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Review Article

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The Development and Effectiveness of Dental Caries Vaccination in Reducing Global Dental Health Burden: Scoping Review

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ABSTRACT

Objective: To review the effectiveness of dental caries vaccination globally. This review includes evaluations of vaccine approaches developed both in silico and in preclinical trials (in vitro and in vivo) that could ultimately reduce or control the burden of dental health problems worldwide.

Tooth decay (dental caries) is a multifactorial disease caused by the interaction between the tooth surface, a layer of bacterial biofilm (dental plaque), and the presence of sugars from food. The bacteria in the biofilm metabolize the sugars and produce acids, which over time damage tooth enamel.Streptococcus mutans (S. mutans) is a potential pathogenic bacterium that causes dental caries. Untreated permanent tooth decay has a prevalence of 40% for all ages combined, making it the most common condition among 291 diseases according to the Global Burden of Disease Study, affecting approximately 3.9 billion people worldwide.

Although not yet commercially available, a caries vaccine shows high potential as a long-term preventive solution. Globally, vaccination could be particularly useful in developing countries with limited access to dental care. Therefore, it is necessary to develop and review the effectiveness of dental caries vaccination in reducing the burden of dental health globally.

Method: The type of research used isscoping review. The articles used relate to the development and effectiveness of dental caries vaccination in reducing the global burden of dental health. Search fromdatabasegenerate 25,100 fromGoogle Scholar, 136 ofPubmed, and 2,380 ofScience Directregarding the development and effectiveness of dental caries vaccination in reducing the global burden of dental health. Initial screening of the removal was based on articles from the last 5 years in English,
and the removal of 1,668 unavailable articles and the removal of 25 duplicate articles. Of these, 6 articles were deemed to meet the inclusion and exclusion requirements for evaluation.full text.

Results: A search of PubMed, Google Scholar, and Science Direct yielded 876, 7,195, and 30,400 article records, respectively. Initial screening of titles and abstracts and removal of duplicates yielded 1,652 unique articles. Of these, 6 articles were deemed eligible for full-text evaluation. These 6 articles were selected for full-text analysis, consisting of 3 studies with in silico tests using immunoinformatics, and 3 other studies using in vitro and vivo tests.

Conclusion: The development and effectiveness of a dental caries vaccine have great potential as a preventive approach that can reduce the burden of dental disease globally. Findings from the six selected articles show positive results regarding vaccine effectiveness, both through in silico testing approaches and in vitro and in vivo testing. Further research is needed in the form of preclinical trials, especially in vitro, in vivo, and clinical trials to ensure the safety, effectiveness, and feasibility of mass use of anti-caries vaccines. If proven safe and effective, a caries vaccine will be a long-term and economical solution to reduce the burden of caries, especially in areas with limited access to dental health services.

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Introduction

Dental caries is a common, multifactorial, and chronic global health problem affecting all age groups. The development of dental caries depends on various factors such as fermentable sugars, cariogenic microbial flora, host factors, time, diet, and other related environmental factors. Environmental factors such as socioeconomic status, education level, medical health, lifestyle, diet, and access to dental care can also influence the development of dental caries [1].

Dental caries is a multifactorial non-communicable disease caused by the complex interaction of bacteria, fermentable carbohydrates, and host factors over time. In addition, socio-behavioral risk factors play a significant role, including family history.

low education, poor living conditions, poor eating habits, high sugar consumption, traditions and limited access to general health care and oral health. However, dental caries is largely preventable, new prevention can be used currently in the community by administering fluoride to inhibit tooth demineralization, increase tooth remineralization, and inhibit bacterial metabolism and acid production in teeth [2].

It is characterized by tooth demineralization, leading to cavities and, if left untreated, potentially more severe dental and systemic health problems. More than 30% of the world's population suffers from untreated dental caries, and it remains one of the most important oral health diseases due to its negative impact on growth, cognitive development, and quality of life. As reported in the Global Status of Oral Health Report 2022, due to their large populations, the Southeast Asia and Western Pacific regions reported the highest number of cases among the World Health Organization (WHO) regions, and among the other four WHO regions—Africa, the Americas, Europe, and the Eastern Mediterranean—the African region recorded the highest number of cases, with 480 million cases in 2019. The prevalence of dental caries, with an estimated 3.5 billion people worldwide affected by oral diseases, is projected to increase. Overall, an estimated 2 billion people experience caries in permanent teeth and 514 million children experience caries in primary teeth, WHO also reported a global prevalence of caries in primary teeth of 43%, with the African region recording a caries prevalence of 30% in primary teeth in 2019. The lowest caries prevalence is in the Americas and Europe while the highest prevalence is in Southeast Asia and Africa [3, 4].

The prevalence of early caries in children aged 3–5 years varies globally. It is higher in most low-income countries such as Southeast Asia and Africa, which show higher prevalence among socioeconomically disadvantaged groups. The United States shows a higher prevalence than European countries with 40% of children experiencing caries by kindergarten age, while 12% of children have visible caries by around 3 years of age in the United Kingdom. Accumulating evidence suggests a high prevalence of 36%–85% in Asian countries, 38%–45% in Africa, and 22%–61% in the Middle East [5].

Dental caries remains a major global public health challenge due to its widespread impact not only on oral health but also on the social and economic aspects of individuals and communities. Risk factors for dental caries are not limited to these aspects.

It is not merely a biological factor, but is influenced by complex social determinants of health such as access to adequate health care, awareness of the importance of oral hygiene, and health policies that support primary prevention [6]. In some low- and middle- income countries, resource constraints and the lack of effective prevention programs make it difficult to control caries prevalence, thus reinforcing the need for multidisciplinary interventions and community-based approaches. Technological advances in microbiology and immunology open up opportunities for new approaches that focus not only on prevention with fluoride and sealants, but also on the development of immunological therapies for specific and personalized caries prevention [7].

Current research focuses on the importance of an interdisciplinary approach

involving public health education, nutrition, vaccine development, and other biotechnologies to reduce the global burden of this disease. Strengthening the capacity of local oral health systems is a key factor in reducing caries prevalence, especially in areas with high social and economic disparities [8].

Currently, various strategies for preventing dental caries are being used, such as oral health education, chemical and mechanical plaque control, fluoride use, and pit and fissure sealant application. Many of these approaches are generally effective. However, economic, behavioral, or cultural barriers to their use have contributed to the continued epidemic of dental disease in many communities globally. A recent approach to combating dental caries is through the development of an effective vaccine suitable for public health contexts, particularly in settings where routine health care is not readily available [9].

Caries vaccination, also known as anti-caries immunization, is a proposed method for preventing dental caries by using a vaccine to stimulate the production of antibodies that target the bacteria responsible for tooth decay. The idea of using vaccination to prevent dental caries originated in the 1920s, when researchers first discovered that immunization with cultures ofStreptococcus mutansInactivated vaccines can reduce the prevalence of cavities in animal studies. However, early attempts at caries vaccination in humans were largely unsuccessful, as the vaccines were ineffective in inducing a strong immune response or protecting against natural infection [10].

Streptococcus mutansIt is a gram-positive facultative anaerobic bacterium that plays a role in plaque formation and acid production, which are the primary causes of dental caries pathophysiology. This bacterium thrives in the oral cavity, especially when...

Fermentable carbohydrates such as sucrose, glucose, and fructose are present. This produces extracellular polysaccharides, mostly glucans, which promote oral biofilm formation and give it a remarkable capacity to adhere to enamel surfaces. Plaque development creates a restrictive microenvironment in which Streptococcus mutancan grow while evading the host's immune system and salivary purification system. Due to its acidogenic

nature, the pH of the biofilm decreases, increasing the acidity of the oral environment. Because hydroxyapatite, the main mineral component of enamel, dissolves at low pH, the enamel undergoes demineralization due to the sustained acidic conditions.

Repeated acid attacks will erode the enamel over time, ultimately leading to the formation of cavities [11].

In the 1970s and 1980s, researchers developed a new approach to initiate research on caries vaccination, which involved the application of isolated live cultures of strains ofS. mutansusing recombinant DNA technology to produce antigens that can stimulate an immune response. Vaccines using this DNA technology have shown promising results in animal studies and early clinical trials, but further research is needed to assess how well they work in humans [10].

Caries vaccines are designed to play a protective role against the process of tooth decay. Streptococcus mutansis the main etiology in the pathogenesis of dental caries because its cells contain substances such as adhesins, GTF, GBP, 13 kDa protein antigen (antigen D), 39 kDa protein (AgIII), 29 kDa protein antigen (antigen A), 70 kDa protein antigen (antigen C), and 190 kDa protein (AgI/II). These substances play a role in the interaction between the organism and the host, so that most of the experimental designs of dental caries vaccines are directed at these compounds [5]. Glucan biofilms produced by GTF fromStreptococcus mutansknown as the main component of cariogenic plaque and the enzyme is known as one of the pathogens of dental caries because the enzyme plays an important role in the formation of dental plaque [12]. In other studies exploring the mucosal immune system related to the occurrence of dental caries. It is said that IgA antibodies play a central role in mucosal immunity, so in this study it was concluded that IgA induction, especially specific immunity againstStreptococcus mutansis a logical and scientifically significant strategy in the development of a caries vaccine [13].

The aim of this study was to review the effectiveness of dental caries vaccination globally. This review included an evaluation of vaccine approaches developed both in-house and in-house. in silico and preclinical trials (in vitro and in vivo) which will ultimately reduce or control the burden of dental health throughout the world.

Materials and Methods

The type of research used isscoping reviewThe articles used relate to the development and effectiveness of dental caries vaccination in reducing the global burden of dental health. Data extraction began with a data search on 3 databasethat is Google Scholar, PubMed,AndScience Directby using keywords (VaccineOR Immunization)AND(Dental CariesORDental DecayORDental Cavity)AND (Dental Health OROral Health), the articles obtained were filtered based on inclusion criteria, namely research articles that have been published in international journals related to the development and effectiveness of dental caries vaccination in reducing the burden of dental health globally; articles published within the last 5 years, 2020 - 2025; type of research articleoriginal research articles; research articles are fully accessible (full text); English language articles.

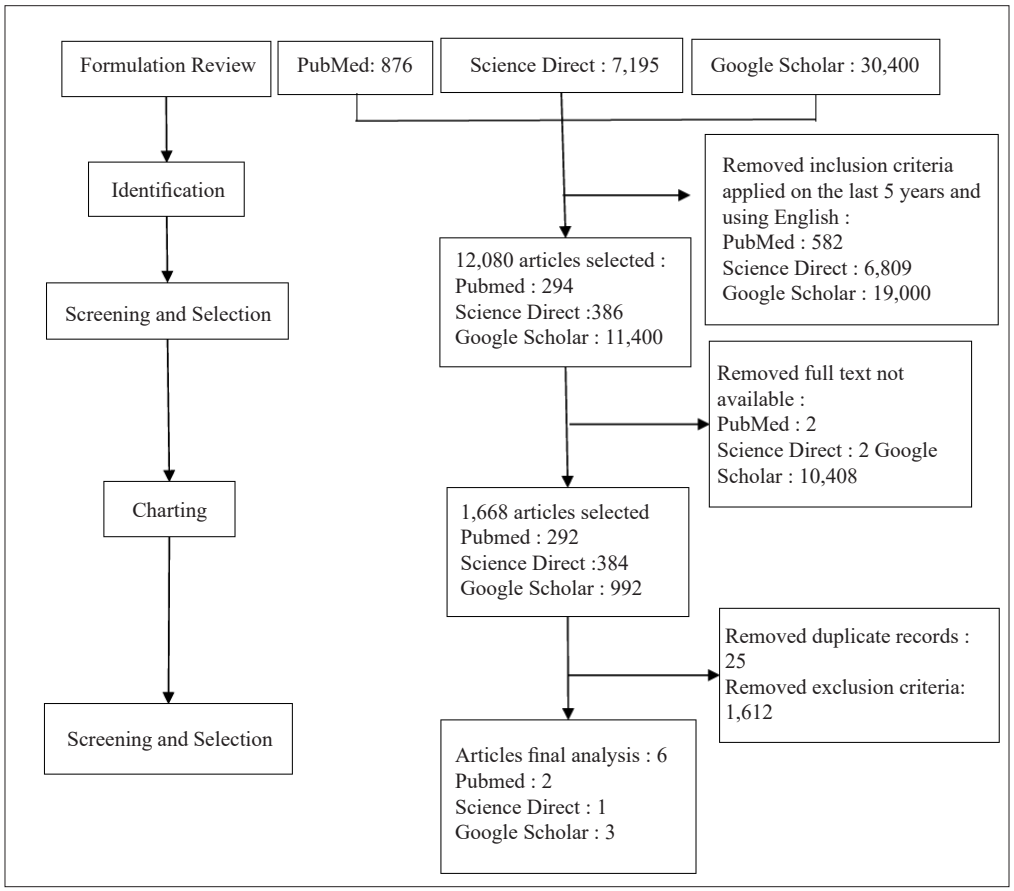

Figure 1: Item Report forScoping Review Diagram

Exclusion criteria were publications that focused solely on vaccines against bacteria that do not cause dental caries, vaccines targeting areas other than the oral cavity, and the use of probiotic bacteria in caries prevention. The search was conducted from three sources.database in May 2025 produced 30,400 ofGoogle Scholar, 876 ofPubmed, and 7,195 ofScience DirectThis study examined the development and effectiveness of dental caries vaccination in reducing the global burden of dental health. Initial screening was based on English-language articles from the last 5 years, as well as the removal of unavailable articles, resulting in 1,668 articles and 25 duplicate articles. Of these, 6 articles were deemed to meet the inclusion and exclusion criteria for evaluation.full text.

Scope Review: The initial electronic search yielded 28,471 potentially eligible articles, and no additional studies were identified through manual searches. Rigorous selection, including application of inclusion criteria, based on articles from the last 5 years and English- language articles yielded 12,080 articles, then removal of articles not available in full text yielded 1,668 and removal of duplicates yielded 1,643. Finally, 6 articles were selected and analyzed, thus providing a focus on caries vaccination in reducing the global dental health burden.

A search of PubMed, Google Scholar, and Science Direct yielded 876, 7,195, and 30,400 article records, respectively. Initial screening of titles and abstracts and removal of duplicates yielded 1,652 unique articles. Of these, 6 articles were deemed eligible for full-text evaluation. The data retrieval flow is illustrated in Figure 1

Results

Table 1: Characteristics of Eligible Articles

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All included studies were of moderate to low quality. All articles were peer- reviewed publications describing studies using a control group for outcome assessment. After assessing the eligibility of the full text based on the inclusion criteria (last 5 years, English language, original research), six articles were deemed eligible for further analysis. The six articles analyzed covered various approaches to caries vaccine development: three articles used to immunoinformatics-base in silico assays and three others used in vitro assays.

with streptococcus mutans bacterial culture, followed by in vivo testing based on experimental animals.

Three of the six studies used a cross-sectional approach. immunoinformaticsto design a multi-epitope vaccine in silico. The developed vaccine demonstrated high immunogenic potential, good structural stability, and strong interaction with immune receptors such as TLR-4 and MHC-I. Predicted immune responses showed good activation of B and T cells and increased IgG and IgA antibodies [14-16].

Three other studies tested the effectiveness of vaccines in animal models, which had previously cultured mutans streptococci. Subunit vaccines such as KFD2-rPAc and ZIF-8@PAc successfully demonstrated reduced colonization.S. mutanssignificantly and prevent caries development. Systemic and mucosal immune responses were demonstrated by increased specific antibody titers and decreased biofilm formation, demonstrating the vaccine's effectiveness in preventing the initial caries process. A study evaluating a mucosal vaccine based on rGlnH protein in mice with sublingual immunization resulted in a significant increase in IgG titers and a reduction in bacterial colonization, demonstrating the vaccine's protective effectiveness against the early colonial phase of S. mutans [17-19].

These results indicate that multiepitope-based vaccines exhibit predictive high immunogenicity and interact strongly with immune receptors such as TLR4 and MHC. Subunit vaccines such as ZIF-8@PAc and KFD2-rPAc successfully increased IgG and IgA antibodies and inhibited S. mutans colonization in mice. The mucosal rGlnH + LTK63 vaccine resulted in significant colonization reduction and a robust immune response. Most vaccines demonstrated high potency in preventing initial colonization and biofilm formation by S. mutans, which are key to caries prevention.

Table 2: Risk of bias assessment of 6 selected articles

https://docs.google.com/spreadsheets/d/1It6OO69amqJkOIIxtIsgLS1Bw1V6MoE-jlMtBIfCS1k/edit?usp=sharing

Risk of bias assessment (Risk of Bias) of the six journals analyzed showed variations in the level of methodological quality. Three journals [17-19] had a high level of compliance. low risk of bias. In contrast, two in silico journals [14, 15] had low compliance rates indicatinghigh risk of bias. Meanwhile, journal [16] has a moderate level of compliance which indicateslow to moderate risk of bias [20]. In general, in vivo and in vitro studies demonstrate stronger methodological quality than in silico studies. This reflects the need for experimental validation on computer simulation-based vaccine design before it can be applied to preclinical or clinical trials.

Discussion

The burden of dental health, especially on dental caries disease in permanent teeth, reviewed from 1990 - 2019 according to the World Health Oral, was found with the highest level in the European region at 33.63% and the lowest in the Western Pacific region at 25.41%, but if reviewed from the cases found, the most were in the Southeast Asia region (526 million cases) and the Western Pacific region (464 million cases) [21]. Meanwhile, in research to find caries vaccine studies in the last 5 years, only 6 articles were found originating from India (2 articles), Brazil (1 article), China (2 articles) and Switzerland (1 article).

The lack of research from countries with the highest caries prevalence, such as Africa, highlights the research gap and the need for international collaboration.

Furthermore, no studies have yet reached the human clinical trial stage, so long-term safety and immunological responses in humans remain uncertain

According to the WHO graph above, the highest number of caries cases, with 525 million, is found in the African region. However, in the past five years, no researchers have found any research or articles on caries vaccines. Therefore, research is needed in this region with the most recent caries cases so that it

can be a source of relevance for caries vaccine products that can be used in the global community. Most of the scientific research on the development of dental caries vaccines was published in China and in Q1 quartile journals [22].

Caries vaccines are primarily designed to play a protective role against the process of tooth decay. It is a well-known fact that S. mutans is a bacterium that attacks the central and peripheral nervous systems [23], playing a major etiological role in the pathogenesis of tooth decay because its cells mainly contain substances such as proteins - proteins used in the 6 articles that have been previously studied proteins (PBP2X, PBP2b, MurG, ATP-F, AGPAT), virulent proteins Dextranase, GbpA, GbpB, GbpC, Gtf I, Gtf D, Glnh, Pac, pstS, WAPA), proteins (PBS, PBS1PAc, ZIF-8@PAc, CTB1PAc, Alum+1PAc), KFD2-rPAc, rGlnH, LTK63. Since these substances are thought to play an important role in the interaction between the organism and the host, most of the experimental designs of caries vaccines are mainly directed at these compounds.

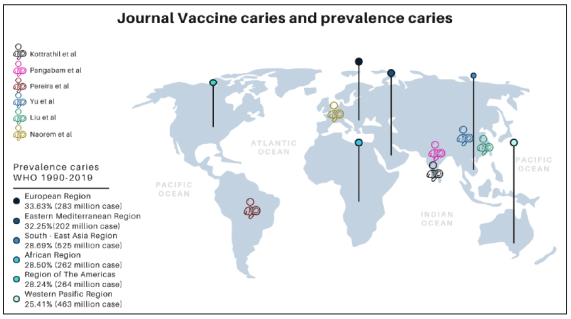

Figure 2: Graph of Caries Vaccine and Caries Prevalence Globally

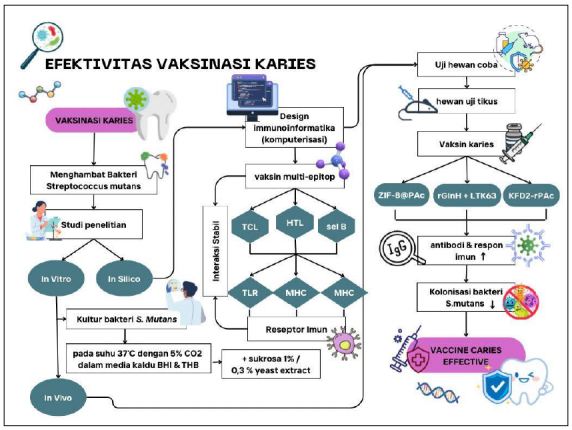

Figure 3: Caries Vaccination Effectiveness Scheme

Figure 3. Reviewing six scientific journals published in the past five years since 2020, we found scientific journals that have researched and developed caries vaccines. This article reviews the evidence for the effectiveness of caries vaccination, which requires research using various approaches. The approaches used are In Silico Testing based on immunoinformatics or computerization, and In Vivo Testing based on test animals. In previous research, the In Silico Testing, an immunoinformatics approach was used to identify potential antigens suitable for successful vaccine design in designing a multi-epitope vaccine for dental caries, consisting of CTL, HTL, and B cell epitopes from antigenic proteins, along with appropriate adjuvants and linkers.

Docking and molecular dynamics studies with TLR, MHC, and MEV receptors demonstrated potential immunological activation and recognition, and molecular dynamics simulations demonstrated stable interactions between the vaccine and immune receptors. Advances in immunoinformatics have contributed significantly to the improvement of peptide-based vaccine predictions. By targeting specific antigens involved in the pathogenesis of dental caries, this in silico-designed vaccine promises long-term protection against this caries disease. Although in silico approaches provide valuable insights into vaccine design, experimental validation remains essential to confirm the efficacy and safety of vaccine candidates. To verify research results, vaccine proteins must undergo experimental validation, which involves in vivo testing [14-16].

The In Vitro Test approach was carried out first before being carried out on experimental animals or In Vivo Tests, namely by culturing Streptococcus mutans bacteria at 37ºC with 5% CO_2 in BHI (Brain Heart Infusion) and THB (Todd-Hewitt) broth media aerobically and anaerobically, then given 1% sucrose and 0.3% yeast extract. The animals used for this research test were mice. In previous studies, the immunological response to the ZIF-8@PAc vaccine was evaluated in mice by subcutaneous injection of the vaccine. The results showed that the ZIF-8@PAc vaccine produced significantly higher levels of IgG and its subclasses with good biocompatibility, pH response, and the addition of high PAc antigen as an adjuvant significantly increased internalization and caused a strong immune response, including high levels of antibody and cytokine titers, high splenocyte proliferation index, In addition, the PAc-specific immune response effectively inhibited colonization byStreptococcus mutanson teeth and provides sufficient protection against caries in mice. This advantage showed that ZIF-8@PAc is a promising anti-caries vaccine candidate [19].

Experimental animal studies using five female mice aged 6–8 weeks were given sublingual rGlnH and LTK63 vaccinations, showing that administration of rGlnH together with the LTK63 adjuvant induced antigen-specific serum IgG responses in the mucosa that were able to recognize native proteins expressed in bacterial cells.

Streptococcus mutansand provide protective immunity. Collectively, these results indicate promising prospects for the development of antibacterial vaccines based on ABC transporter components [18]. In contrast to other animal studies, it was shown that vaccination of mice with KFD2-rPAc effectively inhibited early infection.

Streptococcus mutansIn addition to assessing the effectiveness of the caries vaccine, researchers also need to demonstrate that the KFD2-rPAc vaccine infection model is suitable for evaluating the vaccine's prophylactic effects. Researchers found that the bacteria in mice Streptococcus mutansCultured in confined air conditions showed a rapid increase in colonization efficiency in the development of vaccines to prevent dental caries compared to those cultured in unrestricted air conditions (free air). These results indicate that culture in confined air conditions can improve the prophylaxis of vaccines in inhibiting bacteria.Streptococcus mutans, thus helping in evaluating the prophylactic efficacy of vaccines and anticaries drugs [17].

In research that examines inoculationStreptococcus mutansinto the dental pulp of mice showed an immune response characterized by an increase in the Th1 (IFN-γ) response. This study states that successful therapeutic interventions in recruiting oral immunity to eradicateStreptococcus mutansaffecting the ERK/MAPK, NF-κB, and inflammasome signaling pathways that support the suppression of Th1 responses. The most effective caries prevention vaccine produces a combination of Th1, Th2, and Th17 responses. In addition, an in vitro study that utilized the utility of genetically modified tomatoes, namely transgenic tomatoes, by incorporating the PAc proteinStreptococcus mutansand the gene encoding the cholera toxin B subunit showed a predominance in the expression of dental caries antigens [24,25].

Therefore, research with in silico and in vivo tests resulted in a vaccination design with an immunoinformatics approach using a computerized system, then continued by validating the caries vaccination using research with in vivo tests.

with an animal test approach that is effective in inhibiting bacteriaStreptococcus mutansin caries prevention, in order to suppress the increasing prevalence of dental caries globally. This analysis reviews the six scientific research articles that show that vaccines are relevant for preventing dental caries and can be applied immediately to the community. In addition to computer testing and animal trials, direct human research is needed. Previously, there was a vaccine study in humans in 2012. Various small-scale trials in adults, caries vaccines have shown that they increase salivary S-IgA antibody levels against mutans streptococci, and in some cases, inhibit mutans streptococcal colonization. This vaccine can also be given to children in conjunction with other vaccines such as diphtheria and tetanus before the eruption of primary teeth so that caries inhibition can be maximized. The vaccine was administered orally in capsules to 14 subjects, resulting in an increased salivary IgA antibody response. In addition, oral immunization with this antigen has been associated with disrupting the Streptococcus mutans bacterial population in the oral cavity. There is still a need for the latest supporting research involving direct human trials, before the vaccine is applied to the public [26].

Conclusion

Based on a global review from 1990–2019, the highest prevalence of dental caries was found in the European region (33.63%) and the lowest in the Western Pacific region (25.41%). However, the highest number of cases was found in Southeast Asia (526 million) and the Western Pacific (464 million). Despite dental caries being a significant health burden, in the past five years, only six scientific studies on caries vaccine development have been reported, originating from India, Brazil, China, and Switzerland.

Dental caries vaccination offers a promising preventive approach, especially in areas with limited access to dental health services. The combination of in silico-based multi- epitope vaccine design with biological validation in animal models (in vivo) strengthens the scientific evidence for this vaccine's potential. However, before this vaccine can be widely applied, further preclinical trials involving variations in dosage, duration of immunogenicity, and long-term effects are needed; human clinical trials (phases I–III) to assess safety and effectiveness in target populations; and population-based studies in caries-endemic areas (Africa, Southeast Asia). Global implementation of this vaccine could be a cost- and logistically efficient long-term preventive solution.

The development and effectiveness of a dental caries vaccine hold great potential as a preventive approach that could reduce the global burden of dental disease. Findings from six selected articles demonstrate positive results regarding vaccine effectiveness, using both in silico and in vivo approaches. These studies focused on the role of Streptococcus mutansas the main cause of caries, with vaccine targets in the form of various antigenic proteins such as GbpA, Gtf I, PAc, and others.

Overall, the results of these six studies demonstrate that caries vaccines have significant potential to reduce the prevalence of dental caries globally. Vaccine development, using a combination of immunoinformatics approaches and animal model validation, is considered effective and relevant for implementation in caries prevention efforts in the wider community.

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