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Short Review

Seal The Entry, Win The War: Mucosal Vaccines For A Safer Tomorrow

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ABSTRACT

Mucosal vaccines represent a transformative approach to immunization by stimulating immune responses at mucosal surfaces—the primary entry points for many infectious agents. These vaccines can induce localized mucosal immunity, which is characterized by secretory IgA (SIgA) and robust systemic immune memory. Despite these advantages, mucosal vaccine development faces significant barriers, including antigen degradation, low mucosal absorption, and insufficient immunogenicity. Recent advances in adjuvant technology, antigen delivery platforms, and recombinant expression systems offer promising solutions to overcome these limitations. This review provides a comprehensive overview of current mucosal vaccine strategies, highlights state-of-the-art innovations in formulation and delivery, and identifies critical challenges and future research directions necessary to accelerate clinical translation and global implementation.

Keywords: mucosal immunity, secretory IgA, vaccine delivery systems, adjuvants, mucosal vaccination strategies, oral and nasal vaccines.

INTRODUCTION

Mucosal surfaces—including the respiratory, gastrointestinal, and genitourinary tracts—serve as the primary entry points for over 90% of human pathogens [1]. While parenteral vaccines have revolutionized disease prevention, they typically fail to induce robust mucosal immunity, particularly the production of secretory immunoglobulin A (SIgA), critical for pathogen neutralization at mucosal barriers [2,3]. This gap has fueled growing interest in mucosal vaccination strategies that target these frontline tissues directly.

Mucosal vaccines offer several advantages over conventional intramuscular immunization, including the ability to elicit local and systemic immune responses, reducing pathogen transmission through sterilizing immunity, and enhancing memory B and T cell responses [4]. Additionally, their non-invasive routes of administration—oral, nasal, sublingual, or rectal—simplify mass immunization logistics, minimize needle-associated risks, and improve patient compliance, especially in pediatric and needle-phobic populations [5,6].

In addition to their immunological advantages, mucosal vaccines present logistical and practical benefits that enhance their applicability in real-world settings. By avoiding needles, mucosal administration reduces the risks of needlestick injuries and bloodborne pathogen transmission while simultaneously minimizing

psychological barriers associated with injections [7,8]. This ease of administration makes them ideal for mass vaccination campaigns, particularly in low-resource settings or during pandemic outbreaks where rapid deployment is essential [9].

Immunologically, mucosal vaccines stimulate the production of secretory IgA at the site of pathogen entry, creating a robust first line of defense that blocks infection at the mucosal surface before systemic dissemination occurs [10]. These vaccines elicit systemic IgG responses and promote the development of long-lived memory B and T cells, offering comprehensive protection [11]. This dual response is particularly important in respiratory and enteric infections, where early neutralization is critical to disease control.

Furthermore, mucosal immunization activates the common mucosal immune system (CMIS), allowing immune cells primed at one mucosal site to home to distant mucosal tissues, thereby enhancing cross-site protection [12]. This unique property opens new avenues for non-invasive immunization against sexually transmitted infections, gastrointestinal diseases, and respiratory viruses with pandemic potential. As a result, mucosal vaccines are promising as stand-alone strategies and powerful boosters that enhance systemic and mucosal immunity in heterologous prime-boost regimens.

Despite this promise, mucosal vaccines face significant challenges, such as antigen instability in harsh mucosal environments, enzymatic degradation, and poor uptake by antigen-presenting cells [13]. Recent innovations in adjuvant development, delivery platforms (e.g., nanoparticles, liposomes, bacteriophage-based carriers), and mucosal immunology are rapidly reshaping the landscape of mucosal vaccine design [14,15].

Given the rapid progress in this field, there is an urgent need for a consolidated synthesis of recent advances to inform research priorities and clinical translation. In this review, we critically evaluate emerging mucosal vaccine platforms, assess their technological promise, and examine key challenges that must be overcome to enable widespread implementation (Figure 1).

Licensed Mucosal Vaccines

Only a limited number of mucosal vaccines have received licensure for human use, primarily via oral or intranasal routes. These include vaccines targeting enteric pathogens—such as Vibrio cholerae (Dukoral®, Shanchol®), Salmonella typhi (Vivotif®), and rotavirus (Rotarix®, RotaTeq®)—as well as respiratory viruses like Influenza A/B (FluMist®) and SARS-CoV-2 (iNCOVACC®, Convidecia Air®) [16,17]. The global introduction of rotavirus vaccines alone has prevented an estimated 200,000 child deaths annually and reduced diarrhea-related hospitalizations by up to 84% in some countries [18]. Similarly, intranasal influenza vaccines have demonstrated up to 93% efficacy in children in certain seasons, outperforming inactivated injectable vaccines [19,20].

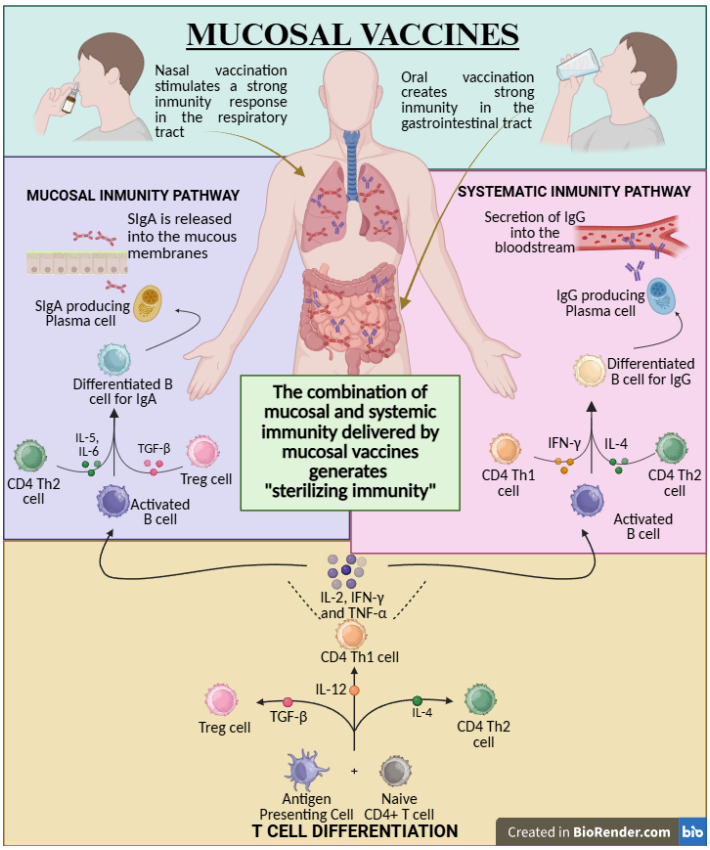

Figure 1. Overview of immune mechanisms triggered by mucosal vaccines. Mucosal vaccination activates both secretory IgA-mediated immunity at the mucosal surface and systemic IgG-mediated immunity, promoting CD4+ T cell differentiation and the development of sterilizing immunity.

In the veterinary field, mucosal immunization has been widely adopted due to its ease of administration and impact on disease control in livestock and wildlife. For example, through bait-based immunization campaigns, oral rabies vaccines (e.g., RABORAL V-RG®) have led to near-elimination of rabies in foxes and raccoons in parts of Europe and North America [21]. These successes underscore the real-world potential of mucosal vaccine platforms and provide a valuable foundation for expanding their use in human populations.

Vaccine Name	Target Pathogen	Delivery Route	Composition	Use	Impact on Public Health	Ref
Rotarix®	Rotavirus	Oral	Live attenuated human G1 strain	Human	↓200,000 deaths/year; ↓84% hospitalizations in some countries	[17,20,]
RotaTeq®	Rotavirus	Oral	Live reassortant (G1–G4 + P1A)	Human	Broad efficacy; introduced in >100 countries	[17,20]
FluMist®	Influenza A/B	Intranasal	Live attenuated, cold-adapted virus (4 strains)	Human	Up to 93% efficacy in children in some seasons	[21]
Dukoral®	*Vibrio cholerae*	Oral	Inactivated O1 + recombinant cholera toxin B subunit	Human	Used in outbreak response and travelers; short-term protection	[16]
Shanchol®	*Vibrio cholerae*	Oral	Inactivated O1 and O139 serotypes	Human	Used in WHO-prequalified stockpiles; effective in endemic areas	[16]

Vivotif®	*Salmonella typhi*	Oral	Live Ty21a strain	Human	Long-term protection: used in travelers and endemic areas	[16]
iNCO-VACC®	SARS-CoV-2	Intranasal	ChAd36 vector expressing spike protein	Human	India's first intranasal COVID-19 vaccine; emergency use authorization	[18]
Convidecia Air®	SARS-CoV-2	Inhaled aerosol	Ad5 vector expressing spike protein	Human	Approved in China; targets upper airway immunity	[18]
RABORAL V-RG®	Rabies virus	Oral (bait)	Recombinant vaccinia expressing rabies glycoprotein	Veterinary	Eradication of rabies in foxes/raccoons in Europe and North America	[22]
Nobivac® KC	*Bordetella bronchiseptica*, canine parainfluenza	Intranasal	Live attenuated B-C2 and Cornell strains	Veterinary	Prevents kennel cough outbreaks; used in shelters and clinics	[23]

Table 1. Summary of licensed mucosal vaccines approved for human or veterinary use, including delivery routes, antigen composition, and real-world public health impact. This expanded version highlights clinical applications and measurable outcomes in disease prevention programs.

Adjuvants and Delivery Systems for Mucosal Vaccines

One of the primary challenges in mucosal vaccine development is overcoming the biological barriers of mucosal tissues—such as enzymatic degradation, low pH, mucus trapping, and epithelial impermeability—which significantly reduce antigen stability and uptake [22]. To enhance immune responses, mucosal vaccines increasingly rely on adjuvants and delivery systems (Figure 2) that protect antigens and promote their interaction with mucosa-associated lymphoid tissues (MALT).

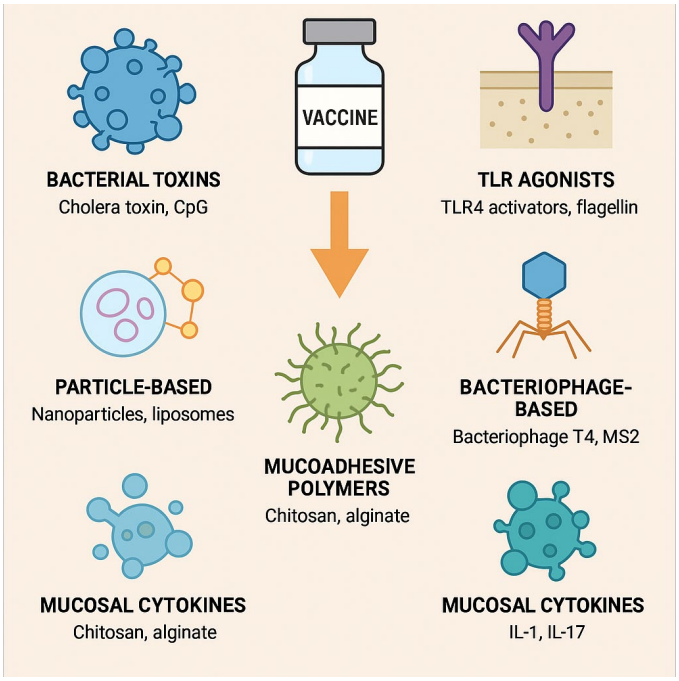

Figure 2. Summary of key adjuvant and delivery strategies for mucosal vaccines. These include detoxified bacterial toxins (e.g., cholera toxin, CpG), Toll-like receptor agonists (e.g., TLR4 activators, flagellin), mucoadhesive polymers (e.g., chitosan,

alginate), nanoparticle-based systems (e.g., liposomes, PLGA), bacteriophage vectors (e.g., T4, MS2), and mucosal cytokine adjuvants (e.g., IL-1, IL-17). These technologies enhance antigen uptake, epithelial penetration, and immune activation at mucosal surfaces.

1. Bacterial Toxin Derivatives

Among the most well-studied mucosal adjuvants are detoxified bacterial toxins such as heat-labile toxin (LT) from Escherichia coli and cholera toxin (CT) from Vibrio cholerae [23]. Modified versions like dmLT (double mutant LT) and mmCT (multiple mutant CT) retain strong immunostimulatory properties while reducing toxicity [24]. These adjuvants enhance antigen uptake by opening tight junctions, promoting dendritic cell activation, and inducing SIgA responses [25]. For example, dmLT combined with oral or sublingual antigens has enhanced Th17 and SIgA responses in animal models [26].

2. Toll-like Receptor (TLR) Agonists

TLR agonists represent a promising class of mucosal adjuvants due to their ability to mimic pathogen-associated molecular patterns (PAMPs) and activate innate immunity. Monophosphoryl lipid A (MPL, a TLR4 agonist) is already used in licensed systemic vaccines (e.g., Cervarix®) and is under evaluation for mucosal applications [27]. When administered intranasally, TLR9 agonists like CpG oligodeoxynucleotides have enhanced mucosal IgA and systemic IgG responses [28].

3. Mucoadhesive Polymers

Mucoadhesive agents such as chitosan and carboxymethylcellulose prolong antigen contact with mucosal surfaces, improving uptake and stability. Chitosan interacts with mucins to form bioadhesive gels, enhances epithelial permeability, and has shown adjuvanticity in intranasal influenza vaccines [29,30]. These polymers also allow nanoparticle co-formulation, facilitating antigen protection and sustained release.

4. Nanoparticle-Based Delivery Systems

Nanocarriers—such as liposomes, PLGA nanoparticles, and virus-like particles (VLPs)—enable targeted delivery and immune cell uptake [31]. Particle size and surface charge are critical; particles between 100–200 nm are preferentially taken up by M and dendritic cells, stimulating robust mucosal and systemic responses [32]. Lipid-based vesicles, such as liposomes and ISCOMs, have also shown promise in oral and nasal vaccine delivery [33].

5. Recombinant and Viral Vectors

Recombinant vectors such as adenovirus (e.g., Ad5, ChAd) and bacteriophage-based systems provide effective antigen presentation while protecting cargo from degradation [34]. Bacteriophage T4-based platforms have recently been shown to induce sterilizing mucosal immunity against SARS-CoV-2 in preclinical models without compromising safety or stability [35].

6. Cytokine-Based Adjuvants

Certain cytokines—including IL-1β, IL-12, and IL-7—have been investigated as mucosal adjuvants to recruit immune cells and modulate local immune responses [36]. For instance, intravaginal administration of recombinant IL-7 in non-human primates enhanced mucosal chemokine expression and immune cell homing, supporting its use as a potent mucosal immunomodulator [37].

These advances in adjuvant design and delivery technology have significantly improved the immunogenicity of mucosal vaccines and offer promising pathways toward clinical translation. However, further human trials are needed to optimize safety profiles and regulatory approval pathways. The key differences between mucosal and systemic vaccines are systematically compared in Table 2.

Parameter	Mucosal Vaccines	Systemic (Parenteral) Vaccines
Administration route	Oral, nasal, sublingual, rectal	Intramuscular, subcutaneous, intradermal
Immune response	Mucosal (SIgA) + systemic (IgG)	Primarily systemic (IgG)
Induces sterilizing immunity	Often, yes (at the site of entry)	Rarely
Needle-free	Yes	No
Cold chain requirements	Often more flexible (in oral forms)	Typically strict
Patient compliance	Higher (especially children and needle-phobic individuals)	Lower in some populations
Self-administration potential	High	Very low
Barriers to efficacy	Enzymatic degradation, mucosal tolerance, low absorption	Injection site inflammation, low mucosal response
Formulation complexity	Higher (adjuvants, delivery systems needed)	Lower
Clinical examples	Rotarix, FluMist, Dukoral, iNCOVACC	Pfizer-BioNTech, Moderna, DTP, MMR

Table 2. Comparative summary of key characteristics of mucosal and systemic vaccines. This table highlights the strengths and limitations of each approach and supports the rationale for expanding mucosal vaccination strategies.

DISCUSSION

Mucosal vaccines hold transformative potential in infectious disease prevention by targeting immune responses at the body's most vulnerable entry points. Unlike traditional systemic immunization, mucosal vaccines can provide localized SIgA-mediated immunity and systemic protection, offering a dual barrier against pathogen colonization and dissemination [4,10,25]. This unique immunological profile allows mucosal vaccines to induce sterilizing immunity, which is particularly valuable for preventing transmission during pandemics or in high-risk environments [38]. One notable application of mucosal vaccine development is tuberculosis (TB), a respiratory disease ideally suited for mucosal immunization due to its pulmonary transmission route. A promising candidate mucosal vaccine expressing the antigen 85B of *Mycobacterium tuberculosis*, delivered intranasally in a murine model, demonstrated strong induction of secretory IgA, elevated Th1 cytokine levels in bronchoalveolar lavage fluid, and significant reductions in bacterial burden in both lungs and spleen. These findings illustrate the potential of intranasal vaccination strategies to prevent initial infection and limit systemic dissemination of *M. tuberculosis*, aligning with the central goal of mucosal

vaccines: to block pathogens at their point of entry and achieve sterilizing immunity in diseases spread by aerosol transmission [38].

In addition to immunological benefits, mucosal vaccines present compelling logistical advantages, including needle-free administration, improved patient compliance, and suitability for self-administration and mass campaigns in resource-limited settings [5,7,9]. However, antigen stability, mucosal permeability, and consistent immunogenicity challenges persist across diverse populations [13,22]. Biological barriers such as acidic environments, mucus viscosity, and mucociliary clearance hinder antigen access to inductive immune sites [31].

Emerging technologies—including mucoadhesive polymers, bacterial toxin derivatives, cytokine-based adjuvants, and nanocarrier-based delivery systems—are actively being developed to address these barriers [23,24,27,32]. Some platforms, such as bacteriophage-based vaccines or virus-like particles, have shown preclinical success in achieving mucosal and systemic protection with high safety margins [34,35].

Mucosal adjuvants function by overcoming physicochemical (e.g., low pH, enzymatic degradation) and immunological barriers (e.g., mucosal tolerance) using targeted molecular mechanisms.

For example, the B subunits of bacterial toxins such as LT and CT bind to GM1 gangliosides on epithelial cells, facilitating antigen uptake via endocytosis and stimulating dendritic cell activation through cAMP/PKA signaling pathways [12,13]. Engineered mutants such as dmLT and mmCT reduce enterotoxicity while retaining the ability to promote Th17-polarizing cytokines like IL-17 and IL-22—key drivers of mucosal IgA production [15,16,18].

Similarly, Toll-like receptor (TLR) agonists such as CpG (TLR9) and MPL (TLR4) activate antigen-presenting cells (APCs) through the MyD88/NF-κB signaling cascade [19,20]. This leads to the secretion of pro-inflammatory cytokines, including IL-6 and TNF-α, promoting APC maturation and the induction of IgA responses in mucosa-associated lymphoid tissues (e.g., GALT, BALT) [21,22,25].

Nanoparticle-based delivery systems—particularly those made of PLGA or liposomes—further enhance mucosal immunogenicity by protecting the antigen cargo, controlling its release over time, and promoting uptake by M cells and APCs due to their optimized size (100–200 nm) and surface charge [34]. Positively charged particles exhibit enhanced mucoadhesion and translocation across the mucosal epithelium [31,42].

Innovative hybrid systems combining polymeric nanoparticles with molecular adjuvants (e.g., CpG or dmLT) are being developed to synergize multiple immune pathways [24,25,35]. These strategies aim to achieve durable and site-specific mucosal immunity while accounting for interindividual variability due to microbiota composition or enzymatic degradation (Figure 3) [44].

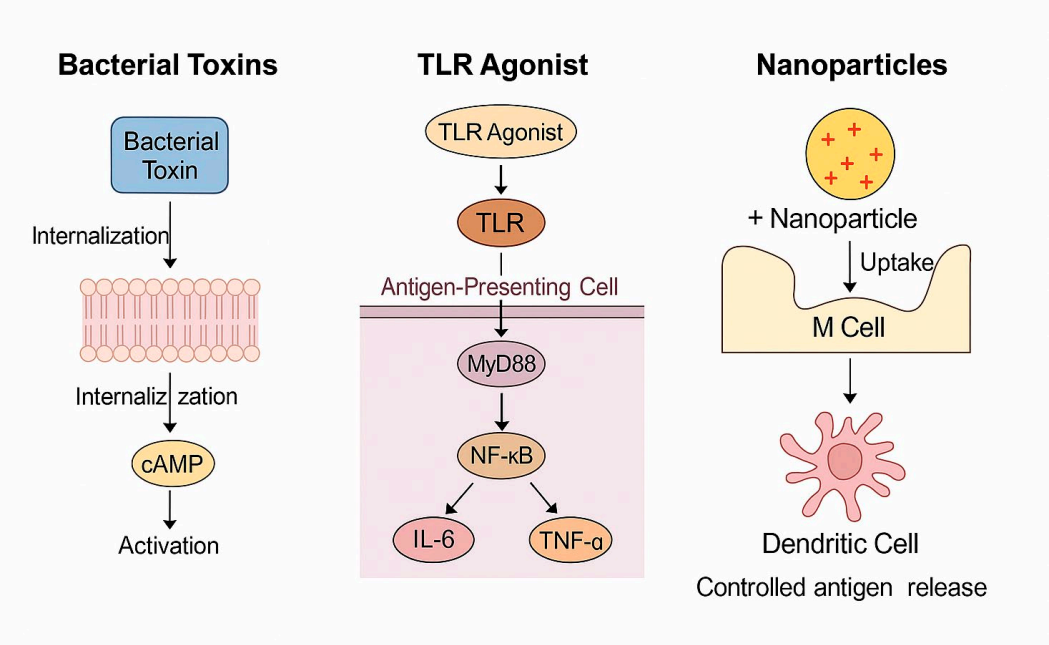

Figure 3. Molecular mechanisms of mucosal adjuvants. Bacterial toxin derivatives bind to GM1 ganglioside receptors, triggering cAMP-dependent pathways that facilitate epithelial permeability and immune activation. TLR agonists stimulate antigen-presenting cells through the MyD88/NF-κB pathway, inducing IL-6 and TNF-α production. Nanoparticles (~100–200 nm, positively charged) are taken up by M and dendritic cells, enabling controlled antigen release and enhanced mucosal immune responses.

Despite these advances, regulatory pathways for mucosal vaccines remain underdeveloped. Most current licensures are limited to oral and intranasal routes, with few sublingual or rectal vaccines reaching clinical trials [16,39]. Furthermore, the lack of standardized correlates of protection for mucosal immunity complicates efficacy assessment in humans [42]. Investment in translational studies, particularly Phase I/II trials focusing on immune correlates and delivery optimization, will be crucial for future clinical implementation.

Future Directions

The field of mucosal vaccinology is poised for rapid expansion, yet several knowledge and implementation gaps must be addressed. First, developing thermostable formulations that can withstand ambient conditions remains critical for deployment in low-resource settings [41]. Second, identifying correlates of protection specific to mucosal immunity is urgently needed to support regulatory evaluation and licensure [40]. Third, emerging innovative platforms that combine antigen delivery with immune modulation—such as AI-guided epitope mapping and mucosal microbiome-targeted adjuvants—warrant further exploration [42].

Furthermore, integrating mucosal vaccines into pandemic preparedness frameworks, particularly through stockpiling and rapid-deployment strategies, will enhance global response capacity [43]. Finally, increased investment in translational research, including human challenge models and standardized delivery systems, will be essential for bringing next-generation mucosal vaccines from bench to bedside. Table 3 summarizes leading mucosal adjuvant technologies' mechanisms, advantages, and development status.

Adjuvant Type	Mechanism of Action	Immune Pathways Activated	Advantages	Limitations	Development Stage
dmLT / mmCT (Bacterial Toxins)	Bind GM1 → cAMP ↑ → epithelial opening → antigen uptake	Th17, IL-17, IL-22, IgA	Strong mucosal response; effective in oral/sublingual routes	Residual toxicity; variable efficacy across species	Phase I/II trials
CpG (TLR9)	TLR9 activation → MyD88 → NF-κB → proinflammatory cytokines	Th1, IL-6, TNF-α, IgA	A safe, defined mechanism, stable	Poor uptake alone; needs a delivery carrier	Clinical trials
MPL (TLR4)	TLR4 stimulation via MyD88-independent/TRIF pathway	Th1, IgG, IgA	Licensed in parenteral vaccines; under study mucosally	Low mucosal retention requires formulation support	Clinical/exploratory
Chitosan	Mucoadhesive opens tight junctions and enhances antigen stability	SIgA, APC recruitment	Biocompatible, low-cost	Degraded by mucosal enzymes; sensitive to pH	Preclinical/Clinical
PLGA Nanoparticles	Antigen protection; controlled release; uptake by M cells/APCs	Mixed Th1/Th2, SIgA, CD8+	Controlled release; co-delivery of adjuvants	Complex manufacturing requires tuning surface charge	Advanced preclinical
Bacteriophage T4	Antigen display; natural tropism to the mucosa	SIgA, CD4+, CD8+ T cells	Self-adjuvanted, stable	Novel platform; regulatory experience limited.	Preclinical

Table 3. Comparative characteristics of mucosal adjuvants under development or clinical testing. The table summarizes mechanisms, immune targets, strengths, limitations, and current translational stages, aiding in selecting optimal adjuvant systems for mucosal vaccine formulation.

CONCLUSIONS

Mucosal vaccines represent a highly promising yet underutilized class of immunization strategies. Their potential to generate broad immune coverage, reduce transmission, and improve global vaccine accessibility positions them as central to next-generation vaccinology.

As advances in immunology, formulation science, and delivery platforms converge, mucosal vaccination is expected to transition from a niche innovation to a mainstream approach. Continued interdisciplinary collaboration among immunologists, formulation scientists, and public health experts is essential to unlock their full potential and bring these innovations globally.

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