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Effects of Povidone-iodine foam in children with active decay

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Effect of Povidone-iodine Foam in Children with Active Decay

by

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THESIS

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ABSTRACT

Effect of Povidone-iodine Foam in Children with Active Decay

Purpose: The purpose of this investigation was to conduct a randomized clinical study on the efficacy of four weekly applications of a povidone iodine/fluoride (PVPI-F) foam on the reduction of cariogenic bacterial levels, namely mutans streptococci (MS) and *Lactobacillus* (LB) species. The hypothesis was that four weekly applications of PVPI-F would suppress MS and LB.

Methods: Fifty-three healthy assenting 6-9 year olds with 1-5 frank caries lesions were enrolled in the study, randomized to either a control group (F-only, 5,000 ppm F foam) or a test group (PVPI-F foam). The treatment was performed at baseline and then once/week for 3 consecutive weeks. Stimulated saliva samples were taken at the initial visit before treatment (S1), then 1 month after the four weekly treatments were completed (S2). MS and LB were enumerated on selective media as colony forming units per ml (CFU/ml) of saliva. CFU/ml were converted to $\log_{10}$MS and $\log_{10}$LB for statistical analyses.

Results: Log_{10}MS at S2 was not significantly different from S1 in either group nor between groups at either S1 or S2 (P=0.32). Log_{10}LB in the PVPI-F group was suggestive of reduction from S1 to S2 but this was not statistically significant (P= 0.57)

Conclusions: The F-only control group showed no change in MS or LB. In contrast to previously reported bacterial reductions by PVPI in solution in younger children, MS and LB levels were not significantly reduced in the PVPI-F foam group compared to the F-only control group.

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Literature Review

1. 1 Epidemiology

Dental caries, also known as tooth decay, is the pathologic process of tooth destruction by oral microorganisms that can affect individuals of all ages and cultural, ethnic and socio-economic backgrounds. In 2000 it was determined that dental caries was the most common chronic disease of childhood, with a rate five times greater than that seen for the next most prevalent disease of childhood – asthma [1] . Because dental infections are common and usually non-life-threatening in nature, the significance of dental decay in overall human health has historically been minimized.

In 1981 the World Health Assembly of the World Health Organization (WHO) declared that the global goal for oral health by the year 2000 should be that the mean number of decayed, missing or filled permanent teeth (DMFT) for the 12-year-olds should not exceed 3. Over a period of twenty years, nearly 70% of the countries in the world have succeeded in achieving this goal, or have never exceeded this borderline value – a great step towards "Health for All". However, a detailed analysis of the caries situation in many countries shows that there is a skewed distribution of caries prevalence – meaning that a proportion of 12-year-olds still have high or even very high DMFT values even though a proportion is totally caries free. A new index, the *Significant Caries Index (SiC Index)* was introduced in order to bring attention to the individuals with the

highest caries values in each population under investigation. The SiC Indexes published by WHO showed, for example, although the mean DMFT for 12 year-old in the USA and UK were each 1.4, the SiC indexes were 3.6 and 3.5 respectively. Therefore, WHO has set a new goal of oral health for those countries, which reached the WHO/ World Dental Federation (FDI) global goal of 3 DMFT, to achieve the SiC Index to be less than 3 DMFT in the 12-year-olds by the year 2015 (http://www.whocollab.od.mah.se) [2].

Although overall dental caries prevalence and severity has been notably reduced in several western world countries over the past couple of decades, dental caries continues to be a major health issue in the United States. The Third National Health and Nutrition Examination Survey (NHANES III)-Phase 1,which collected data from 1988 to 1994 which indicated that 50% of 5-8 year old children in the United States had experienced caries in the primary dentition [3]. Remarkably, when the data are examined, approximately 25% of children and adolescents in the 5-17 age range accounted for 80% of the caries experienced in the permanent teeth. These facts indicate that caries continues to be a major oral health concern in children in the USA and worldwide [4]. It is evident from numerous studies that dental decay continues to affect individuals through childhood and beyond [4].

Despite the fact that some individuals remain highly susceptible to dental decay, the generalized overall decrease in caries prevalence experienced by a large percentage of the population cannot be associated with any single event. It is a common belief that this overall decrease in caries prevalence is due most

notably to the incorporation of fluoride in toothpastes, mouth rinses, and selected water supplies since the mid- 1970s [5, 6]. Unfortunately, the beneficial effects credited to fluoride seem to have reached a plateau since the 1990s [7].

Untreated dental decay continues to persist regardless of thorough and consistent oral hygiene instruction, cutting edge restorative techniques and continued development of new and improved dental materials. Based on data collected from 1993-1994, in California, it was found that 55% of children 6-8 years old had untreated dental decay [8, 9]. A survey completed recently by the Dental Health Foundation found that 54% of the kindergartners and 71% of the 3rd grade children in California had a history of tooth decay [10].

Despite various caries preventive methodologies and procedures currently in use, a portion of the population continues to remain at high risk of developing caries. Unfortunately routine treatment protocols do not include a viable preventive approach based upon the control of the bacterial factors involved in decay over and above the benefits given by fluoride therapy [11]. These high-risk individuals are most likely in need of added preventive measures such as antibacterial treatments in order to reduce their cariogenic bacterial loading and consequently decrease the intensity of their caries challenge.

Currently dental caries is one of the most common infectious diseases inflicting humans. Due to issues related to access to care, such as finances, location of providers and patient education, dental decay remains untreated in many underdeveloped countries. Untreated dental decay leads to considerable suffering that is often alleviated only by the loss or extraction of the infected tooth

[12]. The impact of dental caries extends beyond the boundaries of health: the resulting oral pain and chronic discomfort may affect speech, eating, sleeping, swallowing, breathing, and the altered appearance it causes to any visible teeth may undermine self-image, self-esteem and social acceptance [13].

1.2 Etiology

1.2.1 Caries Process

Dental Caries is a multifactorial, transmissible, bacterial disease. In 1960, Keyes demonstrated that specific microorganisms are responsible for dental caries [14]. Dental caries is an infectious disease caused by acid producing bacteria, primarily mutans streptococci and lactobacilli in adults and children [15]. Cariogenic (decay causing) bacteria in the dental "plaque" feed on fermentable carbohydrates from the human diet and produce acids. These acids travel into the tooth and dissolve calcium and phosphate from the tooth mineral, in a process known as demineralization. If demineralization is allowed to continue, it eventually produces a cavitation in the tooth structure. The initial demineralization process can be reversed or inhibited by saliva, which contains minerals, fluoride, protective proteins and antibacterial reagents. The partially demineralized tooth can be repaired by the re-incorporation of calcium and phosphate from the saliva, promoted by the presence of fluoride. This tooth repair process is called remineralization.

Demineralization and remineralization occur numerous times daily. The delicate balance between caries progression and its reversal is determined by

many factors including the quantity and quality (virulence) of the bacteria present in the mouth, the content and flow rate of saliva, and the presence or absence of fluoride [15]. Fluoride from drinking water and dental products has played a considerable role in the reduction of caries prevalence and its severity during the past few decades [15]. However fluoride therapy alone cannot overcome the severe bacterial challenge in high caries risk individuals. Caries prevalence and its severity have been greatly reduced in the past few decades. This observed decrease in caries has been associated with factors such as fluoride dentifrices and water fluoridation. Despite the use of these various caries-preventive procedures and methodologies, a portion of the population continues to remain at considerable risk of caries progression [15]. Further, results of an ongoing caries management study with caries risk assessment in adults showed the cariogenic bacterial challenge remained high despite the conventional dental treatment completion (data unpublished). These high-risk individuals may benefit from added preventive measures such as antibacterial treatment to reduce their "caries challenge". The benefit of additional antibacterial therapy could be particularly applicable in lower socioeconomic populations due to the large number of high caries risk individuals for whom fluoride alone appears insufficient to control the level of caries challenge. The following sections outline the various factors alluded to in further detail.

1.2.2 Cariogenic Bacteria

Many oral microorganisms participate in the formation of caries, but specific bacteria, namely mutans streptococci (in humans, *S. mutans* and *S. sobrinus*) and lactobacilli, have demonstrated a greater cariogenicity [15, 16,17, 18].

Considerable data has linked mutans streptococci to the formation of caries because they are acidogenic and aciduric, which allow the organisms to produce acid and survive in the acidic environment necessary for caries formation [15].

Mutans streptococci are believed to initiate the dental caries process within the enamel while lactobacilli are thought to be involved in the progression of decay further into tooth structure [19, 20].

Mutans streptococci are able to metabolize a great variety of carbohydrates. Carbohydrates that can be metabolized by mutans streptococci include, but are not limited to: glucose, fructose, sucrose, lactose, galactose, mannose, starch, and isomaltosaccharides [21].

Although the general category "mutans streptococci" or MS is often found in dental literature it is important to mention that this is a term used to refer to a collection of bacterial species. Streptococcus mutans is considered by some to be the most cariogenic of all the mutans streptococcal species and according to Loesche the principle causative agent implicated in human dental caries [21]. *S. sobrinus* is the second most commonly isolated species of mutans streptococci in humans. Some studies indicated that this species might be more virulent than *S. mutans*. Clinical studies had found that subjects with a mixed infection of *S. mutans* and *S. sobrinus* tended to have more dental decay than subjects with infection of only a single mutans streptococci bacterial species [22]. Other studies

indicated that children with *S. sobrinus* infection developed more smooth surface decay than children without this mutans streptococci species [22].

Pediatric patients most often acquire mutans streptococci from their caregivers as it is transmitted via saliva [15]. Studies have also shown that children colonized with mutans streptococci possess the same bacterial serotype as their infected mothers [23]. The presence of high levels of mutans streptococci in saliva does not mean that caries formation is inevitable for this patient but rather that there is an increased risk of caries development. Kohler and Bratthall determined in their study that caries-free children had less than 10,000 colony forming unit/ml (CFU/ml) of saliva [24]. Featherstone (unpublished data) concluded that in pediatric patients, a high caries risk exists if the saliva contains ≥ 10,000 CFU/ml of mutans streptococci and below this threshold; the patient has a moderate to low caries risk. Ramos-Gomez *et al.*; concluded that children with $\log_{10}$ MS $\geq$ 3.0 &/or $\log_{10}$ LB $\geq$ 1.5 were about five times as likely to have early childhood caries than those with lower cariogenic bacterial levels [25].

The presence of lactobacilli has also been associated with caries formation and tooth decay [26]. Various lactobacilli species have been consistently associated with caries and are thought to be important secondary pathogens in the process of dental decay [26, 27]. Lactobacilli are highly acidogenic with the ability to produce lactic acid from the fermentation of glucose and other carbohydrates. These bacteria have been associated with advancing caries rather than the formation of a carious lesion [28]. High counts of lactobacilli in saliva and plaque are often indicative of a high total carbohydrate consumption

and is therefore considered an indirect indicator of caries risk [26]. Furthermore, lactobacilli are difficult to eradicate since they can use many oral surfaces for colonization including the teeth, the tongue and the cheeks.

Featherstone (unpublished data) concluded that in pediatric patients, a high caries risk exists if the saliva contains ≥ 10,000 CFU/ml of mutans streptococci, ≥ 100 CFU/ml of lactobacilli and below this threshold, the patient has a moderate to low caries risk.

1.2.3 Host factors

Many host factors can have a direct effect on the balance of protective and pathogenic factors. Factors that can change this balance and possibly increase or decrease a patient's caries risk include the mechanical and chemical functions of saliva, irregularities in the enamel surfaces of the tooth, and diet.

Saliva

The influence of saliva on oral health is well documented. It is one of the key host defense systems in caries development and progression. Saliva contains antibacterial, antiviral, and antifungal properties as well as proteins, phosphates, and bicarbonate molecules that have a buffering capacity, which helps maintain the oral environment at an optimum pH [29]. This optimal salivary pH effectively neutralizes acids and therefore will decrease the mineral dissociation of teeth as well as protect the oral soft tissue. The salivary pH usually stays around the

neutral point of 7. The breakdown of fermentable carbohydrates by cariogenic bacteria, namely *Streptococcus mutans*, *Streptococcus sobrinus*, and lactobacilli causes a drop in salivary pH and creates a gradient allowing acid to enter the tooth. Once the salivary pH drops, minerals move out of the tooth, and are dissolved [13]. Any fluctuations in salivary pH are largely due to diet and the frequency of carbohydrate intake. If the pH of the saliva is not kept sufficiently high, the teeth may erode or be susceptible to caries formation.

Diet

Another important host factor is the dietary profile of the patient. A change in the quantity and frequency of carbohydrate consumption can affect the balance between protective and pathologic factors. Even in the presence of cariogenic bacteria, if little or no suitable dietary substrates are present, little or no acid will be produced through carbohydrate metabolism, ultimately reducing the risk of caries development.

Frequency of consumption of fermentable carbohydrates can also influence caries challenge. Increased frequency of carbohydrate (i.e. sucrose, fructose, and cooked starch) increases the acidity of plaque and prolongs the length of time that an acidic environment is maintained in the mouth. The extended time that an acidic environment is maintained, increases the potential for enamel demineralization, and provides inadequate time for remineralization by various components of saliva. The result is that the balance between the protective and

pathological factors shifts significantly in favor of pathological factors leading to demineralization of the tooth structure [30]

1.3. Clinical Management of Caries

Until recently, clinical management of dental decay consisted solely in physical removal of decay from the tooth and restoration of the defect with a stable material. Dental restorations are commonly placed as treatment for dental decay. Gregory *et al.*, showed that there were no significant differences in pre- and post-restoration concentrations of mutans streptococci or total oral streptococci in children [31]. It has been shown that removal of decay and placement of restorations does have a temporary effect of decreasing levels of mutans streptococci and lactobacilli, but shortly thereafter these levels gradually returned to the pre-treatment levels in most subjects studied [11]. Therefore, standard restorative treatment alone is not effective for eliminating mutans streptococci or lactobacilli from tooth surfaces throughout the mouth or eliminating caries risk. Because of the demonstrated ability of cariogenic organisms to rapidly re-establish throughout the mouth it is essential to effectively reduce the numbers of salivary cariogenic bacteria in the plaque by antibacterial treatment in order to have a significant effect on an individual's caries risk [31].

1.4. Medical Management of Caries

Since dental decay is bacterial in etiology, the use of antibacterial agents against cariogenic microorganisms is logical. Nevertheless, there are no specific antibiotics or vaccines available.

Various antibacterial approaches have been attempted to control intraoral bacterial levels. Of those, the four most extensively researched antibacterial agents are discussed below.

1.4.1Fluoride

Fluoride has been utilized in oral health since the 1940s. It is known for its well-established effects on the remineralization processes [15]. It is an anion that when incorporated into the apatite of the tooth structure can decrease tooth solubility making it more resistant to acid challenge [32]. It is available for delivery to individuals in many forms including, liquid, tablets, toothpastes, mouthrinses, water, gels, foam and varnishes.

ADA (American Dental Association) recently published evidence-based clinical recommendations for professionally applied topical fluoride. The council recommends use of fluoride gels or foam for four minutes. Interestingly, even though foam is commonly used in dental practice; the weight of the clinical evidence of its effectiveness is not as strong as that for fluoride gel and varnish. Further clinical trials are recommended to establish the effectiveness of fluoride foam [33].

1.4.1.1 Mechanism of action

Fluoride can also act as an inhibitor of cariogenic bacteria [32]. Fluoride can not enter the cell as the ion, but can readily diffuse into the cell as HF, so when the bacteria produce acid, the hydrogen ion combines with fluoride present in the plaque and diffuses into the cells [32]. Inside the cell the HF dissociates, producing fluoride ion, which interferes with enzymatic pathways. Fluoride interferes with enolase, a critical enzyme in the metabolic pathway, thereby reducing the acid by-product [32]. Additionally, fluoride may act to reduce the function of the membrane gradient for H^+ which directly inhibits the glucose uptake necessary for bacterial metabolism to occur at low pH [32].

Fluoride is routinely used to reinforce good oral hygiene, but its use has been shown to be effective only up to a point; a high bacterial challenge cannot be completely overcome by even high-concentration fluoride therapy [34].

1.4.2 Chlorhexidine

Chlorhexidine is the most widely used antibacterial agents currently available [35]. At concentrations ranging from 0.1% to 40% in solutions, gels, chewing tablets and varnishes, chlorhexidine has been shown to reduce MS to low levels in saliva and dental plaque in children and adults who have high caries risk [36]. Many studies show chlorhexidine products reduce the levels of MS in the mouth, but its efficacy on lactobacilli is limited [37-40].

Currently in the United States 0.12% chlorhexidine gluconate oral rinse containing ethyl alcohol is available by prescription. Chlorhexidine is a positively charged bis-biguanide with bactericidal activity against both gram-positive and gram-negative bacteria [35, 41]. Its positive charge allows the chlorhexidine to bind to the enamel pellicle, hydroxyapatite and bacterial cell walls. When bound to the bacterial cell wall, it disrupts cell membranes by binding to their negatively charged sites [41]. When chlorhexidine is in the presence of fluoride, fluoride has an antagonistic effect. When fluoride interacts with chlorhexidine, the small negatively charged fluoride ion inhibits the bactericidal effects of chlorhexidine on cariogenic bacteria [42]. Hence the recommendation that the interval between toothbrushing with fluoride toothpaste and rinsing with chlorhexidine be more than 30 minutes [43].

A major disadvantage of chlorhexidine use continues to be difficulty in maintaining patient compliance. In addition to its unpleasant taste, it may also cause temporary tooth staining, formation of supra-gingival calculus and temporary loss of sense of taste [44]. Therefore, an antibacterial with increased efficacy against cariogenic bacteria with improved patient acceptance is needed.

1.4.3 *Xylitol*

Xylitol is a naturally occurring carbohydrate sweetener discovered in the early 1980s. It is commonly found in many plants and fruits such as strawberries, plums, pears, and even in the human body [45]. Naturally sweet, lower in calories than sugar with no aftertaste, xylitol has various medical uses. It is independently

metabolized from insulin and therefore can be used by diabetics [45]. Drawbacks in the use of xylitol are: it is a laxative in large amounts, it is not cheap, it is most effective if used multiple times a day [45].

Xylitol is a five-carbon sugar alcohol that is not a fermentable substrate for mutans streptococci [46]. Xylitol is taken up, by mutans streptococci (MS), via a constitutive fructose- phosphotransferase system (PTS). MS are not able to utilize the metabolite, xylitol phosphate, which results in a toxic effect [47]. Thus xylitol inhibits growth of the bacteria. Xylitol also disturbs the protein synthesis of mutans streptococci. This in turn decreases mutans streptococci ability to adhere to the tooth surface in the presence of fermentable carbohydrates [48]. A study conducted by Miake *et al.*, shows that xylitol induces remineralization of demineralized enamel in the deep and middle layers. Xylitol combines with calcium in aqueous solution. Thus xylitol might act as a Ca^{2+} ion carrier supplying Ca^{2+} to enamel for remineralization [49].

Xylitol in the form of chewing gum displays an increase in natural salivary buffering capabilities against caries by increasing salivary flow. This is an additive effect of preventing and fighting off decay [50].

1.4.4 *Povidone Iodine*

1.4.4.1 Introduction

Povidone Iodine (PI) is known to be a powerful broad spectrum antibacterial agent, effective against a wide range of bacteria, viruses, fungi, protozoa and spores [51]. It is an effective antiseptic and used widely in medicine for

management of wounds, as a pre-surgical antiseptic, and as a disinfectant [51]. In dentistry, topical application of iodine solutions has demonstrated suppression of oral *S. mutans* populations. An early investigation indicated that a single application of 0.2% potassium iodine solution (KI) eliminated mutans streptococci from accessible human tooth sites for up to 13 weeks following treatment [52].

In 1979, Caufield *et al.*, demonstrated that use of 2% iodine-potassium iodide solution (I_2-KI) could significantly reduce the levels of *S. mutans* in fissure and proximal plaques and in saliva for 20 to 24 weeks [53]. After dental prophylaxis an aqueous solution containing 2.0% I_2 and 2.0 KI in 53% glycerin was applied to the teeth for 4-5 minutes. A total of 2-3 ml of iodine solution was used for each treatment. Two additional iodine applications were completed 3 and 5 days later [53].

More recently, a randomized placebo-controlled clinical pilot study found that multiple topical applications of 10% Povidone iodine every two months could reduce the incidence of dental caries in young dental patients with a high caries risk [54, 55]. Maltz-Turkienicz *et al.* studied the effects of both chlorhexidine and iodine on *S. mutans in vitro*. Both of the antibacterial agents were found to be effective on *S.mutans* [56]. However, contradictory results were found by Schaeken *et al.* [57]. Amin *et al.* used 10% povidone-iodine solution, applied 3 times at 2 monthly intervals. Study dose for each application was approximately 0.20 ml—a dose that contains 2 mg iodine, which is nontoxic when applied bimonthly [58]. Povidone-iodine did not significantly reduce plaque *S mutans* levels in children 6 months after dental treatment under general anesthesia (GA) [59].

A pilot study at UCSF with 20 children showed that a single application of PVPI solution following treatment for early childhood caries in children under 5 years of age, under GA after restoration of all active caries, reduced MS and LB levels significantly for up to 3 months[60], but the one time application did not reduce caries incidence over 12 months. This strongly supports the notion that multiple applications of 10% PVPI could provide a positive effect on future caries activity by reducing populations of the two major cariogenic bacterial groups in the oral cavity of children with ECC. A pilot study just completed at UCSF using PVPI foam on children (aged 6 to 9 years) with active caries gave reduced MS and LB levels at 1 week compared to baseline, but the effects were diminished by 1 month. Further, the PVPI foam formulation was well accepted by the participating children. These results suggest that four PVPI foam treatments repeated at weekly intervals would likely be a good treatment regimen to substantially reduce or eliminate MS and LB.

1.4.4.2 Povidone Iodine Structure

Povidone iodine is available commercially as Betadine, as a 10% povidone iodine solution. A 10% povidone iodine solution contains 90% water, 8.5% polyvinylpyrrolidone and only 1% of available iodine and iodide. Polyvinylpyrrolidone povidone iodine (PVPI) is an iodophor consisting of a combination of a complex of iodine (I) with polyvinylpyrrolidone (PVP) surfactant [61]. Combining iodine with PVP increases its ability to dissolve in water, reduces its irritability and decreases the staining caused by pure iodine. In the presence of water, PVP liberates a small amount of free iodine to solution [59]. When iodine

dissociates from the PVP complex, it becomes biologically active. When iodine is in its unbound form, it is active and able to assert its germicidal action. The equilibrium between the complex-bound iodine and the non-complex is presented in detail in the literature [59].

1.4.4.3 Adverse Reactions

Allergic reactions to povidone iodine are rare, occurring in the general population at a rate of one person in one-thousand [61]. The allergic reactions associated with iodine include irritation, sensitivity, skin burns, bad taste and staining. Systemic symptoms associated with general iodine toxicity include fever, diarrhea, mental status changes, metabolic acidosis and abnormal thyroid function [61]. There is enough evidence about povidone iodine's safety and efficacy for use as a topical antimicrobial agent [62].

Significance of the study

The prevalence of dental decay shows that we need an antibacterial/ antimicrobial agent to overcome the bacterial challenge in a high caries risk patient. Povidone iodine has the potential to be efficacious against these cariogenic bacteria. Furthermore the beneficial effects of a high concentration fluoride (5,000 ppm F) foam or gel are well known in enhancing remineralization of carious lesions. Chemically, povidone-iodine and fluoride can be combined to enhance the antibacterial effect of povidone-iodine and the remineralizing effect of fluoride. Potentially a PVPI-F combined foam could be applied to the teeth of children at appropriate intervals throughout a year, reducing both the MS and LB bacterial challenge, enhancing remineralization, and markedly reducing or even eliminating new caries formation. The advantage expected by using this antibacterial/fluoride combination in a flavored foam form is improved taste and easier application for routine treatment, which may broaden its future use in dental practice or home dental care for caries prevention in children with high caries risk.

Povidone iodine foam is expected to have the same efficacy as the previously used povidone iodine solution.

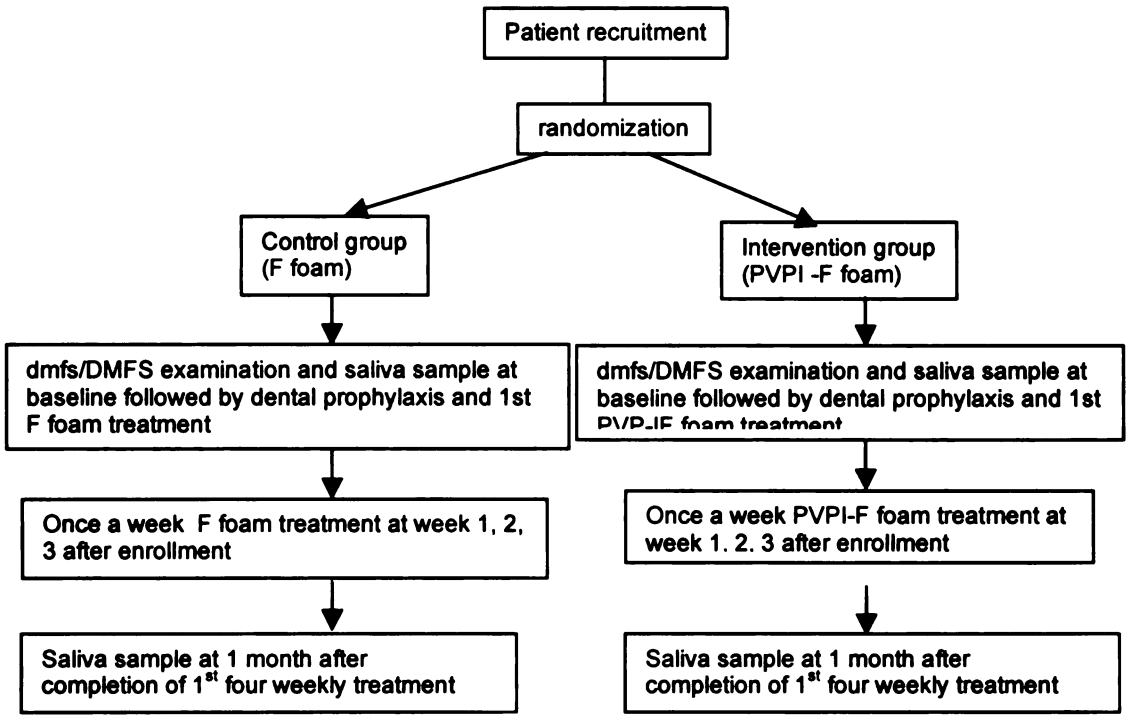
Specific Aim

The aim of the study was to conduct a randomized clinical study to determine the efficacy of four weekly applications of a povidone iodine/ fluoride (PVPI-F) foam at baseline and 1 month on the reduction of oral cariogenic bacteria levels, namely mutans streptococci (MS) and *Lactobacillus* (LB) species, in children with active caries. The hypothesis to be tested was that four weekly application of PVPI-F would suppress MS and LB colonization.

If the hypothesis is proven, it will indicate that PVPI-F foam is a convenient antibacterial treatment as a strategy in caries prevention for children in the U.S.A. and beyond, especially for children with high caries risk from socioeconomically disadvantaged families.

Experimental Design and Methods

4.1 Overview of Study- Flow Diagram



dmfs – decayed, missing and filled surfaces in primary dentition
DMFS- decayed, missing and filled surfaces in permanent dentition
PVPI-F – Povidone iodine fluoride
F- Fluoride

4.2 Subject Recruitment, Randomization and Blinding

UCSF Committee on Human Subject Research (CHR) approval was obtained prior to recruitment of any patients (CHR # H9136-26344). Parents or legal guardians of eligible subjects received a verbal and written explanation of the study procedures and the study protocol (see appendix for forms). Consenting parents signed an informed consent document approved by the UCSF CHR. The nature of the study, details of the study and any questions related to the study were answered. Children who agreed to participate in the study signed an informed assent, previously approved by the UCSF CHR (see appendix).

Other than the collection of saliva samples, all office procedures were identical to what the patients would otherwise normally receive. There was no extra cost to the subjects for participation in this study.

The study population was patients in the Postdoctoral Dental Clinic and the Predoctoral Dental Clinic at the Division of Pediatric Dentistry at UCSF.

The study population was planned for sixty children ranging from ages 6-9 years old. Subjects were selected based on appropriate age range and history of past (within 1 year) or present dental decay.

Inclusion criteria for subjects enrolled in the study included:

- Patients with a history of at least 1 active dental carious lesion within the past 1 year.
- Patients whose medical history is non-contributory.

- Residents of San Francisco or residing within 20-mile radius.
- Parent and child both willing to participate in the study.

Exclusion criteria for subjects included:

- Children with serious chronic systemic diseases or periodontal diseases.
- Children who had taken medicines within the past 3 months that might affect the oral flora.
- Children with dry mouth or who had difficulty spitting.

A randomization schedule was used to assign patients to either a) control: F-only foam group or b) intervention: the PVPI-F foam group. Details of the products used are described below. The clinician administering treatments assigned each subject either to foam A or foam B based on the randomization sheet. Placebo foam (fluoride only, control group) with similar color to the PVPI-F was used and containers for collecting saliva were uniquely coded. Only the statistician knew subject group assignments. The corresponding treatment was performed at baseline and then once a week for 3 further consecutive weeks. Stimulated saliva samples were taken at the initial visit before treatment, then at 1 month after the last foam treatment. The investigator coordinated with the Predoctoral Pediatric Dental Clinic and the Post Graduate Pediatric Dental Clinic to have all cavities of the enrolled subjects treated within six months after enrollment as they are indicated in the conventional treatment plan.

A pharmaceutical company (Omnii Oral Pharmaceuticals) collaborated with us and provided the prototype PVPI-F foam (1% active iodine [I] and 5000 ppm F) and F-foam (5000 ppm F) for the study free of charge.

4.3 Clinical Examination

Medical history was reviewed, and the presence of at least one caries lesion was confirmed, or the subject's history of having at least one dental carious lesion in the past 12 months was confirmed. Caries diagnosis was carried out by an intraoral mirror and explorer, which was supplemented by bilateral bitewing and periapical radiographic films. The following information was recorded on a dental charting form for each subject: teeth present, carious surfaces, restored surfaces and teeth missing as a result of dental decay. This dmft/DMFT and dmfs/DMFS index was recorded using WHO criteria (WHO, 1997) at the initial treatment and at the 1 year final visit by one examiner. Lowercase letters were used to specify primary dentition (dmft = decayed missing and filled teeth; dmfs = decayed missing and filled surfaces) and upper case letters (DMFT, DMFS) were used to specify permanent dentition. A pilot tested questionnaire was handed out at each foam treatment to ask the child to evaluate their acceptance of the foam treatment. The investigators recorded potential side effects and complaints of the treatment at each visit.

4.4 Saliva Sample Collections and Treatment

After the clinical examination, a stimulated saliva sample was collected. Saliva flow was stimulated by having the subject chew on a 2x2 cm square of paraffin (Parafilm "M" Laboratory Film, Pechiney Plastic Packaging, Chicago, IL) followed by expectoration into a 15 ml sterile tube (Becton Dickinson, USA). Two ml of stimulated saliva was collected for microbiological assessment prior to any dental treatment and the sample was stored in the refrigerator immediately after collection prior to plating for microbiological assessment within 24 hours (see below).

At the initial visit, a thorough prophylaxis using a disposable prophylaxis cup and prophylaxis paste was performed for each subject after saliva sample collection. After prophylaxis, either foam "A" or "B" (based on patient's randomization assignment) was placed into disposable fluoride trays (Oral B, USA). The trays with treatment foam were placed into the patient's mouth for 4 minutes. Upon completion of treatment, the tray was removed and excess removed with low vacuum suction. Subjects were instructed not to eat or drink anything for 30 minutes. The patient acceptance of the foam and any other complaint were reviewed immediately after the foam treatment.

4.5 Saliva Sample Processing, Microbiology, and Laboratory Procedures

Once saliva samples were collected, the tube was chilled on ice for transport to the microbiology laboratory. The tubes were uniquely coded for each subject. The microbiologist (Dr. C. Hoover) responsible for plating saliva samples

and quantifying bacterial content was blinded to subject assignment to control/intervention group. All saliva samples were plated for mutans streptococci (MS), lactobacilli (LB), and total viable count (TVC). Each sample was sonicated for 20 seconds, and an aliquot was removed for microbiological assays. Saliva samples were plated within 24 hours of sample collection on Mitis Salivarius Sucrose Bacitricin (MSSB) agar for MS enumeration, on Rogosa agar for LB enumeration and on rabbit blood agar for TVC enumeration. All plates were incubated in 85% nitrogen, 10% hydrogen, and 5% carbon dioxide for 48-96 hours before enumeration of bacterial colonies. The enumerations of MS, LB and TVC in saliva were calculated as colony forming units per ml of saliva (CFU/ml).

4.6 Statistical Analysis

The colonization levels of the bacteria were determined for all subjects at initial and 1-month visit. The values obtained were converted to $\log_{10}$(CFU/ml + 1) values so that parametric statistical tests could be applied to the data. Means and standard deviations in $\log_{10}$MS, $\log_{10}$LB, and $\log_{10}$TVC were calculated for each group. For each subject the reduction in $\log_{10}$MS and $\log_{10}$LB was calculated by comparing pre-treatment bacterial counts with log transformed bacterial counts at 1 month. The two mean log transformed reductions were compared to determine whether there were any statistically significant differences at the initial visit and 1 month follow-up to calculate the short-term

impact of the repeated PVPI-F treatment on cariogenic bacteria recolonization. For each subject, the changes of MS, LB and TVC as log CFU/ml at 1month after 1st three weekly treatments were also calculated against baseline. The two mean changes were compared to determine statistical differences at the initial visit and 1 month follow-up to calculate the short-term impact of the repeated PVPI-F treatment on MS infection levels. All the baseline data (age, dmfs/DMFS, snacking frequencies and microbiology) between the two groups were compared using the t test. Gender distributions of the two groups were compared with a chi-square test. Pearson correlations were estimated for snacking frequencies, dmfs/DMFS, ds/DS, and age with MS, LB and TVC reduction at 1 month. Also, correlations between baseline microbiology, snack pattern and caries condition were estimated.

Data was also analyzed to assess the familial contribution to baseline oral health status (microbiological and dental caries). We fitted maximum likelihood variance components models to estimate the within family and between family variance components; then we calculated the percentage of variation within family relative to total variation.

RESULTS

5.1 *Subjects at Baseline*

A total of 53 children (33 males and 20 females) were enrolled in the study with 26 subjects in Fluoride group (control) and 27 subjects in PVPI-F (intervention group). There were six families with two siblings enrolled in the study and two families with three siblings enrolled in this study. Randomization was at the child level (not the family level). One family of 2 children was in the fluoride group, two families of 2 children were in the PVPI-F group and three families of two children had one child in each group. One family with 3 children enrolled had two children in fluoride and one child in the PVPI-F group; the other family of three children had one child in fluoride and two children in PVPI-F group.

At baseline, the mean age of the subjects was 7.2 years (range: 6-9) in control group and 7.4 years (range: 6-9) in the intervention group. There was no statistically significant difference in gender distribution nor age between the two groups ($P>0.05$). Table 1 shows the subject parameters at baseline.

Table 1 Subject Parameters at baseline

	Fluoride (n=26)	PVPI-F (n=27)	P value (statistical test)
Average Age, years	7.2	7.4	0.40 (t-test)
Male:Female	15:11	18:9	0.58 (χ^2)
Mean(SD)* dmfs/DMFS	21.2 (13.4)	18.7 (13.3)	0. 50 (t-test)
Mean(SD)* ds/DS	3.9 (4.2)	3.9 (4.4)	0.98 (t-test)

* denotes standard deviation

All subjects enrolled in the study were confirmed to have or to have had active dental decay within the past year. The mean dmfs/DMFS values are given in Table 1. There was no statistically significant difference in dmfs/DMFS or ds/DS between the two groups at baseline (Student t-test, P>0.05). There was no relation of age and gender to any microbiological and decay measures.

5.2 Familial Aggregration

The percentage of variation due to families was calculated. The percent variation was calculated for the following variables: dmfs/DMFS, ds/DS, log MS, log LB and log TVC. The intrafamily correlation was 0.6 for Dmfs/DMFS, 0.81 for ds/DS, 0.6 for logMS, 0.5 for logLB, and 0 for logTVC.

5.3 Questionnaire Data

At the time of enrollment parents answered a questionnaire stating the snacking frequency habit of the child and type of toothpaste used by the child.
All patients stated that they were using fluoridated toothpaste.
Snacking frequency did not correlate to microbiological levels nor to decayed surfaces ($r = -0.17 < r < 0.12$ Spearman correlation, $p > 0.22$).

5.4 Subjects at completion

All but two subjects in the fluoride group completed all of the four foam treatments. One patient dropped out of the study after the initial appointment and one other missed one foam application. All subjects in the PVPI-F group completed all four treatments.
The mean time between the four weekly appointments was 6.1 days. The one-month saliva sample was collected on day 30.5 on average (range: 26-36 days) for the fluoride group and on day 31.6 on average (range: 26- 47 days) for the PVPI-F group.

Five subjects in the PVPI-F group complained of an unpleasant taste of the foam, while three subjects in fluoride group complained of an unpleasant taste of the foam. All of the subjects who complained about the taste of the treatment foam were able to complete the 4-minute foam treatment and graded their experience as tolerable. No long-term complaints or adverse effects resulting from foam treatment were noted in either group.

5.5 Microbiological Data at Baseline

The bacterial counts were converted into $\log_{10}$(CFU/ml + 1).

Approximately seventy-seven percent of the patients had detectable levels of LB. No significant correlation was found between bacterial levels and the subjects' ds or ss-ds scores (- 0.24 < r < 0.20, p>0.05). No significant correlation was found between snacking pattern and microbiology measures {r=0.67 logMS,r=0.73 logLB, r=0.5 logTVC, Spearman correlation test} Moreover, there were no statistically significant differences in MS, LB, and TVC levels at baseline between the two groups (Student t-test, P=0.79)

Table 2 shows the mean levels of mutans streptococci, lactobacilli, and the total viable count calculated for each group at baseline.

Table 2 Mean (SD)* $\log_{10}$ Bacterial Counts at Baseline

	Fluoride (n=26)	PVPI-F (n= 27)
Log_{10} MS	4.9 (1.6)	5.0 (1.7)
Log_{10} LB	2.7 (2.2)	3.6 (1.9)
Log_{10}TVC	8.4 (0.4)	8.2 (0.5)

* denotes standard deviation

Pearson Correlation tests showed that log MS counts at baseline positively correlated to log LB level (r = .46, p <0.01).

5.4 Microbiological Data: Changes at follow-up visit

We compared the bacterial measurements at baseline to those at one-month after the four weekly foam treatments. Table 3 shows the mean levels of mutans streptococci, lactobacilli, and the total viable count calculated for each group at one-month.

Table 3 Mean (SD)* $\log_{10}$ Bacterial Counts at One-month

	Fluoride (n= 25)	PVPI-F (n= 27)
$\log_{10}$ MS	4.6 (1.6)	5.0 (1.6)
$\log_{10}$ LB	2.6 (2.0)	3.3 (1.9)
$\log_{10}$ TVC	8.2 (0.4)	8.3 (0.5)

* denotes standard deviation

The mean (SD) change in $\log_{10}$ MS, $\log_{10}$ LB and $\log_{10}$ TVC at one-month are listed in Table 4. There were no statistically significant differences in $\log_{10}$ MS, $\log_{10}$ LB and $\log_{10}$ TVC found between the two groups at the one-month visit (t-test, P= 0.32, 0.57, 0.07 respectively). There was no significant difference in the two groups taking into account families.

Table 4 Mean (SD)* change in microbiological data between baseline and one month

	Fluoride (n= 25)	PVPI-F (n= 27)
$\Delta Log_{10}MS$	- 0.22 (0.62)	0.00 (0.91)
$\Delta Log_{10}LB$	- 0.03 (1.55)	- 0.27 (1.51)
$\Delta Log_{10}TVC$	- 0.17 (0.37)	0.09 (0.60)

*denotes standard deviation

The following figures 1, 2 and 3: show the mean change (+/- 95%CI) in log_{10}MS, log_{10}LB and log_{10}TVC

Figure 1 **Mean change (95% CI) in log_{10} MS levels from Baseline**

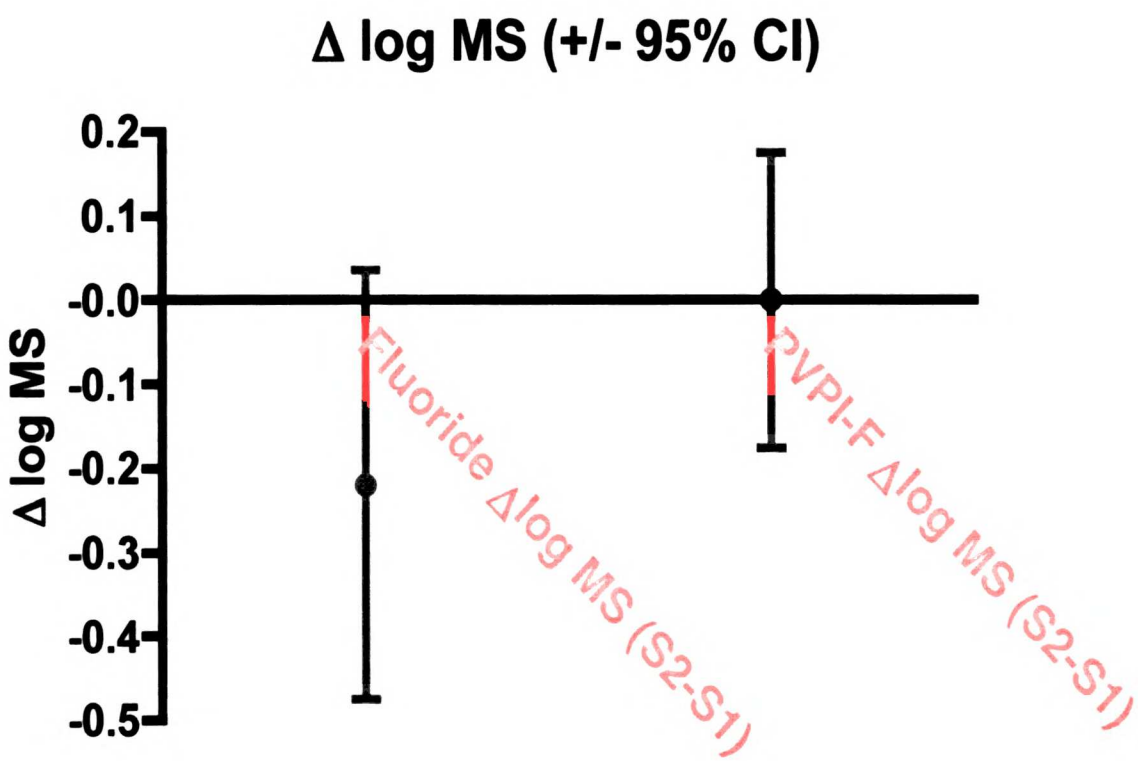


Figure 2 **Mean change (95% CI) in log_{10} LB levels from Baseline**

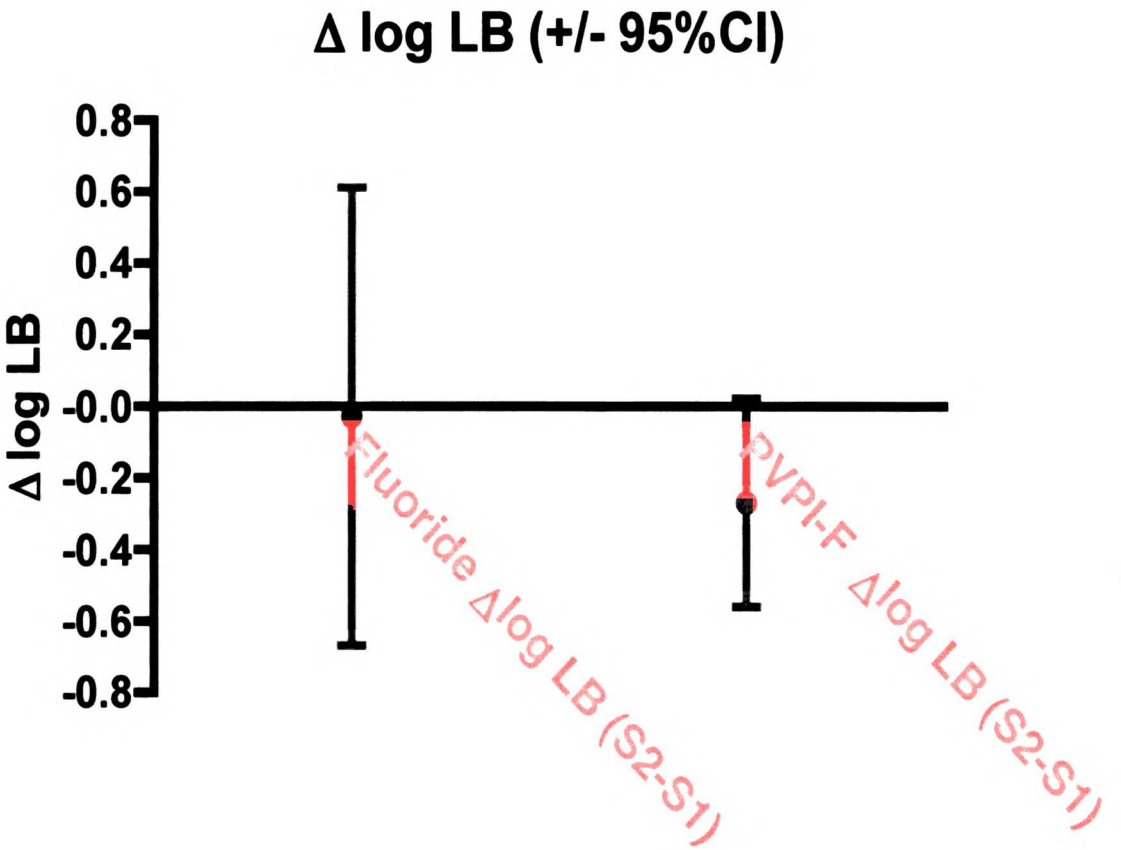
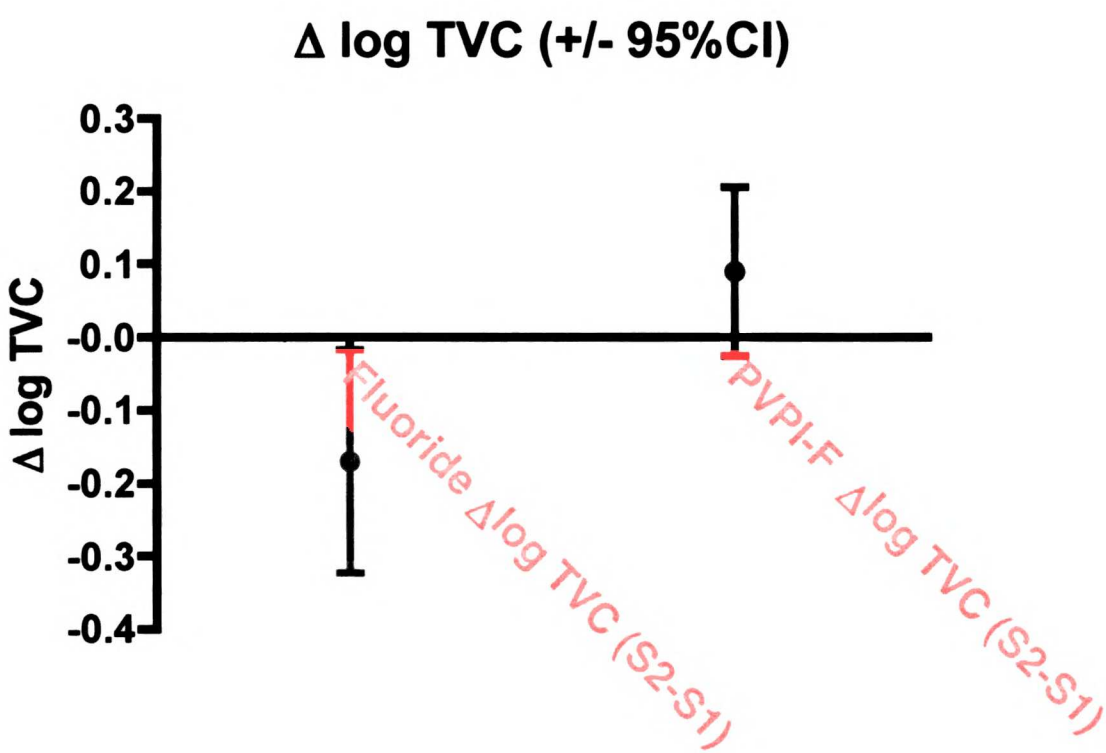


Figure 3 **Mean change (95% CI) in log_{10} TVC from Baseline**



DISCUSSION

Dental caries is characterized by an overwhelming infectious challenge by mutans streptococci (MS) and *Lactobacillus* species (LB). The current standard of care is usually limited to surgical removal and restoration of carious tooth structure, application of topical fluoride, oral hygiene, and dietary counseling [30, 63]. As dentistry evolves, it is becoming more apparent that a new approach needs to be taken in order to address this bacterially mediated disease in a comprehensive manner [64, 65]. This study was designed specifically to contribute to the concerted efforts of many to identify and evaluate antibacterials and regimens with the potential to reduce cariogenic challenge in individuals at high risk for developing dental decay.

Previous studies have supported the possible usefulness of povidone iodine in caries prevention. Caufield and Gibbons showed that after three topical applications of iodine solution MS levels in plaque and saliva could be reduced for 20-24 weeks after treatment [53]. Other studies demonstrated that either I_2-KI solution or iodine could decrease detectable levels of *S. mutans*, and lactobacilli in the plaque of occlusal fissure caries by 98% [57, 66].

The present study followed a study by Fujino and colleagues at UCSF in 2003. In their well-controlled *in vivo* study, children going to the operating room for dental rehabilitation were recruited to evaluate efficacy of PVPI. Treatment was administered in the OR immediately following full mouth rehabilitation. Saliva samples were collected one-hour, three-weeks, and three-months after treatment. What they found was that the mean MS and LB levels were

significantly decreased at all follow-up visits in the PVPI group up to 3 months but the single PVPI treatment did not reduce the formation of new caries in one year [60].

Similarly, Berkowitz *et al.*, have found a significant reduction in MS levels in children with Early Childhood Caries (ECC)[67]. They recruited 2-5 year olds undergoing treatment under general anesthesia. A 0.2 ml solution of 10% povidone iodine was applied to the dentition immediately after dental surgery was completed. Povidone iodine solution (10%) had a significant suppressive effect on salivary MS levels in the setting of severe ECC [67]. However, we did not demonstrate MS or LB reduction by four weekly treatments of PVPI-F in the current study.

There are many possible reasons why Berkowitz and colleagues noted significant MS reductions after PVPI treatment but the present study did not.

1) In the Berkowitz and Fujino studies, povidone iodine was applied to subjects under general anesthesia with little or no saliva present. Saliva may act to dilute povidone iodine or interfere with its attachment to oral structures and ultimately decrease its efficacy. Iodine could also possibly bind to the various proteins in the saliva and not be easily available for interaction with the bacteria.
2) The oral bacteria namely mutans streptococci and lactobacilli may be more susceptible to the iodine in the general anesthesia environment. As mentioned earlier, the salivary flow is reduced in the oral cavity when the subject is being treated under general anesthesia. Typically the surgical

procedure lasted for 2-3 hours. In both the studies the iodine was applied after all the restorative work was completed (i.e. after 2 –3 hours). It is possible that due to the dry conditions the bacteria may be desiccated and more susceptible to iodine.

3) Subjects from these two studies had full mouth rehabilitation before treatment. Although research has historically supported that removal of dental infection in cavities alone does not have any significant effect on overall bacterial loading in the remainder of the mouth, recent studies by Amin *et al.*, have demonstrated that extensive one-time restorative dental treatment results in a significant suppression of *S. mutans* levels at 6 months after treatment [59]. It may be the case that there is a temporary decrease in bacterial challenge after dental restorations as dental decay is removed as well as plaque.
4) In this study, all the restorative needs of the subjects were not met at one-month.
5) Application vehicle i.e. foam might not be as effective as the solution. All the previously mentioned studies used 10 % povidone iodine solution and found significant reductions in mutans streptococci and lactobacilli counts. During application the foam is placed in a tray and held in the oral cavity for 4 minutes, after which the foam is suctioned out of the oral cavity. The solution, gel or varnish vehicle tends to stick to the teeth, oral mucosa more than the foam hence iodine is available for longer periods of time. It

may be that the application time must be considerably longer for PVPI foam to have a beneficial effect.

6) PVPI may be effective when a different application vehicle is used (gel or varnish).

Further research is needed to find another effective antibacterial for the pediatric population.

CONCLUSIONS

In this randomized blinded study PVP-I foam was ineffective in reducing cariogenic bacterial counts in children aged 6-9 with active decay. In contrast to previously reported bacterial reductions by PVPI in solution in younger children, MS and LB levels were not significantly reduced in the PVPI-F foam group compared to the F-only control group. This is in contrast to the other studies with povidone iodine and may be due to the different application conditions. The previous studies used povidone iodine solution in younger patients undergoing comprehensive dental treatment under general anesthesia.

Future studies should consider randomizing siblings to different treatment groups in order to eliminate any familial effects.

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9. Appendix A

Group A: Microbiology Raw Data

	S1			S2		
ID	MS	LB	TVC	MS	LB	TVC
PR01	40,000	8,000	100,000,000	3,330	1,620	60,000,000
PR02	326,000	400,000	170,000,000	99,000	38,000	110,000,000
PR05	700,000	400,000	260,000,000	1,100,000	230,000	410,000,000
PR06	76,000	330	370,000,000	290,000	1,250	690,000,000
PR11	500,000	0	130,000,000	243,000	60	130,000,000
PR12	12,000	0	320,000,000	26,000	0	470,000,000
PR13	59,000	0	270,000,000	7,700	0	670,000,000
PR14	104,000	240	90,000,000	35,000	0	40,000,000
PR15	800,000	10	310,000,000	800,000	420	210,000,000
PR17	34,000	0	380,000,000	700,000	0	530,000,000
PR 18	78,000	0	120,000,000	92,000	10	130,000,000
PR 21	3,500,000	58,000	800,000,000	N/A	N/A	N/A
PR 24	2,600,000	2,100,000	440,000,000	800,000	700,000	260,000,000
PR 27	119,000	0	140,000,000	73,000	0	90,000,000
PR 28	0	0	230,000,000	0	380	110,000,000
PR 32	0	0	110,000,000	0	0	40,000,000
PR 35	1,800,000	43,000	190,000,000	600,000	7,000	360,000,000
PR 37	59,000	12,000	20,000,000	3,000	260	10,000,000
PR38	1,400,000	28,000	1,230,000,000	700,000	120,000	60,000,000
PR40	6,000	330	250,000,000	13,000	1,020	130,000,000
PR 42	76,000	60	1,100,000,000	46,000	23,000	180,000,000
PR 44	3,400,000	500,000	360,000,000	110,000	3,000	140,000,000
PR45	1,000,000	199,000	380,000,000	400,000	20,000	100,000,000
PR46	600,000	210	230,000,000	1,000,000	181,000	250,000,000
PR48	19,000	9,000	90,000,000	3,000	360	80,000,000
PR53	140,000	990	130,000,000	291,000	0	150,000,000

Group B Data: Microbiology Raw Data

ID	MS	LB	TVC	MS	LB	TVC
PR03	2,400,000	800,000	490,000,000	135,000	137,000	200,000,000
PR04	419,000	116,000	340,000,000	1,100,000	6,000	140,000,000
PR07	106,000	5,000	90,000,000	137,000	42,000	140,000,000
PR08	1,100,000	1,200,000	480,000,000	27,000	110	190,000,000
PR09	1,300,000	42,000	410,000,000	700,000	34,000	310,000,000
PR10	73,000	2,910	80,000,000	359,000	0	290,000,000
PR16	270	600	10,000,000	1,980	620	510,000,000
PR19	123,000	111,000	180,000,000	2,400,000	337,000	380,000,000
PR20	1,500,000	23,000	380,000,000	700,000	40	310,000,000
PR22	2,100,000	73,000	240,000,000	1,700,000	75,000	190,000,000
PR23	186,000	82,000	200,000,000	196,000	32,000	90,000,000
PR25	800,000	119,000	120,000,000	395,000	99,000	10,000,000
PR26	29,000	910	270,000,000	171,000	1,130	180,000,000
PR29	0	0	250,000,000	0	0	90,000,000
PR30	0	1,450	310,000,000	0	390	90,000,000
PR31	43,000	271,000	560,000,000	2,170,000	600,000	590,000,000
PR33	19,000	3,000	130,000,000	50,000	15,000	140,000,000
PR34	108,000	64,000	60,000,000	1,400,000	294,000	620,000,000
PR36	12,000	0	110,000,000	25,000	170	140,000,000
PR39	400,000	71,000	10,000,000	337,000	63,000	130,000,000
PR41	5,500,000	7,000	850,000,000	4,300,000	15,000	1,260,000,000
PR43	2,000,000	1,140	420,000,000	11,000	0	150,000,000
PR47	88,000	920	70,000,000	151,000	19,000	200,000,000
PR49	7,000,000	239,000	160,000,000	154,000	88,000	760,000,000
PR50	284,000	10	830,000,000	201,000	70	1,060,000,000
PR51	500,000	0	110,000,000	3,000,000	60	800,000,000
PR52	42,000	0	40,000,000	9,000	0	20,000,000

Group A: Log Values of Microbiology Data
Baseline (S1) and One Month (S2)

	S1log			S2log		
ID	logMS	logLB	logTVC	logMS	logLB	logTVC
PR01	4.60	3.90	8.00	3.52	3.21	7.78
PR02	5.51	5.60	8.23	5.00	4.58	8.04
PR05	5.85	5.60	8.41	6.04	5.36	8.61
PR06	4.88	2.52	8.57	5.46	3.10	8.84
PR11	5.70	0.00	8.11	5.39	1.79	8.11
PR12	4.08	0.00	8.51	4.41	0.00	8.67
PR13	4.77	0.00	8.43	3.89	0.00	8.83
PR14	5.02	2.38	7.95	4.54	0.00	7.60
PR15	5.90	1.04	8.49	5.90	2.62	8.32
PR17	4.53	0.00	8.58	5.85	0.00	8.72
PR 18	4.89	0.00	8.08	4.96	1.04	8.11
PR 21	6.54	4.76	8.90			
PR 24	6.41	6.32	8.64	5.90	5.85	8.41
PR 27	5.08	0.00	8.15	4.86	0.00	7.95
PR 28	0.00	0.00	8.36	0.00	2.58	8.04
PR 32	0.00	0.00	8.04	0.00	0.00	7.60
PR 35	6.26	4.63	8.28	5.78	3.85	8.56
PR 37	4.77	4.08	7.30	3.48	2.42	7.00
PR38	6.15	4.45	9.09	5.85	5.08	7.78
PR40	3.78	2.52	8.40	4.11	3.01	8.11
PR 42	4.88	1.79	9.04	4.66	4.36	8.26
PR 44	6.53	5.70	8.56	5.04	3.48	8.15
PR45	6.00	5.30	8.58	5.60	4.30	8.00
PR46	5.78	2.32	8.36	6.00	5.26	8.40
PR48	4.28	3.95	7.95	3.48	2.56	7.90
PR53	5.15	3.00	8.11	5.46	0.00	8.18

Group B Data: Log Values of Microbiology Data
Baseline (S1) and One Month (S2)

	S1log			S2log		
ID	logMS	logLB	logTVC	logMS	logLB	logTVC
PR03	6.38	5.90	8.69	5.13	5.14	8.30
PR04	5.62	5.06	8.53	6.04	3.78	8.15
PR07	5.03	3.70	7.95	5.14	4.62	8.15
PR08	6.04	6.08	8.68	4.43	2.05	8.28
PR09	6.11	4.62	8.61	5.85	4.53	8.49
PR10	4.86	3.46	7.90	5.56	0.00	8.46
PR16	2.43	2.78	7.00	3.30	2.79	8.71
PR19	5.09	5.05	8.26	6.38	5.53	8.58
PR20	6.18	4.36	8.58	5.85	1.61	8.49
PR22	6.32	4.86	8.38	6.23	4.88	8.28
PR23	5.27	4.91	8.30	5.29	4.51	7.95
PR25	5.90	5.08	8.08	5.60	5.00	7.00
PR26	4.46	2.96	8.43	5.23	3.05	8.26
PR29	0.00	0.00	8.40	0.00	0.00	7.95
PR30	0.00	3.16	8.49	0.00	2.59	7.95
PR31	4.63	5.43	8.75	6.34	5.78	8.77
PR33	4.28	3.48	8.11	4.70	4.18	8.15
PR34	5.03	4.81	7.78	6.15	5.47	8.79
PR36	4.08	0.00	8.04	4.40	2.23	8.15
PR39	5.60	4.85	7.00	5.53	4.80	8.11
PR41	6.74	3.85	8.93	6.63	4.18	9.10
PR43	6.30	3.06	8.62	4.04	0.00	8.18
PR47	4.94	2.96	7.85	5.18	4.28	8.30
PR49	6.85	5.38	8.20	5.19	4.94	8.88
PR50	5.45	1.04	8.92	5.30	1.85	9.03
PR51	5.70	0.00	8.04	6.48	1.79	8.90
PR52	4.62	0.00	7.60	3.95	0.00	7.30

Group A: Difference in Log Values at One Month

	S2-S1		
ID	logMS	logLB	logTVC
PR01	-1.08	-0.69	-0.22
PR02	-0.52	-1.02	-0.19
PR05	0.20	-0.24	0.20
PR06	0.58	0.58	0.27
PR11	-0.31	1.79	0.00
PR12	0.34	0.00	0.17
PR13	-0.88	0.00	0.39
PR14	-0.47	-2.38	-0.35
PR15	0.00	1.58	-0.17
PR17	1.31	0.00	0.14
PR 18	0.07	1.04	0.03
PR 21			
PR 24	-0.51	-0.48	-0.23
PR 27	-0.21	0.00	-0.19
PR 28	0.00	2.58	-0.32
PR 32	0.00	0.00	-0.44
PR 35	-0.48	-0.79	0.28
PR 37	-1.29	-1.66	-0.30
PR38	-0.30	0.63	-1.31
PR40	0.34	0.49	-0.28
PR 42	-0.22	2.58	-0.79
PR 44	-1.49	-2.22	-0.41
PR45	-0.40	-1.00	-0.58
PR46	0.22	2.93	0.04
PR48	-0.80	-1.40	-0.05
PR53	0.32	-3.00	0.06

Group B: Difference in Log Values at One Month

	S2-S1		
ID	logMS	logLB	logTVC
PR03	-1.25	-0.77	-0.39
PR04	0.42	-1.29	-0.39
PR07	0.11	0.92	0.19
PR08	-1.61	-4.03	-0.40
PR09	-0.27	-0.09	-0.12
PR10	0.69	-3.46	0.56
PR16	0.86	0.01	1.71
PR19	1.29	0.48	0.32
PR20	-0.33	-2.75	-0.09
PR22	-0.09	0.01	-0.10
PR23	0.02	-0.41	-0.35
PR25	-0.31	-0.08	-1.08
PR26	0.77	0.09	-0.18
PR29	0.00	0.00	-0.44
PR30	0.00	-0.57	-0.54
PR31	1.70	0.35	0.02
PR33	0.42	0.70	0.03
PR34	1.11	0.66	1.01
PR36	0.32	2.23	0.10
PR39	-0.07	-0.05	1.11
PR41	-0.11	0.33	0.17
PR43	-2.26	-3.06	-0.45
PR47	0.23	1.31	0.46
PR49	-1.66	-0.43	0.68
PR50	-0.15	0.81	0.11
PR51	0.78	1.79	0.86
PR52	-0.67	0.00	-0.30

DMFS Data Group A:

	primary						Permanent						total							
Patient ID#	Teeth #	ds	ss-ds	fs	ss-fs	ms	Teeth #	DS	ss-DS	FS	ss-FS	MS	# Teeth	ds/DS	ss-ds/DS	fs/FS	ss-fs/FS	ms/Ms	ss-dfs/DFS	dmfs/DMFS
PR01	17	6	3	6	3	5	2	0	0	0	0	0	19	6	3	6	3	5	6	17
PR02	18	1	0	12	5	0	5	0	0	0	0	0	23	1	0	12	5	0	5	13
PR05	7	0	0	23	20	15	14	2	0	3	0	0	21	2	0	26	20	15	20	43
PR06	19	3	3	23	14	0	5	0	0	0	0	0	24	3	3	23	14	0	17	26
PR11	5	0	0	8	3	5	17	6	0	1	0	0	22	6	0	9	3	5	3	20
PR12	12	1	1	13	6	5	10	0	0	0	0	0	22	1	1	13	6	5	7	19
PR13	13	0	0	7	0	0	6	0	0	0	0	0	19	0	0	7	0	0	0	7
PR14	11	1	1	16	8	5	12	0	0	0	0	0	23	1	1	16	8	5	9	22
PR15	12	3	2	14	6	0	12	4	1	0	0	0	24	7	3	14	6	0	9	21
PR17	11	7	3	6	3	5	12	0	0	0	0	0	23	7	3	6	3	5	6	18
PR18	12	1	0	0	0	0	12	1	0	0	0	0	24	2	0	0	0	0	0	2
PR21	2	2	2	2	0	0	22	10	0	0	0	0	24	12	2	2	0	0	2	14
PR24	17	19	11	5	4	0	5	0	0	0	0	0	22	19	11	5	4	0	15	24
PR27	14	4	2	23	14	0	10	0	0	0	0	0	24	4	2	23	14	0	16	27
PR28	17	0	0	0	0	0	6	3	0	0	0	0	23	3	0	0	0	0	0	3
PR32	20	0	0	4	2	0	0	0	0	0	0	0	20	0	0	4	2	0	2	4
PR35	11	2	1	23	17	0	12	4	1	0	0	0	23	6	2	23	17	0	19	29
PR37	6	0	0	30	20	26	12	0	0	0	0	0	18	0	0	30	20	26	20	56
PR38	16	2	0	31	22	9	6	1	0	0	0	0	22	3	0	31	22	9	22	43
PR40	18	3	2	14	9	0	2	0	0	0	0	0	20	3	2	14	9	0	11	17
PR42	12	0	0	25	13	0	11	0	0	0	0	0	23	0	0	25	13	0	13	25
PR44	13	3	0	29	20	10	8	0	0	0	0	0	21	3	0	29	20	10	20	42
PR45	16	2	1	17	7	4	7	1	0	0	0	0	23	3	1	17	7	4	8	24
PR46	1	1	1	2	0	0	23	4	0	2	0	0	24	5	1	4	0	0	1	9
PR48	12	2	1	19	12	0	12	0	0	0	0	0	24	2	1	19	12	0	13	21
PR53	19	3	1	2	1	0	5	0	0	0	0	0	24	3	1	2	1	0	2	5

DMFS Data Group B:

	primary						Permanent						total							
Patient ID#	Teeth #	ds	ss-ds	fs	ss-fs	ms	Teeth #	DS	ss-DS	FS	ss-FS	MS	# Teeth	ds/DS	ss-ds/DS	fs/FS	ss-fs/FS	ms/Ms	ss-dfs/DFS	dmfs/DMFS
PR03	14	2	2	24	16	10	11	1	0	0	0	0	25	3	2	24	16	10	18	37
PR04	18	0	0	17	13	0	4	0	0	0	0	0	22	0	0	17	13	0	13	17
PR07	12	0	0	10	1	0	12	2	0	0	0	0	24	2	0	10	1	0	1	12
PR08	2	0	0	5	2	0	19	0	0	0	0	0	21	0	0	5	2	0	2	5
PR09	11	3	1	2	1	5	10	2	0	0	0	0	21	5	1	2	1	5	2	12
PR10	12	3	2	10	8	0	12	0	0	0	0	0	24	3	2	10	8	0	10	13
PR16	13	3	3	6	2	0	10	2	0	0	0	0	23	5	3	6	2	0	5	11
PR19	5	2	1	11	9	15	15	3	1	5	0	0	20	5	2	16	9	15	11	36
PR20	12	0	0	26	17	0	6	2	0	0	0	0	18	2	0	26	17	0	17	28
PR22	8	2	1	8	4	0	15	6	0	0	0	0	23	8	1	8	4	0	5	16
PR23	12	0	0	30	20	0	10	0	0	1	0	0	22	0	0	31	20	0	20	31
PR25	8	2	2	12	7	36	8	2	0	2	0	0	16	4	2	14	7	36	9	54
PR26	11	0	0	33	22	5	13	2	0	0	0	0	24	2	0	33	22	5	22	40
PR29	20	2	0	0	0	0	0	0	0	0	0	0	20	2	0	0	0	0	0	2
PR30	12	0	0	3	1	5	10	4	0	0	0	0	22	4	0	3	1	5	1	12
PR31	11	5	5	0	0	5	12	0	0	0	0	0	23	5	5	0	0	5	5	10
PR33	10	0	0	4	2	5	12	0	0	0	0	0	22	0	0	4	2	5	2	9
PR34	13	4	2	9	5	15	10	0	0	0	0	0	23	4	2	9	5	15	7	28
PR36	12	2	0	11	4	0	12	0	0	0	0	0	24	2	0	11	4	0	4	13
PR39	10	2	1	6	3	0	12	1	0	2	0	0	22	3	1	8	3	0	4	11
PR41	12	1	1	28	19	0	12	0	0	0	0	0	24	1	1	28	19	0	20	29
PR43	0	0	0	0	0	0	23	1	0	6	0	0	23	1	0	6	0	0	0	7
PR47	14	0	0	4	2	0	10	0	0	0	0	0	24	0	0	4	2	0	2	4
PR49	14	15	8	10	7	0	10	5	0	0	0	0	24	20	8	10	7	0	15	30
PR50	21	12	5	13	7	0	2	0	0	0	0	0	23	12	5	13	7	0	12	25
PR51	14	10	10	0	0	0	6	0	0	0	0	0	20	10	10	0	0	0	10	10
PR52	10	2	2	0	0	0	12	0	0	0	0	0	22	2	2	0	0	0	2	2

Group A: Age, Gender and Ethnicity

Patient ID#	age	gender	ethnicity
PR01	6	F	Arabic
PR02	6	F	Arabic
PR05	9	M	CenAme
PR06	6	M	Mid Eas
PR11	9	F	Chinese
PR12	8	M	AA
PR13	7	M	CenAme
PR14	8	F	Mex
PR15	8	F	Mex
PR17	8	F	Mid Eas
PR18	7	F	Mid Eas
PR21	9	M	AA
PR24	6	M	Filipino
PR27	7	M	SAmer
PR28	7	M	Mex
PR32	6	M	Mex
PR35	9	M	Mex
PR37	7	F	CenAme
PR38	6	M	Mex
PR40	6	M	Mex
PR42	7	M	AA
PR44	6	F	Korean
PR45	6	M	Euroasian
PR46	8	F	AA
PR48	8	M	Mex
PR53	6	F	Mex

Group B: Age, Gender and Ethnicity

Patient ID#	age	gender	ethnicity
PR03	8	F	Arabic
PR04	6	M	Mex
PR07	8	M	Mex
PR08	9	M	Mex
PR09	8	F	CenAme
PR10	8	M	Cauc
PR16	7	F	Mex
PR19	7	F	Mex
PR20	6	F	Mex
PR22	7	M	AA
PR23	7	M	Filipino
PR25	6	F	Mex
PR26	9	M	
PR29	6	M	Mex
PR30	8	M	Mex
PR31	8	M	CenAme
PR33	8	M	Mex
PR34	6	M	Filipino
PR36	8	M	Filipino
PR39	8	F	SAmer
PR41	8	M	CenAme
PR43	9	F	Mex
PR47	6	F	Cau/Ch/fili/
PR49	7	M	Mex
PR50	6	M	CenAme
PR51	7	M	CenAme
PR52	9	M	Mex

Group A Questionnaire Data:

Patient ID#	Brushing frequency/day	Toothpaste used	Brand	Snacking frequency/day	Flossing Frequency/week	Seen dentist	Know result
PR01	2	Y	Crest	1	1	Y	Y
PR02	2	Y	Crest	2	Daily	Y	Y
PR05	2	Y	Colgate	1	0	Y	Y
PR06	2	Y	Crest	2	1	Y	Y
PR11	2	Y	Crest	2	Daily	Y	Y
PR12	2	Y	Crest	1	2	Y	Y
PR13	2	Y	Colgate	2	0	Y	Y
PR14	2	Y	Colgate	3	3 to 6 times	Y	Y
PR15	2	Y	Crest	3	0	Y	Y
PR17	2	Y	Colgate	2	0	Y	Y
PR18	1	Y	Colgate	3	0	Y	Y
PR21	1	Y	any with FL	3	1	N	Y
PR24	2	Y	Colgate,Crest	3	1	Y	Y
PR27	2	Y	Closeup	1	0	Y	Y
PR28	2	Y	Colgate	3	1	Y	Y
PR32	2	Y	Colgate Total	1	Daily	Y	Y
PR35	1	Y		1	3 to 6 times	Y	Y
PR37	2	Y	Colgate	3	1	Y	Y
PR38	1	Y	Crest	1	0	Y	Y
PR40	2	Y	Crest	3	3 to 6 times	Y	Y
PR42	2	Y	Colgate	2		Y	Y
PR44	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PR45	Not every Day	Y		2	3 to 6 times	Y	Y
PR46	2	Y	Colgate	2	1	Y	Y
PR48	2	Y	Oral B	1	N/A	N/A	N/A
PR53	1	Y	Colgate	1	2	Y	Y

Group B Questionnaire Data:

Patient ID#	Brushing frequency/day	FL Toothpaste used	Brand	Snacking frequency/day	Flossing frequency/week	Seen Dentist	Know Result
PR03	2	Y	Crest	1	1	Y	Y
PR04	1	Y	Colgate	1	don't Know	Y	Y
PR07	2	Y	Colgate	2	1	Y	Y
PR08	1	Y	Crest	2	1	Y	Y
PR09	2	Y	OralB	1	2	Y	Y
PR10	2	Y	N/A	2	Daily	Y	Y
PR16	2	Y	Colgate	2	2	Y	Y
PR19	2	Y	N/A	2	2	Y	Y
PR20	2	Y	N/A	2	2	Y	Y
PR22	2	Y	Colgate	3	not at all	Y	Y
PR23	2	Y	Colgate	2	1	Y	Y
PR25	2	Y	Colgate	1	Daily	Y	Y
PR26	2	Y	Colgate	2	N/A	N/A	N/A
PR29	2	Y	Colgate	3	1	Y	Y
PR30	2	Y	Colgate	1	0	Y	Y
PR31	2	N	Colgate	3	N/A	Y	Y
PR33	2	Y	Colgate Total	1	Daily	Y	Y
PR34	2	Y	Crest	1	don't Know	Y	Y
PR36	2	Y	kids Col/k crest	3	2	Y	Y
PR39	2	Y	Crest	3	3 to 6 times	Y	Y
PR41	Not every day	Y	Colgate	2	not at all	Y	Y
PR43	1	Y	Crest	3	Daily	Y	Y
PR47	2	Y	Crest	2	7+	Y	Y
PR49	2	Don't Know	N/A	3	2	Y	Y
PR50	2	N	Colgate	2	not at all	Y	Y
PR51	2	N	Colgate	2	not at all	Y	Y
PR52	1	Y	Colgate	1	1	Y	Y

Group A: Days between Appointments

Visit 2	Visit 3	Visit 4	1 Month
6	4	8	33
6	4	8	33
6	6	5	27
6	7	4	27
6	6	6	28
7	6	6	26
5	7	5	27
5	6	6	28
5	6	6	32
6	6	6	27
6	6	6	27
n/a	n/a	n/a	n/a
missed	14(7)	6	36
6	7	6	31
6	6	8	34
6	7	7	27
4	8	6	29
6	6	6	34
7	5	6	36
6	6	6	27
7	5	6	34
6	6	6	31
7	7	5	35
6	6	6	28
7	5	8	32
6	7	6	34

Group B: Days between appointments

Visit 2	Visit 3	Visit 4	I Month
6	4	8	33
5	7	5	28
6	5	7	33
6	6	6	33
7	5	7	27
6	6	6	27
6	7	6	26
6	6	6	29
6	6	6	29
5	7	5	35
5	7	5	35
7	6	6	27
6	7	5	27
6	6	8	34
6	6	8	34
6	5	7	29
6	7	7	27
6	7	4	29
6	6	6	34
6	6	6	27
6	6	6	28
5	6	6	34
6	6	6	32
6	8	4	27
9	3	7	47
9	3	7	47
6	7	6	34

10. Appendix B

UCSF **Please date form:** 07/19/05
COMMITTEE ON HUMAN RESEARCH
FULL COMMITTEE REVIEW APPLICATION

General Instructions | View Complete Set of Linked Instructions

PART 1: ADMINISTRATIVE REQUIREMENTS

- Eligibility requirements for Principal Investigator, Co-Principal Investigator and Contact Person
- Training requirements

A. Principal Investigator:		
Name and degree John D. B. Featherstone, PhD., M.Sc.	University Title Professor	Department Prev & Rest Dental Sciences
Campus Mailing Address (Box No.) Box 0758	Phone Number 415/ 476-0456	E-mail Address jdbf@ ucsf.edu
Co-Principal Investigator:		
Name and degree Ling Zhan, DDS, PhD	University Title Postdoctoral Researcher	Department Prev & Rest Dental Sciences
Campus Mailing Address (Box No.) Box 0758	Phone Number 415/476-0921	E-mail Address zhanl@dentistry.ucsf.edu
Additional Contact Person (if any):		
Name	University Title	Department
Campus Mailing Address (Box No.)	Phone Number	E-mail Address
Send correspondence to (check *one*):	[ ]PI only [X]PI and Co-PI [ ]PI and Additional Contact Person	
Study Title: Effectiveness of Specific Antimicrobial Treatment Against Bacteria that Cause Dental Decay in Children in Pacific Rim Countries		Application Type: []New Full Committee Application []Response to "Contingent" or "Return" letter [X]Modification [ ]Renewal Current CHR #: __ Expiration date: __
Sites (Check all that apply): [X]UCSF [ ]SFGH [ ]VAMC [ ]Fresno [ ]Cancer Center [ ]UC Berkeley [ ]GCRC (Moffitt/Mt. Zion) [ ]GCRC (SFGH) [ ]PCRC [X]Foreign Country [ ]Other(s):		

B. Funding: If this study is eligible for "Just in Time" NIH review, do not submit your application to the CHR until you have received notification from the federal granting agency that your study appears to be in a fundable range. Check all that apply:

Type of funding	Source of funding	Funds will be awarded to/through:
[X]Contract/Grant [ ]Subcontract [ ]Drug/device donation [ ]Student project [ ]Other: __ Have funds been awarded? [X]Yes [ ]Pending [ ]No Award No.: 04TPRRP 02-0012__	[ ]Federal Government [ ]Other Gov. (e.g., State, local) [ ]Industry* [ ]Other Private [X]Campus/UC-Wide program [ ]Departmental Funds [ ]Other: **Sponsor Name: UC Pacific Rim Research Program and IADR/GSK innovative research award (see below)**	Dept./ORU: *Institution* *Federal Wide Assuran* [X]UCSF ..... [ ]Blood Centers of the Pacific ..... [ ]Gallo Institute ..... [ ]Gladstone Institute ..... [ ]Goldman Institute on Aging ..... [ ]NCIRE ..... [ ]S.F. Dept. of Public Health ..... [ ]VA Research Office .....

*UCSF (or affiliate) financial contact person for IRB review recharge:	Normita Santore, AC Phone: 4-0495 AC Fax: 6-0858 AC E-mail: santore@itsa.ucsf.edu
Grant Title and PI (if different from above):	
Secondary sponsors: If there are multiple sources of funding for this study, please describe the additional funding:	
IADR/GlaxoSmithKline Innovation in Oral Care Awards Title: A NOVEL ANTIBACTERIAL APPROACH TO REDUCE CARIES IN CHILDREN	

C. Key Personnel: All key personnel including the PI and Co-PI must be listed below along with a brief statement of their qualifications. *If the SF VAMC is a study site*, please identify the principal VAMC investigator, unless already listed as PI or CoPI above. For questions regarding the VAMC application process, please contact the VA Clinical Research Office at 221-4810 ext.4655.

Investigator (and institution):	Qualifications:
John Featherstone (PI), UCSF Ling Zhan(co-PI),	Dr. John D.B. Featherstone is professor and Chair of the Department of Preventive and Restorative Dental Sciences at UCSF. Dr. Featherstone is internationally recognized for studies relating to de- and remineralization of the teeth, and clarification of the mechanisms of action of fluoride in preventing or reversing dental caries. He has been principal investigator or co-investigator on numerous

UCSF Pamela Den Besten (co-investigator), UCSF Purvi Zavery (co-investigator, UCSF) XueDong Zhou(Co-investigator), West China College of Stomatology (WCCS)	NIH/NIDR funded studies. Dr. Ling Zhan is now a postdoctoral researcher in the Department of Preventive and Restorative Dental Sciences at the UCSF. She came from West China College of Stomatology as a visiting professor 4 years ago. She is a trained dentist with over 10 year clinical practice experience. Her research career has been focused on microbiology aspects of caries and caries prevention. She has led one pilot project funded by NIH/NIDCR on cariogenic bacteria in children, and she has participated in several clinical studies related to caries risk assessment and caries prevention by antibacterial agents in children and adults funded by NIH/NIDCR. She is Professor and Chair of the Division of Pediatric Dentistry at UCSF and has 20 years of clinical and research experience. Dr. Den Besten was the principal investigator on two key studies using PVP-I to reduce MS and LB bacteria in children with early childhood caries (ECC). She will be co-investigator responsible for the overall clinical aspects of the study at UCSF. Dr. Zavery is a resident in the pediatric dentistry specialty program at UCSF. She will work closely with Dr. Zhan and will be responsible for recruiting, scheduling subjects, clinical treatment of the subjects, applying the test agents, and will actively participate in data analyses. Dr. Zhou is the dean of the college and the chair of the Operative Dentistry Department at WCCS. She is internationally recognized for her research in caries etiology and prevention and is now the president of Chinese Association of Caries Research. She has been principal investigator and co-investigator on numerous caries research projects funded by the Chinese government and international foundations. She is co-investigator of the study and will be responsible for leading the study at WCCS.

D. Drugs, Devices and Biologics:		
List any investigational drugs, biologics and IND Numbers:	name	IND #
List any investigational devices and IDE Numbers:	name	IDE#
	[ ] Non-Significant Risk Determination Requested .... **Attach NSR Supplement**	
Who holds the IND/IDE?	[ ]Sponsor [ ]Investigator	

List any approved drugs, biologics and/or devices being *studied*:	10% povidone iodine solution 2% sodium fluoride foam
Are investigational drugs, devices, or biologics prepared or manufactured in UCSF research labs?	[ ]Yes [X]No If "Yes," identify the lab:

E. Other Approvals/Regulated Materials: Does this study require approval or authorization from any of the following regulatory committees, or involve the use of the regulated materials listed below? Follow the hyperlinks for more information. If "Yes," complete the applicable section(s) below.			[ ]Yes [X]No
[x]	Biological Safety Committee		BUA #: 2308-BU-01-INC (expiration 4/1/06)
	[ ]	Gene Transfer/Therapy	
[ ]	Institutional Animal Care and Use Committee		IACUC #:
	[ ]	Xenotransplantation Clinical Trial	
[ ]	Controlled Substances		
[ ]	Human Stem Cells		**Attach Stem Cell Supplement**
	[ ]	Embryonic Stem Cell Clinical Trial	
[ ]	Radiation Safety Committee		RUA #:

F. Scientific Merit Review: This study has received or will receive scientific merit review from (check all that apply):
[ ]NIH [ ]Cancer Center* [ ]GCRC or PCRC [ ]SFVAMC [ ]Dept. Review [
*Required prior to final CHR approval for oncology studies.

G. Statement of Financial Interest: Do you or the other investigators have a financial interest in the outcome of this study? If "Yes," please describe below and describe briefly in Purpose and Background section of the consent form.	[ ]Yes [X]No

H. Principal Investigator's Certification:

- I certify that the information provided in this application is complete and correct.
- I accept ultimate responsibility for the conduct of this study, the ethical performance of the project, and the protection of the rights and welfare of the human subjects who are directly or indirectly involved in this project.
- I will comply with all policies and guidelines of UCSF and affiliated institutions where this study will be conducted, as well as with all applicable federal, state and local laws regarding the protection of human subjects in research.

- I will ensure that personnel performing this study are qualified, appropriately trained and will adhere to the provisions of the CHR-approved protocol.
- I will not modify this CHR-certified protocol or any attached materials without first obtaining CHR approval for an amendment to the previously approved protocol.
- I assure that the protected health information requested, if any, is the minimum necessary to meet the research objectives.
- I assure that the protected health information I obtain, if any, as part of this research will not be reused or disclosed to any parties other than those described in the CHR-approved protocol, except as required by law.

Principal Investigator's Signature _____ Date _____

PART 2: STUDY DESIGN

Complete items A-E using clear, concise, non-technical, lay language (i.e., the type of language used in a newspaper article for the general public) wherever possible. Define all acronyms. Use caution when cutting and pasting from another application or protocol to ensure that information is complete, supplemented where necessary, is pasted in a logical order, and is relevant to the specific section.

Space limits are recommendations and should be adjusted as needed, but the total length for sections A-E should not exceed 5 pages.

For modifications and renewals, please highlight in *italics* all changes from previously approved version.

A. Synopsis (Briefly summarize the study.)

Aim: The aim of the study is to conduct a one year randomized clinical study to determine the efficacy of four weekly applications of a povidone iodine/fluoride (PVP-IF) foam at baseline and 6 months on the reduction of oral cariogenic bacteria levels (mutans streptococci (MS) and Lactobacillus (LB) species), the genetic diversity of MS, and caries increment in children with active caries. The hypothesis to be tested is that bi-annual four weekly application of PVP-IF will suppress MS and LB colonization, decrease the genetic diversity of MS, enhance remineralization and reduce future caries formation. Methods: 60 healthy 6-9 year olds with 1-5 frank caries lesions will be randomized to 30 per each of the intervention and control groups, namely a) control: F-only foam group or b) intervention: the PVP-IF foam group. Treatments will be performed at baseline and then once a week for 3 consecutive weeks. The four weekly treatments will be repeated 6 months after enrollment. Stimulated saliva samples will be taken at the initial visit before treatment, then 1 month, 5 months, and 1 year after the first four weekly treatments are complete and assayed for MS, LB, and MS genetic diversity. The DMFT and DMFS (decayed missing and filled teeth and surfaces) will be recorded using NIDCR modified WHO criteria at the initial treatment and at the 1 year final visit by one

examiner. Quantitative light florescent (QLF) images on occlusal and buccal surfaces of molars for early caries lesion detection will also be used to augment the examination. The instrument includes a repositioning software to enable a 95% positioning match for each re-assessment. Ecological shifts in selected flora will be followed by checkerboard analyses at baseline, 1 month and 1 year. Significance: Potentially a PVP-IF combined foam could be applied to the teeth of children at appropriate intervals throughout a year, reducing both the MS and LB bacterial challenge, enhancing remineralization, and markedly reducing or even eliminating new caries formation. **If the hypothesis is proven, this novel PVP-IF foam will be a convenient antibacterial treatment as a strategy in caries prevention for children in U.S.A. and beyond, especially for children with high caries risk from socioeconomically disadvantaged families.**

B. Purpose (Specify the hypotheses, aims and/or objectives.)

The aim of the study is to conduct a one year randomized clinical study to determine the efficacy of four weekly applications of a novel povidone iodine/fluoride (PVP-IF) foam at baseline and 6 months on the reduction of oral cariogenic bacteria levels (namely mutans streptococci (MS) and *Lactobacillus* (LB) species), the genetic diversity of mutans streptococci, and caries increment in children with active caries. The hypothesis to be tested is that bi-annual four weekly application of PVP-IF will suppress MS and LB colonization, decrease the genetic diversity of MS, enhance remineralization and reduce future caries formation.

C. Background (Summarize previous studies. Explain rationale for the proposed investigation.)

Prevalence of dental decay worldwide and in the United States

Dental caries continues to be a major oral health concern in children in the USA and world wide. The third National Health and Nutrition Examination Survey-Phase I showed 50% of 5-8 year old children in the US had experienced caries in the primary dentition (baby teeth) and 67% of 12-17 year olds had experienced caries in the permanent dentition [1]. Remarkably, 11% of children aged 6-11 years had 75% of the caries[2].

Caries prevention measures and antibacterial therapy

Dental caries is an infectious disease caused by acid producing bacteria, primarily MS, and LB in adults and children[3]. Its initiation and progression depend on a balance between demineralization of the enamel, by acids produced by cariogenic bacteria, and remineralization by calcium and phosphate from saliva enhanced by fluoride. Fluoride from drinking water and dental products has played a considerable role in the reduction of caries prevalence and its severity during the past few decades[3]. However fluoride therapy alone can not overcome the severe bacterial challenge in high caries risk individuals.

In addition to cariogenic bacteria quantity, recent studies by us and others found that high caries active children and adults displayed high genetic diversity (numerous different strains) in MS infection[4-6]. Studies have shown that "restoring" carious lesions has a minimal effect on the bacterial loading in the remainder of the mouth. High-risk individuals therefore need antibacterial treatment to reduce their "caries

challenge" in both quantity and virulence.
Although the concept of using antibacterial therapy is logical, it is not much used in the prevention of tooth decay[3]. To date, there are no specific effective antibiotics or vaccines available against cariogenic bacteria.
Chlorhexidine has been the most often used antibacterial for caries prevention, but it has yielded limited success. Chlorhexidine reduces the levels of MS in the mouth if used daily for two weeks, but its efficacy on lactobacilli is limited[3]. The unpleasant taste and staining reduce patient compliance. Therefore, an antibacterial with increased efficacy against cariogenic bacteria with improved patient acceptance is needed.
PVP-I (10% povidone-iodine, with 1% active iodine) has been approved for application to the skin and mucous membranes of children in general clinical practice, as a pre-surgical antiseptic, and is considered safe for intraoral use. It appears to be a promising antibacterial for cariogenic bacterial infection. Topical use of iodine showed prolonged suppressive effects on oral populations of MS[7]. Very importantly, a recent study by Lopez et al showed that bi-monthly topical application of a 10% povidone iodine solution to the dentition of babies at high risk for early childhood caries (ECC) prevented the development of white spot lesions[8].
PRELIMINARY RESULTS: (pilot studies, unpublished)
a) A pilot study(CHR approval # H8693-17428-01) at UCSF with 20 children showed that a single application of PVP-I solution following treatment for early childhood caries in children under 5 years of age, under general anesthesia after restoration of all active caries, reduced MS and LB levels significantly for up to 3 months[9], but the one time application did not reduce caries incidence over 12 months. B) We have just completed a pilot study (CHR approval # H8693-22998-01A) using PVP-I foam on children (aged 6 to 9 years) with active caries. The fruit flavored PVP-I foam gave reduced MS and LB levels at 1 week compared to baseline, but the effects were diminished by 1 month. Further, the PVP-I foam formulation was well accepted by the participating children. These results suggest that four PVP-I foam treatments repeated at weekly intervals will likely be a good treatment regimen to substantially reduce or eliminate MS and LB. c) A study (CHR approval # H8693-22805-01) in high caries and caries free children showed that MS infection diversity (number of strains in one individual) is positively correlated with ds (decayed surfaces) scores of subjects. These results indicate that genetic diversity may contribute to MS virulence[5, 6]. D) We have just completed a five year NIH-funded study on "Caries management by risk assessment" in adults(CHR approval #H9136-13891-03A). Results showed the cariogenic bacterial challenge remained high despite the completion of conventional dental treatment[10], unless aggressive antibacterial therapy was used in conjunction with restorative work in high caries individuals. However, PVP-I has not frequently been used in full mouth dental rehabilitation and its related efficacy in decreasing the risk for recurrent decay by multiple applications is unknown. Furthermore the beneficial effects of a high concentration fluoride (5,000 ppm F) foam or gel are well known in enhancing remineralization of caries lesions. There is no chemical reason why we can not combine PVP-I and F in one treatment regimen. This novel approach will be used in the present study.

D. Design
General Study Design and inclusion criteria:
The study will be carried out at two sites, namely (1) UCSF, and (2) West China College

of Stomatology (WCCS). The study at UCSF will be carried out at the Predoctoral Pediatric Dental Clinic (PDPDC) and the Postgraduate Pediatric Dental Clinic (PGPDC). The study at WCCS will be carried out at the Operative Dentistry clinic. A separate human subject approval will be obtained in China for the study conducted at WCCS, and it will use the identical protocol. A total of 60 healthy 6-9 year olds with 1-5 frank caries lesions (who assent and their parents give consent) will be enrolled in the study at each site, randomized to 30 per each of the test and control groups. Eligible children who reside within a 25 mile radius will be randomly assigned to one of the two study groups, a) **control:** F-only foam group or b) **intervention:** the PVP-IF foam group. The corresponding treatment will be performed at baseline and then once a week for 3 consecutive weeks. The four weekly treatments will be repeated 6 months after enrollment. Stimulated saliva samples will be taken at the initial visit before treatment, then 1 month, 5 months, and 1 year after the first four weekly treatments are complete. The investigator will coordinate with the PDPDC and PGPDC department to have all cavities of the enrolled subjects treated within 6 month after enrollment as they are indicated in the conventional treatment plan. The DMFT and DMFS will be recorded using NIDCR modified WHO criteria at the initial treatment and at the 1 year final visit by one examiner and with the aid of radiographs. The quantitative light fluorescent (QLF) images of occlusive and buccal surfaces of molars will be taken at the oral examination visits to evaluate early non-cavitated lesions and to augment the visual exams.

Dr. Ling Zhan is from WCCS and is currently a postdoctoral fellow at UCSF. She will act as the liaison between the two sites. She is competent in all aspects of the study, including the microbiology. She will work with Dr. Den Besten (see below) at UCSF in subject recruitment and clinical treatment procedures, and will work with personnel in Dr. Hoover's lab at UCSF for microbiology plating and enumeration. Dr. Ling Zhan will be responsible for supervising these procedures when she travels to WCCS in the early part of the study year. We have the unique opportunity to capitalize on the knowledge and experience of Dr. Zhan to commence this exciting collaboration between the two universities. She will return to UCSF during the year of the study to coordinate between the two sites.

Sample size: Based on our study on ECC children (see above) we predict that 65% of subjects in the control group will have new caries within a year. For a predicted 30% reduction in new caries in the PVP-IF group the sample size needed to detect that difference at alpha (two sided)= 0.05, power 80%, is estimated as 26 (Chi-square test) per group. We will use 30 subjects in each group to allow for about 15% attrition.

Human Subjects Approval. UCSF Committee on Human Research (CHR) approval will be obtained prior to recruitment of any children at UCSF. The CHR has previously approved the use of PVP-IF foam and salivary assays for our pilot studies. Payments to the subjects (children) and their parent will be as per the payment schedule table below. At UCSF, each child will receive a $10 gift card and the parent/guardian will receive $10 cash for each treatment and saliva visit. Both of the child and his/her parent/guardian will get $4 per visit cash bonus at the final visit that will be $40 cash for each of them if they complete all ten study visits. That is a total of $280 reimbursement for each subject and their parent/guardian if they complete the study.

Parents or legal guardians of eligible subjects will receive an explanation of the study procedures. If they agree to allow their children to participate, they will be asked to sign an informed consent document approved by the UCSF committee on human research (CHR). The CHR approval from WCCS will be obtained before any children are enrolled in China.

Exclusion criteria are children: a).with serious chronic systemic or periodontal diseases; b).with medicines taken within the past 3 months that might affect oral flora; c).with a dry mouth or difficulty spitting

Blinding. Placebo foam (fluoride only, control group) with similar color to the PVP-IF will be used and containers for collecting saliva will be uniquely coded. Only the statistician will know subject group assignments.

PVP-IF and F foams: A pharmaceutical company (Omnii Oral Pharmaceuticals, West Palm Beach, FL) has agreed to collaborate with us and to provide the prototype PVP-IF foam (1% active I and 5000 ppm F) and F-foam (5000 ppm F) for the study free of charge. The company has already supplied the product for our pilot studies described above.

Clinical Procedures and Saliva Sample Collection. At UCSF, assenting eligible subjects will be scheduled for the initial visit. Before any treatment, 2 ml of paraffin-stimulated saliva will be collected for microbiological assessment, including the checkerboard assessment. An oral examination will be conducted by Dr. Zhan, who is trained in the use of WHO criteria, and the DMFS and DMFT will be recorded.(Fifteen subjects from the study will be re-examined to assess the reliability). The subject will then receive either F-foam or PVP-IF foam treatment in pre-made trays for 4 minutes, and excess foam will be removed by suction. The patient will be instructed not to rinse for 30 minutes after treatment. The foam treatment will be repeated three times, once weekly for the next 3 weeks, and four times at weekly intervals 6 months after enrollment. Three additional saliva samples will be collected at 1 month, 5 months and 12 months after the first four weekly treatments, for bacterial assays.

A pilot tested questionnaire will be handed out at each foam treatment to ask the child to evaluate their acceptance of the PVP-IF treatment. Potential side-effects and complaints of the treatment will be recorded by the investigators at each visit. After subjects are recruited into the study, a treatment plan will be written to include all detected cavities to be treated in six months at UCSF after the initial visit. A second caries examination for each subject will be done by the same examiner at the one year follow-up visit

Microbiology. Saliva samples will be sonicated for 20 seconds, and an aliquot will be plated within 24 hours of collection on MSSB agar for MS, on Rogosa agar for LB and on rabbit blood agar for TVC (Total Viable Counts). Plates will be incubated in 85% N_2, 10% H_2, & 5% CO_2 for 48 hours before enumeration of bacterial colonies. Five typical MS colonies will be isolated from MSSB agar based on the colony morphology. Fermentation tests will be used for MS identification. The strains confirmed as MS will be stored in glycerol TSB broth at -80°C.

Checkerboard assay. 1 ml of the saliva sample will be added to a buffer containing 0.25M NaOH, 5 mM Tris, 0.5 mM EDTA and stored at -20 deg C prior to shipping frozen to the Sissons lab for checkerboard analysis according to Wall-Manning, Sissons et al., 2002[11]. A range of oral bacterial species will be assessed and the ecological shifts determined over time.

AP-PCR assay will be used to determine the genetic diversity (# of species & strains within a single subject). In brief, stored MS isolates will be cultured in TPY broth. The bacterial DNA will be extracted by QIAamp DNA Mini Kit (Qiagen Sciences, Maryland, USA). Five μL of the extracted DNA will be place in a standard AP-PCR reaction buffer with 1 single primer (primer OPA-5: 5'-AGGGGTCTTG-3' or primer OPA013: 5'-CAGCACCCAC-3', Invetrogen, U.S.A.). Following 35 PCR amplification cycles the products will be analyzed by agarose gel electrophoresis. The DNA fragment banding patterns observed allow us to differentiate between MS species & strains.

1. (Check all that apply):

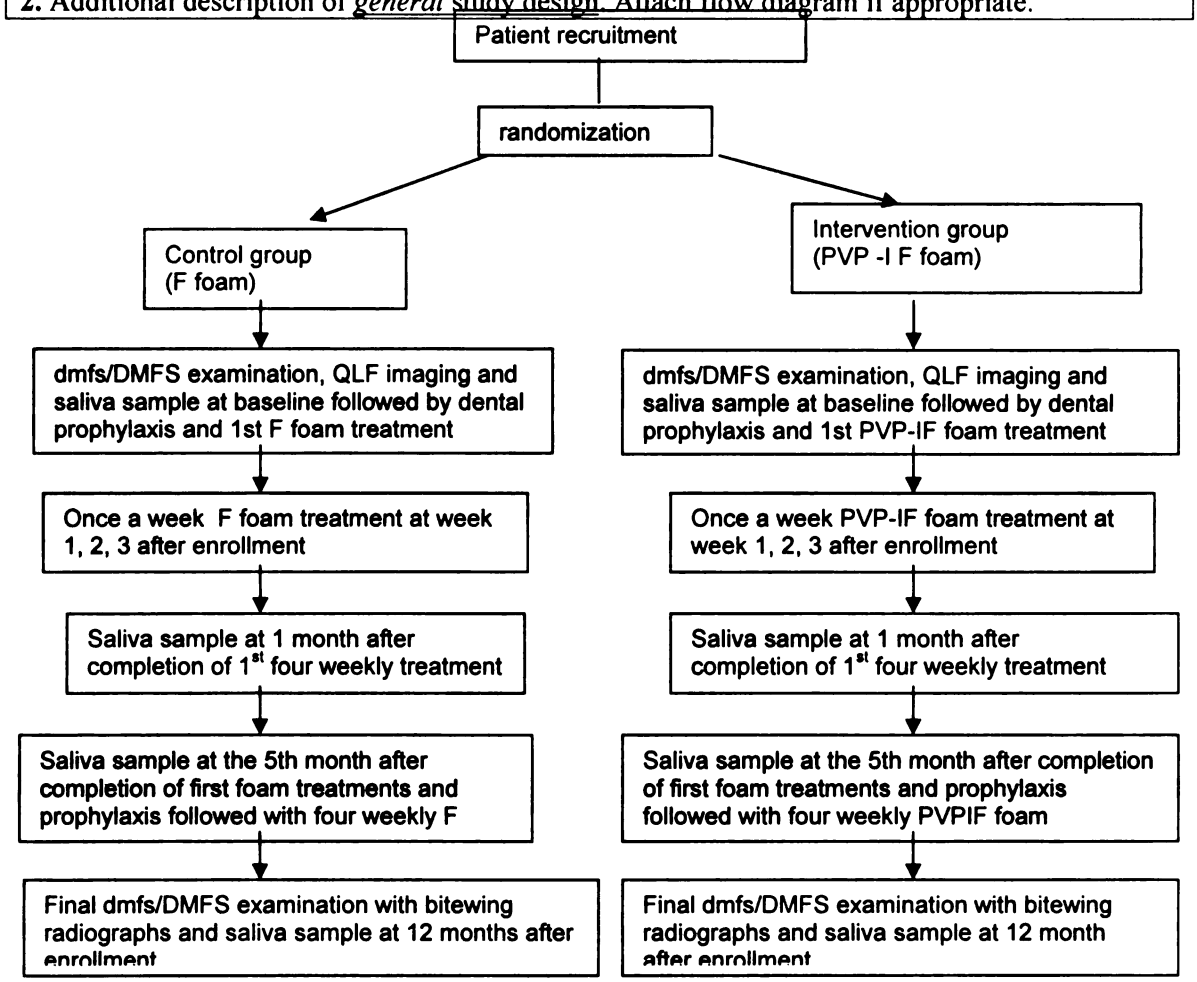
[ ]Phase I [ ]Phase II [ ]Phase III [ ]Phase IV [X]Randomized [X]Blinded

[X]Multicenter: If so, is UCSF the coordinating center? [X]Yes [ ]No

[ ]Open Label Extension: If so, specify CHR Approval Number for original study: —

[ ]Behavioral

2. Additional description of *general* study design. Attach flow diagram if appropriate.



E. Data Analysis (How and by whom will data be analyzed?)

The DMFS increment and percentage of the subjects with new decay will be calculated in both groups. The difference in DMFS increment between the two groups will be analyzed by the 2 sample Student t test. The percentage of the subjects with new decay will be analyzed by the Chi-square test. The QLF parameters of lesion area and fluorescence will be similarly analyzed. Counts of MS, LB and TVC (CFU/ml saliva) will be determined for each time point. Regression analyses (linear or logistic) will be used to test differences while adjusting for covariates such as age and gender. For each subject the reduction in logMS and logLB will be calculated by comparing

the logarithms of the pre-treatment bacterial counts with logarithm of the bacterial counts at each time point. The two mean log reductions will be compared to determine statistical differences at the initial visit, 6 month and 12 month follow-up to calculate the long term impact of the repeated PVP-IF treatment on cariogenic bacteria recolonization. For each subject, the changes of MS amplitypes at 1month and 1 year after the 1st four weekly treatments will be calculated against baseline. The mean and standard deviation from the change of amplitypes will calculated for both groups. The two means will be compared to determine statistical differences at the initial visit, 1 month and 12 month follow-up to calculate the long term impact of the repeated PVP-IF treatment on MS infection diversity.
Dr. Stuart Gansky will be responsible for overseeing the study design, data management, generating data analysis plan and performing multifactor regression analysis. Dr. Ling Zhan will be responsible for data entry and simple data analysis under Dr. Gansky's guidance.

PART 3: PROCEDURES

A. Check all that apply.

[ ] Human Biological Specimen Banking... **Attach Banking Supplement**
[ ] Genetic Testing [ ] HIV Testing

B. Please list, in sequence, all study procedures, tests, and treatments required for the study. Indicate which would be done even if a subject does not enroll in the study. Include a detailed explanation of any experimental procedures. Attach table if available.

Refer to flow chart in section 2 above for a summary of all procedures in sequence.

C. List the clinics and/or other specific locations where study procedures will be performed. Indicate how much time will be required of the subjects, per visit and in total for the study.

The study at UCSF will be carried out at the Predoctoral Pediatric Dental Clinic (PDPDC) and Postgraduate Pediatric Dental Clinic(PGPDC) at 707 Parnassus Ave. The study at WCCS will be carried out at the Operative Dentistry Clinic. A copy of the Chinese IRB approval letter will be submitted to UCSF CHR before the study in China starts. The Subjects will have a 50/50 chance of being randomly assigned to each of the study groups. The first visit for saliva sample, baseline dental examination, QLF imaging, dental prophylaxis and foam treatment will take about 1 hour. The following seven foam treatments will take about 10 minutes each time. The saliva sample visit at 1 month after completion of 1st foam treatments will take about 10 minutes. The final saliva and dental examination visit will take about 45 minuets. A total of about 3 hours will be involved for completion of the study. The dental examination at baseline and 1 year follow-up will be done by the addition of bitewing radiographs. Annual bitewing radiographs are a part of standard dental care for children with active dental decay. If there are no radiographs within 6 months available, the study will pay for the radiographs of the 1 year follow-up examination. One set of the radiographs will be provided to the patients' charts for their regular dentist and the other set will be kept with the subject's study charts.

D. Will any interviews, questionnaires, surveys or focus groups be	[X]Yes [ ]No

conducted for the study? If "Yes," please list any standard instruments used for this study and attach any non-standard instruments.	

Dental examination will be performed at baseline and 1 year after enrollment at the UCSF Predoctoral Dental Clinic with the standard dental setting and dental examination kit including a dental explorer and mirror. The dmfs/DMFS scores will be recorded using the standard recording form. QLF images will be taken after the initial and final dental exam, using QLF by Inspektor Pro (Omnii Oral Pharmaceuticals, USA). The Inspektor Pro QLF is a FDA approved non-invasive imaging instrument for early dental decay detection that uses filtered visible to induce fluorescence from the underlying dentin and the interference of this by a carious lesion is quantitatively determined. A brief questionnaire about their diet and oral care will be handed out at initial visit.
The patient will receive four weekly applications of either 2% NaF foam(control) or 10% povidone iodine plus 2% NaF foam(intervention) treatments consecutively in the first four weeks after enrollment. A dental prophylaxis will be performed immediately before the first foam treatment. The treatment will be repeated at the sixth month after enrollment. All treatments will be conducted in a regular pediatric dental setting. The subjects will be asked to bite on a commercial tray filled with either kind of the foam for 4 minutes and the excess foam will be removed by suction. The children will be asked not to rinse or eat for at least 30 minutes after the treatment.
The subjects will also be asked to chew on a piece of parafilm wax and spit into a sterile tube for 2ml of saliva at baseline, then 1 month, 5month and 1year after the first four foam treatments. The risk for this procedure is minor.

E. Will subjects undergo any study procedures or tests off-site by non-UCSF personnel? If "Yes," please explain.	[ ]Yes [X]No

F. Will subjects or their health care provider be given the results of any <u>experimental tests</u> that are performed for the study? If "Yes," please describe the tests, provide a rationale for providing subjects with the experimental test results and explain what, how and by whom subjects and their health care provider will be told about the meaning, reliability, and applicability of the test results for health care decisions.	[X]Yes [ ]No

The guardians and subjects will be asked if they would like to know their salivary cariogenic bacterial levels at baseline and final visit after they complete the study. If they do want to know, a letter will be drafted to send them the results by the investigator in charge. The bacterial challenge category using the criteria previously devised by Dr. Featherstone will be used to interpret whether each subject is in high, medium or low bacterial challenge category. Patients will be encouraged to discuss their concerns and/or oral care plans with the investigators.

PART 4: ALTERNATIVES

A. Describe the <u>alternatives to study participation</u> that are available to prospective subjects.

Subjects who choose not to participate will continue to receive normal dental care in the appropriate clinic.

B. Is study drug or treatment available off-study? If "Yes," discuss this in the consent form.	[ ]Yes [X]No [ ]N/A

PART 5: RISKS AND BENEFITS

A. Risks and Discomforts:

1. Describe the risks and discomforts of any investigational or approved drugs, devices and procedures being used or assigned for study purposes. Describe the expected frequency of particular side effects. If subjects are restricted from receiving standard therapies during the study, please also describe the risks of those restrictions.

The 2% NaF foam has been approved to be used in children for caries prevention in U.S.A. 10% Povidone iodine is approved for intraoral use in the US. The risks resulting from saliva collection are minimal, although a small percentage of the population shows allergic reaction to iodine. According to our previous studies and those of other investigators, the oral use of povidone iodine has not been associated with any risks or discomforts above and beyond that associated with routine dental care.

QLF images will be taken after the initial and final dental exam, using an Inspektor Pro QLF device (Omnii Oral Pharmaceuticals, USA). The Inspektor Pro QLF is a FDA approved non-invasive imaging instrument for early dental decay detection. The risk of the QLF imaging is minimal.

2. Describe the steps you have taken to minimize the risks/discomforts to subjects (e.g., stopping rules, special monitoring):

Discomfort or delayed side-effects of either the fluoride or the povidone iodine plus fluoride foam will be built into the recording sheets for treatment and follow-up visits. The investigator in charge of the treatment and follow-up visit will ensure that this information is recorded and will report any side-effect to the principal investigator. The treatment will be stopped for any subjects with complications due to the treatment. Any side-effect related to the study treatment will be reported to CHR on time as required. A contact phone number of the responsible clinical investigator will be given to the patient for their questions and concerns about the treatment.

The annual bitewing x-ray is a part of your child's standard dental care. The study will pay the one year follow-up x-rays if they are not available. We will use the existing x-rays within 6 months and no new x-rays will be taken. The amount of radiation the child will be exposed to is relatively small. These doses of radiation could be potentially harmful, but the risks are so small that they are difficult to measure.

B. Data and Safety Monitoring Plan:

The guidelines for a Data and Safety Monitoring Plan state that the degree of monitoring should be commensurate with the risk. Because the risk of adverse events related to the study is minimal and because we will take appropriate

measures to ensure confidentiality the study will not require a Data Safety Monitoring Board. This study is a small scale pilot study to test if the combination of the two approved drugs, namely 2% sodium fluoride and 10% povidone iodine in a foam delivery system, will reduce the cariogenic bacteria and enhance resistance of the teeth to demineralization, thereby preventing future tooth decay in children at high risk. However we will conduct our own monitoring according to recognized procedures to prepare for and respond to any adverse events.

C. Confidentiality and Privacy: Describe the consequences to subjects of a loss of privacy (e.g., risks to reputation, insurability, other social risks):

Participation in research may involve a loss of privacy; however, the research records will be handled confidentially. All records will be coded, and kept in locked files so that only the study investigators have access to them. No individual identities will be used in any reports or publications resulting from this study.

1. Identifiers: Please indicate all identifiers that may be included in the research records for the study. Check all that apply.

[X] Names	[ ] Social Security Numbers	[ ] Device identifiers/Serial numbers
[X] Dates	[ ] Medical record numbers	[ ] Web URLs
[X] Postal address numbers	[ ] Health plan numbers	[ ] IP address
[X] Phone numbers	[ ] Account numbers	[ ] Biometric identifiers
[ ] Fax numbers	[ ] License/Certificate numbers	[ ] Facial Photos/Images
[ ] Email address	[ ] Vehicle id numbers	[ ] Any other unique identifier

[ ] None of the 18 identifiers listed above

2. Determining Whether HIPAA Regulations Apply to This Study: Please answer the questions below for the identifiers marked in the above section. Check all that apply:

Are study data: [ ] Derived from a medical record? ***Please identify source***: [X] Added to the hospital or clinical medical record? [X] Created or collected as part of health care? [ ] Used to make health care decisions?	**HIPAA regulations apply.** The identifiers marked in section C.1 are PHI.
[X] Obtained from the subject, including interviews, questionnaires? [ ] Obtained from a foreign country or countries only? [ ] Obtained from records open to the public? [ ] Obtained from existing research records? [ ] None of the above.	**HIPAA regulations do not apply.** The identifiers marked section C.1 are not PHI.

If HIPAA regulations apply, you are required to obtain individual subject authorization or a CHR-approved waiver of authorization, or both, to be allowed access to medical records. For the VA, use the SFVAMC authorization. (The one exception to these requirements is the use of a Limited Data Set along with a Data Use Agreement.)

3. Use and Disclosure of Personal Health Information: Please indicate to whom or where you may disclose any of the identifiers listed above as part of the study process. Check all that apply:

[X] We do not plan to share any of the personally identifying information listed above outside the research team.
[ ] The subject's medical record
[ ] The study sponsor: ***please indicate***:
[ ] The US Food & Drug Administration (FDA)
[ ] Others: ***please indicate***:
[ ] A Foreign Country or Countries

4. Data Security: Please indicate how study data are kept secure. Check all that apply:

[ ] Data are coded; data key is destroyed at end of study or ***provide date***:
[X] Data are coded; data key is kept separately and securely
[X] Data are kept in locked file cabinet
[X] Electronic data are protected with a password
[X] Data are kept in locked office or suite
[ ] Data are stored on a secure network

5. Describe any additional steps taken to assure that identities of subjects and any of their health information which is protected under the law is kept confidential. If video or audio recordings will be made as part of the study, disposition of these recordings should be addressed here and in the consent form.

6. Reportable Information: Is it reasonably foreseeable that the study will collect information that State or Federal law requires to be reported to other officials (e.g., child or elder abuse) or ethically requires action (e.g., suicidal ideation)? If "Yes," please explain below and include a discussion of the reporting requirements in the consent form.	[ ]Yes [X]No

D. Benefits: **1.** Are there potential direct benefits to study subjects? If "Yes," please describe below.	[X]Yes [ ]No

The subjects recruited into the study will be at high risk of further tooth decay. They will get two free oral prophylaxis (about $60 each time) and eight fluoride foam treatments (about $50 each time), which will help to them to reduce the risk for future decay. They will also get a free set of x-ray bite wings at the end of the study, which is worth $45. Besides, the results of the bacterial analysis will be available to the subjects by the end of the study, which indicates the subject's risk for future dental decay. It is hoped that the study will determine

that the proposed regimen is a practical antibacterial treatment to reduce tooth decay causing bacteria and generate a new treatment regimen to prevent caries in children at high risk.

2. What are the potential benefits to society?

Potentially a PVP-I/F combined foam could be applied to the teeth of children at appropriate intervals throughout a year, reducing both the MS and LB bacterial challenge, enhancing remineralization, and markedly reducing or even eliminating new caries formation. The advantage expected by using this antibacterial/fluoride combination in a flavored foam form is improved taste and easier application for routine treatment, which may broaden its future use in dental practice or home dental care for caries prevention in children with high caries risk.

If the hypothesis is proven, it will indicate that PVP-IF foam is a convenient antibacterial treatment as a strategy in caries prevention for children in U.S.A. and beyond, especially for children with high caries risk from socioeconomically disadvantaged families.

E. Risk/Benefit Analysis: How do the benefits of the study outweigh the risks to subjects?

The subjects in the control group could get benefits from the study by 2 free prophylaxes and fluoride treatments, which will help them to improve oral hygiene and tooth resistance to decay. The subjects in the intervention group will get 2 free prophylaxes and PVPI/F foam treatment, which will have at least equivalent effect to fluoride foam treatment if it is not better, based on our preliminary study. The subjects will also get a free set of bite-wing x-rays of their tooth as a diagnostic tool for caries status assessment. Subjects in the control group will receive F foam treatment which is a part of routine care at UCSF for high caries risk children. Subjects in the intervention group will receive PVP-IF treatment. PVPI has been approved to be used in oral cavity topically. The complication for PVPI is very rare although there are a small number of individuals who are allergic to iodine. Precautions are built into the recording system and the treatment will be stopped immediately and reported to CHR if any complication happens. The patient will be referred to the appropriate physician for treatment. The risk from other research procedures, such as saliva sampling, is minor. Therefore, the benefits to the subjects outweigh the risks in the study.

PART 6: SUBJECT INFORMATION

A. Number of Subjects:	
1. How many subjects will be enrolled at UCSF and affiliated institutions?	60
2. How many subjects will be enrolled at all sites (i.e., if multicenter study)?	120
3. How many people do you estimate you will need to consent and screen here	120

(but not necessarily enroll) to get the needed subjects?	

B. Types of Subjects: Check all that apply. Click on links for additional instructions.	
[X]	Minors.....**Attach "Inclusion of Minors" Supplement**
[ ]	Subjects unable to consent.....**Attach Surrogate Consent or Emergency Waiver of Consent Supplement**
[ ]	Subjects unable to read or speak English
[ ]	Pregnant Women
[ ]	Fetuses
[ ]	Neonates
[ ]	Prisoners .....**Attach "Inclusion of Prisoners" Supplement**
[ ]	Inpatients
[X]	Outpatients
[ ]	Healthy Volunteers
[ ]	Staff of UCSF/affiliated institution

C. Eligibility Criteria:

1. General description of subject population(s):

A total of 60 healthy 6-9 year olds with 1-5 frank caries lesions (who assent and their parents give consent) will be enrolled in the study at each site, randomized to 30 per each of the test and control groups. Eligible children who reside within a 25 mile radius and will be randomly assigned to one of the two study groups.

2. Inclusion Criteria:

Children: a) 6-9 years old, b) registered patients at UCSF Predoctoral Pediatric Dental Clinic or Postgraduate Pediatric Dental Clinic, c) have 1-5 frank caries lesions, d) resident within a 25 miles radius of San Francisco.

3. Exclusion Criteria:

children: a).with serious chronic systemic or periodontal diseases; b).with medicines taken within the past 3 months that might affect oral flora; c).with a dry mouth or difficulty spitting

D. How (chart review, additional tests/exams for study purposes), when and by whom will eligibility be determined?

A dental examination of dmfs/DMFS will be conducted by Dr. Ling Zhan. She is a postgraduate researcher in the Department of Preventive and Restorative Dental Sciences at the UCSF. She is a trained dentist with over 10 years of clinical practice experience. Her research career has been focused on microbiology aspects of caries and caries prevention. She has worked closely with Dr. Jane Weintraub in one NIH funded caries management study and has been trained as an examiner for dmfs/DMFS scores using WHO criteria.
All prophylaxis and foam treatments will be done at PDPDC or PGPDC by one postgraduate dental resident (Dr. Purvi Zavery) under supervision of Dr. Pamela Den Besten, who is the chair and professor of the Division of Pediatric Dentistry. The final bite-wing x-rays will be also taken by the resident.

E. Are there any inclusion or exclusion criteria based on *gender, race* or [ ]Yes [X]No

ethnicity? If "Yes," please explain the nature and rationale for the restrictions below.

PART 7: RECRUITMENT

A. Please review CHR Recruitment Guidelines for more information about acceptable recruitment methods. Note that all advertisements, whether posted or broadcast, and all correspondence used for purposes of recruitment require CHR review and approval before they are used. Check all that apply:	
[X]	Study investigators recruit their own patients directly and/or nurses or staff working with researchers approach patients. ***Please explain in Section B.***
[ ]	Study investigators send a CHR-approved letter to colleagues asking for referrals of eligible patients interested in the study. The investigators may provide the referring physicians a CHR-approved Information Sheet about the study to give to the patients. If interested, the patient will contact the PI. Or, with documented permission from the patient, the PI may be allowed to talk directly with patients about enrollment. ***Attach letter for review.***
[ ]	Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing. ***Attach letter for review.***
[X]	Advertisements, notices, and/or media used to recruit subjects. The CHR must first approve the text of these, and interested subjects will initiate contact with study investigators. ***Attach ads, notices, or media text for review. In Section B, please explain where ads will be posted.***
[ ]	Study investigators request a Waiver of Consent/Authorization for recruitment purposes. This waiver is an exception to the policy but may be requested in circumstances such as:
[ ]	Minimal risk studies in which subjects will not be contacted (i.e., chart review only);
[ ]	Review of charts is needed to identify prospective subjects who will then be contacted. (Explain in Waiver form);
[ ]	Large-scale epidemiological studies and/or other population-based studies when subjects may be contacted by someone other than personal physician. (Explain in Waiver form.)
[ ]	Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study. ***Please explain in Section B.***
[ ]	Study investigators list the study on the UCSF Clinical Trials Seeking Volunteers web page or a similarly managed web site. Interested subjects initiate contact with investigators.
[ ]	Study investigators recruit potential subjects who are unknown to them. Examples include snowball sampling, use of social networks, direct approach in public situations, random digit dialing. ***Please explain in Section B.***

B. Provide detail in the space below (*i.e., how, when, where and by whom are potential subjects approached?*).

The students, faculty and staff in the PDPDC and PGPDC will be informed about the study and be asked to refer potentially qualified patients to the study investigators or give the patient the study contact phone number for them to contact the investigators. The investigator will approach the patient's guardian when the patients come for their regular treatment and ask if they are interested in the study. A screening appointment will be scheduled if the patient and their guardian are interested.
Fliers about the study with contact information will also be posted in the UCSF School of Dentistry Clinics to recruit subjects.

PART 8: INFORMED CONSENT PROCESS

A. Check all that apply:

[X] Signed consent will be obtained from subjects and/or parents (if subjects are minors),

[ ] Verbal consent will be obtained from subjects, using an

[ ] Information sheet (attach)

[ ] Script (attach)

[ ] Signed consent will be obtained from surrogates..... **Attach Surrogate Consent Supplement**

[ ] Informed consent will not be obtained. .... **Attach either the Waiver of Consent/Authorization or the Emergency Waiver of Consent Supplement as appropriate.**

B. In the space below, describe *how*, *where*, *when* and *by whom* informed consent will be obtained. How much time will prospective subjects be given to consider study participation? If special subject populations will be included, be sure to describe any additional plans for obtaining consent from particular populations. Justify any plans to use verbal consent instead of signed consent.

Informed consent from subject's guardian and assent from the subject will be obtained by Dr. Den Besten, Dr. Ling Zhan and/or the Pediatric Dental resident who will work on the study, at the scheduled screening visit in PDPDC or PGPDC. The above named doctors will discuss the procedures, benefits, risks and rights of the subject in the study and answer questions. The subjects will have 30 minutes to decide whether they want to participate in the study. If they can not decide in 30 min, they will always be welcome to call back to schedule a visit for their enrollment while the study recruitment is going on.

C. How will you make sure subjects understand the information provided to them?

The investigator will ask the subject to repeat the outline of the study procedures and their benefits and risks to make sure they understand the provided information.

PART 9: FINANCIAL CONSIDERATIONS

A. **Payments to Subjects:**		
1. Will subjects receive payments or gifts for study participation? If "Yes," please review CHR Subject Payment Guidelines and complete the following:		[X]Yes [ ]No
2. Payments will be (check all that apply):	[X] Cash (describe below) [ ] Check	[ ] Other
3. Please describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.		

Each child will receive a $10 gift card and their parent/guardian will receive $10 cash for each of the treatment or saliva visits. Both of the child and his/her parent/guardian will get $4 per visit cash bonus at the final visit that will be $40 cash for each of them if they complete all ten study visits. That is a total of $100 gift card and $40 cash reimbursement for each subject and $140 cash for their parent if they complete the study. The reimbursements to the parents/guardians are calculated to cover their parking and transportation expenses for the visit. We added the cash bonus at the final visit to show our appreciation for their participation in the study and encourage them to complete the study.

The subjects and the parents in China will receive 20 Chinese Yuan gift card and the parent/guardian will receive 20 Chinese Yuan for completion of each four weekly treatment visit at the beginning and the 6th month after enrollment. The child will receive a 10 Chinese Yuan gift card and their parent/guardian will receive 10 Chinese Yuan for the 1 month saliva sample visit and the 12 month final visit. The subject and their guardian will get 4 Chinese Yuan per visit cash bonus at the final visit that will be 40 Yuan cash bonus for each of them if they complete all study visits. That will be a total of 200 Chinese Yuan reimbursement for the child and their parent/guardian if they complete the study.

B. Costs to Subjects: Will subjects or their insurance be charged for any study procedures? If "Yes," describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.	[ ]Yes [X]No

C. Treatment and Compensation for Injury: The investigators are familiar with and will follow the University of California policy and (if applicable) Veteran's Affairs policy regarding treatment and compensation for injury. If subjects are injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California, by the Department of Veteran's Affairs (for subjects eligible for veteran's benefits, if the SF VAMC is a study site), or by the study sponsor, if any, depending on a number of factors. The University does not normally provide any other form of compensation for injury.

PART 10: BIBLIOGRAPHY

LITERATURE CITED:

1. Kaste LM SR, Oldakowski RJ, Brunelle JA, Winn DM, Brown LJ. Coronal caries in the primary and permanent dentition of children and adolescents 1-17 years of age: United States, 1988-1991. J. Dent. Res. 1996;75:631-641
2. Macek MD, Heller KE, Selwitz RH and Manz MC. Is 75 percent of dental caries really found in 25 percent of the population? J Public Health Dent 2004;64:20-5
3. Featherstone J. The science and practice of caries prevention. J Am Dent Assoc 2000;131:887-899
4. Napimoga MH, Kamiya RU, Rosa RT, et al. Genotypic diversity and virulence traits of Streptococcus mutans in caries-free and caries-active individuals. J Med Microbiol 2004;53:697-703
5. KHOO MA, DENBESTEN PK, FUJINO T, et al. MS Genetic Diversity and Cariogenic Bacterial Levels in ECC Subjects. J Dent Res 2004;83:A3431
6. Zhan L, Hoover C, Li W and Featherstone JDB. Genetic Diversity of Mutans Streptococci in High Caries Risk People. J. Dent Res 2002;81:A-351
7. Caufield PW, Gibbons RJ. Suppression of Streptococcus mutans in the mouths of humans by a dental prophylaxis and topically-applied iodine. J Dent Res 1979;58:1317-26
8. Lopez L, Berkowitz R, Spiekerman C and Weinstein P. Topical antimicrobial therapy in the prevention of early childhood caries: a follow-up report. Pediatr Dent 2002;24:204-6
9. Zhan L, DenBesten PK, Gansky SA, Hoover CI, Fujino T and Featherstone JD. Povidone-iodine as an oral antiseptic in children with early childhood caries. Caries Res 2003;37:272
10. Hoover C, Weintraub JA, Gansky SA, White JM, Wilson RS and Featherstone JD. Effect of a Caries Management Regimen on Cariogenic Bacterial Population. J. Dent Res 2004;83:A0779
11. Wall-Manning GM, Sissons CH, Anderson SA, Lee M. Checkerboard DNA-DNA hybirdisation technology focused on the analysis of gram-positive cariogenic bacteria. J Microbiol Methods 2002;51:301-311.

PART 11: ATTACHMENTS

Please list Attachments, Supplements and Appendices	Version number(s) or date(s)

consent form
assent form
flyer
Form A. Baseline visit
Baseline dmfs/DMFS record form
Baseline questionnaire
Form B. 1 week- 2 month follow-up

visit record form
Form C. 6 month follow-up record form
Form D. Final visit record form
Final dmfs/DMFS record form

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO BE A RESEARCH SUBJECT

Effectiveness of Specific Antimicrobial Treatment against Bacteria that cause Dental Decay in Children in Pacific Rim Countries

A. PURPOSE AND BACKGROUND

Dr. John Featherstone, Dr. Ling Zhan from the Department of Preventive and Restorative Dental Sciences and Dr. Den Besten from the Division of Pediatric Dentistry are conducting a study to investigate using Povidone Iodine Foam as an antibacterial treatment to reduce new tooth decay in children with high risk. This study is being funded by a Pacific Rim Grant from the University of California, and a grant from the International Association for Dental Research.

Your child is being asked to participate in this study because he/she is at high risk for tooth decay and is 6 to 9 years old.

B. PROCEDURES

If you agree to have your child in this study, the following will happen to your child:

1. Your child will have a 50/50 chance (like flipping a coin) of being placed in one of two groups. Neither your doctor nor you will make the choice, so that bias in the study is reduced. The two groups are (a) fluoride foam (control group) or (b) povidone iodine/fluoride (treatment group). He/she will be scheduled for an initial visit. A dental examination will be done to record his/her tooth decay status. Pictures of his/her back teeth will be taken with a intra oral camera with a blue light shine on the teeth. He/she will be asked to chew on a piece of parafilm wax and spit into a sterile tube and give 2ml of saliva. The saliva will be used to test the tooth decay causing bacteria. He/she will receive a dental prophylaxis (professional tooth cleaning). Then he/she will be asked to bite on a tray filled with fluoride foam (control group) or povidone iodine/fluoride foam (treatment group) for 4 minutes based on which group he/she will be randomly assigned to. He/she will be asked not to rinse or eat for 30 minutes after the treatment. The initial visit will take about 1 hour.
2. Your child will be asked to come back for three more foam treatments, one each week for the next 3 weeks after the initial treatment. Each of these foam treatments will take about 10 minutes.
3. Your child will be asked to come back one month after the last foam treatment and spit into a sterile tube to give 2 ml of saliva. The visit will take about 10 minutes.
4. Four months later, he/she will be asked to come back to repeat the foam treatment once a week consecutively for four weeks. He/she will spit into a tube to give 2ml of saliva and receive a prophylaxis before the first foam treatment. Each visit will take about 10 minutes.

5. One year after enrollment, your child will be asked to come back for the final visit. A set of bitewing x-rays of the teeth will be taken if there are no existing bitewing x-rays taken within 6 months. One set of the x-rays will be available for your child's dentist. He/she will be asked to spit to give 2ml of saliva.He/she will also receive a dental examination and pictures on his/her back teeth will be taken again, using an intra oral camera with blue light. The visit will take about 45 minutes.
6. Arrangement will be also made in the UCSF Pediatric Dental Clinic to have all cavities of your child fixed within 6 month after he/she enters the study. Payment for this routine treatment will come either from your dental insurance or from you.

Participation in the study will take a total of about 2 hours 50 minutes over a period of 1 year with a total of 10 visits.

C. RISKS/DISCOMFORTS

The 2% NaF foam is a standard treatment that is approved for use in children for caries (tooth decay) prevention in U.S.A. The 10% Povidone iodine antibacterial treatment is approved for use in the mouth in the US. The risks resulting from saliva collection are minimal, although a small percentage of the population shows allergic reaction to iodine. According to previous studies, the oral use of povidone iodine has not been associated with any risks or discomforts above and beyond that associated with routine dental care.

The annual bitewing x-rays are a part of your child's standard dental care. The study will pay for the one year follow-up x-rays if they are not available. We will use any existing x-rays taken within 6 months and no new x-rays will be taken. The amount of radiation your child will be exposed to is relatively small. These doses of radiation could be potentially harmful, but the risks are so small that they are difficult to measure. If your child has had a lot of x-rays already, you should discuss this with the investigator.

Randomization: Your child will be randomly assigned to a treatment program by 50/50 chance. The treatment your child receives may prove to be less effective or to have more side effects than the other study treatment or than other available treatments. This will not be known until after the study is completed and the data has been analyzed.

Confidentiality: Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. Records will be coded, and kept in locked files so that only the study investigators have access to them. No individual identities will be used in any reports or publications resulting from this study.

Treatment and Compensation for Injury:

If your child is injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California depending on a number of factors. The University does not normally provide any other form of

compensation for injury. For further information about this, you may call the office of the Committee on Human Research at (415) 476-1814.

D. BENEFITS

The potential benefit to your child is that the treatment he/she receives may prove to be more effective than the other study treatment or than other available treatments, although this cannot be guaranteed. It is hoped that the information gained from the study will help to prevent or reverse dental decay in children at high risk in the future. Further, the results of the bacterial analysis will be available to you at the end of the study. This information will be explained to you as indicators of your child's risk for future dental decay. It is hoped that the study will determine that the proposed regimen is a practical antibacterial treatment to reduce the number of tooth decay causing bacteria. If successful this will be a new treatment for preventing or reversing dental decay in children at high risk.

E. ALTERNATIVES

Your child and you may choose not to participate in this study at any time and no further exam, treatment, or saliva samples will be taken but you will continue to receive normal dental care in the appropriate clinic.

F. COSTS

You will only pay for the usual treatments that are needed to fix your child's tooth decays as a part of their routine dental care. Your child will not be charged for any exam, fluoride or antibacterial treatments or saliva collection that are part of the study.

G. PAYMENT

You will receive $10 cash and your child will receive a $10 gift card for each study visit. You and your children will also get $4 cash bonus for each visit at the final visit. That is a total of $140 for each of you if your child completes the study.

H. QUESTIONS

This study has been explained to you by Dr. John Featherstone, or Dr. Ling Zhan, or the person who signed below and your questions were answered. If you have any other questions about the study, you may call Dr. John Featherstone at (415)476-0456, or Dr. Ling Zhan at (415) 476-0921.

I. CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate, you should sign below, and you will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about your child.

The person being considered for this study is unable to consent for himself/herself because he or she is a minor. You have been asked to give your permission to include your child in this study. You know of no reason why he/she would refuse were it possible to do so now.

Date	Parent/Legal Guardian's Signature
Date	Person Obtaining Consent

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
ASSENT TO BE A RESEARCH SUBJECT

Effectiveness of Specific Antimicrobial Treatment against Bacteria that cause Dental Decay in Children in Pacific Rim Countries

What is this study about?

Dr. John Featherstone and Dr. Ling Zhan are doing an experiment to see if a special tooth foam will help to stop cavities better than regular tooth foam.

What will happen to you if you are in the experiment?

1. First the dentist will look at your teeth. A picture of your back teeth will be take by a mini camera with blue light. You will chew on a piece of wax and spit into a cup until a teaspoon of spit is collected.
2. Your teeth will be cleaned and then you will bite into a tray that is filled with fruit flavored foam for 4 minutes.
3. The extra foam in your mouth will be removed with a suction straw.
4. You will come back 3 more times in the next 3 weeks to bite the foam trays. One month later, you will come back to chew on wax and spit into a cup again.
5. Four months later, you will come back to chew on wax and spit into a cup for one teaspoon of spit. Your teeth will be cleaned and you will bite the foam trays once a week for four times.
6. Then you will come back 5 months later to have the dentist look at your teeth and take the picture of your back teeth with the mini camera. You will chew on a piece of wax and spit into a cup.

Will any parts of the experiment hurt?

There is no part of this experiment that will hurt. It is like your regular check up with your dentist.

Will the study help you get better?

Yes, we hope the study will find new ways to keep children from getting new tooth decay in future. The tooth cleaning and fluoride foam treatments you will receive in the study are going to help you keep your teeth clean and strong.

What if you have questions?

You can ask Dr. John Featherstone or Dr. Ling Zhan or their friends any questions you have about the experiment. You can ask your questions now or later, any time you like.

What are your choices?

You will be in this experiment only if you want to. You will not be in it if you don't want to. If you decide to be in this experiment and you change your mind later, that is okay too. You just have to tell the dentist and then you can stop. No body will get mad at you if you don't want to be in this experiment.

If you are in the experiment, you will get a $10 gift card for each study visit and you will get $4 bonus for each visit at the final visit. If you finish all 10 study visit, you can get $100 in gift cards and $40 cash.

If you want to be in this experiment, please sign your name on the line at the bottom of this paper.

Date Signature of Child

UCSF COMMITTEE ON HUMAN RESEARCH
APPLICATION SUPPLEMENT
(BETA VERSION)

Please date form: __

INCLUSION OF MINORS

Principal Investigator on CHR Application:	CHR # (if known):
John Featherstone	
Study Title (may not exceed 500 characters):	
Effectiveness of Specific Antimicrobial Treatment Against Bacteria that Cause Dental Decay in Children in Pacific Rim Countries	

Age Range
Please specify the eligible age range for minors in this study:

six to nine years old.

45 CFR 46, Subpart D: Minors	
Research on minors must fall under one of the following categories. Please check all that apply:	
]	**Minimal Risk** (45 CFR 46.404). The risks (physical or emotional) are no greater than those encountered in daily life or during the performance of routine physical or psychological examinations or tests. **Obtain the consent of one parent/legal guardian and the assent of the minor** (if over 7 years of age).
X]	**Greater than Minimal Risk** (45 CFR 46.405) but presenting the prospect of **direct benefit** to the individual subject. **Obtain the consent of one parent/legal guardian and the assent of the minor** (if over 7 years of age).
]	**Greater than Minimal Risk** (45 CFR 46.406) (though only a **minor increase over minimal risk**) and **no reasonable prospect of direct benefit** to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. **Obtain the consent of both parents/legal guardians and the assent of the minor** (if over 7 years of age) unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor.
[ ]	**Research not otherwise approvable** (45 CFR 46.407) which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. • **Requires approval by the Secretary of the U. S. Department of Health and Human Services.** • Requires consent of both parents/legal guardians.
If there is more than one group of minors being studied, e.g., patients and normal controls, and the groups fall into different risk/benefit classifications, explain the differences below, citing the applicable section of 45 CFR 46 for each group.	

Informed Consent and Minor's Assent
Please indicate below the consent and assent forms that will be used for this study.

[ ] Consent form addressed to the subject, for subjects 13 and older, with signature lines for subjects and parent(s)
[X] Simplified Assent form for subjects 7-12 years of age
[X] Consent form addressed to parent(s)

Waiver of parental consent (45 CFR 46.408(c)): The requirement for parental/guardian consent may be waived under limited circumstances (e.g., homeless youth, youth seeking health care which does not require parental consent) where parental/guardian permission is not a reasonable requirement to protect the subject if an appropriate mechanism for protecting the children is implemented and the waiver is consistent with Federal, State, or local law.

If you are requesting a waiver of parental/guardian consent, please explain why parental consent is not necessary and what other protections are in place to substitute for parental consent.

A Study to Prevent Tooth Cavities in Children

Recruiting Volunteers!

It is a one year study with fruit flavored antibiotic foam treatments.

- We need children age **6 - 9 years** with 1 to 5 cavities
- The child will receive **$100 gift certificate, $40 cash**, two free tooth cleaning and a free set of tooth x-ray in one year.
- The parent will receive **$140 cash**.

For details of the study please contact:

Dr. Ling Zhan
Phone: (415) 476-0921
University of California, San Francisco
Department of Preventive and Restorative Dental Sciences
Division of Clinical General Dentistry

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SCHOOL OF DENTISTRY
PVP-I Foam Study **Form A1 Subject's Contact Information and Ethinicity**
Subject initial:_____. Study ID:PR___/____/____.

Please fill in the following information (It will only be used for contact in this study):

Child's Name: _____ _____
First Last Middle Initial

Child's Birth date: ____/____/_____.
MM DD YYYY

Child's gender: Male____ Female_____

Parent/guardian's Name: _____
First Last

Contact phone number: _____(day) _____(night)

Contact Address:

_____
Number Street Apt#

_____
City State Zip Code

Information about you child's ethnicity:

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

☐ No
☐ Yes

☐ Central American ☐ Puerto Rican

☐ Cuban ☐ South American

☐ Mexican ☐ 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/Myanmarese
  - ☐ 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

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SCHOOL OF DENTISTRY
PVP-I Foam Study **Form A2 Subject Oral Care Survey**
Subject initial: _____. Study ID: PR___/___/___.

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: ____/____/_____.
MM DD YYYY

Child's gender: Male____ Female_____

1. How often does your child brush his/her teeth?

- □ Not every day
- □ 1 time each day
- □ 2 times each day

2. Does your child use fluoride toothpaste when he/she brushes his/her teeth?

- □ Yes
- □ No
- □ I do not know.

What kind of toothpaste does your child use? _____

3. How many times each day does your child eat or drink sweet snacks like soda, juice, cookies and candy etc.?

- □ Never
- □ 1 time each day
- □ 2 times each day
- □ 3 or more times each day

4. How many times did your child floss his/her teeth in the past week?

- □ Not at all
- □ One Time
- □ Two Times
- □ Three to six times
- □ Daily (seven times)
- □ More than seven times
- □ Don't know

5. Did your child see a dentist at least once a year in the past two years?

- □ Yes.
- □ No.

5. Would you like to know your child's test results at the end of the study?

- □ Yes
- □ No

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SCHOOL OF DENTISTRY

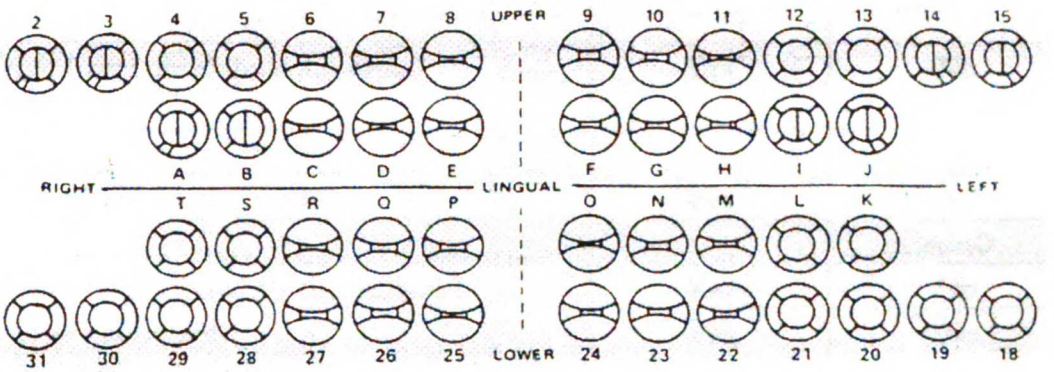
PVP-I Foam Study

Form A3 Baseline DMFS/dmfs record sheet

Subject's initials: _____. Study ID: PR____/_____/_____.

Visit Date: ____/____/_____

Charting: Red=current decay, Blue= previous restorations



Comments:

_____

_____

_____

_____

_____

Patient's Name _____	Date of visit: ___/___/	Patient Study ID Number PR___/___/___

PROCEDURES

Subject Qualification			
1. 1-5 active caries in past year?		**Yes**	No
2. No antibiotics within 2 weeks?		Yes	**No**
3. No medicine that will cause dry mouth?		Yes	**No**
4. No hepatitis and HIV etc. systemic disease.		Yes	**No**
5. Will stay in the Bay Area for another 1 year.		**Yes**	No
6. No significant developmental dental diseases.		Yes	**No**
Patient qualified for the study		**Yes**	No
Consent form signed by the patient?		**Yes**	No
Saliva sample collected? (1 tube, 2 ml in ≤ 4 minutes)		Yes	No
DMFS/dmfs exam done?		Yes	No
Oral prophylaxis done?		Yes	No

First Foam Treatment

Randomization(check one group)	Group A ___ Group B
Foam treatment done (record the foam group)	Foam
Record any unpleasant feeling or complaint after the foam treatment. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. unpleasant taste _____ c. staining _____ d. allergy _____ e. others _____

Schedule the date for the second foam visit(include week day also):
___/___/____(____)

Comments:_____

_____

Investigator's Signature:

Patient's Initials	Patient treatment group: _____.	Patient Study ID Number PR___/___/___

Second Foam Treatment:

Date of visit	___/___/_____.
Record any unpleasant feelings or complaints after the **previous** foam treatment. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. unpleasant taste _____ c. staining _____ d. allergy _____ e. others _____
Foam treatment done? (record the foam group)	Group _____.
Record any unpleasant feelings or complaints after the **present** foam treatment. **If yes, report it to Dr. John Featherstone.**	f. None ____. a. unpleasant taste _____ b. staining _____ c. allergy _____ d. others _____

Schedule the date for the third foam visit(include week day also): ___/___/___(_____)

Investigator's Signature:

Third Foam Treatment

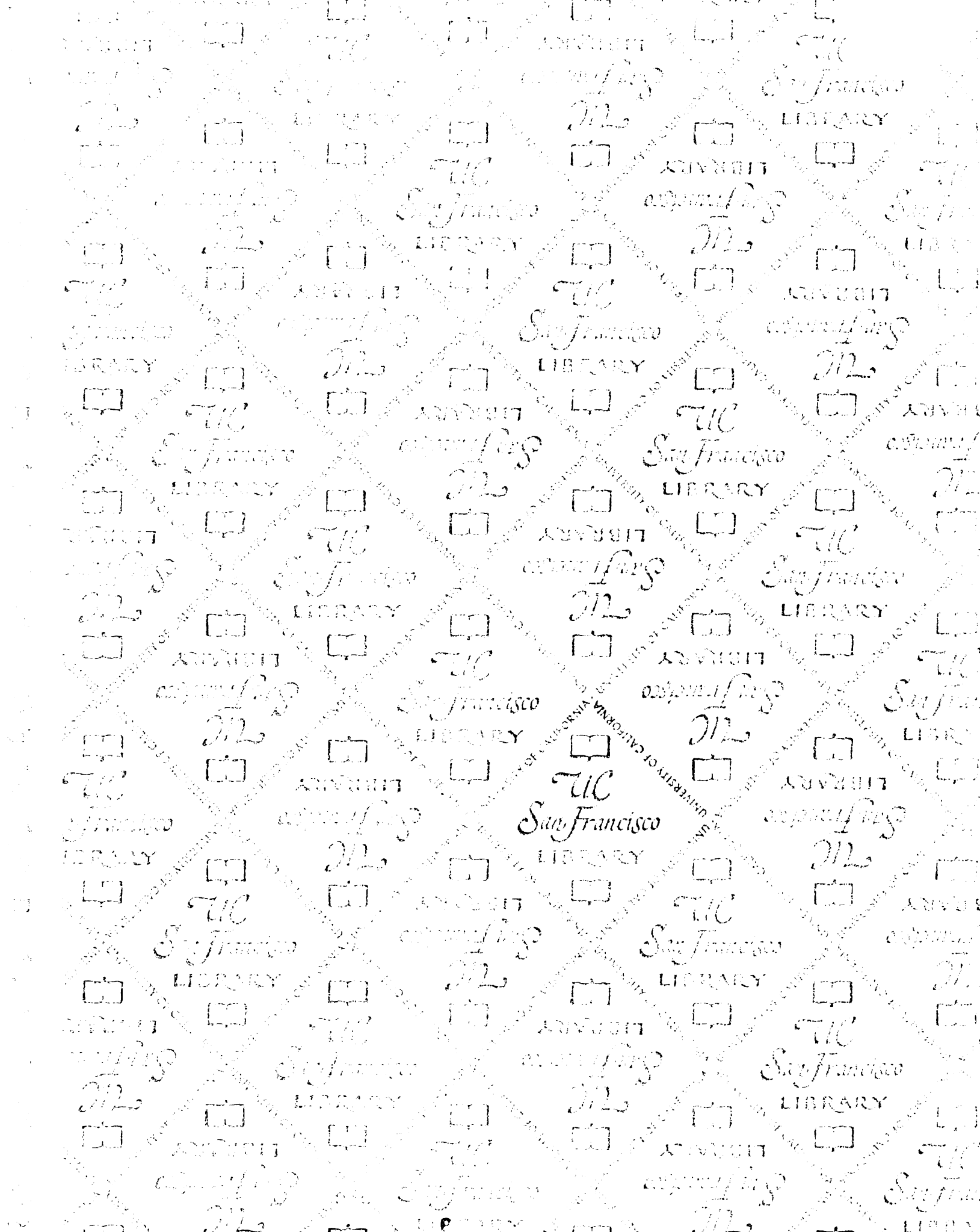
Date of visit	___/___/_____.
Record any unpleasant feelings or complaints after the **previous** foam treatment. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. unpleasant taste _____ c. staining _____ d. allergy _____ e. others _____
Foam treatment done? (record the foam group)	Group _____.
Record any unpleasant feelings or complaints after the **present** foam treatment. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. unpleasant taste _____ c. staining _____ d. allergy _____ e. others _____

Schedule the date for the fourth foam visit(include week day also):___/___/___(_____)

Investigator's Signature:

Fourth Foam Treatment	
Date of visit	___/___/_____.
Record any unpleasant feelings or complaints after the **previous** foam treatment. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. unpleasant taste _____ c. staining _____ d. allergy _____ e. others _____
Foam treatment done? (record the foam group)	Group _____.
Record any unpleasant feelings or complaints after the **present** foam treatment. **If yes, report it to Dr. John Featherstone.**	a. None ____. b. unpleasant taste _____ c. staining _____ d. allergy _____ a. others _____
Schedule the date for 1 month saliva visit(include week day also): _____/___/___(____)	
Investigator's Signature:	

1 month saliva sample	
Date of visit	___/___/_____.
Record any unpleasant feelings or complaints after the **previous** foam treatment. **If yes, report it to Dr. John Featherstone.**	a. None ____. a. unpleasant taste _____ b. staining _____ c. allergy _____ d. others _____
Saliva sample collected? (1 tube, 2 ml in ≤ 4 minutes)	Yes.
Schedule the date for 2nd set of foam treatment visit at 6th month (include week day also): _____/___/___(____)	
Does the patient have any change on their contact information: Yes. No. **If "Yes", please update the patient contact information.**	
Investigator's Signature:	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