Emerging horizons in periodontal vaccine development: From concept to clinical translation (Review)

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Abstract. Periodontal disease is a multifactorial chronic inflammatory disease of tooth-supporting tissues that initiates with a dysbiotic microbial biofilm and a dysregulated host immune response. Conventional treatment with mechanical debridement and antimicrobials is beneficial only in the short term and does not address the underlying immune pathological process or prevent recurrence. Currently, one of the novel approaches for combating periodontal disease involves preventive and therapeutic strategies, by modulating the host immune system in order to safeguard them over a prolonged period of time from periodontal infection caused by *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Treponema denticola* and *Prevotella intermedia*, is the utilization of periodontal vaccines. Recent advances in reverse vaccinology, epitope prediction using artificial intelligence, lipid nanoparticle delivery systems and messenger RNA vaccines as a delivery platform have facilitated periodontal vaccine development. Several immunogenic responses have been demonstrated in animal studies and early human trials, such as blocking adherence and colonization with neutralizing antibodies. There are, however, challenges, such as antigenic variability, potential cross-reactivity with host tissues and the need for safe and sustained immune activation in the oral setting. However, recent advances in areas, such as molecular biology, immunogen design, bioinformatic approaches, mucosal adjuvant systems and nanoparticle-based delivery technologies may render these confounders obsolete. The present review aimed to present a comprehensive and integrated overview of periodontal vaccine development that merges classic vaccine development methods with emerging technologies, as well as translation challenges and clinical perspectives. Periodontal vaccines may provide immunological protection against periodontal disease, support a paradigm shift away from mechanical plaque control, and offer long-term, host-modulated protection.

Contents

1. Introduction

Periodontal disease is widely recognised as a complex, multifactorial inflammatory disorder that targets the tooth-supporting tissues. The disease process is triggered by a significant shift in the subgingival microflora, which elicits a destructive, hyperactive host immune response that ultimately leads to progressive attachment loss and tooth loss. Within these dysbiotic microbial biofilms, keystone and accessory pathogens, including *Porphyromonas gingivalis* (*P. gingivalis*), *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*), *Tannerella forsythia* (*T. forsythia*), *Treponema denticola* (*T. denticola*), *Prevotella intermedia* (*P. intermedia*),

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Fusobacterium nucleatum (*F. nucleatum*) and *Campylobacter rectus* utilise virulence factors, such as lipopolysaccharides (LPS), proteases and fimbriae to exploit host immunity and sustain localised tissue degradation (1).

While conventional mechanical debridement via scaling and root planing, combined with adjunctive antimicrobials, remains the current clinical standard, it lacks long-term immunoprotection, and rising global antibiotic resistance limits repeated drug delivery. Thus, the preventive treatment of clinically healthy individuals with periodontal vaccines that inactivate pathogens prior to the development of clinical disease represents a critical paradigm shift (2). The present review summarises the classical milestones of vaccinology, and combines the current state-of-the-art in mucosal immunobiology, the oral-gut-immune axis, biomaterial nanocarriers and artificial intelligence (AI)-driven reverse vaccinology to chart the path ahead for clinical applications (3,4).

Literature search strategy and methodological transparency. The present review was conducted through a structured literature search to ensure methodological transparency. Relevant articles were identified using electronic databases, including PubMed, Scopus and Web of Science. The search was performed using pre-defined keywords related to periodontal vaccine development, periodontal pathogens and host immune responses. Studies published between 1985-2026 were considered; the selection process involved screening titles and abstracts, followed by full-text evaluation. Studies were included if they were relevant to periodontal vaccine research, including *in vitro*, animal and clinical studies.

2. The oral-gut axis: Systemic immunity and periodontal pathogens

The oral-gut axis is a key modulator of systemic and immunological processes, as well as periodontal vulnerability. In normal physiological circumstances, the gut microbial community is in a state of eubiosis (microbial diversity, metabolic balance, balance among host and micro-organisms, promoting immune homeostasis and maintaining the integrity of the intestinal barrier), while during dysbiosis, there is a qualitative and quantitative change in microbial community structure, the loss of beneficial micro-organisms, increases in potentially pathogenic micro-organisms and alterations in normal microbial functions, ultimately leading to a predisposition of the host toward inflammatory and chronic diseases (4,5). In addition, dysbiosis allows the systemic delivery of bacterial components, such as LPS, into the circulation, which also affects the process by which oral mucosal dendritic cells are primed, thereby accelerating tissue destruction caused by subgingival pathogens (4,5). Thus, the control of this axis is crucial for optimising the efficacy of future periodontal vaccines (5,6).

3. Historical evolution of periodontal vaccine research

The developments in microbiology, immunology and molecular biotechnology have paralleled the evolving concept of periodontal disease immunisation. Early experiments performed in the 1920s and 1930s employed unrefined extracts of oral micro-organisms; however, none were taxonomically specific, standardised, or provided information on the mechanisms of periodontitis (7). The advances in periodontal vaccines can be subdivided into four stages, as follows:

i) 1940s to 1960s: The first phase involved whole-cell killed or attenuated bacterial formulations assigned to early suspected pathogens, such as *A. actinomycetemcomitans*. These formulations did improve systemic antibody levels; however, they lacked consistency and caused local inflammatory effects, limiting their clinical use (7,8).

ii) Subunit vaccines, shifted during the second phase (1970s to 1980), in the wake of understanding of periodontitis as a polymicrobial biofilm disease. Specific surface virulence factors have been purified from *P. gingivalis*, and organisms lacking these factors fail to elicit a protective immune response in animal models (9).

iii) Third phase (1990s to 2000s): Developed recombinant DNA technology and molecular cloning that allowed for the precise production of purified bacterial antigens, such as gingipains produced by *P. gingivalis*. This period established the foundation for the use of synthetic peptide antigens, DNA vaccines and mucosal vaccine strategies (10).

iv) Current phase (2010s to present): This phase is directed towards the precise design of antigens. Novel approaches use the combined technologies of computational immunoinformatics, reverse vaccinology, sophisticated multi-epitope targeting, and nanoparticle technologies to enhance protection at mucosal sites and achieve ideal safety profiles (7-9).

4. Immune system, immune molecules and immune cells in association

Understanding the local immune network within the periodontium will be critical for the development of an effective periodontal vaccine. Pathogen-associated molecular patterns displayed by periodontal pathogens are primarily recognised by Toll-like receptors (TLRs) on resident epithelial cells, fibroblasts and infiltrating leukocytes, which trigger innate and adaptive immune responses to periodontal antigens through activation of processing and migration of professional antigen-presenting cells (APCs), in particular dendritic cells and macrophages (11). Exposed periodontal tissue breakdown depends on the status of the cytokine balance, as follows:

Pro-inflammatory cascade. Upon activation and pathogen stimulation, the secretion of IL-1 superfamily members, as well as TNF-α and IFNγ is markedly increased; these secretions, under conditions of imbalance, are factors involved in osteoclastogenesis and alveolar bone loss (11,12).

Anti-inflammatory regulation. Counter-regulatory cytokines, specifically IL-10 and TGF-β, function to suppress excessive inflammatory responses, facilitating tissue remodelling and the preservation of periodontal attachment (12). These observations are consistent with broader Toll-like receptor-mediated immunomodulatory mechanisms reported in inflammatory and immune-mediated diseases (13,14).

To achieve therapeutic viability, vaccine design needs to bypass these destructive pro-inflammatory loops. Formulations must employ targeted antigens and optimised adjuvants to selectively stimulate protective immunological

memory predominantly secretory IgA (sIgA) and neutralising IgG, thereby shifting the immune response toward a regenerative phenotype rather than a destructive, hyper-inflammatory state (11-14).

5. Pathogenicity and virulence determinants of major periodontal pathogens

Periodontitis is sustained by a dysbiotic polymicrobial biofilm, in which specific keystone and accessory pathogens express distinct virulence determinants that drive colonisation and tissue destruction. As these molecules dictate disease pathogenesis and are highly immunogenic, they serve as the primary antigenic targets for current periodontal vaccine development (15-17). These pathogens are the following:

P. gingivalis. As regards virulence, as a keystone pathogen, *P. gingivalis* manipulates host immunity through its cysteine proteases (gingipains: RgpA, RgpB and Kgp), which degrade host structural proteins and dysregulate cytokine signalling. It also utilises fimbriae (FimA and Mfa1) for tissue attachment, capsular polysaccharides and LPS for immune evasion, and outer membrane vesicles to deliver proteases deep into periodontal tissues (15,16).

Accessory and associated pathogens. *A. actinomycetemcomitans* secretes potent leukotoxins (LtxA) and cytolethal distending toxin (CDT) to induce apoptosis in host leukocytes, neutralising local surveillance. *T. forsythia* utilises its surface layer (S-layer) proteins and Mi09 proteases to delay host recognition, while the motile spirochete *T. denticola* leverages dentilisin to degrade extracellular matrix components. *F. nucleatum* and *P. intermedia* express specialised surface adhesins that serve as structural bridges, stabilising the polymicrobial architecture (16).

6. Antigenic targets in periodontal pathogens

Characterising highly immunogenic and neutralising virulence determinants is a key prerequisite for the development of immunoprophylactic strategies. Research has mainly focused on the major periodontopathogens, *P. gingivalis*, *A. actinomycetemcomitans* and *T. forsythia*. These organisms each have surface molecules of unique structure, which enable them to colonise their host, subvert the host immune response and cause localised tissue destruction, and therefore constitute potential candidate antigens (18-23). The key antigenic targets are summarised in Table I, including their biological roles, experimental vaccine vectors and preclinical vaccine efficacy data.

Pathogen-specific antigenic profiles

P. gingivalis. *P. gingivalis* has been described as a keystone pathogen, meaning that it has several highly antigenic surface molecules. In addition to the structure-determinant FimA and Mfa1 fimbriae, which mediate primary events of tissue adhesion and the highly destructive gingipains. These molecules aid bacterial aggregation and adherence to erythrocytes, and targeting the conserved peptide epitopes consistently elicits protective mucosal responses. In addition, outer membrane proteins, such as OMP85 and RagB, and modified LPS formulations are being tested to trigger active, non-destructive systemic and mucosal antibody responses while preventing hyper-inflammatory cytokine loops (18-21).

A. actinomycetemcomitans. Targeting the *A. actinomycetemcomitans* vaccine focuses on neutralising the secretome and cell-wall proteins associated with rapidly progressive periodontitis presentations. The primary target is leukotoxin (LtxA); in these cases, toxoid-based vaccines elicit neutralising antibodies that prevent leukocyte lysis, thereby maintaining local immune surveillance. In addition, recombinant vaccines against the CDT components are useful for reducing the arrest of the host cell in its cell cycle, and targeting outer membrane proteins (Omp29, Omp100) and fimbrial adhesins is effective in inhibiting bacterial adherence and, therefore, subgingival colonisation (18,22).

T. forsythia. *T. forsythia* is characterised by distinctive surface structures, which are suitable targets. BspA_{lr} serves as an immunodominant protein for epithelial attachment and TLR activation, and its availability as a recombinant protein demonstrates substantial promise to confer protection. Furthermore, the structural layer proteins of the crystal-like architecture are located on the exterior, rendering them available to the immune system for recognition as an external glycoprotein coat. As they are highly stable, they are an excellent target to elicit robust and sustained humoral protection. The emergence of sialidases and proteases that catalyse the degradation of host glycoproteins in localised activities is also a target (23,24).

Next-generation multivalent and conserved antigen strategies. Multivalent vaccine strategies have been proposed to address the polymicrobial nature of periodontal disease by targeting multiple virulence-associated antigens .These platforms aim to provide broad cross-protection across the subgingival microbiome by combining key antigenic epitopes from different periodontal pathogens (23).

At the same time, investigators are identifying highly conserved, cross-reactive antigens, such as bacterial heat shock proteins (HSP60) and outer membrane proteins, which are conserved across all bacteria. The incorporation of these highly conserved antigenic determinants, which aim to optimise immunological memory, maximise biosecurity and provide full protection against polymicrobial dysbiosis (19-25).

7. Immunological mechanisms and contemporary vaccine platforms

The main goal of periodontal vaccination is to establish long-lasting, antigen-specific immunologic memory that neutralises subgingival virulence factors, prevents bacterial colonisation, and reduces the osteolytic inflammatory cascade. To attain this site-specific protection, a multifaceted response from the innate and adaptive arms has to be coordinated, namely one that relies heavily on how antigens are presented and the immune cells at the mucosal site (26,27). The clinical translation of these vaccines depends critically on five basic parameters: The selection of an antigen, platform architecture, the formulation of an adjuvant, the route of administration and host immune competence.

Table I. Comparative overview of major antigenic targets explored for periodontal vaccine development.

Pathogen	Antigen	Function/virulence mechanism	Vaccine type investigated	Protective efficacy in animal models	(Refs.)
Porphyromonas gingivalis	FimA fimbriae	Bacterial adhesion, colonization, biofilm formation	Recombinant protein, DNA vaccine	Elevated IgG/IgA; reduced bacterial colonization and alveolar bone loss	(8,22)
	Gingipains (RgpA, RgpB, Kgp)	Proteolytic enzymes driving tissue destruction and immune evasion	Subunit vaccine	Neutralization of protease activity; attenuated periodontal destruction	(18,19)
	Hemagglutinins (HagA/HagB)	Adhesion to host tissues and erythrocytes	Peptide vaccine	Enhanced mucosal immune responses; protection against infection	(10,39)
	Outer membrane proteins (OMP85, RagB)	Host-cell interaction and immune stimulation	Recombinant protein vaccine	Robust antibody response; reduced bacterial burden	(8,39)
Aggregatibacter actinomycetemcomitans	Leukotoxin (LtxA)	Leukocyte lysis and localized immune suppression	Toxoid/subunit vaccine	Protection of host immune cells; reduced disease severity	(10,26)
	Cytolethal Distending Toxin (CDT)	Host cell-cycle arrest and tissue injury	Recombinant protein vaccine	Attenuated toxin-mediated cellular damage	(10,26)
	Omp29/Omp100	Adhesion and invasion of host barrier tissues	Recombinant subunit vaccine	Protective antibody responses *in vivo*	(10,26)
Tannerella forsythia	BspA protein	Epithelial adhesion and activation of inflammatory loops	Recombinant protein vaccine	Blunted inflammatory response; reduced bacterial colonization	(10,26)
	S-layer proteins	Host interaction and protective surface shielding	Subunit vaccine	High immunogenicity; protective adaptive immune responses	(10,26)

To overcome mucosal tolerance in the oral cavity, newer approaches include combining machine learning with immunoinformatics via reverse vaccinology to rapidly screen bacterial genomes. Compared to conventional culture guarantees, this strategy circumvents their need to detect those non-allergenic, immunodominant linear and/or conformational epitopes that are highly conserved (27-30).

The use of modern formulations that optimise prime-boost protocols and targeted delivery forces the helper T-cell response to deviate from a bone-resorptive Th1/Th17 profile towards a regulatory, neutralising humoral phenotype. This polarisation of this type is targeted to control alveolar bone destruction driven by the host's immune response and to provide long-term, highly specific immunoprophylaxis against periodontal pathogens (27-30).

8. Vaccine delivery systems and mucosal adjuvants

In general, traditional systemic immunisation fails to induce local protective immunity against periodontitis. To achieve effective immunoprophylaxis, it is essential to target the common mucosal immune system to induce the production of localised secretory IgA (sIgA) and the transudation of IgG subgingivally via sublingual, intranasal, or topical gingival pathways (31,32).

To avoid the 'fast enzymatic degradation' of soluble antigens in the oral cavity, these vaccine architectures are mostly based on advanced particulate, polymeric, lipidic and microbial vector delivery systems. The technical parameters of these platforms and their abilities to protect vulnerable payloads, retain them in the mucous layer and improve uptake by APCs are summarised in Table II.

Optimisation for safety is achieved by using modern formulations that have shifted away from classic bacterial enterotoxins toward well-defined synthetic molecular adjuvants, such as CpG oligodeoxynucleotides and monophosphoryl lipid A (MPLA) (33-36). These well-defined bio-adjuvants, when complexed with lipid nanoparticles (LNPs), provide the necessary immunomodulatory platform to protect the messenger RNA (mRNA) payload and enable rapid antigen expression in the intracellular space, which is necessary for long-term immunoprophylaxis via the oral route (37-39).

9. Preclinical evaluation: Experimental models and translational barriers

Preclinical *in vivo* studies are essential for establishing the safety, immunogenicity and efficacy of candidate periodontal vaccines prior to clinical translation. Employing animal models to mimic the complex host-pathogen interactions of human periodontitis, evaluating different vaccine formats assesses their ability to modulate the immune system, leading to decreased subgingival bacteria and prevention of progressive alveolar bone resorption (8).

Based on the recent preclinical characterisation of nanoscale mucosal vaccination in the murine periodontitis model, the recent study by Qin *et al* (40) demonstrated that sublingual vaccination with nano-programmable DNA scaffolds yields a substantial increase in saliva sIgA levels. This targeted immunoprophylaxis effectively reduces subgingival colonisation by periodontal pathogens, locally suppresses the periodontal inflammation cascade, and ultimately reduces progressive alveolar bone loss *in vivo* (40).

Experimental periodontitis is typically induced by either the oral or subgingival inoculation of major pathogens, such as *P. gingivalis,* or by ligature placement around the teeth to allow polymicrobial plaque to accumulate. In all these models, different immunoprophylactic strategies have demonstrated considerable therapeutic promise. Animal studies have consistently shown increased systemic IgG and mucosal IgA levels, decreased pro-inflammatory cytokine cascades and reduced alveolar bone loss following the administration of subunit or recombinant formulations containing target proteins, including *P. gingivalis* fimbriae, gingipains and outer membrane proteins, compared to the placebo groups (8). At the same time, some studies have used nucleic acid platforms based on DNA vaccine constructs that express fimA (40) or gingipain genes (41), which can induce potent, long-lasting cellular and humoral immunity. Comparative studies highlight that the route of administration is a key factor in determining protective effectiveness, as intranasally administered fimbrial proteins, in combination with mucosal adjuvants, are effective in inducing a protective sIgA response in rodents that protects against subgingival colonisation and the subsequent tissue degradation (41,42).

The extrapolation of vaccine efficacy from experimental animals to human clinical trials is one of the greatest challenges due to inherent biological differences between species (43-45). Each of these unique characteristics can influence the choice of profile, and is thus critical for translating and simulating models of human periodontal disease, as outlined in Table III.

The issue with the development of a periodontal vaccine is that, traditionally, endpoints have been mechanical or radiographic measurements of alveolar bone loss and quantitative changes in subgingival bacterial counts. The field should focus on validating non-invasive, standardised surrogate vaccine efficacy biomarkers to facilitate successful human translation (45,46).

Therefore, future protocols should include quantitative measurements of both antigen-specific sIgA in the saliva and IgG in the gingival crevicular fluid. These panels can be standardised by monitoring localised inflammatory mediators (IL-1β and TNF-α), the RANKL/OPG ratio, matrix metalloproteinases and systemic bone turnover markers, such as C-terminal telopeptide of type I collagen, thereby enhancing the comparability of studies and helping fill the gap between animal and human clinical trials (45,46).

10. Biological and adjunctive preventive strategies

The multifactorial aetiology of periodontitis cannot necessarily be treated within a framework of 'monotherapy' through targeted vaccination to achieve lasting periodontal stability. Prevention strategies thus include immunological interventions, as well as microbiome-targeted interventions, to create an oral environment that is resistant to pathogen recolonization (30,46-48). The active suppression of keystone pathogens by probiotics occurs through the competitive exclusion and secretion of bacteriocins (49,50). Probiotic strains, such as *Lactobacillus reuteri*, *Lactobacillus rhamnosus* and

Table II. Comparison of mucosal delivery systems and adjuvants used in periodontal vaccine development.

Delivery system/adjuvant	Material	Particle Size Range	Target Site	Induced Immune Response	Limitations	(Refs.)
Liposomes	Phospholipid bilayer vesicles	50-5,000 nm	Oral and nasal mucosa	Humoral and cellular immunity; enhanced antigen uptake	Limited stability; relatively high production cost	(31,32)
Polymeric nanoparticles (PLGA)	Poly(lactic-co-glycolic acid)	100-1,000 nm	Dendritic cells, mucosal tissues	Sustained antigen release; strong cellular and humoral responses	Manufacturing complexity; potential burst release effect	(31,32)
Chitosan nanoparticles	Chitosan biopolymer	50-500 nm	Oral mucosa	Enhanced mucosal adhesion and secretory IgA responses	Variable stability and drug-loading capacity	(31,32)
Microspheres	Biodegradable polymers	1-100 μm	Oral and gastrointestinal mucosa	Controlled antigen release; prolonged immune stimulation	Reduced penetration through mucosal barriers	(31,32)
Lipid nanoparticles (LNPs)	Ionizable lipids, cholesterol, phospholipids	60-150 nm	Antigen-presenting cells	Efficient nucleic acid delivery; robust humoral and cellular immunity	Strict cold-chain requirements; formulation challenges	(37,38)
Tetrahedral framework nucleic acids (tFNAs)	Programmable self-assembled DNA nanostructures embedded in bioadhesive MixPEG hydrogel	Nanoscale (scaffold architecture)	Sublingual mucosa/local dendritic cells	Enhanced salivary sIgA production; targeted DC activation; suppressed *P. gingivalis* colonization	Complex structural engineering; long-term degradation kinetics require further optimization	(40)
Recombinant *Lactobacillus* vectors	Live bacterial vectors	1-5 μm	Oral and gastrointestinal mucosa	Strong mucosal immunity and antigen presentation	Biological safety and stringent regulatory concerns	(33)
Adenoviral vectors	Recombinant viral vectors	70-100 nm	Mucosal and systemic tissues	Potent cellular and humoral immune responses	Pre-existing host vector immunity	(33)
Cholera toxin B subunit (CTB)	Bacterial protein adjuvant	N/A	Mucosal surfaces	Strong secretory IgA and T-cell responses	Potential toxicological concerns	(34-36)
Heat-labile enterotoxin (LT)	*E. coli* enterotoxin derivative	N/A	Mucosal surfaces	Potent enhancement of antigen presentation	Safety concerns at clinical doses	(34-36)
CpG oligodeoxynucleotides	Synthetic DNA motifs	N/A	Antigen-presenting cells	TLR9 activation; Th1-biased responses	Variable inter-individual efficacy	(34-36)
Monophosphoryl lipid A (MPLA)	Detoxified LPS derivative	N/A	Mucosal and systemic tissues	Enhanced innate and adaptive immune responses	Favorable safety profile but limited periodontal-specific data	(36,39)
Cytokine adjuvants (e.g., IL-12)	Recombinant cytokines	N/A	Immune-cell microenvironment	Enhanced T-cell activation and cellular immunity	Risk of systemic adverse effects	(36,39)

Table III. Comparative analysis of preclinical animal models in periodontal vaccinology.

Animal Model	Advantages	Key translational limitations (Refs.)
Rodents (mice/rats)	• Cost-effective with short breeding cycles. • Wide availability of genetically modified strains. • Well-characterized immunogenetic profiles.	• Dissimilar oral microbiota and salivary composition. • Contrasting gingival architecture and tooth morphology. • Divergent innate and adaptive immune responses (42,43).
Non-human primates	• High anatomical similarity to the human periodontium. • Comparable microbial ecology and immune function. • Closely mirrors natural disease progression.	• Severe ethical and regulatory constraints. • Prohibitive procurement and maintenance costs. • Small sample sizes that restrict statistical power (44).

Bifidobacterium species also activate dendritic cells at the mucosa, resulting in increased sIgA secretion upon vaccination. Likewise, a selective prebiotic substrate supports the growth of health-associated commensal micro-organisms, thus maintaining metabolic balance in the subgingival biofilm and preserving the normal abundance of these micro-organisms, thereby avoiding a dysbiotic shift in subgingival composition that precedes tissue destruction (46-48).

At the same time, combinations of immunisation with host-modulatory therapies reduce collateral damage of inflammation, which is mediated by hyperinflammatory host responses. Although conventional anti-inflammatory drugs have the inherent side-effect of non-specifically dampening immune responses, specialised pro-resolving mediators (SPMs). such as lipoxins, resolvins, protectins and maresins are specifically pro-resolving therapies that actively promote inflammation to progress toward resolution. SPMs are known to limit the local network of cytokines, such as IL-1β and TNF-α, prevent neutrophils from damaging tissue and activate macrophages to remove cells through efferocytosis (51). This alteration in local immune profile results in the loss of the bone-resorbing Th1/Th17 phenotype and promotes a regenerative phenotype. A holistic paradigm for durable periodontal protection is achieved by integrating pathogen-specific vaccines, probiotic management of the microbiome and SPM-based inflammation control.

11. Challenges encountered in periodontal vaccine development

The impediments to the development of a clinically viable periodontal vaccine are numerous, given the complex biology of the oral cavity and of periodontitis itself. The key scientific deficiencies are the following:

Polymicrobial aetiology. As opposed to traditional vaccines that target only a monopathogenic organism (e.g., tetanus or measles), periodontitis is a polymicrobial disease, and the dysbiotic biofilm is a community of micro-organisms that act in synergy. Blocking a single virulence factor or species may result in outbreaks of accessory or alternative pathogens and in synergistic interactions that maintain the chronic inflammatory condition (10).

Immune evasion mechanics. Primary target pathogens have sophisticated adaptive mechanisms that actively dismantle host immune responses. For example, *P. gingivalis* has proteins termed gingipains that are capable of degrading complement proteins and IgG antibodies, and *A. actinomycetemcomitans*, with its leukotoxin (LtxA), can induce the apoptosis of infiltrating leukocytes, rendering classic opsonisation by antibodies ineffective.

Mucosal immune tolerance. The oral mucosa is designed to be tolerant to avoid hypersensitivity reactions to the constant bombardment of dietary antigens and the commensal organisms. Achieving an effective local and systemic response in terms of the production of sIgA and IgG, which can be maintained for longer periods of time, leading to an efficient and effective bioengineering process without inducing local irritation and/or systemic toxicity, remains a major bioengineering challenge (7,29).

Translational discordance. As described above, there are key differences between preclinical models of animals and the human clinical scene, both from an anatomical and microbiological standpoint, as well as from an immunological view; thus, the degree of clinical efficacy observed in a preclinical model cannot be readily translated into clinical reality (39,48,49).

12. Ethical, regulatory and translational perspectives in periodontal vaccine development

Periodontitis is a chronic, non-communicable disease, and as such, any vaccine candidate will undergo intensive risk-benefit analysis, with absolute safety in clinical development as the primary concern (50). A major potential biological and ethical issue is the possibility of molecular mimicry (bacterial antigens with structures resembling human proteins, leading to an unwanted antibody response that could trigger cross-reactive autoimmune diseases targeting cardiovascular or connective tissues). To mitigate this risk, informed consent is essential, as is complete transparency in the conduct of phase 1, 2 and 3 human trials, and a dedication to bioequity on a global scale, so that such therapies eventually reach

vulnerable, underprivileged populations (50). In parallel, emerging host-modulation strategies such as pro-resolving lipid mediators have been investigated for their potential role in restoring inflammatory homeostasis in periodontal disease (51).

The regulatory approval processes of the FDA and EMA require robust quality management systems based on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP). The challenge is particularly unique in that clinical efficacy endpoints are not easily defined as these vaccines do not function in the systemic circulation. There is also additional complexity from next-generation platform technologies, such as DNA or mRNA, necessitating new regulatory regimes for evaluating persistent intracellular expression, LNP clearance and localised tissue safety profiles (52).

The key to successful clinical integration, however, is the cross-disciplinary collaboration among immunologists, clinicians and biotech manufacturers to address scale-up logistics. There will be a need to change public health policies, educate dental practitioners and address patient vaccination hesitancy in a sector that previously relied on mechanical rather than medical models of intervention (52,53).

13. Integrating periodontal vaccination into clinical practice

A preventive paradigm shift in dentistry involves moving from mechanical plaque control to immunological protection, representing the next phase in the implementation of periodontal vaccination in clinical practice. Successful incorporation would necessitate a structured process, whereas integrating the vaccine into existing periodontal care would facilitate this. Subsequently, vaccination could be directed toward the high-susceptibility patient cohort, in which susceptibility and disease severity are higher, such as people with a family history of periodontitis, individuals with a history of tobacco use, patients with diabetes or those with compromised oral hygiene, etc (26,51).

Lastly, regulatory acceptance, public awareness and long-term monitoring would be required for clinical integration to be successful. The standardisation of practice and professional confidence among clinicians can be achieved by clear regulatory guidelines and evidence-based recommendations from professional bodies, such as the American Academy of Periodontology (AAP) and the World Dental Federation (FDI). However, post-market surveillance systems, as well as immunisation registers, would be required to monitor vaccine efficacy, safety and population-level impact longitudinally. Implementing periodontal vaccination in clinical practice thus requires a multidisciplinary approach that combines scientific innovations, clinical skills and public health policy to make it a reliable and sustainable tool for prevention within comprehensive periodontal care (39,54).

14. Immunoinformatics, artificial intelligence and future horizons

The landscape of periodontal vaccine development has witnessed recent advances in structural immunoinformatics, machine learning and reverse vaccinology, transitioning vaccine development from an empirical, laboratory-driven process to one in which antigens can be readily identified *in silico* at high speed (39,55). Advances in high-throughput genomic sequencing render the genome-wide exploration of the microbiome residing under the gum line possible, screening thousands of proteins at once and maximising the selection of highly conserved, non-allergenic proteins across a number of different species (56). At the same time, the epitope prediction tools with the use of AI and machine learning algorithms simulate the interactions between the peptide of the pathogen and human major histocompatibility complex receptors. These computational approaches can successfully identify immunogenic peptide sequences that can induce protective responses by both helper T-cells and B-cells, thus helping to accelerate the design of precision-engineered, multiple-valence vaccines targeting microbial polymorphism and host genetics (56,57).

These computationally optimised antigens are combined with next-generation vaccine delivery platforms to enable the safe evasion of local mucosal tolerance and with advanced structural engineering platforms. Nanoparticle-based carriers could provide a promising approach to induce long-lasting immunogenic responses at the oral mucosal surface, in combination with nucleic acid (DNA or mRNA) vaccine platforms (5,39). In addition, the engineering of adjuvants and the design of targetable polymeric nanocarriers takes into account the stability of the vehicle and the engineering of localised antigen release kinetics, delivering significantly improved systemic IgG and sIgA mucosal responses. The integration of AI-driven epitope mapping with specific nanotechnology introduces a highly personalised approach to creating effective, multi-target and long-lasting immunoprophylaxis in the fight against intricate periodontal diseases.

15. Conclusion

The development of a periodontal vaccine represents a major evolutionary paradigm shift in dental medicine, providing a targeted immunoprophylactic strategy to supersede conventional, reactive mechanical debridement and non-specific antimicrobial interventions. By neutralising keystone virulence determinants within the subgingival biofilm and stabilising dysregulated host inflammatory cascades, periodontal immunoprophylaxis provides a viable pathway toward permanent pocket homeostasis and the preservation of alveolar bone architecture. While complex translational bottlenecks persist most notably in navigating the polymicrobial nature of periodontitis, surmounting sophisticated bacterial immune evasion tactics, refining the fidelity of preclinical animal models, and optimising localised mucosal delivery systems without systemic toxicity, the convergence of structural biology, immunology and nanotechnology continues to accelerate the development of clinically viable formulations.

As an overarching synthesis, the path of periodontal vaccinology evolution from primitive whole cell killed formulations to highly defined recombinant subunit vectors to next-generation nucleic acid platforms is well-established. The combination of modern computational biology,

epitope mapping by AI and sophisticated reverse vaccinology approaches will provide an objective framework for rapid *in silico* antigen discovery that accounts for genetic variations between host and pathogen. Moreover, their combination with the most advanced LNPs or polymeric carriers, and with oral mucosal bioadjuvants (e.g., MPLA), is efficacious in disrupting oral tolerance to induce strong and protective sIgA responses. Finally, the switch from individual mechanical plaque management to an integrated whole-of-mouth multimodal approach that combines tailored immunity, probiotic DNA management of the oral microbiome, and host-response modulation could propel the discipline of prevention into a novel paradigm and markedly reduce the biological and socio-economic impact of periodontal disease worldwide.

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Authors' contributions

SM contributed to the conceptualisation and design of the study, conducted the literature search, synthesised the data and prepared the original draft of the manuscript. SRB, HJ and VAB contributed to the reviewing of the manuscript, critical revision for important intellectual content, and provided academic guidance and supervision. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (Grammarly, and QuillBot) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript).

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