Insight into status of dental caries vaccination: A review

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Abstract

Despite advances in the 21st century, dental caries still remains to be one of the most common infectious diseases. Its prevalence was confirmed by the World Health Organization and affirms dental caries as a major health problem in all over the world. Even though the process of tooth decay is multifactorial, the oral bacteria, mutans streptococci, such as Streptococcus mutans and Streptococcus sobrinus, are considered to be causative agents of dental caries in human. Numerous studies carried out on animals and various categories of vaccines were developed such as whole cell vaccine, subunit vaccine, and synthetic peptides. Irrespective of success from active and passive immunization based on animal trials, it is the phenomenon of human heart reactivity that limited the applicability of these trials in humans. Continuous efforts are being made to overcome these limitations and for further success in human trials. With the advent of various antibodies against antigens of mutans streptococci, local passive immunization has become the safer approach in humans against the colonization of bacteria and caries induction. This review provided insight into epidemiology, active and passive immunization in both animal and human trials, as well as the prospects of caries vaccination.

Keywords: Active immunity; dental caries vaccine; passive immunity; Streptococcus mutans

INTRODUCTION

Oral health is considered to be a significant component and is integral and essential to reflection of general health, well-being, and quality of life. Unfortunately, dental caries that is an infectious microbial disease affecting the teeth remains to be a prime concern affecting oral health and not limited to developed countries but also becoming prevalent in poor countries in world. Its prevalence was in turn confirmed by the World Health Organization and affirms dental caries as a major health problem in all over the world.[1] According to Oral Health Atlas by the FDI World Dental Federation, untreated decay of permanent teeth has a prevalence of 40% for all ages combined, which is the most prevalent condition among 291 diseases as per the Global Burden of Disease Study with approximate 3.9 billion people affecting worldwide.[2] On global scale, 60%–90% of schoolchildren and nearly all the adults have tooth decay, which often leads to pain and discomfort.[3] Therefore, clinicians must identify patients who are at higher risk for caries or who have active caries and must apply appropriate treatment or preventive measures such as immunization, fluoride treatment, salivary functioning, and antimicrobial agents.[4]

Global epidemiology of dental caries

As per the review of literature and the epidemiological data of many countries, there is a marked decreased in the prevalence of dental caries.[5] However, the situation was reversed during the past decade indicating alarmed increase in global prevalence of dental caries in both children and adults, primary and permanent teeth, as well as coronal and root surfaces. To obtain epidemiological data on the
prevalence and incidence of dental caries, a systematic literature review was performed by Frencken et al. In this review, the authors divided the prevalence and severity of cavitated dental carious lesions as per broader age groups, based on mean decayed, missing, and filled teeth (dmft) scores in five countries. Among 4–5 and 5–6-year-old age groups, reduction in the rate of prevalence was observed in the United Kingdom (UK) countries (46%) and Sweden (45%). For 12-year-olds, median prevalence of lesions was 69.4% in upper-middle-income groups compared to others, with higher mean dmft score. In adolescents and adults, there is big reduction in the prevalence as well as mean dmft scores. In adults, the median mean dmft score among 35–44-year-olds was high in high-income group and vice versa in low-income groups.

The prevalence of early childhood caries among children aged 3–5 years varied on global scale. Mainly, it is higher in most of the low-income countries such as Southeast Asia and Africa, suggesting more among socioeconomically disadvantaged groups. The USA has showed higher prevalence than European countries with 40% of children effecting around kindergarten age, while 12% of children had visible caries around 3 years of age in the UK. Accumulating evidence showed high prevalence of 36%–85% in Asian countries, 38%–45% in Africa, and 22%–61% in the Middle East. Studies also revealed that preschool children with oral disease and decay have shown poorer quality of life.

**Microbiota and dental caries**
The process of tooth decay (dental caries) is multifactorial, which is caused due to interaction of the surface of the tooth, dental plaque, and the presence of sugars obtained from food. An approximate of 700 different species of bacteria has been found from human oral microbiome. Among all, bacteria that plays vital role in process of cariogenesis are oral streptococci, especially the mutans group and lactic acid bacteria, i.e., *Lactobacillus* species. In 1924, Clark found that *Streptococcus mutans* grows best in a medium simulating saliva and is found in the earliest stages of decay process. In a study by Meiers et al., the authors collected water spray during restorative process of carious and noncarious lesions of naval recruits and found multiple organisms among which *S. mutans* was only bacterium found in significantly larger numbers in carious lesions than in noncarious lesions.

Microbial community is quite diverse, and often, the dentinal lesions contain many facultatively and obligately anaerobic microorganisms that belong to genera such as *Actinomyces*, *Eubacterium*, *Parvimonas*, *Bifidobacterium*, and *Rothia*. Dental decay can also be caused by other bacteria which were *mitis*, *anginosus*, and *salivarius* groups of *Streptococcus*, *Propionibacterium*, *Enterococcus faecalis*, and *Scardovia*.  

**Streptococcus mutans and dental caries**
*S. mutans* is the leading causative microorganism of dental caries worldwide and also considered as most cariogenic among all oral streptococci. *S. mutans* refers to a group of seven closely related species which were collectively referred to as mutans streptococci. Multiple factors such as adherence to tooth surfaces, acid production, building glycan reserves, and synthesis of extracellular polysaccharides are involved in dental caries formation. These bacteria change the environmental conditions of the oral flora, which allows other fastidious organisms to colonize and further enhances dental plaque formation. Specially equipped receptors with *S. mutans* allow them to attach to tooth surface, thereby creating a slimy environment. Once they adhered to enamel salivary pellicle, strong acid producers such as mutans streptococci and *Lactobacillus* create acidic environment to promote the process of cavity formation.

The ability of *S. mutans* as potent initiator of caries is mainly due to virulence factors that are mainly unique to itself, thereby playing an important role in caries formation. Further, it produces lactic acid as part of metabolism and also its ability to adhere to tooth surfaces in the presence of sucrose by formation of water-insoluble glucans, which are polysaccharides that help in binding bacteria to tooth surface. These characteristics of production of large amounts of lactic acid at rapid rate and tolerance to extremes of sugar concentration, ionic strength, and pH make mutans streptococci efficient at causing dental caries.

**Molecular pathogenesis of dental caries**
Initiation of dental decay mainly occurs due to the dissolution of minerals of enamel and dentine of teeth in the organic acids, such as lactic acid which is produced by the microorganisms that were present in the plaque. The molecular pathogenesis of mutans streptococci-associated dental caries was divided into three possible phases by Taubman and Nash. In the initial phase, attachment of bacterium to the dental pellicle takes place which is mediated by adhesion from mutans streptococci, known as antigen I/II. The second phase involves accumulation depending on the presence of sucrose, glucosyl transferases (GTFs), and glucan-binding proteins (GBP) from mutans streptococci. After the breakdown of sucrose into glucose and fructose, the GTFs of mutans streptococci synthesize glucans which have various α-1,3-linkages and α-1,6-linkages and different solubilities in water. In the third and final phase, glucans that were produced interact with GBP and with glucan-binding domain of GTFs, on the surface of mutans streptococci. Further, colonization and multiplication of these bacteria result in the accumulation of biofilms, leading to formation
of dental plaques, with large masses of mutans streptococci. When these accumulations of bacteria are of sufficient in magnitude with adequate available sugars, it results in production of large amounts of lactic acid, which further leads to dissolution of enamel structure and leading to dental decay.[14]

**Historical background on caries vaccination**

Clarke was the first to isolate streptococcus from carious lesions and identified its association with disease and further named his new species as *S. mutans*.[9] Later, its role in caries etiology was further questioned and led to disappearance of *S. mutans* from the literature. Approximately 40 years later, again, the role of mutans streptococci in caries pathogenesis was resurfaced, establishing its infectious and transmissible nature.[21-23] Further, insight into the details of specific immune factors was provided following the isolation of immunoglobulin A (IgA) by Heremans *et al.*[24] and Tomasi *et al.*[25] who identified the secretory form of IgA (S IgA) in the saliva. The principle of immunization against dental decay was introduced by Bowen,[26] where the author showed that monkeys that were immunized with *S. mutans* developed less caries than those that were not immunized. Later, many authors in the early 1970s conducted animal studies, regarding immunization against dental decay and demonstrated that caries is preventable by induction of specific salivary IgA response to the salivary gland region.[27,28] As tooth surfaces are continually flushed by saliva and S IgA being its principle immunoglobulin, induction of a salivary S IgA response against mutans streptococci would provide first line of defense against formation of bacterial colonies on tooth surfaces.[29] Later, other studies used local immunization in rats to induce salivary S IgA that further exhibited reduction in mutans streptococci as well as the extent of dental caries.[30] Russell *et al.* have explained the possible mechanisms of action of salivary IgA antibodies through interference of sucrose-dependent and -independent attachment of mutans streptococci to the surfaces of the tooth.[31]

Many efforts have been made continuously so far for its prevention and cure, both in developing and in developed countries. Currently, many caries prevention strategies were in practice such as topical fluoride applications, chemical and mechanical control of plaque, and application of pit and fissure sealants and through oral health education. Despite all these strategies, this dental disease is still remained to be an epidemic owing to economic, behavioral, and cultural barriers on a global level.[31] Keeping in mind about such barriers, it is vital for dental public health to develop an effective caries vaccination, particularly for those who fails to receive regular healthcare.

**ANTICARIES VACCINATION**

Vaccines are immunobiological substances designed to produce specific protection against any given disease. They mainly act through stimulation for the production of a protective antibody and other immune mechanisms. They are mainly prepared from live-modified organisms, nonvital organisms, extracted cellular fractions, toxoids, or a combination of these substances.[31,32] A caries vaccine is mainly designed to play protective role against the process of tooth decay. It is of a known fact that *S. mutans* plays a major etiological role in the pathogenesis of tooth decay as its cell mainly contains substances such as adhesins, GTFs, GBP, a 13 kDa protein antigen (antigen D), a 39 kDa protein (AgI), a 29 kDa protein antigen (antigen A), a 70 kDa protein antigen (antigen C), and a 190 kDa protein (AgII). As these substances were thought to play a vital role in interactions between the organism and host, most of the caries vaccine experimental designs were mainly directed toward these compounds.

Similar to any other vaccine, caries vaccine should also be administered before the introduction of the infectious agent into the system.[33] When hosts were immunized with antigens from mutans streptococci, antibodies then formed within saliva will induce a process called cellular aggregation. These large number of aggregates in turn reduce the number of organisms adhering to the tooth surfaces.[34] These antibodies also act by interfering the epitopes of adhesins, the AgII (PaC), and the saliva-binding region of the antigen strongly inhibits sucrose-independent adherence of *S. mutans* cells to tooth surfaces.[35] It was also found that the formation of aggregates, fine-meshed colonies, and long chains of bacteria promotes easy removal of these bacteria and further reduces their pathogenic potential. Antibodies to GTFs further inhibit the synthesis of glucans by these enzymes, thereby the accumulation of mutans streptococci on tooth surfaces.

**Active immunization against dental caries**

**Animals**

Many studies in the past have addressed active immunity for dental caries in experimental animals such as rats and monkeys. It was found to be that in human unstimulated saliva, sIgA is in higher concentrations, with IgG being the most abundant immunoglobulin in the human serum and gingival crevicular fluid. In animal models, the induction of salivary IgA and serum IgG has been studied using various immunization routes, such as subcutaneous, oral, intranasal, and topical routes.[36] Lehner *et al.* in their study has reported a 70% reduction in dental caries following the subcutaneous immunization of Rhesus monkeys with AgII in Freund’s incomplete adjuvant or “Alhydrogel”. [37] Subcutaneous immunization of rats with peptide constructs and GTFs near salivary glands induced high serum IgG and salivary...
IgA responses. Gut-associated lymphoid tissue (GALT) is considered to be one of the principal inductive sites of mucosal immune responses, especially sIgA responses. Stimulation of IgA precursor B-cells in GALT induces sIgA responses in remote secretions, including saliva, and to enhance its response in saliva, various mucosal adjuvants and delivery vehicles such as liposomes have been used. When orally administered, these liposomes will be ingested into GALT through M-cells of Peyer’s patches which further enhance the mucosal responses. The anti-idiotype vaccine, which is specific for antibodies against S. mutans when incorporated into liposomes and administered orally in rats, has significantly reduced caries and its colonization in the oral cavity.

In addition to GALT, nasal-associated lymphoid tissue is a major inductive site for mucosal immune responses. Advantages of nasal delivery for vaccine include lower doses of vaccine doses and relatively easier administration, and it induces both systemic and mucosal immunities. Further, few authors attempted topical immunization routes using 3.8 kDa antigen applying on gingiva resulted in significantly lower incidence of dental caries and colonization of S. mutans. Despite availability of different routes and significant lowered incidence of dental caries in animals, main drawback of streptococcal vaccine regarding its applicability in humans is its cross-reactivity with heart tissue antigens, which might due to whole cell vaccines. This further pointed out for the need of identification and isolation of fractionated “protective antigens” for the development of a safer vaccine for use in humans.

Human heart cross-reactivity and caries vaccination

Even though various types of vaccines have been developed, tried, and proved to be successful in providing protection against dental caries, literature evidence has reported for the evidence of cross-reactivity with human heart tissues and skeletal muscle tissues by the antibodies generated. In 2013, Zhang tried to overcome the cross-reactivity of heart tissue using subunit vaccines; however, he reported less immunogenicity. Alam et al. believed that the dextranseurase antibodies might have inhibitory effect on the cariogenic potential of S. mutans, and they may be helpful in combating the dental caries. Recently, in 2020, Rather et al. indicated that dextranseurase antibodies inhibited acid production and reduced hydrophobicity of S. mutans, indicating the further enhancement of anticariogenic potential of dextranseurase antibodies. Moreover, no cross-reactivity with dextranseurase antibody was seen indicating no harmful physiological effects in the humans. This has given the hope that effective, safer, and acceptable vaccines against human dental caries can be achieved in the near future.

PROSPECTS OF CARIES VACCINATION

Conventionally available vaccines provide immunization to the before to the development of disease. It is important to make a note that the immunization following the eruption of the primary teeth can prevent the colonization of S. mutans, which may also provide extra benefit to the permanent teeth through early immunization until their eruption. And also, as the dental caries is a slow undergoing process throughout life, it would be considerably equal to have an effective immunization mechanism that can exhibit similarly long-lasting immunity against caries. It is also of equal importance that developed caries vaccination must not cause phenomenon of any human heart cross-reactivity following its consumption. The National Institute of Dental
and Craniofacial Research in 2010 has continued their support for basic research in mucosal immunology and also made passive immunization approach as priority. It is often a dilemma that whether if caries vaccine is a viable option in dental caries and decay prevention? To answer this, the caries vaccination trials must be conducted in stages such as in infants (Phase 1, 2, 3 studies), preschool children (Phase 1, 2 studies), and preadolescent children (Phase 1, 2 studies), and these stages have to be strictly considered. To make these immunization techniques more practical, one has to make sure that these human experiments must be transferred successfully humans as well. Despite any number of advances regarding caries immunization, it finally comes to adequate oral health behaviors that continue to be the key for good oral health and for decrease in caries occurrence.

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There are no conflicts of interest.

### REFERENCES

1. Petersen PE. The World Oral Health report 2003: Continuous improvement of oral health in the 21st century – The approach of the WHO global oral health programme. Community Dent Oral Epidemiol 2003;31 Suppl 1:3-23.
2. The Challenge of Oral Disease; 2015. Available from: http://www.fdworlddental.org/resources/oral health atlas/oral health atlas 2015. [Last accessed on 30th January 2021].
3. Oral Health Fact Sheet; 2012. Available from: http://www.who.int/mediacentre/factsheets/fs638/en/. [Last accessed on 30th January 2021].
4. Ramachandran Nair P. What is on the horizon? J Conserv Dent 2009;12:1-1.
5. Bagrampur RA, Garcia-Godoy F, Volpe AR. The global increase in dental caries: A pending public health crisis. Am J Dent 2009;22:3-6.
6. Frencken JE, Sharma P, Stenhousen L, Green D, Laverty D, Dietrich T, et al. Global epidemiology of dental caries and severe periodontitis - A comprehensive review. J Clin Periodontol 2017;44 Suppl 18:S94-105.
7. Colak H, Dulgergil CT, Dalli M, Hamidi MM. Early childhood caries update: A review of causes, diagnoses, and treatments. J Nat Sci Biol Med 2012;4:23-28.
8. Prakash P, Subramaniam P, Durgesh BH, Konde S. Prevalence of early childhood caries and associated risk factors in preschool children of urban Bangalore, India: A cross-sectional study. Eur J Dent 2001;65:1028-37.
9. Clarke JK. On the bacterial factor in the ætiology of dental caries. Br J Oral Maxillofac Surg 1982;61(3):460-4.
10. Chen Y, Chen Q, Chen Z, Li J, Xia J, Wu Y, et al. The role of saliva in dental caries. Curr Med Chem 2009;16:2565-71.
11. Huda S, Jhuma KA, Haq AM. Dental caries vaccine availability: Challenges for the 21st century. J Immuo Immunothe 2017;1:7.
12. Sugit RS, Sachin Naik, Janavathy J, Rajanikanth P. Caries vaccine A review. Indian J Mednodent Allied Sci 2014;2:6.
13. Carounanidy U, Sathyanarayanan R. Dental caries: A complete discussion on causes, diagnosis and treatments. J Conserv Dent 2010;13:209-17.
14. Liljemark WF, Bloomquist CG, Germaine GR. Effect of bacterial aggregation on the adherence of oral streptococci to hydroxyapatite. Infect Immun 1983;39:514-9.
15. Huda S, Jhuma KA, Haq AM. Dental caries vaccine availability: Challenges for the 21st century. J Immunol Immunother 2017;1:7.
16. Sugit RS, Sachin Naik, Janavathy J, Rajanikanth P. Caries vaccine A review. Indian J Mednodent Allied Sci 2014;2:6.
17. Liljemark WF, Bloomquist CG, Germaine GR. Effect of bacterial aggregation on the adherence of oral streptococci to hydroxyapatite. Infect Immun 1983;39:514-9.
18. Brady LJ, Piacentini DA, Crowley PJ, Oyston PC, Bleiweis AS. Differentiation of salivary agglutinin-mediated adherence and aggregation of mutants streptococci by use of monoclonal antibodies against the major surface adhesin P1. Infect Immun 1992;60:1008-17.
19. Koga T, Oho T, Shimazaki Y, Nakano Y. Immunization against dental caries. Vaccine 2002;20:2027-44.
20. Lehner T, Russell MW, Caldwell J. Immunization with a purified protein from Streptococcus mutans against dental caries in rhesus monkeys. Lancet 1980;1:995-6.
21. Taubman MA, Holmberg CJ, Smith DJ. Immunization of rats with synthetic peptide constructs from the glucan-binding or catalytic region of mutants streptococcal glucosyltransferase protects against dental caries. Infect Immun 1995;63:3088-93.
22. Jackson S, Mestecky J, Childers NK, Michalek SM. Liposomes containing anti-idiotypic antibodies: An oral vaccine to induce protective secretory immune responses specific for pathogens of mucosal surfaces. Infect Immun 1990;58:1932-5.
23. Lehner T, Haron J, Bergmeier LA, Mehlert A, Beard R, Dodd M, et al. Selective induction of an immune response in human external secretions by ingestion of bacterial antigen. J Clin Invest 1978;61:731-7.
24. Gahlenberg L, Krasse B. Salivary immunoglobulin A antibodies and recovery from challenge of Streptococcus mutans after oral administration of Streptococcus mutans vaccine in humans. Infect Immun 1983;39:514-9.
25. Childers NK, Zhang SS, Michalek SM. Oral immunization of humans with dehydrated liposomes containing Streptococcus mutans glucosyltransferase induces salivary immunoglobulin A2 antibody
responses. Oral Microbiol Immunol 1994;9:146-53.

44. Childers NK, Tong G, Li F, Dasanayake AP, Kirk K, Michalek SM, et al. Humans immunized with Streptococcus mutans antigens by mucosal routes. J Dent Res 2002;81:48-52.

45. Lehner T, Caldwell J, Smith R. Local passive immunization by monoclonal antibodies against streptococcal antigen I/II in the prevention of dental caries. Infect Immun 1985;50:796-9.

46. Ma JK, Lehner T, Stabila P, Fux CI, Hiatt A. Assembly of monoclonal antibodies with IgG1 and IgA heavy chain domains in transgenic tobacco plants. Eur J Immunol 1994;24:131-8.

47. Ma JK, Hikmat BY, Wycoff K, Vine ND, Chargelegue D, Yu L, et al. Characterization of a recombinant plant monoclonal secretory antibody and preventive immunotherapy in humans. Nat Med 1998;4:601-6.

48. Ayakawa GY, Siegel JL, Crowley PJ, Bleiweis AS. Immunochemistry of the Streptococcus mutans BHT cell membrane: Detection of determinants cross-reactive with human heart tissue. Infect Immun 1985;46:280-6.

49. Zhang S. Dental caries and vaccination strategy against the major cariogenic pathogen, Streptococcus mutans. Curr Pharm Biotechnol 2013;14:960-6.

50. Alam MK, Zheng L, Liu R, Papagerakis S, Papagerakis P, Geyer CR, et al. Synthetic antigen-binding fragments (Fabs) against S. Mutans and S. Sobrinus inhibit caries formation. Sci Rep 2018;8:10173.

51. Rather SA, Sharma SC, Mahmood A. Antibodies generated against dextranucrase exhibit potential anticariostatic properties in Streptococcus mutans. Appl Microbiol Biotechnol 2020;104:1761-72.