Review Article

Anticaries Vaccine as a Promising Alternative for Protection against Dental Caries: A Literature Review

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Abstract

Aim: The aim of this review was to describe the scientific progress regarding anticaries or dental caries vaccines. **Material and Methods:** An electronic search without date restriction prioritizing those scientific articles belonging to the last 5 years was performed in the PubMed and Scopus databases. The following keywords were used: "anticaries vaccine," "vaccine against dental caries," and "caries vaccine." **Results:** A total of 11 studies were considered for the present investigation, of which seven were *in vivo*, one was *in vitro*, two were both *in vivo* and *in vitro*, and one was a theoretical article. The most frequently investigated parameter was the induction of antigen-specific antibodies generated by the administration of the different types of anticaries vaccines. **Conclusions:** More *in vivo* studies aiming at solving the few disadvantages of the current anticaries vaccines need to be carried out to start studies in human samples in the not-too-distant future.

Keywords: Anticaries, Dental Caries, Vaccine

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Introduction

Dental caries is considered a disease with a negative impact on the hard tissues of the teeth and is related to several factors, which is well known as "multifactorial etiology." Carbohydrates from our diet are the main factors contributing to the formation of dental caries lesions, which are subsequently fermented by the action of microorganisms inherent to the oral cavity, including Streptococci and *Lactobacillus*.[1] This microorganism has the capacity to alter the environment or local environment of the oral cavity by forming a medium rich in extracellular polysaccharides and low pH, indirectly creating a favorable environment for the development of other acid-genetic and uric acid bacterial species such as *Lactobacillus*.[2,3]

Dental caries remains the most common disease of all health problems in children, outnumbering other well-known chronic diseases such as asthma by a factor of five. According to the most updated report provided by "The Global Burden of Disease (GBD)," untreated caries in the permanent dentition was ranked as the most prevalent worldwide condition. Untreated caries in the primary dentition has been selected as the 10 most prevalent disease on this list.[4] Additionally, dental caries was observed in 100% of children between 6 and 7 years of age in Poland according to reports by the World Health Organization and the Polish National Institute of Public Health. This is an extremely worrying figure for a developed country.[5] Dental caries has long been considered a disease of childhood and continues to spread into adulthood.[6] For example, the prevalence of caries ranges from 27% to 64% in children, whereas it varies from 26% to 85% in adults.[1]

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Recently, Yang *et al.*[7] have reported the use of salivary IgA-targeting surficial antigens of *S. mutans* as a unique target for the prevention of dental caries, as this microorganism has long been considered the main etiological agent of dental caries. In addition, the natural immune component against *S. mutans*, better known as saliva-secreting IgA antibodies (S-IgA), has also been the focus of several investigations. The most important salivary immunoglobulin is S-IgA, which is produced by mucosal plasma cells in the salivary glands and whose mechanism of action relies on two fundamental facts: interference with the binding of cariogenic *S. mutans* to hard surfaces and possible inhibition of the metabolic activities of this microorganism.[8] Furthermore, glycosyltransferases (GTF) and the surface protein antigen (PAc, P1, or Ag I/II) virulence factors that influence the pathogenicity of this microorganism have been studied and analyzed. In addition, the ability of *S. mutans* to activate the immune system and thus induce an immune response is mediated by the glucan-binding region (GBR) and the alanine and proline (A-P). Both considered immunogenic regions of the virulence factors. As a result of multiple investigations in this field, vaccines against GBR and A-P, the very famous "anticaries vaccines," have emerged; however, further studies are required for these to be improved.[9,10]

The aim of this literature review was to describe the status and scientific progress regarding vaccines against dental caries.

Materials and Methods

Search strategy

An electronic search was carried out to identify the studies included in this narrative review, without date restriction, but prioritizing those belonging to the last 5 years. Electronic searches were carried out in two scientific databases (Scopus and PubMed) in order to identify articles relevant to the present study. The following keywords were used: "anticaries vaccine," "vaccine against dental caries," and "caries vaccine." In addition, a supplementary hand search of the bibliography of the single review article was performed to find additional literature. Duplicate articles were removed along with unpublished articles in English. Article titles were carefully screened to exclude those that were clearly not related to the anticaries vaccine.

The following search formula was established: "anti-caries" [All Fields] AND ("vaccin" [Supplementary Concept] OR "vaccin" [All Fields] OR "vaccination" [MeSH Terms] OR "vaccination" [All Fields] OR "vaccinable" [All Fields] OR "vaccinal" [All Fields] OR "vaccinate" [All Fields] OR "vaccinated" [All Fields] OR "vaccinates" [All Fields] OR "vaccinating" [All Fields] OR "vaccinations" [All Fields] OR "vaccination s" [All Fields] OR "vaccinator" [All Fields] OR "vaccinators" [All Fields] OR "vaccine s" [All Fields] OR "vaccined" [All Fields] OR "vaccines" [MeSH Terms] OR "vaccines" [All Fields] OR "vaccine" [All Fields] OR "vaccins" [All Fields]).

Inclusion criteria

The present review focused on articles that were involved in the development of a vaccine against the main caries-causing bacteria such as *S. mutans*. *In vitro* and *in vivo* studies were also included in the article. The search was limited to articles published in English.

Exclusion criteria

Publications focusing on a vaccine against bacteria that do not cause dental caries were excluded. Articles published in any language other than English were also excluded. Articles with a low level of evidence, such as studies with a small or insignificant sample size, were omitted.

Results

This literature review analyzed a total of 11 studies of which seven were *in vivo*, one was *in vitro*, two were both *in vivo* and *in vitro*, and one was a theoretical article. In addition, one study integrated in the background was used for the writing of the introduction [Table 1].

Antigen subunit vaccines

PAc-based caries vaccines

The first studies that addressed the development of anticaries vaccines proposed the use of a surface protein called PAc (*S. mutans* virulence factor) as a candidate antigen to elicit a response from salivary IgA antibodies, thus giving rise to PAc anticaries vaccines characterized using PAc as antigen-inducing immune responses. However, the stand-alone application of PAc had several limitations over time, which is why later research emphasized the incorporation of adjuvants into these vaccines[11-15] [Figure 1].

PAc anticaries vaccine + recombinant FimH-S protein T

Liu *et al.* proposed the use of PAc anticaries vaccine mixed with recombinant FimH-S. T protein, resulting in an induction of salivary IgA 4.5–23.9 times higher than if PAc had been administered alone. In addition, the PAc anticaries vaccine adjuvanted with FimH-S. T induced serum IgG 3.7–224 times more than if it had been immunized with PAc alone. Given these results, it was possible to demonstrate the great capacity and scope of this adjuvant to enhance immune responses and thus provide greater protection against dental caries in mice, making it a great candidate for a future anticaries vaccine that could be used in humans [Figure 2].[12]

PAc anticaries vaccine + recombinant Flagellin protein

The study by Yang *et al.*[13] introduced recombinant flagellin (KF) as an adjuvant to the PAc anticaries vaccine, achieving a 64.2% reduction in caries formation

Table 1: Summary of studies

Authors	Type of study	Sample number	Anticaries vaccine studied	Results
Liu *et al.*[12]	*In vivo* study	32 mice	Anticaries vaccine PAc + recombinant FimH-S T protein	High protective efficacy against dental caries. PAc + FimH-S.T produced a decrease in the formation of dental caries lesions by significantly increasing PAc-specific antibodies at both mucosal and serum levels
Yang *et al.*[13]	*In vivo* study	30 mice	Anticaries vaccine PAc + recombinant flagellin second-generation protein (KFD2)	The second-generation recombinant rPAc-flagellin fusion protein (KFD2-rPAc) is a promising vaccine against dental caries. PAc + KFD2 produces fewer side effects than KF and a high protective efficacy
Rong *et al.*[14]	*In vivo* study	24 mice	DNA anticaries vaccine + attenuation of the inhibition of naturally occurring antigen protein expression by endogenous miR-9	MicroRNA-9 (miR-9) inhibits the expression of GBR and A-P antigen protein
Hao *et al.*[15]	*In vivo* study	48 mice	Salmonella typhimurium-based anticaries vaccine	Mice immunized with Salmonella-based anticaries vaccine expressing SBR and GBR under the control of CMV promoter reduced significantly *S. mutans* in comparison to those immunized with Salmonella-based anticaries
Sun *et al.*[16]	*In vivo* study	30 mice	Anticaries vaccine PAc + recombinant first-generation flagellin protein (KF)	Immunization with the first-generation recombinant rPAc-flagellin fusion protein significantly reduced dental caries lesions in mice *in vivo*; however, it produced significant side effects in mice, one of these being a systemic inflammatory response
Kausar *et al.*[17]	*In vivo* study	15 mice	Vaccine based on antigen-binding fragments (Fabs)	The antigen-binding fragments (Fabs) used in passive immunization inhibited sucrose-induced biofilm formation. In addition, the combination of Fabs of S. mutans and *S. sobrinus*, Fab SM-10, and Fab SS-2, respectively, prevented the formation of dental caries in rats *in vivo*
Bi *et al.*[18]	*In vivo* study	42 mice	PAc anticaries vaccine + chitosan-MPL/chitosan-Pam3CSK4 combinations	PAc anticaries vaccine adjuvanted by chitosan-Pam3CSK4 or chitosan-MPL combinations promoted higher immune responses in both serum and saliva of immunized mice compared with stand-alone application of PAc
Bai *et al.*[19]	*In vitro* study	-	Anticaries PAcA-ctxB vaccine in transgenic tomato plants	Transgenic tomatoes can grant an appropriate system to produce human caries antigens. In addition, they bring with them several advantages, the most outstanding of which is the absence of pain during their application, because they are edible vaccines
Ferreira *et al.*[20]	*In vivo* study	5 mice	PstS-based anticaries vaccine (recombinant PstS anticaries vaccine [rPstS] + LTK4R)	The immunization regimen with the recombinant PstS protein (rPstS) showed no significant differences with respect to the group in which the mucosal adjuvant LTK4R was coadministered. Both regimens can induce IgA antibody-secreting cells
Tavares-Batista *et al.*[21]	*In vivo* study	10 mice	Anticaries vaccine PAc + LTK4R	LTK4R-adjuvanted PAc anticaries vaccine can induce high levels of antigen-specific serum antibodies, as well as enhance antigen-specific IgA antibody production

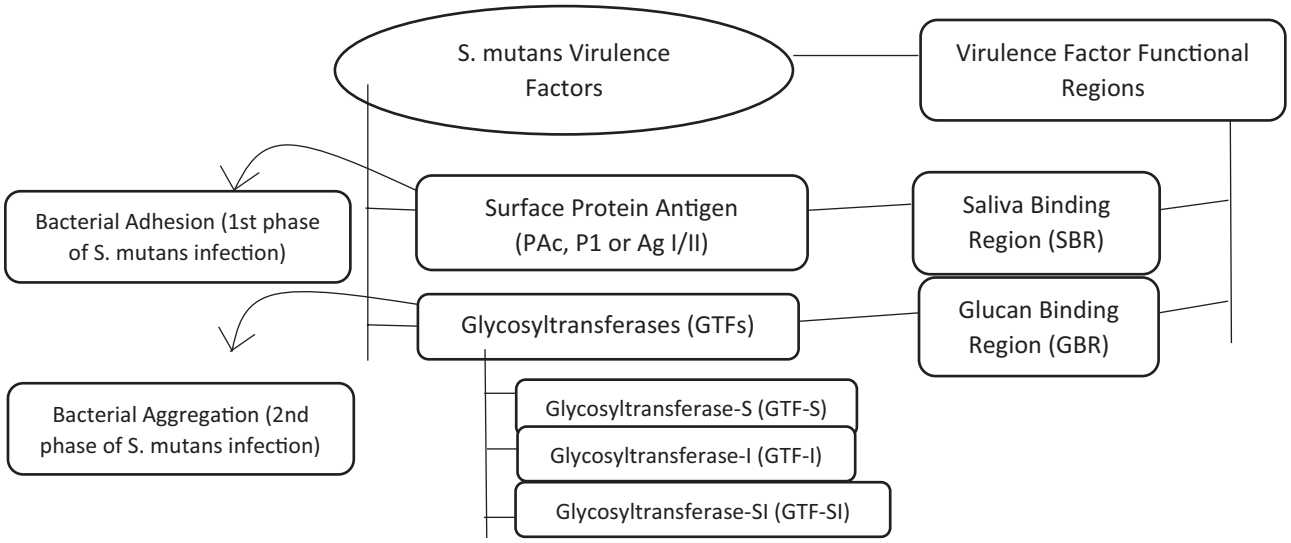


Figure 1: *S. mutans* virulence factors[5,12,15]

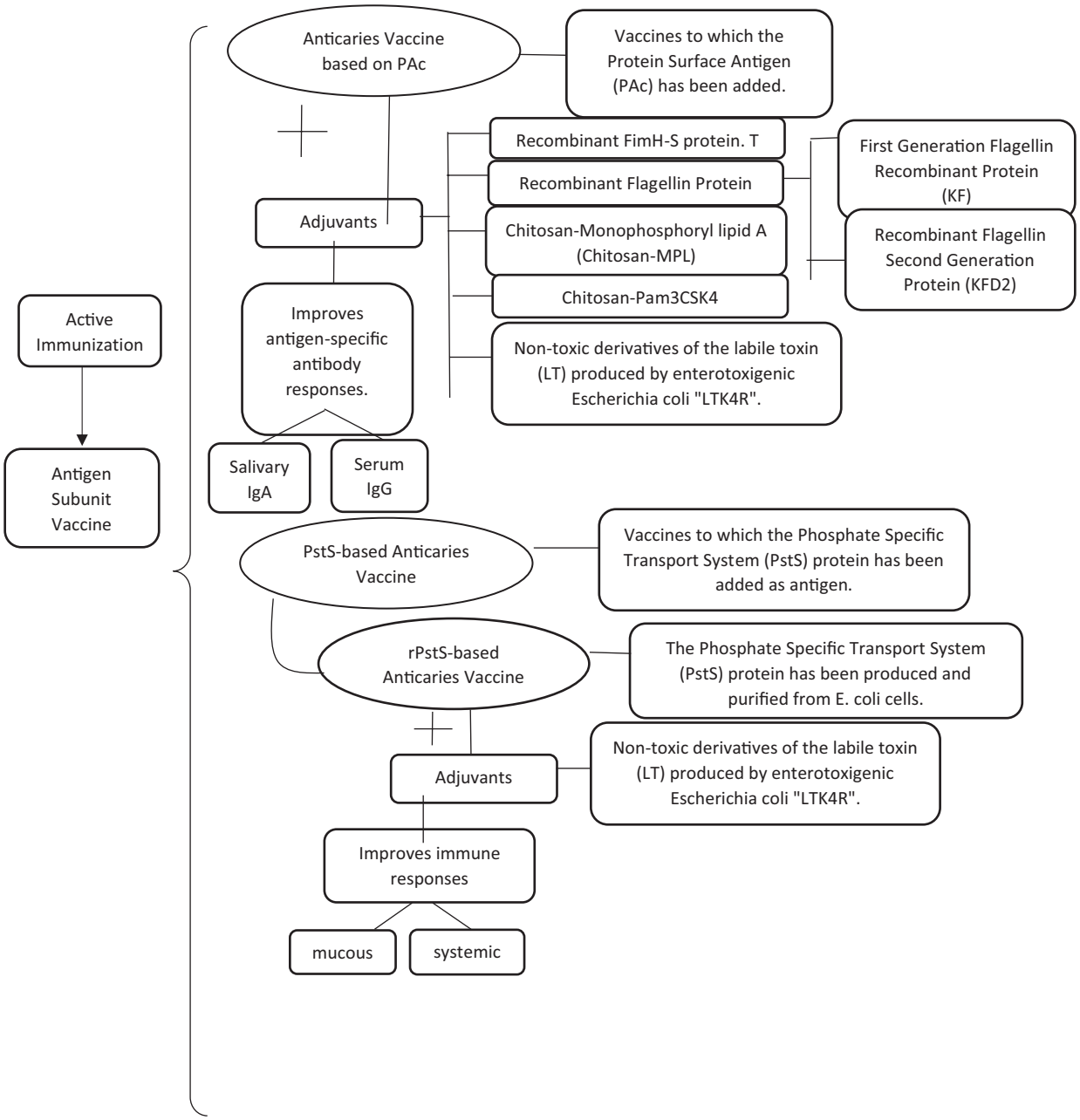


Figure 2: Antigen subunit vaccines[12,13,16,18,20,21]

in immunized rats. On the other hand, recombinant flagellin adjuvant and *Streptococcus mutans* PAc antigen did not achieve significant results when administered independently. They supported the fact that although this new recombinant rPAc-flagellin fusion protein anticaries vaccine (KF-rPAc), resulting from direct fusion of a fragment of the alanine-rich region to the proline-rich (A-P) region of *S. mutans* PAc (rPAc) with recombinant flagellin derived from *E. coli*, provided high efficacy, the KF-rPAc vaccine was not a significant vaccine for *Streptococcus mutans*; *E. coli*-derived recombinant flagellin provided high therapeutic efficacy on dental caries in immunized mice. However, it had potential side effects, the most characteristic of which was the systemic inflammatory response triggered by flagellin application.[13] Because of this drawback, the second-generation recombinant flagellin adjuvant (KFD2) was subsequently developed and demonstrated a lower systemic inflammatory response compared to its predecessor (first-generation recombinant flagellin). Finally, the second-generation recombinant rPAc-flagellin fusion protein anticaries vaccine (KFD2-rPAc) is a promising candidate for administration in humans because of the reduced side effects and high caries protective efficacy.[16]

PAc anticaries vaccine + chitosan-MPL/ chitosan-Pam3CSK4

The literature proposed the combination of two adjuvants to enhance the insufficient and relatively weak immunogenicity of the PAc anticaries vaccine. Two combinations of adjuvants have been studied for this purpose: "chitosan-monophosphoryl lipid A (chitosan-MPL)" and "chitosan-Pam3CSK4," which have been shown after application in mice to improve the speed, magnitude, and longevity of the immune responses by antibodies compared with the stand-alone application of PAc. This was due to improved levels of PAc-specific antibodies in both serum and saliva.[17-20]

PAc + LTK4R anticaries vaccine

It should be noted that *S. mutans* tooth surface adherences ability is due to its interaction between salivary agglutinin (SAG) and a surface protein belonging to *S. mutans* called PAC or P1. This surface protein P1 has two SAG binding sites called "GBR" and "P139-512" by means of which PAc can bind to this protein inherent to the acquired film.[21-25] Also, Tavares-Batista *et al.*[21] tested the administration of a PAc anticaries vaccine composed mainly of P139-512 regarding the induction of antibodies that are able to reduce the initial adhesion colonization of *S. mutans*. The results revealed quantitative increases in immune responses at both mucosal and systemic levels, as well as a decrease in the adhesive properties of *S. mutans* and leading to a marked decrease in the first stage of colonization of these microorganisms on tooth surfaces.[21]

PstS-based anticaries vaccines

The "phosphate specific transport system (PstS)" protein[26] of *S. mutans* as well as PAc has also been integrated as a target antigen in different anticaries vaccines, as it plays an important role in dental caries physiology and pathogenesis.[20,25] However, as with PAc, the immunogenicity induced by the PstS protein can be enhanced using adjuvants, of which LTK4R has been the most extensively studied.[20]

Recombinant PstS anticaries vaccine (rPstS) + LTK4R

The study by Ferreira *et al.* reported on the use of a recombinant form of the PstS protein (rPstS), which was originated from *E. coli* cells, in combination with the mucosal adjuvant "LTK4R." The administration of recombinant PstS (rPstS) protein adjuvant "LTK4R" was shown to quantitatively enhance antibody responses by controlling bacterial cell adhesion to tooth surfaces in a sample of mice *in vivo*.[20]

Recombinant antigen vaccines

PAcA-ctxB anticaries vaccine in transgenic tomatoes

Bai *et al.* in their study constructed a fusion vaccine or recombinant vaccine called PAcA-ctxB, obtained by fusing the A region of the gene encoding the PAc protein (belonging to Streptococcus mutans) and the gene encoding the cholera toxin subunit B followed by subsequent integration of these into the genome of transgenic tomatoes. This research also highlights the advantages of transgenic plant vaccines, including the cost-effectiveness of production, the ease of storage,[19] and the absence of pain (because they are edible vaccines that do not require the use of needles for application).[24] Also, both mucosal and humoral immune responses stimulation without the presence of side effects in animals has been described. This *in vitro* study indicated the usefulness of a genetically modified tomato, i.e., the transgenic tomato, in the expression of dental caries antigens[19] [Figure 2].

Live attenuated vaccines

Salmonella typhimurium-based anticaries vaccine

Firstly, although the study by Huang *et al.*[23] obtained acceptable results, it did not give us the guarantee of expressing long-lasting antigens in large quantities to induce an adequate immune response from the host. A mice sample was administered a Salmonella-based vaccine expressing the saliva-binding region (SBR) under the control of a single promoter. Considering this problem, Hao *et al.*[15] created a Salmonella-based vaccine that expressed not only the SBR but also the GBR. A dual promoter system, also known as a polyvalent vaccine, was formed under the control of two promoters. The results of the latter research demonstrated the great capacity of this system (dual promoter system) to induce significantly higher and long-lasting serum IgA and IgG antibody responses, which is explained by the persistent and higher expression of antigen, which could be maintained for up to 4 weeks in mice immunized with this system [Figure 3].

Cold-adapted influenza virus-based anticaries vaccine

The study by Yang *et al.*[13] theoretically supports a new vaccine candidate called "cold-adapted influenza virus-based influenza vaccine for anticaries." This new proposal is based on the well-known "cold-adapted influenza vaccine" (approved by the FDA), which has been used in humans for more than 15 years with adequate safety rates. In addition, the "cold-adapted influenza vaccine" brings with it several advantages, including intranasal administration in the form of an aerosol that facilitates inoculation because of the absence of pain, prolonged immune responses especially at the mucosa, the low cost of production that makes it available to all, and the progress in terms of genetic techniques for its modification. For all these reasons, they concluded that the "cold-adapted influenza vaccine" has great potential to be used as a vector for a new and future anticaries vaccine, and the *in vivo* research in humans already carried out with "cold-adapted influenza viruses" makes it possible that

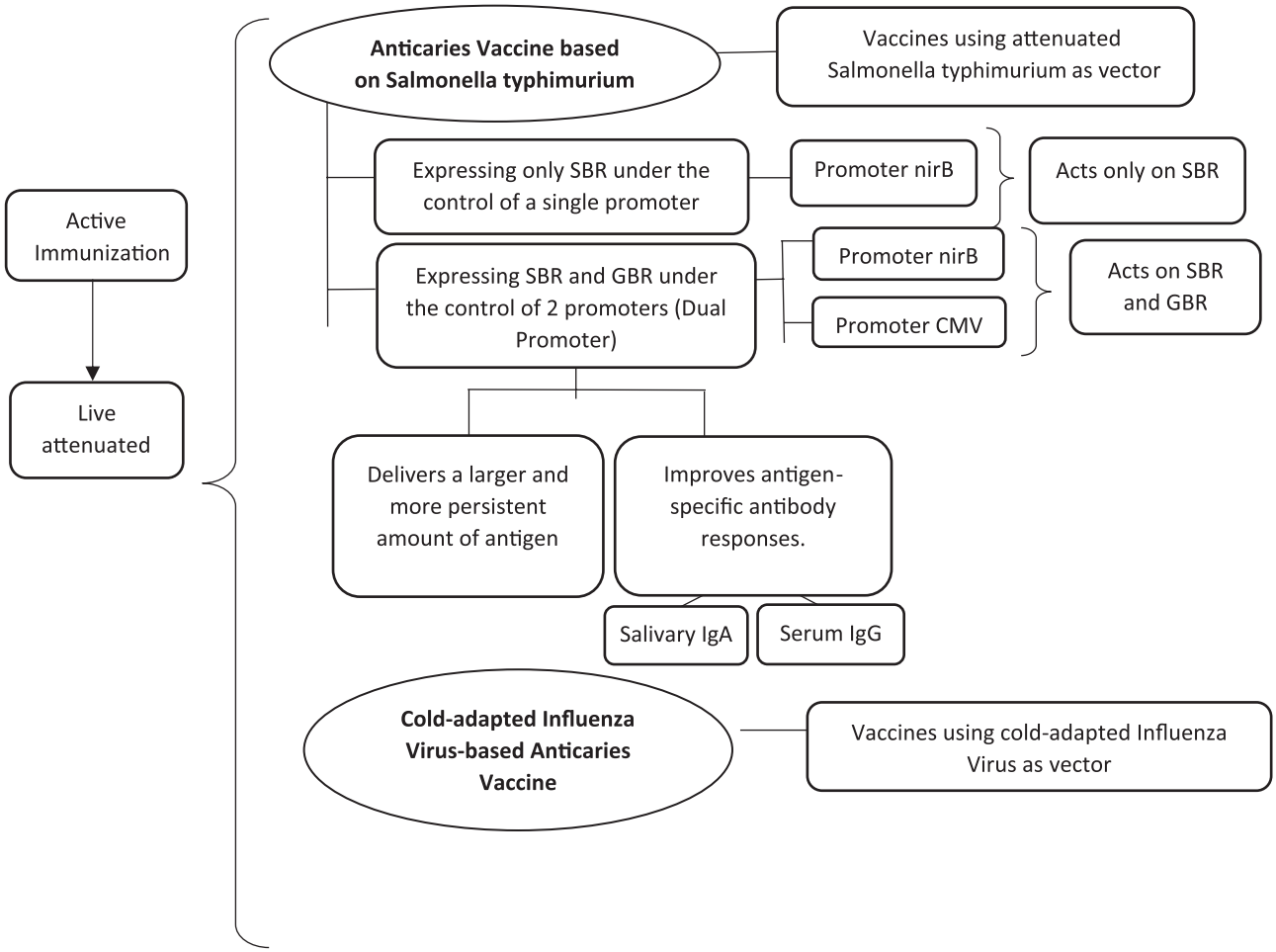


Figure 3: Live attenuated vaccines[7,15]

the future anticaries vaccine will not only be tested in animals but also in humans[7] [Figure 3].

Passive immunization

Vaccine based on antigen binding fragments (Fabs)

The antigen binding fragments (Fabs) used in passive immunization have been shown to bind strongly to *S. mutans* and *S. sobrinus* (main etiological dental caries agents) and block the biofilm formation produced by these cariogenic bacteria, thus preventing the formation of carious lesions in rat samples. In addition, this vaccination approach brings with it the advantages of low production cost, increased tissue penetration, as well as greater safety and ease of application compared with active immunization strategies[17] [Figure 4].

Attenuation of endogenous microRNA inhibition

The study by Rong *et al.*[14] explored new approaches to produce an enhanced immune response induced by anticaries DNA vaccines, the latter having as antigens glucosyltransferase-I and PAc, whose functional regions are the well-known "glucan-binding region (GBR)" and "alanine- and proline-rich regions (A-P)," respectively. Endogenous microRNA-9 (miR-9) inhibits protein expression of the GBR and A-P antigens in these vaccines, so the attenuation of inhibition by this member of the microRNA family resulted in increased protein expression of these antigens, which was beneficial. That said, coimmunization of a DNA anticaries vaccine with nonendogenous miR-9 to produce an attenuation of the inhibition produced naturally by endogenous miR-9 significantly improved both the protein expression of the antigens (GBR and A-P) and the immunogenicity of this type of vaccine, thus generating an improved immune response in mice *in vivo*[14] [Figure 5].

Discussion

The wide variety of anticaries vaccines that have been developed over time has aimed to achieve or induce a potent antibody response against the functional regions, SBR and GBR, of the virulence factors PAc and GTFs, respectively, in order to inhibit the colonization of *S. mutans* on the tooth surface and thus to reduce dental caries.[15]

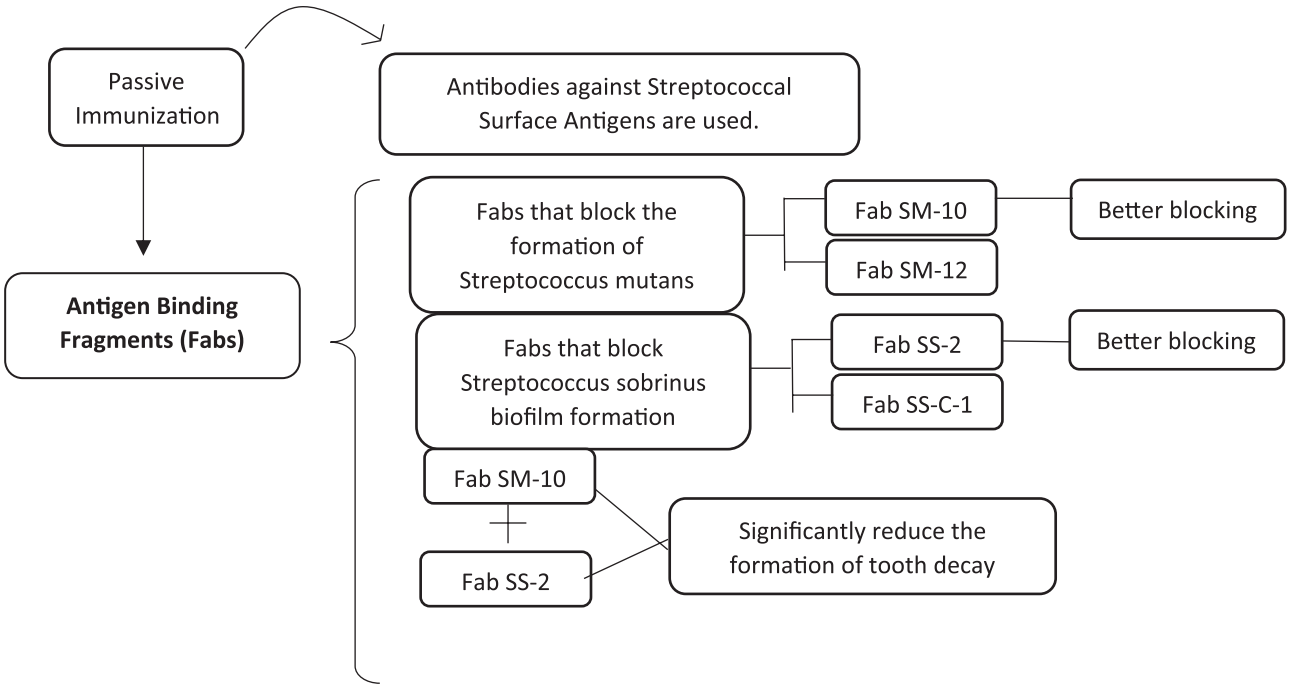


Figure 4: Vaccines based on antigen-binding fragments[17]

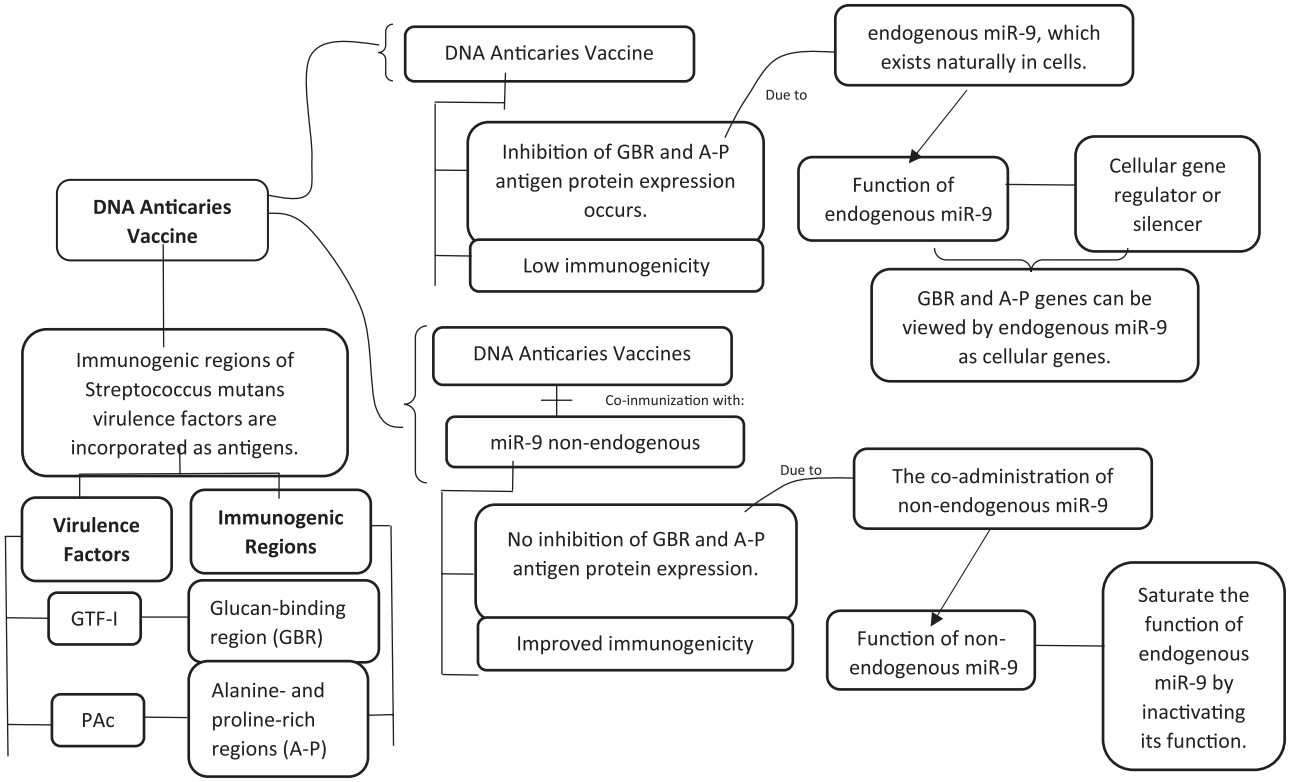


Figure 5: DNA anticaries vaccines + endogenous miR-9 inhibition[14]

It has been shown that the protein surface antigen (PAc) integrated into anticaries vaccines is a great candidate for this purpose; however, PAc anticaries vaccines cannot be applied without the prior inclusion of adjuvants in the vaccine, mainly because of the low immunogenicity of PAc alone. Therefore, the development of adjuvants for integration into PAc vaccines is of great importance to enhance antigen-specific antibody responses (S-IgA antibodies)[12] as well as to ensure their long duration in the oral cavity.[20] One of the most promising adjuvants

at present is recombinant FimH-S T protein, which when mixed with PAc induces 4.5–23.9 times higher salivary IgA (S-IgA) response compared with the application of PAc alone, thus providing a 46.2% reduction of dental caries in immunized rats.[12] Another frequently investigated adjuvant is the first- and second-generation recombinant flagellin (KF and KFD2) with the second generation being the most investigated because of low systemic inflammatory responses and a strong rPAC-specific antibody response, which provides high protection against dental caries.[13,16] Chitosan-MPL and chitosan-Pam3CSK4R are also highly promising adjuvants, as they significantly improve the speed, magnitude, and longevity of the specific antibody response when administered together with protein surface antigen (PAc), thus achieving a protective effect against *S. mutans*, which is not the case when working with PAc alone.[18] Other adjuvants are the derivatives of the labile toxin (LT) produced by enterotoxigenic *E. coli* among which LTK4R stands out; this adjuvant is considered one of the most potent and effective alternatives available to date; this LT derivative increases quantitatively (in number) the production of antibodies both at serum (serum IgG) and mucosal (salivary IgA) level.[21]

Within the antigen subunit vaccines, there is also the anticaries vaccine based on the phosphate-specific transport system protein, better known as PstS (another important antigen of *S. mutans*), which when purified from *E. coli* cells to become recombinant PstS (rPstS) and subsequently adjuvanted by a nontoxic derivative of a LT produced by enterotoxigenic *E. coli* enterotoxin results in decreased adherence of *Streptococcus mutans* on tooth surfaces.[20]

Recombinant antigen vaccines have also been described in the scientific literature, with the PAcA-ctxB anticaries vaccine in transgenic tomato plants being the most prominent within this group. This vaccine was shown to be useful for the human dental caries antigen production, as well as having the advantages of the cost-effectiveness of production, the ease of storage, and the absence of pain during application, because of the fact that this type of vaccine is edible.[19]

Live attenuated vaccines, as well as the previously mentioned antigen subunit vaccines, have also been studied in recent years. Within this group, the single promoter attenuated *Salmonella* vaccine, considered a monovalent vaccine, and the dual promoter attenuated Salmonella vaccine, considered a multivalent vaccine, stand out, the latter being the one that produces a greater immune response by antigen-specific IgA and IgG antibodies, which can be explained due to the integration of two promoters instead of one, thus giving it the possibility to act in the two phases of infection by *S. mutans* infection, initial colonization, and accumulation on the tooth surface, in which the virulence factor functional regions (SBR and GBR, respectively) are of great importance.[15] Despite this, subsequent studies indicate the possible damage that the vector (attenuated Salmonella typhimurium) may receive during its journey from the mouth, where it is administered to the intestinal mucosa, which is considered to be the inductor site, which is why the formulation of the "cold-adapted influenza virus-based anticaries vaccine" has been proposed theoretically. This vaccine, when administered via the intranasal route, is a much more convenient alternative to induce the S-IgA immune response, because of the relative ease and absence of pain during application as well as the presence of fertile mucosal lymphoid tissue and easy transport of immune factors to the salivary glands at the site of application.[7]

Passive immunization, in contrast to active immunization as discussed above, is characterized by the administration of nonhuman antibodies against *S. mutans* antigens. Within this group, the vaccine based on antigen-binding fragments (Fabs), which have been shown not only to inhibit biofilm formation of *S. mutans* but also of *S. sobrinus*, stands out.[17]

Finally, the improvement of the immunogenicity of DNA vaccines by attenuating the inhibition of naturally occurring antigenic protein expression by endogenous miR-9 has been studied recently, but very few studies have been done in this regard; however, the attenuation of antigen protein inhibition by blocking the function of endogenous miR-9 has been shown to result in improved immunogenicity of anticaries DNA vaccines.[14]

One of the limitations of this narrative review is the limited number of *in vivo* studies in humans, most of which were conducted in animals (rats or mice). In addition, the language in which all current articles are written can also be considered a limitation.

Conclusions

Based on this literature review, there are currently several types of vaccines targeted and focused on dental caries disease (from active immunization to passive immunization), some more than others exhibiting better performance in terms of reducing the inherent pathogenicity of acid-gene bacteria of the oral cavity such as *S. mutans*; however, to date no vaccine has been launched on the pharmaceutical market, the main reason being the difficulty in inducing and maintaining antigen-specific antibodies in the salivary fluid, as well as the possible side effects that some of them generate on the host. Therefore, more *in vivo* studies (in mice) are needed to solve these drawbacks, so that in the not-too-distant future studies in human populations can begin to be conducted.

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Conflicts of interest
There are no conflicts of interest.

Author contributions
SC and FMT conceived the ideas. SC, FMT, AMD, RM, CMV, and JBO contributed to data collection. SC and FMT analyzed the data. SC, FMT, AMD, RM, CMV, and JBO led the writing. FMT, AMD, RM, CMV, and JBO critically revised the article and gave final approval.

Ethical policy and institutional review board statement
Not applicable.

Patient declaration of consent
Not applicable.

Data availability statement
As this study is a literature review, we did not use a statistical database, but direct access articles in PubMED and Scopus. The data that support the study results are available from the author Dr. Frank Mayta-Tovalino, e-mail: fmaytat@cientifica.edu.pe, on request.

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