitol

Xylitol is a naturally occurring sugar that has been approved for use by the US Food and Drug Administration (FDA) since 1963 as a sugar substitute. It belongs to the family of "sugar alcohols" because of its similar chemical structure to that both of sugar and alcohol. It was originally produced in Finland through an extraction process using birch wood and can be found in raspberries, cauliflower, and organic substances[34]. Xylitol tastes as sweet as sucrose, but provides one-third fewer calories than sucrose and has no aftertaste usually associated with sugar replacements[34]. Xylitol is one of the most commonly used sweeteners in chewing gum[35]. Relatively large amounts of this polyol (for example, 7-14 grams per day) can be consumed without untoward side effects, though when ingested in quantity, it can act as a laxative[36]. It has proven to be non-acidogenic or hypoacidogenic in plaque telemetric studies[37]. Cariogenic microorganisms do not metabolize xylitol and consuming xylitol does not decrease plaque pH[38]. In addition, xylitol has been shown to reduce the level of MS in plaque and saliva and to reduce tooth decay[39].

There is no consensus as to the exact mechanisms behind xylitol's anti-caries properties. It has been shown that the presence of xylitol in the culture medium may inhibit the *in vitro* growth of MS[40]. This inhibition is postulated to be caused partly by glycolysis-inhibiting intracellular accumulation of xylitol-5-P and partly by an energy-consuming futile cycle related to uptake and phosphorylation of xylitol to xylitol-5-P, subsequent dephosphorylation and expulsion of xylitol[41].

In addition to its non-cariogenic property, some studies have also shown that, in short-term habitual consumption, xylitol reduced the levels of MS assessed both from plaque and from

stimulated saliva[42]; this inhibition effect may last or diminish with long-term xylitol consumption[43]. Some studies indicated that, with long-term use, xylitol may select for natural mutant cell of MS which are "xylitol-resistant"[44]. It was postulated that xylitol-resistant (X-R) mutants shed more easily into saliva from plaque than do xylitol-sensitive (X-S) parental strains[44], though this was never confirmed. In a study by S. Assev, it was found that there was no clear difference in polysaccharide formation between X-R and X-S MS[45], thus raising the question as to how or whether X-R mutants are different or less virulent compared with X-S strains. Clearly, contradictory results have been published in regards to xylitol's effect on MS. Thus, xylitol's specific effect on MS virulence factors needs to be further explored.

Few studies have examined the effect of xylitol on remineralization. In a study by Miake Y. *et al.* in which human teeth were artificially demineralized then immersed in a remineralizing solution with or without xylitol, it was shown that xylitol can induce remineralization on deeper layers of demineralized enamel by facilitating Ca^{2+} movement[46]. Xylitol is known to combine with calcium in aqueous solution and prevent decalcification by inhibiting the translocation of dissolved Ca^{2+} and PO_4^{3-} ions from lesions; xylitol might accelerate remineralization by lowering the diffusion coefficients of Ca^{2+} and PO_4^{3-} within the demineralized layers[46].

Xylitol can be a useful adjunct as a part of an oral health prevention regimen. Maternal use of xylitol has shown great success in the prevention of MS colonization and caries formation in children[47-49]. A study in Finland showed that maternal xylitol consumption during the first 2 years of the children's lives significantly reduced MS colonization in children at 2 years of age[16]. The inhibition of MS colonization resulting from maternal use of xylitol gum extended to 4 years after the maternal xylitol consumption had been discontinued[49].

Although maternal use of xylitol achieved success in reducing MS transmission to infants, recent studies have repeatedly demonstrated that MS transmission from non-maternal sources, such as fathers or playmates, occurs as a major alternative[18-23]. In the presence of both

maternal and non-maternal sources of transmission, it is more efficient to focus caries-prevention strategies on the final destination of the bacteria, the infants, rather than the various points of origin.

2.2.4 Delivery Vehicle for Xylitol

A vehicle that delivers xylitol effectively for infants must be cost effective, appealing, and simple to administer. Chewing gum has been established as the most effective vehicle for xylitol delivery to the oral cavity. Though this is an effective way of consuming xylitol for most adult populations and older children, the American Academy of Pediatrics does not recommend chewing gum use in children under 4 years of age due to risk of choking. As part of the general anticipatory guidance for patients 0-3 years of age, the AAPD recommends cleansing the infant's teeth as soon as they erupt with either a washcloth or soft brush. Thus, wipes could be a suitable medium for xylitol delivery in infants and be a tool for caries prevention. However, up to date, no study has investigated the efficacy of xylitol-wipe use on cariogenic bacteria colonization and caries prevention in infants.

2.3 Significance

ECC is a significant public health problem that severely affects infants, toddlers, and preschool children. Considering that one of the main pathological factors in caries development is acidogenic bacteria, preventing or delaying initial colonization and transmission of cariogenic bacteria in infants may not only decrease the risk of future development of dental caries, but also enhance oral health-related quality of life. Xylitol-containing wipes can be used for infants as a safe adjunct to standard preventive oral hygiene programs to provide an additional mode of protection from high bacterial challenges.

2.4 Purpose

The purpose of the present study was to determine whether daily use of xylitol wipes in infants would reduce levels of colonization of MS and LB and new caries development.

2.5 Hypothesis

The hypothesis to be tested was that xylitol would cause an alteration in the oral bacterial ecological balance that will yield a clinically significant reduction in MS and LB in infants' plaque and saliva and subsequently reduce the infants' caries experience.

3. Materials and Methods

3.1 General Study Design

Figure 1. Study Design Flow Chart

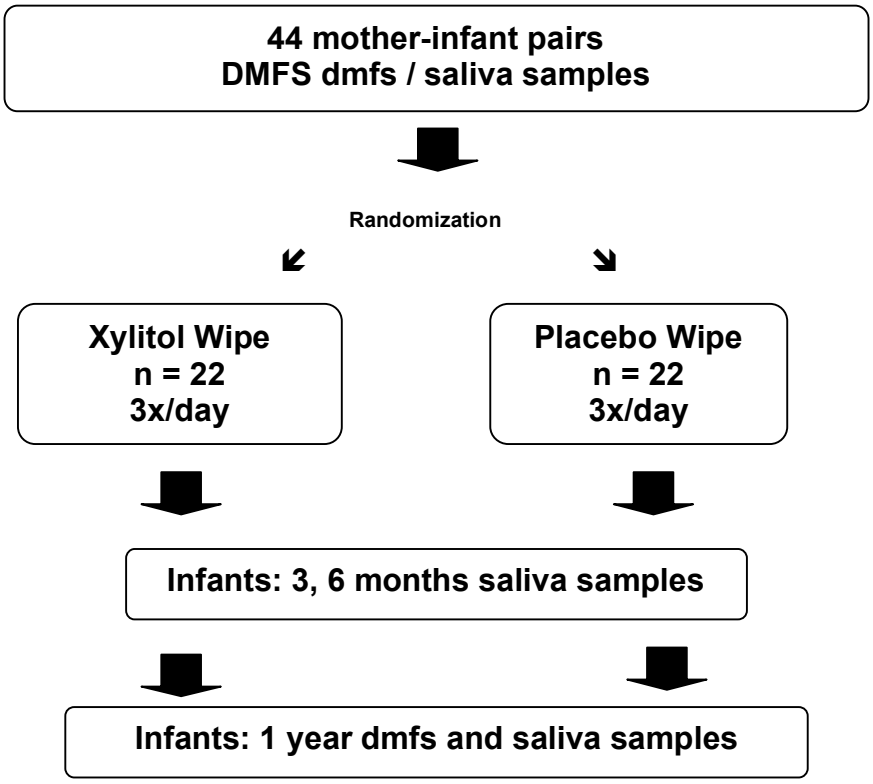


Figure 1 illustrates the design of the study. The Committee on Human Research at the University of California at San Francisco (UCSF) approved the study protocol of this double-blinded randomized controlled clinical trial. Sample size calculation was based on Söderling's study on the effect of maternal use of xylitol gum on transmission of MS to their infants

(Soderling et al., 2000). The sample size needed to detect the difference at alpha (two sided)= 0.05, power = 80%, was estimated as 22 infants per group with a 10% attrition rate. Forty-four mothers with a history of active caries within the past year and their children aged from 6 months to 35 months were recruited for the study.

The mother and the infant received a DMFS/dmfs (decayed missing and filled surfaces) examination prior to saliva collection. Cross-calibration between 2 examiners (MN and PC) were performed before the study started. Repeated exams were done for 7 mother-infants pairs between the examiners to assess consistency.

The mother-infant pairs were randomly assigned to 2 study groups: xylitol-wipe group (Spiffies^{TM} Baby Tooth Wipes, DR Products, Tucson, AZ) or placebo-wipe group (that contained no xylitol) by a computer-generated randomization table. The study design did not include a "no-wipe" group as we simply planned to test the hypothesis that adding xylitol to the wipes would be more efficacious than the wipes alone without the xylitol. However, we invited all subjects who dropped out of the study to return at the final 1-year visit for a dental exam and saliva sample for cariogenic bacteria enumeration. These subjects were defined as the dropout group to evaluate if wipe use alone with or without xylitol would help to prevent caries or to reduce cariogenic bacterial levels.

Mothers received a 3-month supply of wipes at a time and were instructed to use the wipes on their child 3-4 times daily in addition to the child's normal oral hygiene regimen of brushing twice daily with fluoride toothpaste. Mothers were asked to make appointments in 3-month intervals to pick up more xylitol or placebo wipes. Bi-weekly phone calls to the mothers were made to monitor and promote compliance.

Stimulated saliva from the mothers were taken at baseline and swab saliva samples from the infants were taken for determination of MS and LB levels at baseline, 6 months, and 1 year

(see below). Ten MS colonies were isolated from each infant's and each mother's saliva sample and stored for subsequent cariogenic virulence factor analysis.

3.2 Subject Selection

3.2.1 Initial Contact Method

Pediatric dental residents, staff and faculty were briefed on participant recruitment. Posters were also placed at the reception desk and throughout the pediatric dental clinic to notify mothers and caregivers of the study. All infants aged 6-35 months were approached for recruitment. If the mothers agreed to participate in the study, a screening questionnaire was completed prior to final recruitment to assess subject's qualification for the study.

3.2.2 Inclusion/Exclusion Criteria

Inclusion criteria for the study were: 1) mothers with healthy infants aged 6 to 35 months; 2) mothers who were the stated primary caregivers of the infants (>8 hours of care daily) and had at least 1 active caries lesion within the past year. Exclusion criteria included: 1) infants who had other oral or systemic diseases, 2) mothers or infants who had taken antibiotics or other medicine that would affect the oral flora within the last 3 months.

3.2.3 Consent

Informed consent was obtained from the mothers. Procedures, benefits, risks and rights of the subjects in the study were discussed with the mothers. The infants were too young to give written or verbal assent. Mothers were provided ample time to accept or decline participation in this study.

3.2.4 Dental Examination

Mothers who fulfilled the inclusion/exclusion criteria were asked to complete a questionnaire regarding ethnicity, feeding and oral hygiene habits. A DMFS and dmfs (decayed missing and filled surfaces) examination was conducted on the mother and the infant using the modified World Health Organization criteria, which also included non-cavitated lesions, prior to

saliva collection in a routine pediatric dental clinical setting. Subjects who did not enroll in the study received a dental screening exam free of charge.

3.2.5 Randomization/Blinding

This was a double-blinded randomized control study. Computer generated random numbers were used to assign patients to either the control or experimental group. Containers for collecting saliva were uniquely coded for each patient with their study identification number and group number. The clinician administering treatments, subjects, and the laboratory personnel responsible for plating samples and quantifying bacteria were also unaware of the patients' assignment to either the control or experimental group. The data were analyzed as group A and B, prior to the final code being broken.

3.2.6 Saliva Collection

Stimulated saliva collection from the mother: Two ml of stimulated saliva from the mother was collected for microbiological assessment by requesting the subjects to chew on a piece of paraffin wax, and to expectorate into a sterile test tube.

Swab sample collection from the infant: An oral swab sample was obtained from the infant at least 1 hour after the last feeding and at least 2 hours after cleaning of the oral cavity. Sterile cotton-tipped applicators (CITMED Citronelle, AL) were swabbed over the gingiva, tongue, oral mucosa, and tooth surfaces until the swab was saturated with saliva. The tip was broken off and dropped into a pre-labeled 5ml sample tube with 2ml of phosphate-buffer-saline. Collecting saliva with the uncooperative infants was possible with parental help in knee-to-knee position.

The test tubes containing saliva from the mothers and infants were specially coded and no subject identification information used. The samples were transported on ice to the microbiology laboratory at UCSF for MS and LB plating and culture within 24 hrs. All saliva samples were discarded after plating.

3.2.7 Xylitol Wipes Allocation

At the first visit, mothers obtained all the information regarding the study and its duration. Informed consent was obtained and patient study ID number was assigned. After the questionnaire and saliva collection were completed, a 3-month supply of either xylitol or placebo wipes was supplied, based upon the randomization described above. The xylitol wipe and placebo wipe had the identical appearance and were labeled as wipes for Group A or B. Each xylitol wipe contained 0.7 g of xylitol. Other contents included purified water, glycerin, hydroxyethycellulose, sodium benzoate, natural flavor and citric acid. The placebo wipes contained the same ingredients as the xylitol wipes except they did not contain xylitol. Instructions and demonstration of use were given. Mothers were asked to make appointments in 3-month intervals to pick up more xylitol or placebo wipes. At each subsequent visit, any side effects were noted on a tracking form.

3.2.8 Participant Reimbursement

Mothers and infants participating in this study received 10 dollars in cash for each visit to compensate their time in the study.

3.2.9 Confidentiality of Records

All the subjects' personal information, such as names, ages, telephone numbers, was kept in a locked compartment. Information from the participant survey was kept confidential and for use in this research study only. All records were coded with study numbers and kept in locked files so only study investigators had access to them. No individual identities were used in any printed material or reports from this study.

3.3 Laboratory Procedures

3.3.1 Mutans Streptococci and Lactobacilli Enumeration

The test tubes containing the saliva samples from the mothers were sonicated for 20 seconds and 0.1 ml portions were used for microbiological assays as described below for infants.

The swab samples from the infants were vortexed for 30 seconds and 0.1ml portions of resulting bacteria suspension was used to prepare 10-fold serial dilution (10^{-1} through 10^{-5}) in phosphate buffered saline (PBS). One tenth ml of vortexed dispersed bacteria suspension and 0.1 ml of each serial dilution were plated on Mitis Salivarius Sucrose Bacitracin agar (MSSB, Difco) to culture MS and on Rogosa Tomato Juice agar for LB enumeration. Plates were incubated in anaerobic condition of 85% N_2. 5% CO_2, 10% H_2 for 72 hours before enumeration of MS and LB colonies. Enumerations of MS and LB in saliva were calculated as CFU/ml. Ten MS colonies were isolated from each child and each mother and stored at -80ºC for subsequent analysis. The samples were specially coded with no identification information about the subject. All saliva samples were destroyed after the study's conclusion.

3.4. Data Analysis

The primary outcome of the study was the development of new decayed surfaces (ds) at 1 year in the infants. The secondary outcome of the study was the colonization rate and levels of MS and LB. The ds increment and percentage of the subjects with new decay were calculated in the xylitol-wipe, placebo-wipe, and dropout. The difference in ds increments among the 3 groups was analyzed by ANOVA. The percentage of the subjects with new decay was analyzed using the chi-square test.

For each subject, changes in $\log_{10}$MS and $\log_{10}$LB were assessed by comparing pre-treatment logarithm-transformed bacterial counts with those at 6 months and 1 year by paired t-test in order to determine if the treatment had a long-term impact on cariogenic bacteria colonization.

All of the quantitative data (age, dmfs/DMFS) at baseline among xylitol-wipe, placebo-wipe, and dropout groups were compared using the t-test. Gender distributions of the groups were compared with a chi-square test.

4. RESULTS

4.1 Subject Follow-up and Baseline Data

Forty-four mother-child pairs were recruited, 22 in each group. All mothers stated that they were the primary care givers to their children, and all except 1 in the control group had MS infection. The majority (61%) of the study population was Hispanic.

A total of 29 participants, 18 (xylitol-wipe group) and 11 (placebo-wipe group) subjects, completed this 1-year study. See Figure 1 for the follow-up of the study. Eleven subjects from the placebo-wipe group and 4 from the xylitol-wipe group dropped out from the study. In the xylitol-wipe group, 1 cited rejection by her infant, 1 reported being too busy to wipe daily, 1 moved away, and 1 expressed loss of interest. In the placebo-wipe group, 7 out of 11 dropout subjects cited rejection of wipe-use by their infants as a main reason for discontinuation, 2 subjects moved away, and the other 2 subjects lost interest. No adverse side effects such as abdominal pain or diarrhea were reported during the study.

Infants who dropped out from the placebo group were invited to come back for the 12-month assessment. Five infants from the placebo-wipe group returned at 1 year for caries exam and saliva samples. These 5 infants are termed the "drop-out group for subsequent results tabulation.

Figure 1. Infants' Follow-up Chart

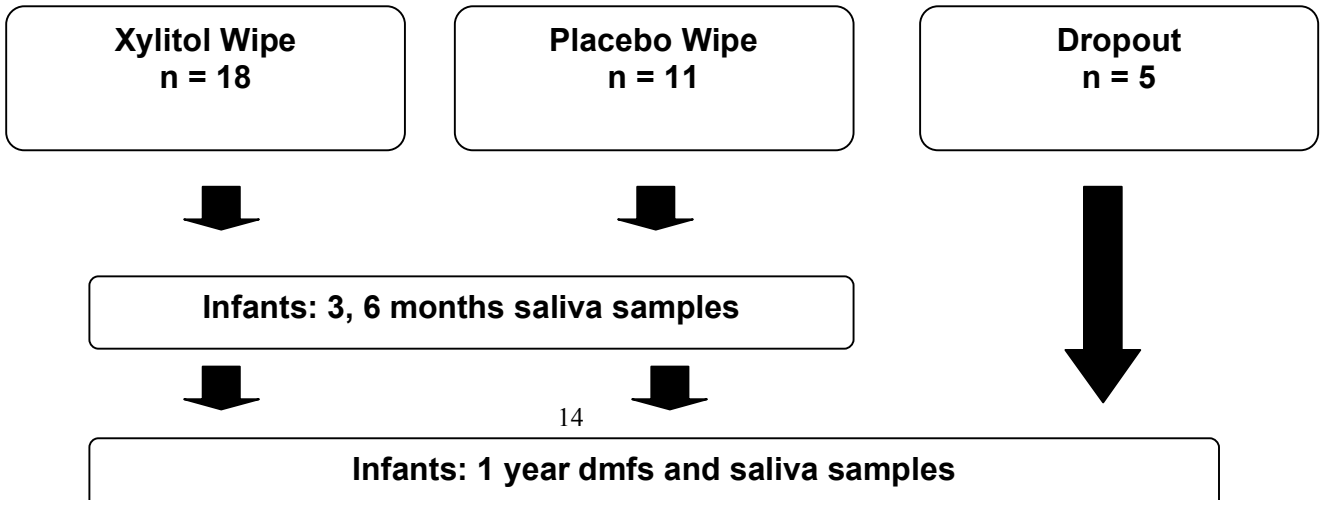


Table 1 illustrates the baseline demographic data of the subjects. No statistically significant differences were found for age, caries status, or cariogenic bacterial levels among the xylitol-wipe, placebo-wipe, and dropout groups (Table 1, $p > 0.05$).

Table 1. **Subject Demographics at Baseline (mean ± SE)**

GROUP	**Xylitol**	**Placebo**	**Dropout**
n at 1 year visit	**18**	**11**	**5**
Mother			
logMS	**5.4 ± 0.2**	**5.3 ± 0.4**	**5.4 ± 0.2**
logLB	**3.7 ± 0.5**	**3.9 ± 0.5**	**2.7 ± 1.2**
DMFS	**23.7 ± 4.5**	**16.4 ± 3.8**	**21.8 ± 8.6**
Infant			
Age(months)	**16.4 ± 1.9**	**16.9 ± 2.5**	**21.6 ± 3.6**
Gender(M/F)	**12 : 6**	**8 : 3**	**5 : 0**
logMS	**1.3 ± 0.6**	**0.0 ± 0.0**	**1.7 ± 1.5**
logLB	**0.0 ± 0.0**	**0.0 ± 0.0**	**0.0 ± 0.0**
dmfs	**1.3 ± 1.2**	**0.0 ± 0.0**	**0.0 ± 0.0**

4.2 MS and LB levels at 3 Months, 6 Months, and 1 Year

Figure 2 shows the incidence of new MS and LB colonization in the study groups. At 1 year, the percent of infants with MS colonization and LB colonization increased in both groups. In the xylitol-wipe group, 40% and 5.5% of the infants acquired new MS and LB colonization, respectively at 1 year, versus 62% and 27% in the placebo wipe group, respectively (Fisher's exact test, $p > 0.05$). Although the xylitol group had a lower increase of MS and LB colonization rate than the placebo group this difference was not statistically significant (Chi-square test, $P>0.05$).

Figure 2. Percentage of New MS and LB Colonization in Infants at 1 Year

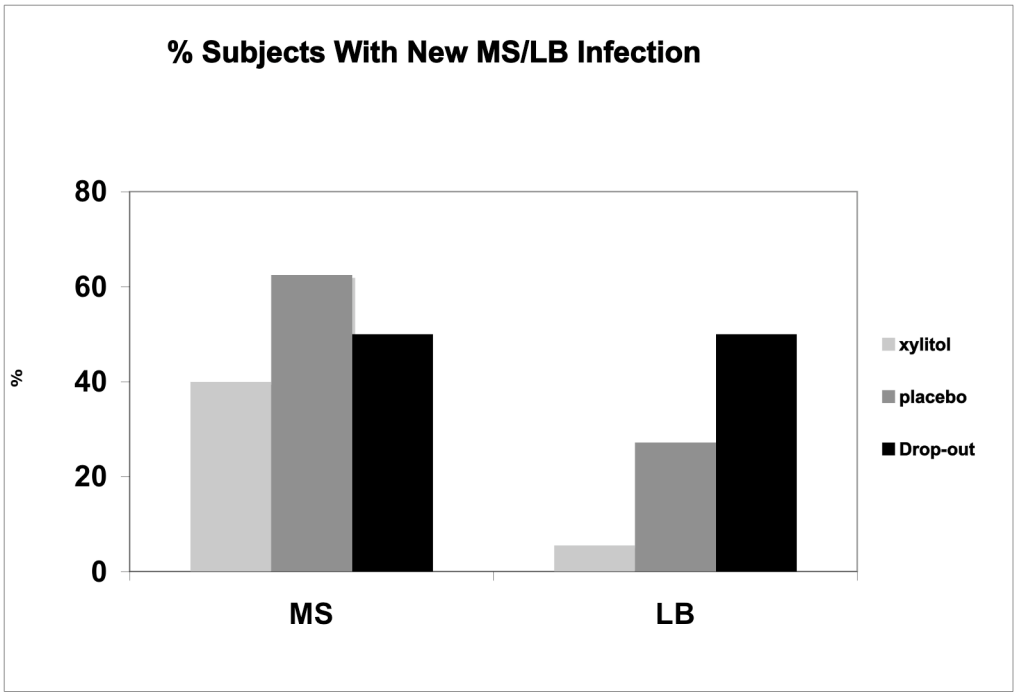
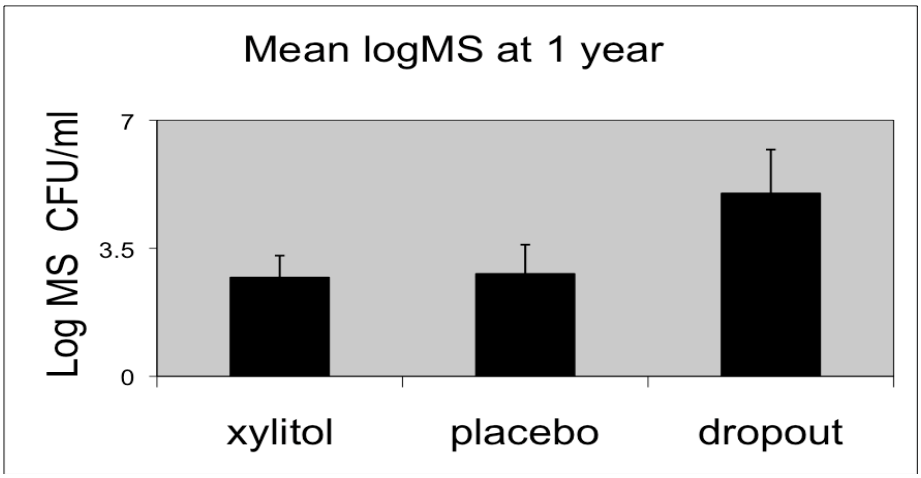


Figure 3 (A, B) illustrates the mean logMS and mean logLB colonization in infants at 1 year for xylitol-wipe, placebo-wipe and the dropout group. Mean logMS values were 2.7±0.6, 2.8±0.8, and 5.0±1.2 with log LB levels as 0.1±0.1, 0.1±0.1, and 1.4±0.9, respectively. Only the dropout group had significantly higher log LB at 1 year compared to the two wipe groups (ANOVA, $p < 0.05$).

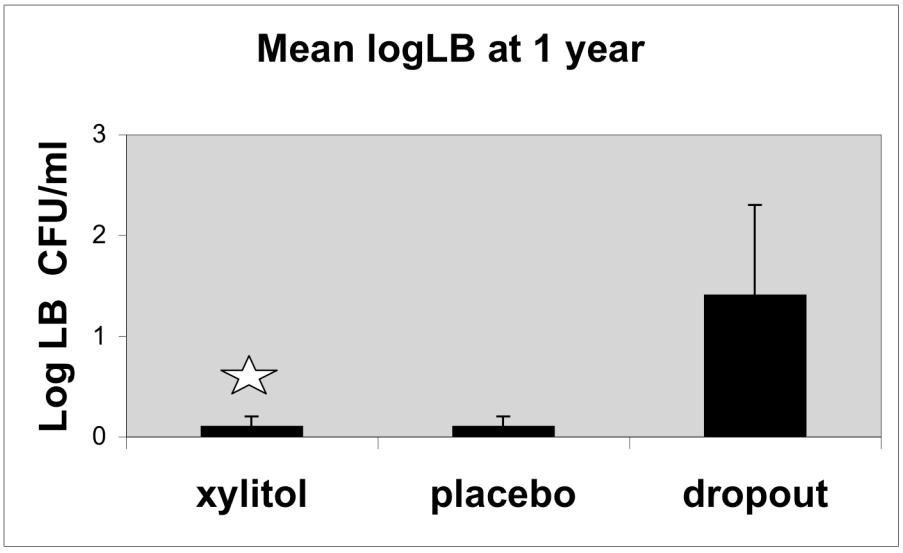
Figure 3. MS and LB levels At 1 Year (error bars stands for SE)

A.



There was no statistically significant difference in MS levels in infants at 1 year among the groups (ANOVA, $p > 0.05$)

B.



Only the dropout group had significantly higher log LB at 1 year compared with the two wipe groups (ANOVA, $p < 0.05$)

Table 2 illustrates MS and LB colonization level changes within the subjects for each group at 3 months, 6 months, and 1 year compared to baseline in infants. No statistically significant differences were found in changes of MS level between the 2 groups at all follow-up visits. However, in the placebo-wipe group, there was a significant increase of MS levels at 1 year compared to baseline (paired t test, $p < 0.05$). In contrast, in the xylitol-wipe group, no significant difference of MS levels was found at any follow-up visits compared to baseline.

Table 2. **MS and LB infection Level Changes of Xylitol-Wipe Group and Placebo-Wipe Group at 3 Months, 6 Months, and 1 Year Compared to Baseline (log mean±SE) in Infants**

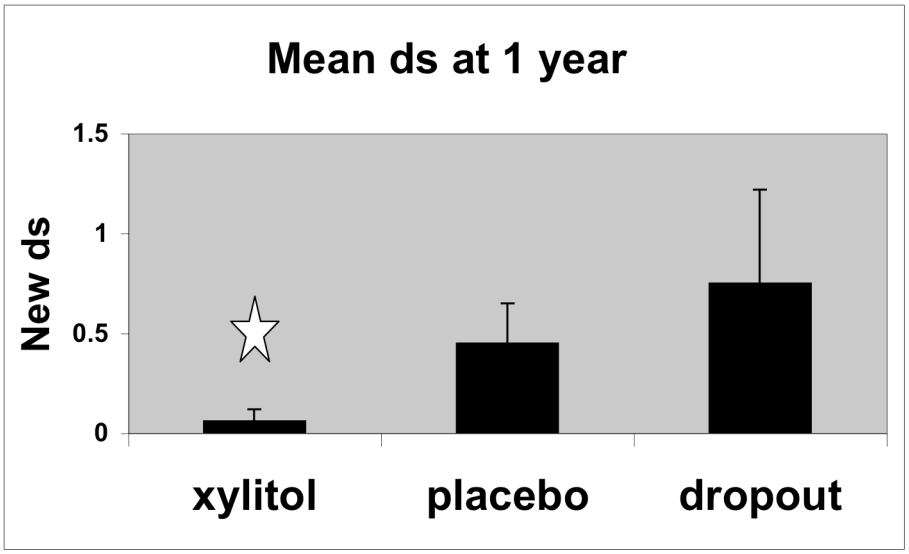
	Xylitol		**Placebo**	
	MS	**LB**	**MS**	**LB**
3 month	-0.1±0.1	0.1±0.2	0.5±0.3	0.2±0.1
6 month	-0.2±0.6	0.5±0.3	0.1±0.4	0.0±0.0
1 year	1.4±0.6	0.1±0.1	1.8±0.4	0.6±0.1

There were no significant differences in the levels of MS and LB at 3, 6, and 12 months between the xylitol wipe group and the placebo wipe group.

4.4 Caries Status at 1 Year

Infants in the xylitol-wipe group had significantly less new decayed surfaces at 1 year (mean ds±SE=0.06±0.06, $p < 0.05$) than the placebo-wipe (mean ds±SE=0.45±0.20) and dropout group (mean ds±SE=0.75±0.47) (Figure 4). Only 1 out of 18 infants in the xylitol-wipe group had any new lesions at 1 year, compared to 5 out of 11 in the placebo-wipe group and 3 out of 5 in the dropout group.

Figure 4. Numbers of new decayed surfaces at 1 year



Infants in the xylitol-wipe group had significantly less new caries at 1 year compared to the placebo-wipe and dropout groups (ANOVA, $p < 0.05$)

5. DISCUSSION

5.1 Effect of Xylitol Use on Caries Prevention

Clinical studies of xylitol have mostly involved chewing gum in school-aged children and dental decay in permanent teeth. A recent study showed, for the first time, successful reduction of dental caries by direct use of xylitol syrup in infants[50]. The aim of our study was to investigate the effect of direct xylitol-wipe use on MS acquisition and dental caries in infants. We found that daily xylitol-wipe use significantly reduced new caries in infants at 1 year compared to the placebo-wipe and the dropout groups. The mean number of new decayed surfaces in the xylitol group was only one seventh of that in the placebo group and one twelfth of that in the dropout group. It is very interesting that only 1 out of 18 infants had any new decay in the xylitol group compared with 5 out of 11 in the placebo group. This result in itself is a clear indication of the marked effect the xylitol wipes had in the present study; xylitol-wipe use almost totally

eliminated new decay in the xylitol group. These results provide further evidence on the anti-caries effect of xylitol use in infants.

In addition to the dramatic caries-preventing effect of xylitol, the study also showed that xylitol-wipes were safe; no mothers reported any adverse side effects such as diarrhea or abdominal stress. This is in agreement with a recent study that found xylitol use at the doses of 5 to 7.5 g daily were well tolerated by infants aged 6 to 36 months[51].

High caries-risk individuals generally display poor commitment to oral hygiene practices. Thus, acceptance of an anti-caries regimen plays an important role on its successful integration into one's daily routine. The xylitol-wipes were much better received by the infants compared to the placebo-wipes. There was a high completion rate of the study by the xylitol-wipe subjects (4 total dropouts) and only 1 mother reported rejection by her infant. The other 3 dropped out subjects moved away from the Bay Area. In contrast, the placebo-wipe group had a 50% (11 subject) dropout rate with 7 subjects reporting rejections of infants to wipe-use. These results support the findings by Galganny-Almedia *el al.* who reported better acceptance of xylitol-wipes by infants at night and equal satisfaction at daytime compared to brushing[52]. The findings also indicated that sweetening of tooth-wipes by xylitol greatly facilitated its acceptance by the infants.

5.2 Effect of Xylitol Wipe Use on Cariogenic Bacterial Colonization

Our study did not show a significant effect of xylitol-wipes in decreasing the colonization rate or levels of salivary MS in infants even though there was a significant decrease in the development of new caries.

The dosage and frequency of xylitol use plays a significant role in its effectiveness. A study by Stecksen-Blicks *et al.* has reported that there were no changes in MS counts in plaque or saliva after the use of xylitol lozenges at doses of 1.7 g/day and 3.4 g/day over an 18-week period[53]. Soderling *et al*., on the other hand, indicated that, among 19-to-35-year-olds,

consumption of 10.9 g xylitol/day for 14 days resulted in the reductions of plaque and salivary MS[38]. Clinical studies in children have suggested that a threshold of 5-10 g/day of xylitol in 3 or more fractionated doses is required to gain a significant anti-caries effect[42]. Milgrom.*et al*. reinforced the need to reach such levels to affect MS level in adults[50]. In our study, each wipe contains 0.7 g of xylitol. The mothers were instructed to use 2 wipes 3 to 4 times a day, with a daily dosage of approximately 4.2-5.6 g. The amount of xylitol in our study, if properly used, theoretically reached the anti-caries effect threshold for infants.

The present study found a trend of MS reduction at 6 months and a non-significant increase at 1 year. This result is consistent with some previous studies that reported short-term use of xylitol products led to a reduction of MS levels; this reduction phenomenon diminished after long-term xylitol use[54, 55]. Several studies demonstrated that long-term xylitol consumption selected for xylitol-resistant MS incapable of accumulating toxic xylitol phosphate and thus not inhibited by xylitol[55].

In the present study the caries rate was markedly reduced with xylitol-wipe use even though there was no significant reduction of cariogenic bacteria levels, suggesting that the virulence factors or the microbial biota might have been modified by consistent xylitol use. Some previous studies hypothesized that xylitol-resistant strains were less virulent compared with X-S strains; they may not adhere as tightly to the teeth and are believed to produce less acid[37]. This notion, however is contradicted by the study by Assev *el al*.[45]. Very few studies have been conducted to verify whether MS not inhibited by xylitol is truly less virulent compared with strains inhibited by xylitol. Further investigation on the impact of xylitol-wipe use on the cariogenic characteristics of MS isolates is necessary for better understanding of the preventive mechanism of xylitol against caries. Such exploration is essential in explaining the puzzling emergence of X-R MS concurrent with caries inhibition.

Currently there is no obvious explanation as to why the xylitol-wipe use did not reduce

the levels of MS. Further investigations are in progress to study the virulence characteristics of the bacteria and changes among the groups, but this is beyond the scope of the present study.

The present study also assessed LB response to xylitol exposure. We found very low levels of LB colonization in both wipe groups at 1 year compared to a significantly higher LB colonization in the dropout group. The literature contains conflicting results with regards to xylitol's effect on LB. The Belize xylitol study reported a decrease in salivary LB[43]. In contrast, the study by Loesche and colleagues, studying the effects of xylitol, sorbitol, and fructose chewing gum for 4 weeks, reported that xylitol only significantly reduced MS levels but not LB levels[56]. Our finding suggests that wiping alone, with or without xylitol, could reduce the level of LB and help in the prevention of caries.

Limitations of the present study include the relatively small sample size and high dropout rate in the placebo group. Studies with a larger sample size, and inclusion of a no-wipe group and a placebo-wipe group sweetened with another sugar substitute are needed to verify whether xylitol or tooth-wiping, or a combination of the two, is beneficial in preventing cariogenic bacteria colonization. Future studies investigating the effect of xylitol on MS cariogenic properties at the genetic level will be crucial in understanding the mechanism behind xylitol's anti-caries effects. Regardless, the present study clearly showed a significant reduction in the formation of new carious lesions as a result of daily xylitol-wipe use. In particular, the present study showed almost complete elimination of new decayed surfaces in infants in the group that used the xylitol-wipes. Regardless of sample size this result is potentially very important clinically.

6. CONCLUSION

This study examined the response of MS and LB levels to xylitol-containing wipes administered directly onto infants' teeth. The notion was that regular use of xylitol-sweetened

wipes would exert a caries-inhibitory action through reduction of salivary MS and LB counts or alterations of bacterial growth and adhesion. The results of this clinical study suggest that even though the protocol of daily wiping with xylitol wipes may reduce the amount of dental plaque and interfere with the microbial composition or characteristics, it did not decrease the proportion of salivary MS. There was a dramatic reduction in the development of new caries, however, in the xylitol-wipe group. Thus, we conclude that xylitol-wipes have a significant protective effect against the development of new carious lesions. There is a great need for effective methods to prevent ECC; the direction towards intervention against oral bacterial colonization may lead to effective caries prevention in light of the fact that dental caries is bacterially based disease. For xylitol to be successfully used in oral health improvement programs, effective delivery methods must be developed and identified. With xylitol's safe side-effect profile and multiple confirmed results of its anti-cariogenic properties, xylitol use shows great potential in being widely accessible and utilized. Additional studies are needed to establish and confirm whether the regimen of wiping with xylitol-wipes in infants does dramatically reduce new caries lesion formation in larger sample sizes, and to establish the mechanism behind such changes. It should be emphasized that such practice is only supplemental, thus not a substitution for a comprehensive dental program that encompasses adequate fluoride exposure, good oral hygiene routines, and regular dental visits.

Based on this study's results, the following conclusions can be made:

1. Xylitol-wipe use showed a significant protection against development of new caries in infants.
2. Addition of xylitol to wipes greatly increased their acceptance of use by the infants.
3. Wiping alone, with or without xylitol, could reduce the level of cariogenic bacteria and aid in the prevention of caries.
4. Future studies are needed to investigate the mechanism of xylitol use on the virulence factors of cariogenic bacteria.

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APPENDIX 1: Subject Questionnaire

Please answer the following questions about your child's oral health care habits as best as you can:

Child's Name: _____
First **Last**

Child's Birth date: _____/_____/_____.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SCHOOL OF DENTISTRY

Xylito wipes Study

Form 2 Subject Oral Care Survey

Subject initial: _____. Subject ID:
MM DD YYYY

Child's gender: Male____ Female_____

Telephone Number: _____

1. How often does your child or you brush his/her teeth?
   - □ Not every day
   - □ 1 time each day
   - □ 2 times each day

2. Is your child using fluoride toothpaste?
   - □ Yes
   - □ No
   - □ I do not know.

   What kind of toothpaste does your child use? _____

3. How many times a day does your child eat sweet things such as soda, juice, sweets and cookies?
   - □ Never
   - □ 1 – 3 times a day
   - □ 4 – 6 times

□ +6 times

4. Please check any that apply regarding your child's feeding habits:
   - □ Breast-fed only
   - □ Bottle-fed only
   - □ Breast and bottle fed
   - □ Fed at regular intervals
   - □ Fed on demand
   - □ I pre-taste my child's food
   - □ child shares food with others

5. Please check any that apply regarding what your child goes to bed with:
   - □ water
   - □ breast milk
   - □ cow's milk
   - □ cow's milk and added sweetener
   - □ juice
   - □ none of the above
   - □ does not apply

6. Have you seen a dentist at least once a year in the past two years?
   - □ Yes.
   - □ No.

7. Have you had a cavity in the last 2 years?
   - □ Yes
   - □ No

8. Have your infant seen a dentist at least once in the past 2 years?
   - □ Yes
   - □ No

9. Would you like to know you and your child's test results at the end of the study?
   - □ Yes
   - □ No

APPENDIX 2: Record Sheet

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SCHOOL OF DENTISTRY
Xylitol wipes Study **Form: Record sheet for participant's ethinicity and contact information**
Subject initial:_____. Subject ID:_____.

Is your ethnic background Hispanic, Latino or other Spanish descent?

☐ No

☐ Yes

- ☐ Central American
- ☐ Cuban
- ☐ Mexican
- ☐ Puerto Rican
- ☐ South American
- ☐ Other Hispanic _____

Please select your racial background (you may select more than one):

☐ African-American / Black / Haitian

☐ American Indian / Native American / Alaskan Native

☐ Asian

- ☐ Bangladeshi
- ☐ Burmese
- ☐ Chinese
- ☐ Filipino
- ☐ Indian
- ☐ Indonesian
- ☐ Japanese
- ☐ Korean
- ☐ Laotian
- ☐ Malaysian
- ☐ Pakistani
- ☐ Thai
- ☐ Vietnamese
- ☐ Other Asian _____

☐

Caucasian / White / Middle Eastern

☐ Native Hawaiian / Pacific Islander

- ☐ Fijian
- ☐ Guamanian
- ☐ Hawaiian
- ☐ Samoan
- ☐ Tongan
- ☐ Other Pacific Islander _____

☐ Other _____

☐ Do not wish to respond

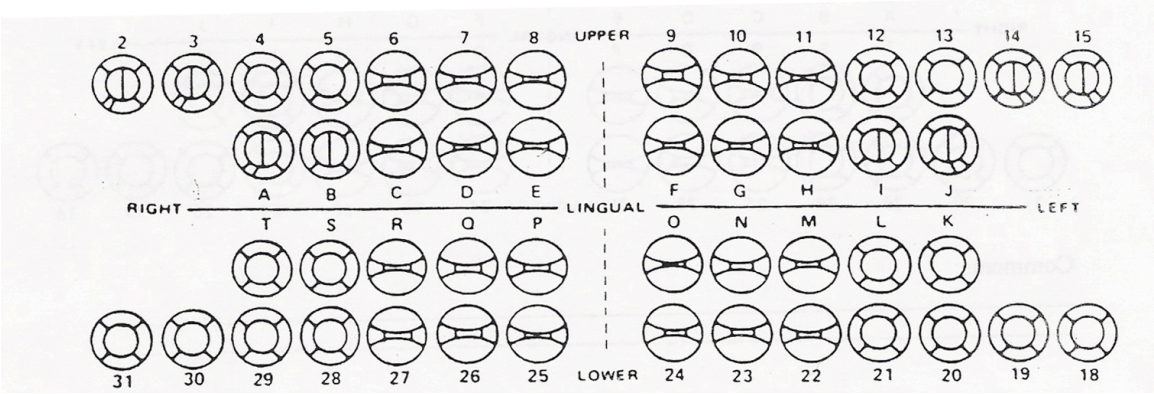
Thank you for your participation!

(Source: Gansky SA: Participant race/ethnicity form compliant with 1997 OMB Directive 15. UCSF CAN-DO internet website, 7/13/2005 accessed, http://www.ucsf.edu/cando/PDF%20Files/race_ethnic.pdf)

APPENDIX 3: Data Collection Sheets

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SCHOOL OF DENTISTRY
Xylitol wipes Study **DMFS/dmfs Record Sheet**
Subject's initials: _____. Subject ID: _____.
Visit Date: ____/____/_____ Mother ____ Child ____

Charting: Red=current decay, Blue= previous restorations, X=missing



Comments:

_____
_____
_____
_____
_____

APPENDIX 4: Enrollment Sheet

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SCHOOL OF DENTISTRY
Xylitol wipes Study **DMFS/dmfs Record Sheet**
Subject's initials: _____. Subject ID: _____.
Visit Date: ____/____/_____ Mother ____ Child ____

PROCEDURES			
Subject Qualification			
1. Mother has at least 1 active caries lesion in the past year?		**Yes**	No
2. Mother or child antibiotics in past 3 months?		Yes	**No**
3. Taking any medicine that causes dry mouth?		Yes	**No**
4. Any hepatitis and HIV etc. systemic disease?		Yes	**No**
5. Will stay in the Bay Area for another 1 year?		**Yes**	No
6. Any significant developmental dental disease?		Yes	**No**
7. Is mother primary caregiver?		**Yes**	No
Patient qualified for the study		**Yes**	No

BASELINE SALIVA SAMPLE			
Consent form signed by the mother?		Yes	No
Questionnaire completed?		Yes	No
dmfs exam for child done?		Yes	No
Saliva sample collected from the **mother**? (1 tube, 2 ml in ≤ 4 minutes)		Yes	No
Saliva sample collected from the **infant**? (Oral swab)		Yes	No
Randomization (check one group)	Group A ___ Group B		
1st -3rd month supply of wipes ☐			
Scheduled date for the next allotment (include week day also): ___/___/____(___)			
Comments:_____ ____ _____			

Investigator's Signature:

Patient's Initials	Patient treatment group: _____.	Patient Study ID Number _____
4th -6th month supply of wipes ☐		
Date of visit	___/___/_____.	
Record any unpleasant effects or irritation after using the wipes. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. crying _____ c. resistant _____ d. allergy _____ e. other _____	
Container of wipes returned?	Number of wipes remaining _____.	
Scheduled date for the next allotment and **6 MONTH saliva sample collection** (include week day): ___/___/_____(_____)		
Investigator's Signature:		

6 month SALIVA SAMPLE **7th-9th month supply of wipes ☐**	
Date of visit	___/___/_____.
Record any unpleasant effects or irritation after using the wipes. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. crying _____ c. resistant _____ d. allergy _____ e. other _____
Container of wipes returned?	Number of wipes remaining _____.
Saliva sample collected from **mother**?	Yes.
Saliva sample collected from **child**?	Yes. _____
Scheduled date for the next allotment (include week day also):___/___/_____(_____)	
Investigator's Signature:	

Patient's Initials	Patient treatment group: .	Patient Study ID Number PR___/___/___
10th-12th month supply of wipes ☐		
Date of visit	___/____/_____.	
Record any unpleasant effects or irritation after using the wipes. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. crying _____ c. resistant _____ d. allergy _____ e. other _____	
Container of wipes returned?	Number of wipes remaining_____.	
Scheduled date for the final visit and **1 year saliva sample** (include week day also): ___/___/_____(_____)		
Investigator's Signature:		
1 year SALIVA SAMPLE		
Date of visit	___/____/_____.	
Record any unpleasant effects or irritation after using the wipes. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. crying _____ c. resistant _____ d. allergy _____ e. other _____	
Container of wipes returned?	Number of wipes remaining _____.	
Saliva sample collected from mother? (1 tube, 2 ml in ≤ 4 minutes)	Yes.	
Saliva sample collected from child? (oral swab)	Yes.	
Investigator's Signature:		
Dose the patient have any change in their contact information: Yes. No. **If "Yes", please update the patient contact information.**		

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