ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2021; 7(2): 461-465

www.oraljournal.com
Received: 28-02-2021
Accepted: 30-03-2021

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Dental caries vaccine: An overview

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DOI: https://doi.org/10.22271/oral.2021.v7.i2g.1249

Abstract
Dental caries is an irreversible microbial disease of the tooth which fulfills the idea of an infectious disease and hence the possibilities of vaccination have been considered.
Many pertinent components of vaccine development, such as protein, recombinant or synthetic peptide, or DNA-based active vaccines, as well as mucosal adjuvants, such as heat-labile enterotoxins from *Vibrio cholera* or *Escherichia coli*, and chitosan, have proven effective through numerous *in vitro* and *in vivo* researches, as well as some human clinical trials. The use of adjuvants and the routes of antigen administration have both been studied to improve the host response. Vaccines such as pGJA-P/VAX, LT derivative/Pi39-512, KFD2-rPAc and SBR/GBR-CMV-nirB are few of the potential vaccines that have been produced and tested in animals in recent years. However, there is still a scarcity of information about the role of caries vaccine in human population. Multicentre collaborative studies and clinical trials of immunologically superior dental caries vaccine formulations are the need of the hour for preventing dental caries.

Keywords: dental caries, caries vaccine, *Streptococcus mutans*, dental caries prevention

Introduction
Dental caries is one of the most prevalent diseases of the oral cavity. It is a microbiologic infection that causes localized breakdown and degradation of the calcified tissue on the teeth. Caries is defined by the World Health Organization as a "localized post-eruptive, externally induced pathological process involving softening of hard tooth tissue and leading to the forming of a cavity."
A national oral health survey in India found that the prevalence of dental caries in 35-44 year-olds is 80-95 percent. According to the National Oral Health Survey, caries prevalence among the elderly in the 65-74 year age group is about 70%, although the current survey in different states finds it to be 51-95 percent. Caries are found to be prevalent in approximately 58 percent of school children in India, according to surveys. Dental caries was observed in 90 percent of late adolescents and young adults in the United States, and 94 percent of all dentate adults had evidence of treated or untreated coronal caries. Dental services cost $70 billion a year in the United States, indicating that this is a growing industry [1].
Various caries prevention methods are currently in use, including oral health education, chemical and mechanical plaque protection, pit and fissure sealants, fluoride use, and so on. Many of these strategies have the potential to be effective. However, economic, behavioral or cultural barriers to their use have continued the epidemic of dental disease of many children globally [2].
Hence, development of caries vaccine is the latest approach for combating dental caries that will be well suited for public health applications especially in the environments that do not lend themselves to regular oral health care.

Role of *S. mutans* in caries
Dental caries is caused by a group of organisms called *Streptococcus mutans* (*S. mutans*) and occurs in three phases:
a) An initial interaction with the tooth surface mediated by adhesions.
b) The accumulation of the bacteria in a biofilm.

c) The production of glucose and glucans by the bacterial enzyme glucosyltransferase and the formation of lactic acid.

Its virulence property is ability to form biofilm known as dental plaque on tooth surfaces. They form Glucosyltransferases (GTFs), Glucan-binding proteins (Gbp proteins) and Cell surface protein antigen c (PAc). Biofilm formation is initiated by interactions between planktonic bacteria and an oral surface in response to appropriate environmental signals.

S. mutans metabolizes carbohydrates to adhere to and form biofilm on tooth surfaces, thus allowing the pathogen to tolerate rapid and frequent environmental fluctuations such as nutrient availability, aerobic-to-anaerobic transitions, and pH changes [3].

In addition, in response to physical and chemical signals, bacteria regulate diverse physiological processes in a cell density-dependent manner, known as quorum sensing, which they utilize to modulate environmental stress responses [4].

Vaccines

Vaccines are immuno-biological substances that provide targeted immunity against a particular disease. It boosts the development of a protective antibody as well as other immune responses. Live, inactivated or killed organism, modified organisms, extracted cellular fractions, toxoids, or a mixture of these are used to make vaccines [1].

Animal studies

In most immunisation trials, rats and monkeys have been commonly used. Rodents are a good choice for laboratory animals because they can make an accurate diagnosis of caries by examining the tooth surface and establishing broad experimental groups. Mutant streptococci (MS) have been shown in numerous studies to cause caries in pits and fissures as well as on smooth, approximal surfaces and root surfaces of the teeth of both gnotobiotic and conventional animals [5].

Human studies

The concept of vaccination in the oral cavity was based on 3 major findings: Transmissible and infectious nature of dental caries, discovery and understanding of secretory immune system and studies in late 1966 and early 1970 to indicate dental caries amenable to immunologic intervention. A study in humans showed that the immunization of glucosyltransferase-enriched preparation (E-GTF) administered by nasal or tonsillar topical spray showed a Significantly higher anti-E-GTF responses in nasal wash samples and indicating that nasal immunization was more effective in inducing mucosal responses in adults [6].

Immunising against *S. mutans* will trigger an immune response, which will help prevent the infection preventing bacteria from colonising the tooth surface, and thus tooth decay can be avoided [1].

Routes of immunization

Oral

Mice immunised orally with a recombinant Streptococcus lactic strain containing the structural gene for a surface protein antigen (PAc) from *Streptococcus mutans* serotype c developed important salivary immunoglobulin A and serum immunoglobulin G responses [7]. In monkeys, *S. mutans* vaccination did not result in major secretory IgA. Immunological memory in secretory IgA responses is minimal, which could reduce the effectiveness of oral immunization [8]. Despite the fact that the oral route was not suitable for a variety of reasons, including the negative effects of stomach acidity on antigen and the fact that inductive sites were relatively far apart, oral route studies established that induction of mucosal immunity alone was sufficient to alter the path of *S. mutans* infection and disease progression in both animal and human models [2, 9, 10].

Intranasal

More recently, researchers have attempted to induce protective immunity in mucosal inductive locations that are closer to the oral cavity anatomically. The nasal associated lymphoid tissue (NALT), which is installed intranasally, has been used to induce tolerance to a variety of bacterial antigens, including those associated with mutans Streptococcal colonisation and accumulation [11].

Experiments in rabbits have shown that topical application of formalin-killed *Streptococcus sobrinus* cells can trigger a salivary immune response, which can substantially reduce the effects of infection with cariogenic *Streptococcus sobrinus*. The presence of IgA antibody-producing cells can be induced by repeated tonsillar application of a particulate antigen. *S. mutans* Ag I/II, the SBR of Ag I/II, the glucan binding domain of *S. mutans*, fimbrial preparations from *S. mutans* with antigen alone or in combination with mucosal adjuvants and GBP-B were also used to demonstrate protection [2].

Nasal or tonsillar topical spray immunisation of glucosyl transferase enriched preparation (E-GTF) resulted in significantly higher anti-E-GTF responses in nasal wash samples, suggesting that nasal immunisation was more successful in inducing mucosal responses in adults [12].

Tonsillar

The ability of antigen to induce immune responses in the oral cavity via tonsillar application is of great interest. Tonsillar application of formal in killer cells of *S. sobrinus* decreased the caries areas in rabbits, according to a report. The IgA antibody-producing cells in both the main and minor salivary glands can be induced by repeated tonsillar application of a particulate antigen. According to Fukuizumi T *et al.*, Tonsillar application of formalin killed cells of S. sobrinus to rabbits decreased caries areas in the rabbits [13].

Intragastric

Mice immunised intragastrically with chimeric proteins containing (saliva binding region) SBR and type II enterotoxins from *E. coli* or cholera toxin (CT) showed an increase in the number of B cells and macrophages in Peyer's patches (PP) and a decrease in the number of B cells in the mesenteric lymph nodes (MLN), indicating a molecular basis for the enhanced immune response [14].

Salivary gland

The CAT-GLU (diepitopic build of catalytic and glucan binding domains of glucosyltransferases) was used to immunise groups of Sprague-Dawley rats subcutaneously in the salivary gland vicinity, suggesting that it may be a potentially significant antigen for a caries vaccine [15].

Subcutaneous: *S. mutans* was successfully administered subcutaneously to monkeys, eliciting primarily serum IgG, IgA, and IgG antibodies. These antibodies are protective against dental caries and enter the oral cavity through gingival crevicular fluid. However, increased serum IgG antibodies were found to be the most important factor in caries

protection [8].
Rectal: The fact that the colo-rectal region has the highest concentration of lymphoid follicles in the lower intestinal tract suggests that it is an inductive location for mucosal immune responses in humans. Preliminary studies have indicated that this route may also be used to elicit salivary IgA responses to mutans streptococcal antigens including GTF [16].

Antigenic components of *S. mutans* for vaccines
While various surface or secreted products of Mutans streptococci have been suggested as vaccine antigen candidates, attention has shifted to three protein antigens: AgI/II, glucosyltransferases, and glucan binding proteins [9].

Adhesins: Adhesins have been isolated from *Streptococcus mutans* (variously known as antigen I/II, PAc, or P1) and *Streptococcus sobrinus* (SpaA or PAg), the two most common human pathogens [17]. Oral immunisation of rats with a recombinant Salmonella typhimurium mutant expressing the *Streptococcus sobrinus* surface protein antigen A (SpaA) resulted in the development of antigen-specific mucosal antibody and provides protection against dental caries [18]. *S. mutans* adherence to saliva-coated hydroxyapatite was blocked by antibodies directed against the intact antigen I/II molecule or its salivary-binding domain [19].

Glucosyltransferases (gtfs): Genes which are responsible for glucan synthesis in *S. mutans* are gtfB, which synthesizes an a-1,3-linked insoluble glucan, gtfC, which synthesizes glucan with both a-1,3 and a-1,6 linkages, and gtfD which produces a soluble 1, 6 linked glucan [2]. Antibodies to glucosyltransferase found in the oral cavity prior to infection may have a substantial impact on the disease's outcome, possibly by interacting with one or more of the enzyme's functional activities [15]. The amount of biofilm on glass surfaces is significantly reduced when mutans streptococci develop in the presence of GTF antibody. Immunization trials using intact GTF vaccines successfully protected animals infected with *S. mutans*. Passive GTF antibody administration in the diet was also protective. Since GTFs from the two most common cariogenic streptococcal organisms in humans, *S. mutans* and *S. sobrinus*, have very similar sequences in these functional domains, antibodies to GTF in the oral cavity before infection may have a significant impact on disease outcome, probably by interfering with one or more of the enzyme's functional activities [16].

Glucan binding proteins: Cell-wall-associated glucan-binding proteins play a role in mutans streptococci's ability to bind to glucans. GbpA, GbpB, and GbpC are three different glucan-binding proteins secreted by *S. mutans*. Only GbpB has been shown to develop a defensive immune response to experimental dental caries among the three *S. mutans* glucan-binding proteins [15]. At least one GbpB subunit vaccine has been shown to be successful in preclinical studies using bioinformatic methods for identifying the molecular regions responsible for this immunogenicity. In contrast to GTF, however, it does not give protection against *S. sobrinus* species [16].

Recent vaccines
New fusion anti-caries DNA vaccine
Cell surface protein PAc and GTFs are two key virulence factors in *S. mutans*. In gnotobiotic rats, a fusion anticaries vaccine, pGJA-P/VAX, encoding two major antigenic domains of *S. mutans*, PAc and GLU, was successful in lowering the levels of dental caries produced by *S. mutans*. However, it was found to be ineffective against *S. sobrinus* infection [20].

Subunit vaccines
Synthetic peptide vaccines: Intranasal immunisation with PAcA in combination with the cholera toxin B subunit inhibited *S. mutans* colonisation in mouse teeth [21].
The development of experimental dental caries was also inhibited by a monoclonal antibody formed by immunising with intact Ag I/II and reacting with the fragment containing the proline-rich region [8].
It provides antibodies in the gingival crevicular fluid as well as in the saliva.

Recombinant vaccines/attenuated expression vectors: Oral immunisation with recombinant Salmonella typhimurium expressing *Streptococcus sobrinus* surface protein antigen A was able to induce long-lasting mucosal immune responses, which may provide safety after a cariogenic *S. sobrinus* challenge in Fischer rats [17]. Salmonella avirulent strains are an effective vaccine vector, hence fusions based on recombinant procedures have been employed.

Conjugate vaccines: Chemical conjugation of functionally related protein/peptide components with bacterial polysaccharides is another vaccine strategy that could cut off more than one aspect of mutans streptococcal molecular pathogenesis [3].
Conjugation of either tetanus toxoid or *S. sobrinus* GTF to the water-soluble glucan synthesised by GTF significantly increased serum in separate studies [22].

Micro-particles: Because of their ability to regulate the rate of release, elude preexisting antibody clearance mechanisms, and degrade slowly without eliciting an inflammatory response to the polymer, micro-particles made of poly lactide-co-glycolide (PLGA) have been used as local delivery systems [1, 15].

Nano-particles: Using anionic liposomes in chitosan/DNA complexes, a nanoparticle system was developed as an effective carrier for nasal mucosal immunisation, demonstrating that nanoparticles give a likely platform for DNA vaccine packaging and delivery for more efficient elicitation of mucosal immunity [23].

Liposomes: They are phospholipid membrane vesicles with two layers that are used to retain and transport drugs and antigens. Anti-idiotype (anti-id) vaccine administered in liposomes offered partial defence against dental caries and can also induce defensive immune responses against pathogens of mucosal surfaces [24]. They facilitate M cell uptake and the delivery of antigen to lymphoid elements of inductive tissue.
Recently, a vaccine with protein p1025 was discovered which tricks *S. mutans* into a belief that there are no vacant tooth sites for it to attack. A surface protein found on the bacteria adheres to the enamel [25].
A vaccine experiment in mice employing LT derivative (detoxified) as an adjuvant with the Pi39-512 subunit and PstS protein has recently been found to elicit antigen-specific antibody production as well as a reduction in Strep. mutans

adherence.

A monomeric vaccine, KFD2-rPAc was administered to rats, containing an alanine-rich to proline-rich region fragment of PAc from *Strep. mutans*, and a partial length flagellin attached with HIV-1 p24, produced significant amounts of rPAc-specific serum IgG, serum IgA and salivary IgA compared with the rPAC alone when administered to rats.

The SBR of PAc, the GB area of GTF-I, and a dual promoter nirB-CMV were used to boost the immune response. This was done with *S. typhimurium*, which functions as an adjuvant on its own. The immune response was improved and *Strep. mutans* colonisation was inhibited in a mouse model utilising this vaccination [26].

Role of passive immunization

Passive immunization completely avoids any risks that might arise from active immunization. However, in the absence of an active response on the part of the recipient, no immunological memory is induced, and the administered antibodies will last just a few hours in the mouth or up to three days in plaque. According to study conducted by Lehner T *et al.*, Mc Ab (monoclonal antibodies) directed against an important *S. mutans* cell surface antigenic determinant (streptococcal antigen I/II) prevented *S. mutans* from adhering to the acquired pellicle on the tooth surface. Cows were immunised systemically with a vaccine made from whole *S. mutans*, which resulted in polyclonal IgG antibodies in their milk and whey [27]. A rat model's diet was then supplemented with it. Caries levels decreased as a result of the immune whey. The need to have a constant supply of antibodies in order to sustain long-term protection remains a major challenge [28]. New technologies for antibody engineering and production in animals, especially plants ("plantibodies"), have the potential to lower costs sufficiently to allow these materials to be integrated into everyday products like mouthwashes and dentifrices [16].

Adjuvants and delivery systems for dental caries vaccine

To address the current drawbacks, a number of new methods have been tried to in the adjuvant field to remove the toxic properties of powerful mucosal adjuvants while maintain their adjuvant properties.

Cholera toxin and *E. coli* heat-labile enterotoxin

Cholera toxin (CT) is a potent mucosal immunoadjuvant that is used to boost mucosal immunity against a wide range of bacterial and viral pathogens. IgA responses are rarely strong or consistent when a soluble protein or peptide antigen is applied to the mucosa [1].

Risk associated with dental caries vaccine

- All vaccines, even if properly manufactured, seem to have risks. Rabbits immunized with killed.
- *Streptococcus sanguis* or *Streptococcus mutans* showed that the findings lend no acceptance to the concept that vaccination of human subjects against dental caries might increase their susceptibility to streptococcal endocarditis [29].
- A study was conducted wherein, rats and rabbits immunized peripherally with ribosomal preparations from *S. mutans* lacked the putative human heart cross reactive determinant and suggested that *S. mutans* ribosomal vaccine against dental caries may not be pathogenic to human heart or renal tissues [30].
- A study, in which rabbits immunized with some strains of *Streptococcus mutans* provided an evidence that antigens in *S. mutans* might elicit antibodies that cross- react with heart tissue, which in turn may induce instances of myocarditis, representing an unacceptable risk to the health of the vaccine recipients [31].
- The potential of Streptococcal whole cells to bring about heart reactive antibodies, the development of a sub-unit vaccine for controlling dental caries has been the focus of intense research [1].

Ideal approach to dental caries vaccine

More effective vaccine targeting has been established using both animated (attenuated bacterial vectors) and inanimate (liposomes and micro-particles) delivery systems. In animal models and human clinical trials, both passive and active immunisation methods have shown to be effective. In an ideal approach, caries vaccine should provide broadest protection against infection by all common cariogenic *S. mutans* strains, last through the critical primary and secondary infection periods, could be given with or as a part of other immunizations, provide secondary immunization to who's not immunized in the population and is easy to deliver.

Conclusion

As the transmission of mutans streptococci appears to be primarily from mother to infant, mothers might be immunised actively or passively with the objective of reducing their oral load of mutans streptococci (possibly in combination with conventional prophylaxis or other interventions). In animal models, a variety of vaccine immunogens, such as protein, recombinant or synthetic peptide, or DNA-based active vaccines, as well as mucosal adjuvants, such as heat-labile enterotoxins from Vibrio cholera or Escherichia coli, and chitosan, have proven effective.

The removal of one of the commensal oral microorganisms is another greater obstacle for the caries vaccine. Vaccines may be developed further with new technology such as nano delivery methods and increased knowledge, allowing them to be tested in human clinical trials. Before any vaccine is released, the long-term effects of disrupting the commensal microflora must be considered.

The evidence supports the association between *Streptococcus mutans* and dental caries. Despite the remarkable decrease in dental caries caused by the use of fluoride mouth rinses, varnishes, and skilled cleaning, there is a high risk of developing caries, particularly in lower socioeconomic backgrounds. However, no vaccines have been commercialised to date, owing to the inability to induce and retain protective antibodies in oral fluids. Caries vaccine will play a major role in the future because it disrupts the metabolism of the main etiological agent. Hence, a caries vaccine can still be the long term most cost-effective solution to the oral health problem of dental caries.

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