

Dental Caries Vaccine Availability: Challenges for the 21st Century

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Abstract

Dental caries (tooth decay) is one of the most common diseases occurring in humans. A considerable research work has established that dental caries is an infectious disease and forms through a complex interaction among many environmental and host factors. Although various caries preventive strategies currently exist, development of an effective vaccine has been studied for more than three decades.

A variety of different categories of vaccines are developed such as whole cell vaccine, subunit vaccine, synthetic peptide vaccine, recombinant vaccine, DNA vaccine, conjugate vaccine, etc. The results of animal trials including active vaccination and passive immunization through different routes were encouraging relevant to protection against dental caries. Based on these results limited small scale human trials have been conducted with some experimental vaccines. Among them, Glucosyltransferase (GTF) from *S sobrinus* combined with aluminum based adjuvant is prominent for protective immune responses. However, the phenomenon of human heart cross reactivity has to be overcome for further large scale human trials. Efforts are being made to modify various modalities of immunization to improve the duration and effectiveness of the immune responses. Two new fusion anti caries vaccines, pGJA-p/VAX and pGJG/GAC/VAX, encoding two important antigenic domains, PAC and GLU of *S mutans* as well as *S sobrinus* and successful in gnotobiotic animals, seemed to be promising for future human trials.

However, the major challenges for the 21st century are to eliminate human heart cross reactivity and rheumatic fever from an anti caries vaccine and improve its various other modalities of vaccination for use in human. In fact, it took nearly half a century to develop vaccines against polio and measles. The quest for an AIDS vaccine is a far greater challenge than sending a man to the moon. Scientists are, therefore, not disappointed due to many odd situations, rather they are cautiously optimistic that dental caries vaccine will be available sooner for global human consumption.

Keywords: Dental caries; Vaccine

Background

Dental caries (Caries from Latin, Decay) means decay or decalcification of the teeth, where there is progressive destruction of enamel, dentine and cementum. Regarding the aetiology and pathogenesis of it, a number of theories had been proposed over the years such as acidogenic (chemicoparasitic) theory, proteolytic theory,

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proteolysis-chelation theory, sucrose-chelation theory and autoimmune theory [1-3]. Other than the acidogenic theory, none of the above propositions have convincing experimental support. These theories appreciated the three essential components of the decay process as the presence of microorganisms, susceptible tooth and dietary factors [4-6]. Infect, a considerable research work has established that dental caries is an infectious disease and forms through a complex interaction over time among many environmental and host factors. These factors and their interactions are presented schematically in figure 1 [1]. The microorganisms (Genera) commonly isolated from dental plaque are shown in table 1 and the microorganisms (Genera, Species) shown to be cariogenic in animals and man are listed in table 2. Among them, streptococci particularly *Streptococcus mutans* (*S mutans*) has been extensively studied amongst the oral microflora [7-9]. Of the many serologically distinct types of *S mutans* (a,b,c,d,e,f,g), *S mutans* serotype c, is thought to be of particular importance in the aetiology of dental caries in human [9,10]. Many different mechanisms are thought to play significant part in the initial colonization of the tooth surfaces by bacteria and their subsequent development into dental plaque such as adherence of bacteria to the exposed tooth surface, formation of plaque matrix and growth of bacteria [11,12]. In many studies of relative cariogenicity of various carbohydrates, sucrose was almost invariably found to be most cariogenic [13,14]. Understanding the biochemical (metabolic) processes of dental plaque producing characteristic disastrous end-products (fermentation products), e.g. lactic acid, are important. Understanding the various modes of pathogenesis is also highly relevant and important towards developing anti caries agents and strategies, particularly anti caries vaccine.

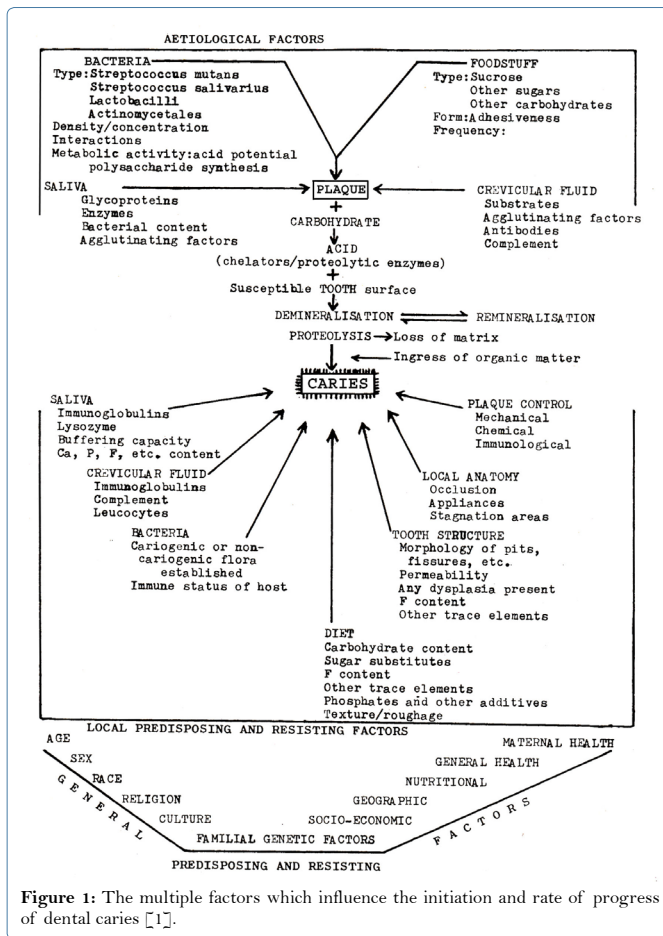


Figure 1: The multiple factors which influence the initiation and rate of progress of dental caries [1].

Bacteria Genera Species	Host	
	Rodent/Primate	Human
<i>Lactobacilli (L) L. acidophilus</i>	+	+
<i>L. Casei</i>	+	+
<i>Streptococci (S) S. mutans</i>	+	++
<i>S. sanguis</i>	+	+
<i>S. salivarius</i>	+	+
<i>S. milleri</i>	+	-
<i>S. Mitior</i>	-	-
<i>Actinomyces (A) A. viscosus</i>	+	+
<i>A. Naestundri</i>	+	+

Table 2: Microorganisms associated with caries in animals and man. '+' means 'carriogenic' '-' means 'not confirmed'

industrialized countries, affecting 60-90% of school children and the vast majority of adults. More than 60% of the children aged 5-17 years in the USA have decayed, missing or filled permanent teeth because of dental caries and 91% of dentate adults have caries experience [15,17]. Bangladesh, Pakistan and other countries are no exceptions as prevalence of dental caries is increasing in these countries also [1,13,15,17-20]. Its prevention and cure are therefore important for both developed and developing countries.

Currently various caries preventive strategies are in use like oral health education, chemical and mechanical control of plaque, use of fluorides, application of pit and fissure sealants, etc. However, economic, behavioral or cultural barriers to their use have continued the epidemic of dental disease in the mouths of many people on a global level. The latest approach for combating dental caries is through the development of an effective vaccine that is well suited for public health applications especially in environments that do not lend themselves to regular health care [1,15]. The prime target population for a dental caries vaccine would be young children/infants for whom safety issues are more stringent. Most adults would have already experienced dental caries and therefore, may not give proper immune responses.

The main aims of the present review article are therefore to highlight and update the progresses made so far in the battle front towards developing preventive and/or curative vaccines against dental caries for global consumption.

Caries Vaccine: A Viable Option

Vaccines are immuno biological substances designed to produce specific protection against a given disease. They stimulate the production of a protective antibody and other immune mechanisms. Vaccines are prepared from live modified organisms, non vital organisms, extracted cellular fractions, toxoids or a combination of these substances. A caries vaccine is a vaccine to prevent and protect against tooth decay. *S mutans* has been identified as one of the major etiological agents of human dental caries. *S mutans* possess various cell surface substances including adhesins, Glucosyltransferases (GTFs) and Glucan-Binding Proteins (GBPs). These substances are used for vaccine preparation. Most of the recent experimental efforts have been directed toward these compounds. Development of a vaccine for dental caries has been studied for more than three decades. A variety of different categories of vaccines are being developed at research centers

Class	Genera	
	Cocci	Rods & Filaments
Gram-positive	<i>Streptococcus</i>	<i>Actinomyces</i>
	<i>Peptococcus</i>	<i>Lactobacillus</i>
	<i>Peptostreptococcus</i>	<i>Bacterionema</i>
	<i>Staphylococcus</i>	<i>Rothia</i>
	<i>Micrococcus</i>	<i>Arachina</i>
Gram-negative		<i>Bifidobacterium</i> <i>Eubacterium</i> <i>Propionibacterium</i>
	<i>Neisseria</i>	<i>Bacteroides</i>
	<i>Branhamella</i>	<i>Fusobacterium</i>
	<i>Veillonella</i>	<i>Haemophilus</i>
		<i>Vibrio (Campylobacter)</i> <i>Leptotrichia</i> <i>Capnocytophaga</i> <i>Selenomonas</i> <i>Spirochaetes</i>

Table 1: Microorganisms (genera) commonly isolated from dental plaque.

Dental caries is one of the most common diseases occurring in human which is prevalent in developed, developing and underdeveloped countries and is distributed unevenly among the populations [1,15-17]. In modern world, it has reached epidemic proportions. This global increase in dental caries prevalence affects children as well as adults, primary as well as permanent teeth, and coronal as well as root surfaces. Dental caries is still a major oral health problem in most

[20,21]. More recently, scientists have started to apply molecular biology technology, i.e., recombinant DNA technology, and others options for developing anti caries vaccines. Some of the important recent developments in the anti caries vaccines research are briefly discussed.

Experimental Studies

A large body of experimental work over several decades has demonstrated the feasibility of inducing protective immunity against *S mutans* and the subsequent development of dental caries in animal models. Information has also accrued from several small scale trials in adult volunteers attesting to the applicability of these approaches to humans.

Animal trials

Since the discovery by Edward Jenner in 1779 that small pox could be prevented by inoculation of pus from the pustules of cowpox patients, quite a large number of effective and safe vaccines have been established which are routinely used all over the world as prophylactics. Similarly, the fact that dental caries is an infectious disease caused by specific pathogens (dental plaque, particularly *S mutans*), has led scientists to explore the possibility that this disease can be prevented by active immunization.

A substantial amount of work concerning active immunization against caries has been done in either rodents (mice, rat and hamster) or monkeys (rhesus, *Macaca mulatta* and *irus*, *Macaca fascicularis*). Until the relatively recent explosion of interest in the role of *S mutans* in dental caries, investigators tried to reduce caries by immunizing against *Lactobacilli* and other organisms but without much success. In recent years the majority of immunization studies have been carried out with vaccines prepared from various strains of *S mutans* [15,22,23]. In some of these studies whole bacterial cell vaccines were used, while in others bacterial components such as Glucosyl-Transferase (GTF) preparations had been employed. In these studies investigators have attempted to stimulate either systemic or local production of antibodies or both by injecting the vaccines at different sites such as intravenously, intramuscularly or submucosally near the salivary glands. Attempts have also been made to mount an immune response by injecting the antigens with adjuvant, e.g., Freund's adjuvant. Although some investigators have used the hamster model with mixed success, the rat model has been used more extensively in immunization studies and a summary of the finding is given in table 3 [24,25]. Although many of these studies have shown a caries protective effect by a variety of immunization regimes, some negative and valuable results were obtained in different experiments.

Probably the best experimental model for dental caries is monkeys, since the dentition and pattern of diseases are more comparable to that of man. Several immunization studies have been carried out in monkeys involving various whole cell vaccines and vaccines composed of purified bacterial antigens. Some of the results of these studies are shown in table 4 [26-29]. A few investigators have also shown that immunity against caries can be transferred passively. These results of passive immunity are summarized in table 5 [24,28,30,31]. In monkeys caries reduction was not achieved by transfer of immune serum alone, but administration of whole immune serum together with transfer factor (a soluble extract obtained from sensitized lymphocytes) did confer immunity to recipient animals [27]. From these findings it would appear that both humoral and cellular immunity

Antigen	Route	Reduction in caries	Antibodies	
			Serum	Saliva
S Faecalis	Intramuscular	+	+	+
Glucosyltransferase	Intraperitoneal	+	+	ND
Glucosyltransferase	Intraperitoneal	-	+	-
<i>S mutans</i> (OMZ 176)	Intravenous	+	+	ND
<i>S mutans</i> (6715)	Subcutaneous	+	+	ND
Glucosyltransferase	Intraperitoneal	+	+	ND
<i>S mutans</i> (6715)	Subcutaneous (Salivary)	+	+	+
<i>S mutans</i> (6715)	Subcutaneous (Salivary)	+	+	+
<i>S mutans</i> (6715)	Subcutaneous (Salivary)	+	+	+
<i>S mutans</i> (6715)	Oral	+	-	+
Glucosyltransferase	Subcutaneous (Salivary)	+	+	+
S Faecalis	Intramuscular	+	+	+

Table 3: Results on immunization studies in rats.

may play roles to confer a protective effect against dental caries. In fact, recent studies have indicated that not only sensitized lymphocytes, but polymorph nuclear leucocytes may also be involved, helping to confer protection by actively phagocytosing microorganisms, including *S mutans* [32]. One approach tried for passive immunity was monoclonal antibodies. The latest in these developments in passive immunization is the use of transgenic plants to give the antibodies. The researchers have developed a caries vaccine from a Genetically Modified (GM) tobacco plant. The vaccine, which is colorless and tasteless, can be painted onto the teeth rather than injected and is the first plant derived vaccine from GM plants. Active and passive immunization strategies, which target key elements in the molecular pathogenesis of *mutans Streptococci*, hold promise to controlling this disease process. Integrating these approaches into broad-based public health programmes may prevent dental caries disease in many of the world's children, among whom those of high risk might derive the greatest benefit [15,26]. The various possible routes by which antibodies (humoral immunity) and immunologically primed cells (cellular immunity) may reach caries susceptible sites of the tooth are illustrated in figure 2 [1]. One of the main drawbacks about the use of any streptococcal vaccine, including *S mutans*, against dental caries is the possibility of inducing antibodies which may cross react with heart tissue antigens [33]. This great risk of side effects is likely to arise particularly from whole cell vaccines. Therefore, identification and isolation of fractionated 'protective antigens' from the causative organism (*S mutans*) may lead to the development of a potentially safer vaccine which will be more acceptable for use in man. The important findings of the immunological studies were that (i) vaccination with antigen 3800 gave rise to humoral as well as cellular immune response, (ii) fluoridation followed by vaccination completely protected the animals against tooth decay, and (iii) no untoward side effects, including heart cross reactivity, were observed in monkeys over the experimental long period [26,29]. This has raised great hope for the future that effective, safer, and acceptable vaccines against human dental caries may not be too distant away. However, such parameters as the optimum dose, route of immunization, immunization schedule, need for adjuvants and other practical considerations remain to be determined. Only when such information is available, it will be appropriate to consider clinical trials in human subjects.

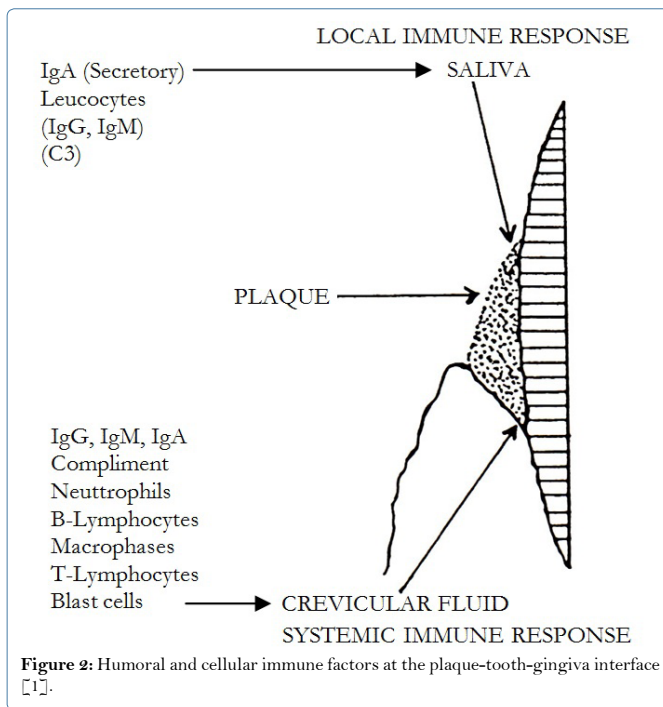


Figure 2: Humoral and cellular immune factors at the plaque-tooth-gingiva interface [1].

Antigen	Route	Reduction in caries	Antibodies	
			Serum	Saliva
<i>S. mutans</i> (Ingbritt)	Intravenous Submucosal	+	+	ND
<i>S. mutans</i> (Ingbritt)	Submucosal	+	+	ND
Glucosyltransferase	Subcutaneous	-	+	ND
<i>S. mutans</i> (C)	Submucosal	+	+	+
	Subcutaneous			
<i>S. mutans</i> (6715)	Parotid	+	+	+
Cell-associated glucan	Subcutaneous	+	+	+
Glucosyltransferase	Intramuscular Subcutaneous	-	+	+
	Subcutaneous, Intramuscular Subcutaneous			
<i>S. mutans</i> (C)	Intramuscular	+	+	+
AgI/II (<i>S. mutans</i> C)	Subcutaneous	+	+	+
	Intramuscular			
AgI (<i>S. mutans</i> C)		+	+	+
Ag 3800 (<i>S. mutans</i> C)		+	+	+

Table 4: Summary of the results published on immunization studies in monkeys. 'ND' means 'not done'

Recent Molecular Vaccines

More recently, scientists have started to apply molecular biology techniques, i.e., recombinant DNA technology, and other options for developing anti caries vaccines. Some of the important and recent developments in this area are noted below:

New Fusion Anti Caries DNA Vaccine

Researchers at Wuhan Institute of Virology, China, tried to develop a new DNA vaccine which showed promising results in preventing

Animal	Preparation	Route	Caries Reduction
Rats	IgG (Intravenously immunized dams)	Oral (Suckling)	+
	IgA (Intravenously immunized dams)	Oral (Suckling)	+
	IgA (Orally immunized dams)	Oral (Suckling)	+
Rat	Hyperimmune Cow's Milk	Oral	+
Monkeys	Immune Serum	Intravenous	-
	Immune Plasma + Transfactor	Intravenous,	+
		Subcutaneous	
	IgG	Intravenous,	+
	IgM	Intravenous,	-
	IgA	Intravenous,	-

Table 5: Summary of Published work on passive transfer of immunity to dental caries.

dental caries. *S. mutans* have two important virulence factors: cell surface protein Pac and Glucosyltransferases (GTFs). GTFs have two functional domains: an N-terminal Catalytic sucrose-binding domain (CAT) and a C-terminal Glucan-binding domain (GLU). A fusion anti caries DNA vaccine, pGJA-P/VAX, encoding two important antigenic domains, Pac and GLU of *S. mutans*, was successful in reducing the levels of dental caries caused by *S. mutans* in gnotobiotic animals [34]. The fusion vaccine induced accelerated and increased specific antibody responses in serum and saliva compared with nonfusion DNA vaccine in rabbits. However, its protective effect against *S. sobrinus* infection proved to be weak. Previous research suggested that antibodies against synthesized peptides derived from the CAT region of GTFs could inhibit water insoluble glucan synthesis by *S. sobrinus*. Therefore another experiment was carried out by utilizing rats and mice models where the CAT fragment of the *S. sobrinus* OMZ176 gtf-I was cloned into the plasmid pGJA-P/VAX to construct a new recombinant plasmid vaccine (pGJGAC/VAX) [35]. The specific serum IgG and salivary IgA anti CAT, anti Pac, and anti GLU responses were induced in mice following immunization with pGJGAC/VAX. More importantly, pGJGAC/VAX immunization provided obvious protection against *S. sobrinus* infection; because rats immunized with pGJGAC/VAX displayed significantly fewer Dental slight (Ds) and Dental moderate (Dm) lesions than did pGJA-P/VAX-immunized rats [35]. This study was possibly the first to construct successfully a new fusion anti caries DNA vaccine encoding antigens of both *S. mutans* and *S. sobrinus*.

Subunit Vaccines

The best experimental model for dental caries is probably the monkeys. Sever immunization studies in monkeys involving purified antigens from *S. mutans*, i.e., subunit vaccines such as GTF, Ag I/II, AgI Ag3800 as stated in table 5 [34-37]. Among them, the studies of Giasuddin et al., & Lehner et al., were promising, as the low molecular weight Ag 3800 showed no heart cross reactivity in monkeys [26,29]. British scientists at Guys Hospital in London have isolated a gene and the peptide that prevents *S. mutans* from sticking to the teeth and they are trying to find ways to deliver the peptide into the mouth through apples and strawberries [15].

Synthetic Peptides

Synthetic peptide approaches have shown the alanine rich repeat region of Ag I/II to be immunogenic and to induce protective

immunity. For example, subcutaneous immunization with a synthetic peptide derived from the alanine rich region of Ag I/II from *S mutans* induced higher levels of serum IgG antibody reactive with recombinant Ag I/II than a synthetic peptide derived from the proline rich region [36]. The synthetic peptides give antibodies not only in the gingival crevicular fluid but also in the saliva. The synthetic peptide used is derived from the GTF enzyme [15,37].

Recombinant Vaccines

Recombinant approaches afford the expression of larger portions of functional domains than can be accommodated by synthetic peptides. The avirulent strains of salmonella are an effective vaccine vector so that fusion using recombinant techniques has been used [37]. Reports of a study indicate that oral immunization with the recombinant salmonella vaccine was effective in inducing protection against *S sobrinus* in rats and that prolonged persistence of recombinant *S typhimurium* in the peyer's patches or spleens was not required for induction of this protective immune response [15,37,38].

Liposomes

These have been used in the delivery of several, particularly anticancer, drugs so as to effectively target the cells to where it should reach. These liposomes are closed vesicles with bilayered phospholipid membrane. Liposomes are thought to improve mucosal immune responses by facilitating M cell uptake and delivery of antigen to lymphoid elements of inductive tissue. The efficacy using liposomes has been found to increase two fold in a rat model. In humans increased IgA antibodies have been found [15,36,37].

Microcapsules and Microparticles

Combinations of antigen in or on various types of particles have been used in attempts to enhance mucosal immune responses. Microspheres and microcapsules made of Poly (lactide-co-glycolide) (PLGA) have been used as local delivery systems because of their ability to control the rate of release, evade preexistent antibody clearance mechanisms, and degrade slowly without eliciting an inflammatory response to the polymer. Oral immunization with these microspheres effectively delivered and released vaccine in the gut associated lymphoid tissue as determined by their ability to induce a disseminated mucosal IgA anti toxin antibody response [15,36].

Conjugate Vaccines

Another vaccine approach which may intercept more than one aspect of *mutans streptococcal* molecular pathogenesis is the chemical conjugation of functionally associated protein/peptide components with bacterial polysaccharides. Added to the value of including multiple targets within the vaccine is that the conjugation of protein with polysaccharide enhances the immunogenicity of the T-cell independent polysaccharide entity [15,36].

Human Trials

Various small scale human trials in adults have shown that it is feasible to increase levels of salivary S-IgA antibodies to *mutans streptococci*, and in some cases to interfere with *mutans streptococcal* colonization [37,38]. The vaccine could also be administered in children

along with the other vaccines like diphtheria, tetanus before the eruption of the deciduous dentition so that maximum caries inhibition can be done. GTF from *S sobrinus* combined with Aluminum Phosphate (AP) was administered orally in capsules to 14 subjects which resulted in an increase in salivary IgA antibody response when combined with an aluminum based adjuvant [37,39]. In addition, oral immunization with this antigen was effective in interference with repopulation of the oral cavity by *S mutans*. While these effects were relatively shortlived, efforts to modify the antigen dose, frequency of administration, composition, route of administration, or presentation of the antigen to appropriate antigen-presenting cells may significantly increase the intensity and duration of the response. Another study was conducted by topically administering GTF from *S sobrinus* onto the lower lips of young adults. It stimulated local antibody production in the minor salivary glands but resulted in delayed oral decolonization with *mutans streptococci* [38,40]. Oral immunization of 7 adult volunteers with an enteric coated capsule containing 500 micrograms of GTF from *S mutans* also resulted in elevating in elevating salivary IgA antibodies to the antigen preparation [40]. When similar antigen preparations were administered intranasally or by topical application to the tonsils, either in soluble form or incorporated in liposomes, salivary IgA antibodies were likewise increased [41,42]. Further clinical trials in younger age groups are therefore necessary to provide substantial evidence whether responses obtained can suppress oral colonization by *mutans streptococci*.

In conjunction with established methods of caries prevention, caries vaccines have the potential of making a highly valuable contribution to disease control. Meanwhile, basic research on the mode of action of caries vaccine and the search for new, more effective, and possibly polyvalent vaccines (vaccines that can protect a person against more than one strain of a causative agent of the disease) must continue if we are to fully explore their potential to minimize dental caries.

Challenges for the 21st Century

Given that dental caries usually develops slowly and can occur throughout life, it may be anticipated that immune protection would need to be similarly long lasting. It is clearly understood that *S. mutans* is not the only cariogenic microorganism and that a series of factors influence the development of disease. Therefore, the main question arises as to what extent successful vaccination against *S mutans* could reduce the incidence of dental caries [43]. Traditional vaccine therapy indicates that immunization should take place prior to infection. Given the apparent pattern of *mutans streptococcal* colonization and the association of these organisms with disease, this would suggest that immunization for dental caries should begin early in the second year of life for those populations under "normal" risk for infection [36]. If bacterial colonization of the dental biofilm is complete after eruption of all primary teeth and if one can, through immunization, prevent *mutans streptococcal* colonization prior to this period, then the benefit of early immunization might extend until secondary teeth begin to erupt, exposing new ecological conditions. Thus a successful vaccination directed against *S mutans* can go a long way in improving the caries status of the vulnerable populations and serve as a major public health measure in others. However, thorough analysis of the need, cost benefits and risk benefits of the vaccine in various societies and communities is mandatory.

Experiments utilizing antisera from rabbits immunized with whole cells of *S mutans* and with a high molecular weight protein antigen of *S mutans* were reported to cross react with normal rabbit and human heart tissues. Polypeptides immunologically cross reactive with human heart tissue and rabbit skeleton muscles myosin are found in the cell membrane of *S mutans* and *Streptococcus ratti* [44]. One of the major challenges for the 21st century is therefore to eliminate the phenomenon of human heart cross reactivity from an anti caries vaccine for human consumption [26]. Any vaccine, to be successful, must be effective, safe, and acceptable to the general public. Although dental caries is undeniably one of the most important diseases in terms of prevalence, suffering, in convenience and cost, it is a condition which rarely if ever leads to death or serious disability of a patient. Consequently, it is most important that any prospective method, including immunization, should not carry even a small risk.

A 'Panel on Caries Vaccine' was constituted by 'National Institute of Dental and Craniofacial Research' (NIDCR) in 2003. Some general issues relating to caries vaccine development were discussed and recommendations were put forward by the panel. They included elements in successful vaccine development, the economic/risk benefit issue, industry partnerships and models of care for access and delivery and an efficient delivery model for a vaccine. In 2010, the NIDCR updated its recommendations with a Summary of Vaccine Panel's Deliberations and Recommendations. They concluded that NIDCR should continue to support basic research on mucosal immunology and suggested that priority be given to the passive immunization approach. The panel also raised several scientific, ethical and economic considerations related to the active immunization approach for the prevention of dental caries [45].

Questions about the possibility of a vaccine ever coming to market were expressed due to public perception about the "risks" of vaccines. The biggest obstacle would be getting a CDC Advisory Committee on Immunization Practices (ACIP: www.cdc.gov/vaccines/recs/acip/default.htm) recommendation for routine use in all children [46]. If that is not obtained, it is feared that industry will not manufacture the vaccine. An ACIP recommendation is based on economic risk benefit, making it necessary to prove that a caries vaccine would be cost saving and cost effective and free from even a small risk. More information about the burden of caries over time in terms of both economics and quality of life and more human trials of experimental vaccines to evaluate efficacy and safety will be required [15,47]. In this regard, stages of human vaccination trials must be considered such as in infants (phase 1,2,3 studies), preschool children (phase 1,2 studies) and pre adolescent children (phase 1,2 studies). Only then one can answer the questions posed: Is a caries vaccine a viable option in dental caries and decay prevention?

In fact, the world waited over a century for vaccine against typhoid once the causative agent had been identified. Later, it took nearly half a century to develop vaccines against polio and measles. The search and quest for an HIV/AIDS vaccine is a far greater challenge than sending a man to the moon [48-50]. Similarly, it is pivotal to prove that a future dental caries vaccine must be cost saving, cost effective and free from even a small risk. Scientists are, therefore, not disappointed due to many odd situations; rather they are cautiously optimistic that protective dental caries vaccine will be available sooner than later for global human usage. Secondly, therapeutic caries vaccine such as KF-rPac could be used as an anticaries therapeutic mucosal vaccine.

Conclusions

As dental caries is a multi factorial disease, various modalities exist to prevent it like use of fluorides, mechanical and chemical control of plaque, pit and fissure sealants, etc. Apparently, the main focus of the dental research is on the development of safe and efficacious oral anti caries vaccines. Animal studies suggested that there is great promise in the development of dental caries vaccine such as subunit vaccines, recombinant DNA vaccines, etc., but few human trials have been undertaken to date. Significant difference of opinions prevails over whether antibody for protection against caries should reside in the IgG or the IgA class of antibodies studied. Active or passive immunization strategies, which target key elements in the molecular pathogenesis of *S mutans*, hold promise. Further advances to make immunization against caries practicable will depend upon clinical trials aimed at establishing whether the findings from animal experiments can be successfully transferred to humans. Also, various routes for inoculation of dental caries vaccine in humans are important to be evaluated with pros and cons of each route of administration. However, the main challenge of the 21st century is to remove human heart cross reactivity and other risks such as rheumatic fever from any future dental caries vaccines, so that it is cost saving, cost effective and free from even a small risk for human use globally. The importance of developing adequate oral health behaviors will also continue to be the key for good oral health and considerable decrease in dental caries occurrence.

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