

Review Article



Bacterial Vaccines in the Era of Antimicrobial Resistance Platforms Challenges and Emerging Approaches

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ABSTRACT

Bacterial infections remain an important cause of disease worldwide, while antimicrobial resistance (AMR) continues to reduce the effectiveness of some antibacterial therapies. Vaccination is therefore a major preventive strategy because it can reduce the probability of infection, severe disease, transmission and, in some settings, antibiotic use. Bacterial vaccines use several platforms, including live attenuated organisms, inactivated whole-cell preparations, toxoids, purified subunits and recombinant antigens, and polysaccharide–protein conjugates. The choice of platform depends on the biology of the pathogen, the protective immune response, antigen stability, manufacturing feasibility and safety requirements. Conjugate vaccines have been particularly important for encapsulated bacteria because protein conjugation can generate stronger, T-cell-dependent immune responses and immunological memory. Established examples include vaccines against tuberculosis, diphtheria, tetanus, pertussis, *Hemophilus influenzae* type b, pneumococcal disease, meningococcal disease and typhoid. At the same time, development remains difficult for pathogens with extensive antigenic diversity, complex intracellular lifestyles, poorly defined correlates of protection or limited natural immunity. Modern research is exploring recombinant proteins, outer membrane vesicles, nanoparticle delivery, reverse vaccinology, structure-guided antigen design and other approaches. WHO analyses have also highlighted a substantial pipeline of bacterial vaccine candidates targeting antimicrobial-resistant priority pathogens. This review summarizes the scientific basis of bacterial vaccines, major vaccine classes, immune mechanisms, clinical applications, development challenges, quality considerations and future opportunities.

Keywords: Bacterial vaccines; immunization; conjugate vaccine; toxoid; antimicrobial resistance.

INTRODUCTION

Vaccines are biological products designed to prepare the immune system to recognize and respond to a pathogen or a defined component of it. Bacterial vaccines are developed against bacterial pathogens or their disease-causing products. Unlike antibacterial medicines, which are generally administered after infection or when disease is suspected, vaccines aim primarily to prevent infection or reduce the severity and consequences of disease. Their public-health value extends beyond the vaccinated person because effective vaccination can reduce circulation of some pathogens and protect people who cannot be vaccinated^{1,2}.

Bacterial vaccine development is strongly influenced by pathogen biology. Some bacteria produce potent toxins, making toxoid vaccination a logical strategy. Others have polysaccharide capsules that are important targets for protective antibodies. Encapsulated organisms such as *Streptococcus pneumoniae* and *Hemophilus influenzae* type b illustrate the value of conjugate technology. Intracellular bacteria create a different problem because protection may require coordinated cell-mediated immunity rather than antibodies alone. WHO maintains vaccine position papers and immunological guidance for important bacterial

diseases, reflecting continual review of evidence and policy^{3,4,5}.

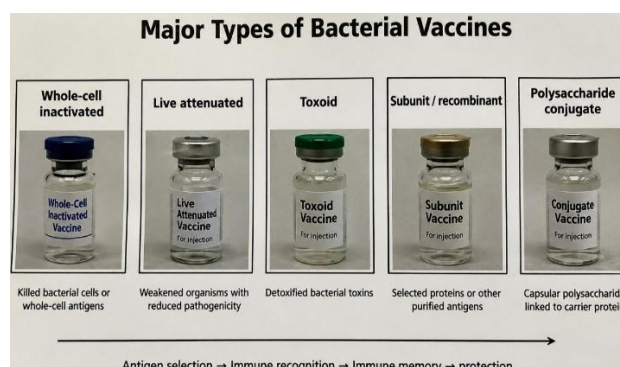


Figure 1: Original schematic showing major bacterial vaccine platforms and the general path from antigen recognition to immune memory.

- To explain the basic principles and immune mechanisms of bacterial vaccination.
- To classify major bacterial vaccine platforms and describe their advantages and limitations.
- To summarize representative licensed bacterial vaccines and their public-health applications.



- To discuss the role of conjugate vaccines, recombinant antigens and newer technologies.
- To examine major scientific, manufacturing and public-health challenges.
- To highlight the importance of bacterial vaccines in the context of antimicrobial resistance and future vaccine development.

2. Major Types of Bacterial Vaccines

Commonly used bacterial vaccine approaches include inactivated whole-cell preparations, live attenuated vaccines, toxoid vaccines, subunit or recombinant vaccines and polysaccharide conjugate vaccines. Experimental approaches include outer membrane vesicles, bacterial vectors, nucleic-acid approaches and nanoparticle-based antigen delivery. A review of bacterial vaccination similarly describes these established and emerging categories.

Table 1: Major types of bacterial vaccines.

Platform	Basic Principle	Representative Example(s)	Main Strength	Key Limitation	Reference
Live attenuated	Weakened organism retains selected antigenic properties	BCG; selected live bacterial vaccines	Broad antigen presentation	Safety and suitability depend on host and strain	^{6,7}
Inactivated whole-cell	Killed organism or whole-cell antigen preparation	Some bacterial vaccines	Multiple antigens presented together	May require adjuvant/boosting	⁸
Toxoid	Detoxified bacterial toxin	Diphtheria, tetanus	Targets toxin-mediated disease	Mainly protects against toxin effects	⁷
Subunit/recombinant	Selected proteins or defined antigens	Acellular pertussis components; recombinant candidates	Defined composition	May require adjuvants and multiple antigens	⁹
Polysaccharide conjugate	Capsular polysaccharide linked to carrier protein	Hib, pneumococcal, meningococcal, typhoid	Strong T-cell-dependent response and memory	Manufacturing and coverage can be complex	¹⁰

2.1 Live Attenuated Vaccines

Live attenuated vaccines contain organisms that have been weakened so that they can stimulate immunity without producing the full disease phenotype in appropriately selected recipients. BCG, derived from *Mycobacterium Bovis*, is a major example of a live bacterial vaccine. WHO's BCG position paper emphasizes the importance of the birth dose in settings where BCG is recommended and provides guidance for special populations¹¹.

2.2 Inactivated Whole-Cell Vaccines

Inactivated bacterial vaccines use organisms that have been rendered non-replicating while retaining antigenic structures. The platform can present many antigens simultaneously, but inactivation and purification must preserve relevant immune targets. Modern vaccine development often prefers more defined antigen compositions when a small number of protective antigens can be identified¹².

2.3 Toxoid Vaccines

Toxoid vaccines are designed for bacterial diseases in which toxins are central to pathology. A bacterial toxin is detoxified while retaining antigenic properties, allowing the immune system to generate antibodies that can neutralize the toxin. Diphtheria and tetanus vaccination are classic¹³.

2.4 Subunit and Recombinant Vaccines

Subunit vaccines contain selected antigens rather than the entire bacterium. Recombinant DNA technology can produce a defined antigen in a suitable expression system, followed by purification and formulation. This can improve composition control and reduce unnecessary components. A key challenge is identifying antigens that generate a sufficiently broad and durable protective response¹⁴.

2.5 Polysaccharide and Conjugate Vaccines

Capsular polysaccharides can be important virulence-associated structures and antibody targets. Pure polysaccharide vaccines generally induce weaker T-cell-independent responses than conjugate vaccines. In conjugate vaccines, a bacterial polysaccharide is chemically linked to a carrier protein. This promotes a more effective T-cell-dependent response, including immune memory. WHO describes conjugate approaches as important for pneumococcal and meningococcal vaccination, and Hib vaccination is another established¹².

3. Immunological Basis of Bacterial Vaccination

Vaccination exposes the immune system to antigens in a controlled context. Antigen-presenting cells capture and process vaccine components and communicate with lymphocytes. B cells can differentiate into antibody-producing plasma cells and memory B cells, while T cells provide helper or effector functions depending on the



vaccine and pathogen. The resulting immune memory allows a faster and stronger response after later exposure.

The protective mechanism differs between pathogens. For toxin-mediated disease, neutralizing antibodies against the toxin are central. For extracellular encapsulated bacteria, antibodies that promote opsonization and complement-

mediated clearance can be especially important. For intracellular bacteria such as *Mycobacterium tuberculosis*, cell-mediated responses are important because the organism can persist within host cells. WHO's immunological basis modules emphasize that vaccine strategies must reflect biological differences among pathogens¹⁵.

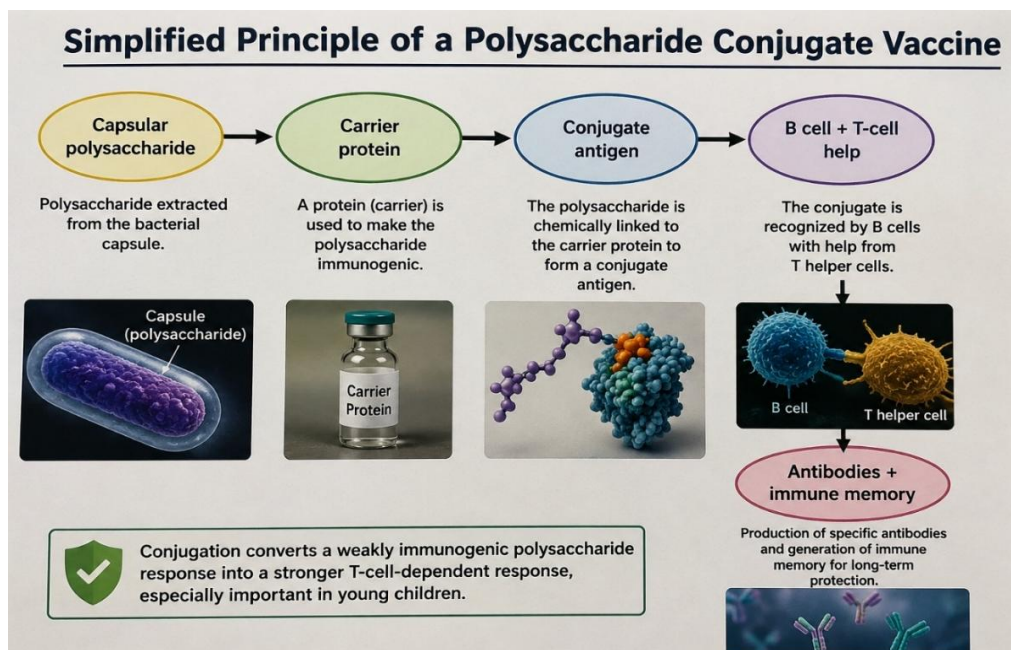


Figure 2: Original conceptual diagram of how polysaccharide–protein conjugation supports a stronger adaptive immune response.

4. Representative Bacterial Vaccines and Applications

Table 2: Representative bacterial vaccines and applications

Disease/Pathogen	Vaccine Approach	Major Target Concept	Public-Health Role	Reference
Tuberculosis/ <i>Mycobacterium tuberculosis</i>	Live attenuated BCG	Mycobacterial antigens; cellular immunity	Important childhood TB prevention strategy	7
Diphtheria/ <i>Corynebacterium diphtheriae</i>	Toxoid	Neutralization of diphtheria toxin	Routine childhood immunization	8
Tetanus/ <i>Clostridium tetani</i>	Toxoid	Neutralization of tetanus toxin	Prevention of toxin-mediated disease	7
Pertussis/ <i>Bordetella pertussis</i>	Acellular subunit and whole-cell approaches	Selected bacterial antigens/toxoids	Routine immunization and boosters	9
Hib disease/ <i>Haemophilus influenzae type b</i>	Polysaccharide conjugate	Capsular PRP linked to carrier protein	Prevention of invasive Hib disease	10
Pneumococcal disease/ <i>Streptococcus pneumoniae</i>	Conjugate vaccines	Selected capsular polysaccharides	Prevention of invasive disease and pneumonia	10
Meningococcal disease/ <i>Neisseria meningitidis</i>	Conjugate and protein-based approaches	Capsular polysaccharides or surface proteins	Prevention of meningitis and invasive disease	16
Typhoid/ <i>Salmonella</i> Typhi	Typhoid conjugate vaccine	Vi polysaccharide linked to carrier protein	Use in endemic settings and outbreak control	17,18

4.1 Tuberculosis and BCG

BCG is the most widely used bacterial vaccine platform and remains important for preventing severe forms of tuberculosis in children. Its effectiveness against different

forms of TB varies, which has stimulated research into improved TB vaccines. WHO's 2018 BCG position paper updated recommendations and re-emphasized the birth dose in settings where BCG is used.

4.2 Pneumococcal Conjugate Vaccines

Streptococcus pneumoniae can cause pneumonia, meningitis, septicemia and other diseases. Pneumococcal conjugate vaccines target selected capsular serotypes. WHO updated its position paper in September 2025, reflecting changes in evidence and vaccine formulations.

4.3 Hemophilus influenzae type b

Hib is an encapsulated bacterial pathogen that can cause invasive disease, particularly in young children. Hib conjugate vaccination transformed prevention by making the capsular polysaccharide antigen more effective at generating immune memory. WHO's Hib position paper summarizes the evidence and vaccination recommendations.

4.4 Meningococcal Vaccines

Meningococcal vaccines include polysaccharide and polysaccharide–protein conjugate approaches, as well as protein-based vaccines for selected serogroups. WHO notes that conjugate vaccines are more immunogenic than plain capsular polysaccharide vaccines and can induce immunological memory. Updated guidance on multivalent conjugate vaccines was issued in 2024 for the African meningitis belt.

4.5 Typhoid Conjugate Vaccines

Typhoid fever is caused by *Salmonella Typhi*. WHO recommended typhoid conjugate vaccine use for infants and children from six months of age in typhoid-endemic countries, based on evidence concerning safety, efficacy, feasibility and affordability. TCVs are also relevant to outbreak control and drug-resistant typhoid.

5. Antimicrobial Resistance and Bacterial Vaccines

Antimicrobial resistance makes prevention increasingly valuable. Vaccines can reduce the number of infections requiring antibiotic treatment and may reduce opportunities for resistant organisms to spread. This does not mean vaccination replaces antibiotics; rather,

vaccination and antimicrobial stewardship are complementary public-health tools.

WHO's analysis of bacterial vaccine candidates in development for priority drug-resistant pathogens reported 61 candidates in active clinical development and 94 in preclinical development in the 2021 analysis. Among active clinical candidates, conjugate/subunit approaches were common and most candidates were prophylactic. These data demonstrate substantial interest in vaccine-based prevention of bacterial disease and AMR¹⁹.

6. Emerging Technologies in Bacterial Vaccine Development

Contemporary bacterial vaccinology is moving from empirical antigen selection toward more rational and data-driven design. Reverse vaccinology uses genome and protein information to identify candidate antigens. Structural biology can help identify conserved or functionally important antigenic regions. Recombinant expression and modern purification systems can then support controlled production.

Outer membrane vesicles (OMVs) are naturally released bacterial membrane structures containing multiple surface-associated components. They have attracted interest as multi-antigen vaccine platforms and have informed meningococcal vaccine development. Research is also exploring nanoparticles, bacterial ghosts, engineered bacterial vectors and nucleic-acid approaches. These technologies remain at different stages of development and must be evaluated for safety, consistency, immunogenicity and manufacturing feasibility.

7. Vaccine Development and Quality Considerations

Development proceeds through discovery, preclinical studies, clinical trials, regulatory review and post-licensure surveillance. Early work asks whether the antigen is biologically plausible and immunogenic. Clinical development evaluates safety, dose, immune responses and, when feasible, protection against disease. Manufacturing development must establish a reproducible process and control critical quality attributes.

Table 3: Emerging technologies in bacterial vaccine development

Emerging Approach	Potential Advantage	Main Scientific Challenge	Reference
Reverse vaccinology	Genome-wide antigen discovery	Predicting which antigens truly correlate with protection	20
Structure-guided design	Focuses responses on conserved/functional regions	Requires structural and immunological knowledge	21
Outer membrane vesicles (OMVs)	Multi-antigen presentation	Consistency, reactogenicity and process control	22,23
Nanoparticle delivery	May improve antigen presentation and stability	Safety, scalability and regulatory characterization	24,25
Recombinant multivalent proteins	Defined composition and scalable production	Antigen folding, expression and breadth	20
Novel adjuvants	Can enhance magnitude and quality of responses	Balancing efficacy with tolerability and safety	26



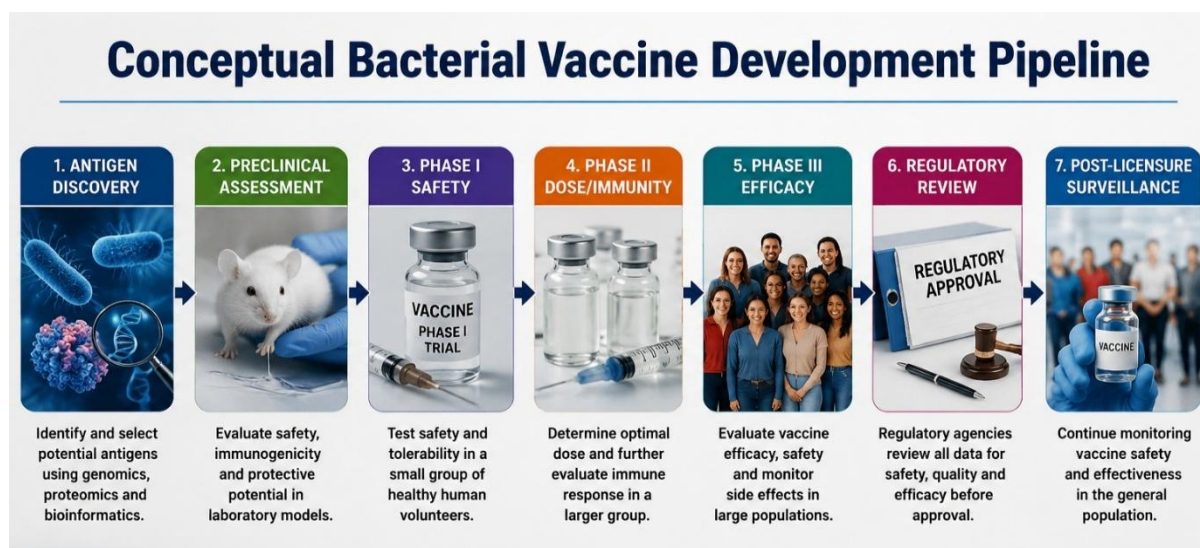


Figure 3: Original conceptual representation of the bacterial vaccine development pipeline.

Table 4: Vaccine development and quality considerations

Quality domain	What is assessed	Why it matters
Identity	Correct antigen(s) and product composition	Ensures the product is what it is intended to be
Purity	Removal/control of unwanted components	Supports safety and consistency
Potency	Biological activity or validated surrogate measure	Helps ensure intended biological effect
Microbiological quality	Absence/control of unacceptable contamination	Critical for patient safety
Stability	Product quality over shelf life	Supports reliable storage and distribution
Consistency	Batch-to-batch reproducibility	Essential for large-scale manufacturing
Safety	Local/systemic reactions and adverse events	Protects vaccinated populations

8. Challenges in Bacterial Vaccine Development

Antigenic diversity

Many bacterial species contain multiple strains or serotypes. A vaccine covering only a subset of circulating types may have limited breadth, creating pressure for broader formulations¹².

Complex pathogen biology

Some bacteria colonize mucosal surfaces, persist intracellularly, form biofilms or change surface antigens. These features can make protective immunity difficult to reproduce²⁷.

Correlates of protection

For several bacterial diseases, the immune marker that reliably predicts protection is not fully defined. This complicates clinical development²⁷.

Manufacturing complexity

Conjugation chemistry, recombinant proteins, vesicle-based products and multivalent formulations can require tightly controlled processes and analytical methods²⁸.

Access and affordability

A vaccine can be scientifically successful but have limited population impact if it is difficult to manufacture, store, deliver or finance²⁸.

Antigenic replacement

When vaccines target a subset of serotypes, ecological changes may alter the distribution of non-vaccine types. Surveillance is important after introduction²⁸.

Regulatory complexity

Novel platforms need validated assays, well-characterized manufacturing processes and sufficient clinical evidence before approval²⁸.

9. Role of Vaccines in Public Health

Vaccination programs work best when integrated with surveillance, diagnosis, infection prevention and appropriate antimicrobial use. For bacterial disease, vaccination can reduce severe outcomes while surveillance identifies changes in serotypes, strain distribution and antimicrobial susceptibility. WHO's vaccine position papers are periodically reviewed as new evidence becomes available and are intended to support national immunization programs.⁶

Conjugate vaccines are particularly important in childhood immunization because they can generate stronger immune responses to polysaccharide antigens than plain polysaccharide formulations. WHO's pneumococcal, Hib and meningococcal guidance illustrate how vaccine policy is linked to pathogen epidemiology, age-specific disease burden and available vaccine technology.

Future Perspectives

The next generation of bacterial vaccines is likely to combine several technologies rather than rely on a single platform. Potential directions include broader multivalent formulations, conserved-antigen targeting, improved mucosal vaccination, better adjuvants, OMV-derived platforms, structure-guided antigen design and vaccine strategies explicitly designed to reduce AMR transmission. The WHO bacterial vaccine pipeline demonstrates that vaccine development against priority resistant pathogens is an active area of research.

For pathogens such as *Mycobacterium tuberculosis*, the central scientific challenge is to generate durable protection against a complex intracellular organism. For encapsulated bacteria, future vaccines may seek wider serotype coverage while maintaining manufacturing feasibility. For highly variable pathogens, combining multiple conserved antigens may improve breadth. Across all platforms, successful development will depend on linking laboratory immunology with rigorous clinical evidence, manufacturing quality, affordability and effective immunization programs.

CONCLUSION

Bacterial vaccines are a diverse and essential component of modern preventive medicine. Their design ranges from live attenuated organisms and toxoids to highly defined recombinant antigens and polysaccharide–protein conjugates. The most appropriate strategy depends on the pathogen's biology and the immune response required for protection. Established vaccines against tuberculosis, diphtheria, tetanus, pertussis, Hib, pneumococcal disease, meningococcal disease and typhoid demonstrate the practical impact of bacterial vaccinology.

At the same time, antimicrobial resistance and persistent bacterial diseases create a strong rationale for continued research. WHO's documented pipeline of bacterial vaccine candidates shows substantial activity against priority pathogens. Future progress will likely depend on improved antigen discovery, structural and computational approaches, advanced delivery systems, robust correlates of protection and scalable manufacturing. Overall, bacterial vaccination should be viewed not only as a method of preventing individual disease but also as an important component of long-term infectious-disease control and antimicrobial stewardship.

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