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REVIEW

From Antibiotic Resistance to Bacterial Vaccines: A New Approach to Controlling Resistant Bacterial Infections

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Abstract: Antimicrobial resistance (AMR) is one of the major threats to global health, with a complex and diverse underlying mechanism. Vaccines reduce the dependence on antimicrobial agents by preventing and treating bacterial and viral infections, as well as secondary infections caused by both, thereby lowering the risk of AMR. Unlike traditional antibiotics, bacterial vaccines trigger a long-lasting immune response that not only prevents bacterial infections but also inhibits the spread of resistant strains. They show significant advantages in reducing antibiotic use and lowering resistance risks. However, the development of bacterial vaccines faces several challenges, including the diversity of bacterial antigens, rapid evolution, and the difficulty of achieving broad-spectrum immune protection. Despite these challenges, advancements in vaccine technology and the optimization of delivery systems are making the application prospects of bacterial vaccines in combating resistant strains increasingly promising. We sequentially discuss resistance mechanisms, existing and emerging vaccine platforms, enabling technologies, and future perspectives.

Keywords: antimicrobial resistance, bacterial vaccines, bacterial infections, challenges, technology

Introduction

The introduction of penicillin marked the beginning of the antibiotic era and is widely regarded as one of the most significant advancements in the field of medicine.[1] The advent and use of antimicrobial drugs have played a crucial role in treating infectious diseases, improving health, and saving millions of lives globally. However, with the increasing problem of antibiotic misuse, the incidence of infectious diseases has risen once again. Drug-resistant bacteria are spreading rapidly worldwide, leading to the expansion of the "superbug" family, which poses a severe pathogenic threat in clinical infections.[2] In 2014, the World Health Organization (WHO) released the Global Antimicrobial Resistance Surveillance Report, highlighting that in the United States, antibiotic-resistant bacterial infections result in approximately 63,000 deaths annually, while in the European Union, the figure is around 25,000.[3] If the global spread of superbugs remains unchecked, the resulting death toll could rise to 10 million annually.[4]

Generally, the development of bacterial resistance is a natural evolutionary process. Several key factors contribute to the emergence of resistance, including bacterial natural selection, environmental conditions in communities and hospitals, excessive use of antibiotics, and the availability of new antibiotics—all of which have significantly accelerated the global spread of AMR.[5,6] Research on the mechanisms of bacterial resistance has long been a major focus of experimental and clinical studies. Addressing the issue of AMR requires not only a focus on developing new antimicrobial drugs but also the adoption of other effective strategies.

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Bacterial vaccines play a crucial role in preventing bacterial infections, with the emergence of new bacterial vaccines providing innovative solutions, particularly RNA and peptide vaccines.[7] These vaccines can prevent bacterial infections by eliciting long-lasting immune responses, suppressing the spread of resistant strains, and triggering specific immune responses in the early stages of infection. Bacterial vaccines help reduce host infections, thereby controlling the spread of infections and decreasing the demand for antibiotic use. Currently, with advances in various biological sciences and technologies, new approaches to bacterial vaccine design have continuously emerged, making it a focus of scientific research. Vaccines represent a promising complementary strategy in combating AMR. This article provides a systematic review of AMR mechanisms, novel bacterial vaccine technologies, and their developmental challenges. Its distinctive contribution lies in explicitly connecting these two fields: we analyze how specific vaccine platforms are designed to counteract particular resistance mechanisms. Beyond this integrative analysis, we offer a critical update on the translational progress of promising platforms like OMVs and mRNA vaccines, discussing their practical challenges and clinical trajectories. Thus, this work serves as a targeted reference that links vaccine design rationale directly to the evolving problem of AMR.

The Resistance Mechanism of Antibiotics

Antibiotic resistance (AR) is primarily divided into two types: intrinsic resistance and acquired resistance.[8] Intrinsic resistance is an inherent trait of bacteria, determined by their chromosomes, hereditary, and predictable based on bacterial species.[9] Acquired resistance, on the other hand, results from bacteria gaining new genetic material through mechanisms like DNA transformation, conjugation, transcription, or mutation.[10] The main mechanisms of antibiotic resistance can be categorized into four types (Figure 1) reduced drug permeability, 2) active antibiotic efflux, 3) enzymatic inactivation of antibiotics, and 4) modification or alteration of antibiotic targets.[8] Gram-positive bacteria lack an outer membrane; consequently, they employ reduced permeability and/or efflux pumps differently from Gram-negatives, and these mechanisms contribute less frequently to clinically relevant resistance.[8,11]

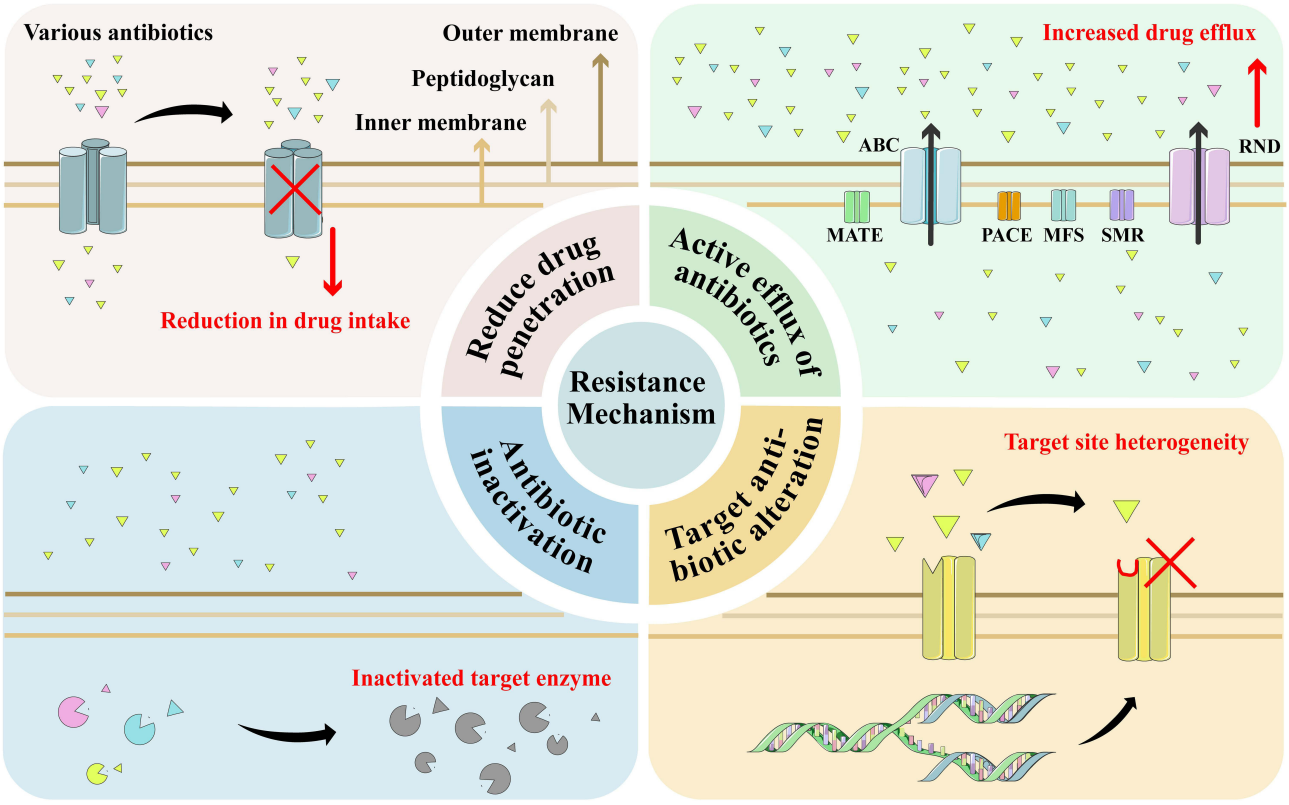

Figure 1 The resistance mechanism of antibiotics.

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Reduce Drug Penetration

Antibiotics exert their effects by penetrating bacterial cell membranes, a process that is particularly critical for Gram-negative bacteria.[12] Due to the double-membrane structure of Gram-negative bacteria, their permeability to certain antibiotics is lower compared to Gram-positive bacteria. The main ways to reduce antibiotic permeability include the regulation of outer membrane porin (Omp) and alterations in membrane structure.[13] Omp are specialized channel proteins composed of phospholipids and lipopolysaccharides, allowing some antibiotics to pass through the outer membrane and enter bacterial cells. The quantity and function of these porins are crucial for antibiotic permeability. Bacteria can significantly reduce the speed and quantity of antibiotic entry by decreasing porin expression or altering porin structure, thereby enhancing resistance. For instance, *Escherichia coli* (*E. coli*) decreases the expression of the OmpF, reducing permeability to antibiotics, especially aminoglycosides and β-lactam antibiotics.[14] *Klebsiella pneumoniae* (*K. pneumoniae*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) enhance their antibiotic resistance by regulating porin expression.[15,16]

In addition to reducing the expression of porins, bacteria can also alter the structure of porins through gene mutations or regulation, making it more difficult for antibiotics to pass through these channels into the cells. For example, *P. aeruginosa* can mutate to change the structure of its outer membrane porin OprD, decreasing the ability of carbapenem antibiotics (such as meropenem and imipenem) to enter the cell.[17] In *E. coli*, mutations in the porin genes OmpC and OmpF can lead to a reduction in pore diameter or changes in surface charge, thereby decreasing the permeability of β-lactam antibiotics (such as penicillin).[14] By reducing the permeability to antibiotics, bacteria significantly lower the accumulation of these drugs within the cells and, in combination with other resistance mechanisms (such as efflux pumps and antibiotic-inactivating enzymes), exhibit high levels of resistance to different classes of antibiotics. This resistance mechanism poses significant challenges to the success of antibiotic therapy, especially in the treatment of difficult-to-treat infections.

In contrast to Gram-negative bacteria, Gram-positive species lack an outer membrane and possess a thick peptidoglycan layer. While this structure generally renders them more permeable to many antibiotics, it also serves as a primary barrier and target.[18] Resistance via reduced penetration in Gram-positives is less common but can occur through modifications in cell wall composition or charge, which can impede the uptake of certain cationic antimicrobial peptides or glycopeptides.[19] For example, alterations in the net positive charge of the cell envelope in Staphylococcus aureus can reduce the binding and efficacy of daptomycin.[20]

Active Efflux of Antibiotics

The expulsion of drugs from the cell through specific or general antibiotic efflux pumps is one of the important mechanisms of antibiotic resistance. Efflux pumps are transmembrane proteins that can transport various toxic compounds, including antibiotics, across the bacterial membrane in an energy-dependent manner.[21] They work in conjunction with the impermeable bilayer membrane, enabling these pathogens to develop intrinsic resistance to many antibiotics. A single antibiotic can be expelled by multiple different efflux pumps, and a single efflux pump can also expel different substrates. Efflux pumps exist in various forms in most bacteria and are currently classified into six main families: ATP-binding cassette (ABC), small multidrug resistance (SMR), large facilitator superfamily (MFS), multidrug and toxic compound extrusion (MATE), and resistance-nodulation-cell division (RND).[22] Efflux pumps from the MFS and ABC families are predominant in Gram-positive pathogens and contribute significantly to their multidrug resistance profiles. Notable examples include NorA and MepA in S. aureus, which export fluoroquinolones and other agents, and the Msr(A) macroide efflux pump in staphylococci and streptococci.[23,24] In Enterococcus faecalis, the EmeA pump confers resistance to biocides and dyes.[25] The regulation of these pumps, often via local transcriptional regulators, is a key factor in the adaptive resistance of Gram-positive bacteria. Different efflux systems have varying impacts on specific drugs, providing different levels of resistance. For example, the Tet efflux pump from the MFS family can use proton exchange as an energy source to expel tetracycline, while MacB, a member of the ABC family, can couple the hydrolysis of cytoplasmic ATP with transmembrane conformational changes to work in the periplasmic space, functioning as a MacAB-TolC tripartite pump to expel macrolide antibiotics.[26,27]

Bacteria precisely regulate the expression of efflux pumps through various signaling pathways to ensure a rapid response to increased environmental stress. Common regulatory mechanisms include global regulators and local regulators.[28] Global regulators, such as MarA, SoxS, and Rob, can sense stress signals in the environment (such as antibiotic pressure and oxidative stress) and activate the expression of efflux pump genes.[29] For example, in *E. coli*, the MarA regulatory system can upregulate the expression of the AcrAB-TolC pump, enhancing the bacteria's resistance to multiple antibiotics.[30] Some local regulators, such as the negative regulatory factors MexR and NfxB in *P. aeruginosa* when mutated or inactivated, can lead to the overexpression of efflux pumps, thereby increasing resistance.[31] Efflux pumps are not only important tools for antibiotic-resistant bacteria to withstand antibiotics but are also core factors in the current global antibiotic resistance crisis. Developing effective efflux pump inhibitors and exploring new antibacterial strategies are of great significance.

Antibiotic Inactivation

Many antibiotics contain easily hydrolyzable sensitive chemical bonds (such as ester bonds and amide bonds), the integrity of which is crucial for their biological activity. Bacteria can evolve enzymes that target and eliminate these vulnerable chemical bonds, thereby developing mechanisms to destroy the activity of antibiotics. This mechanism is particularly widespread in resistance to β-lactam antibiotics, aminoglycosides, and macrolide antibiotics.[32]

β-lactamases are hydrolytic enzymes produced by bacteria that can break down the β-lactam ring. They can be classified into narrow-spectrum β-lactamases and extended-spectrum β-lactamases (ESBLs), as well as higher-level carbapenemases, based on their functional characteristics and molecular structure.[33] Narrow-spectrum β-lactamases primarily hydrolyze penicillin antibiotics and are found in Gram-negative bacteria such as *E. coli* and *K. pneumoniae*.[34] Extended-spectrum β-lactamases can hydrolyze not only penicillin but also most cephalosporins.[35] Carbapenem antibiotics (such as meropenem and imipenem) are the most effective among broad-spectrum antibiotics; however, certain bacteria, particularly *P. aeruginosa* and *Acinetobacter baumannii* (*A. baumannii*), have developed resistance to these antibiotics by producing carbapenemases.[36]

Aminoglycoside antibiotics (such as streptomycin and gentamicin) work by binding to bacterial ribosomes to inhibit protein synthesis. However, bacteria can produce modifying enzymes to chemically alter these antibiotics, preventing them from binding to the ribosome.[37,38] These modifying enzymes are divided into three main types: aminoglycoside acetyltransferases (AACs), aminoglycoside phosphotransferases (APHs), and aminoglycoside adenylyltransferases (ANTs).[39] AACs transfer an acetyl group to the aminoglycoside molecule, thereby blocking its binding to the ribosome. For example, AAC (3)-II, found in E coli and Klebsiella species, can resist the effects of aminoglycoside antibiotics.[40] APHs inactivate aminoglycosides through phosphorylation such as APH (3′).[41] ANTs inactivate aminoglycosides by adenylylation.[42]

Macrolide antibiotics (such as erythromycin and azithromycin) inhibit protein synthesis by binding to the 50S subunit of the ribosome, bacteria can inactivate macrolides by producing macrolide-modifying enzymes that disrupt their molecular structure. For instance, esterases produced by Enterococcus species can hydrolyze erythromycin, preventing it from binding to the ribosome.[43]

Enzymatic inactivation is a cornerstone of resistance in Gram-positive bacteria.[44] Beyond the Enterococcal esterases mentioned, the most clinically significant mechanism is the production of β-lactamases and, more critically, the acquisition of genes encoding alternative, low-affinity Penicillin-Binding Proteins (PBPs).[45] Although not an "inactivation" mechanism in the strict enzymatic sense, the mecA-encoded PBP2a in methicillin-resistant S. aureus (MRSA) functionally renders all β-lactam antibiotics ineffective by providing an alternative cell wall synthesis pathway.[46]

Antibiotic Target Modification and Alteration

Antibiotics bind with high affinity to key targets, inhibiting essential cellular functions, which leads to growth inhibition or cell death. Bacteria can develop antibiotic resistance by altering the structure of these drug targets, reducing the drug's affinity for the cellular target. For example, penicillin and other β-lactam antibiotics inhibit bacterial cell wall synthesis by binding to essential enzymes called PBPs, which prevents cell wall formation and leads to bacterial death.[47] To counteract this effect, bacteria can reduce the affinity of PBPs for β-lactam antibiotics by modifying the PBPs' structure.

Additionally, bacteria can produce erythromycin ribosomal methylases encoded by the Erm gene family. These enzymes methylate the 16S rRNA, modifying drug-binding sites and preventing the binding of macrolides, streptomycin, and lincosamides.[48]

Target modification is arguably the most defining resistance mechanism in Gram-positive pathogens.[49] The paradigm is the aforementioned PBP2a in MRSA. Similarly, vancomycin resistance in enterococci (VRE) is mediated by the alteration of the peptidoglycan precursor target (D-Ala-D-Ala to D-Ala-D-Lac), reducing vancomycin binding affinity.[50] Ribosomal target protection, as seen with tetracycline resistance genes that encode proteins displacing the drug from its ribosome binding site, is also common in streptococci and enterococci.[51] In summary, bacteria develop antibiotic resistance through various mechanisms, which can act independently or synergistically to confer broad-spectrum resistance.

Bacterial Immune Evasion

The immune evasion mechanisms employed by bacteria constitute critical strategies for establishing and sustaining infections within the host, thereby posing a significant challenge in vaccine development.[52] Pathogenic bacteria utilize various tactics to evade detection and elimination by the immune system. One such strategy is antigenic variation and masking; for example, *Streptococcus pneumoniae* achieves antigenic diversity through the expression of over 90 capsular serotypes, while *Mycobacterium tuberculosis* relies on its lipid-rich, thick cell wall to physically shield internal antigens.[53] Another strategy involves the secretion of immune modulatory factors; Staphylococcus aureus, for instance, produces chemokine inhibitory proteins and complement inhibitory proteins that disrupt the recruitment and activation of immune cells.[54] Additionally, some bacteria interfere with phagocytosis and intracellular killing processes, as demonstrated by *Mycobacterium tuberculosis*, which inhibits phagosome maturation, and Legionella pneumophila, which creates an endoplasmic reticulum-like replication niche.[55] Lastly, the formation of biofilms represents another evasion tactic; *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* construct physical barriers and establish immunosuppressive microenvironments through biofilm matrices.[56] These evasion strategies critically influence the rationale and technical methodologies employed in vaccine development. For instance, multivalent conjugate vaccines are necessary for addressing the high variability of capsular antigens;[57] viral vector vaccines should be designed to elicit robust cellular immunity against intracellular parasites;[58] reverse vaccinology can be utilized to identify conserved antigens, thereby mitigating the challenges posed by antigenic variation;[59] and innovative delivery systems, such as nanoparticles and outer membrane vesicles, can improve the presentation efficiency of weakly immunogenic antigens and overcome bacterial immune shielding barriers.[60] Consequently, a comprehensive understanding of bacterial immune evasion mechanisms is essential not only for elucidating their pathogenicity but also as a foundational element in the design of next-generation vaccines capable of circumventing these natural defense mechanisms and providing durable immune protection.

Classification and Characteristics of New Bacterial Vaccines

Bacterial vaccines are regarded as a promising tool in combating AMR by preventing bacterial infections and reducing reliance on antibiotics. Traditional vaccines, such as whole-cell vaccines (WCV) and live attenuated vaccines (LAV), have been in use for many years,[61] although these vaccines provide broad-spectrum protection against bacterial infections, they face limitations. Key bacterial antigens, such as serotype-specific polysaccharides on the cell wall, often exhibit weak immunogenicity, reducing the efficacy of vaccines. Additionally, vaccines based on inactivated bacteria can cause adverse reactions in immunocompromised individuals, highlighting the need for safer and more effective alternatives. Advances in immunology, molecular biology, and multi-omics have paved the way for the development of a diverse array of next-generation bacterial vaccines, which are broadly classified into several innovative platforms as discussed below (Figure 2 and Table 1).

Live Vector Vaccines

Live vector vaccines, as a new type of vaccine, offer significant advantages and promising applications compared to traditional vaccines. These vaccines use attenuated live bacteria or viruses as vectors, into which target antigens are

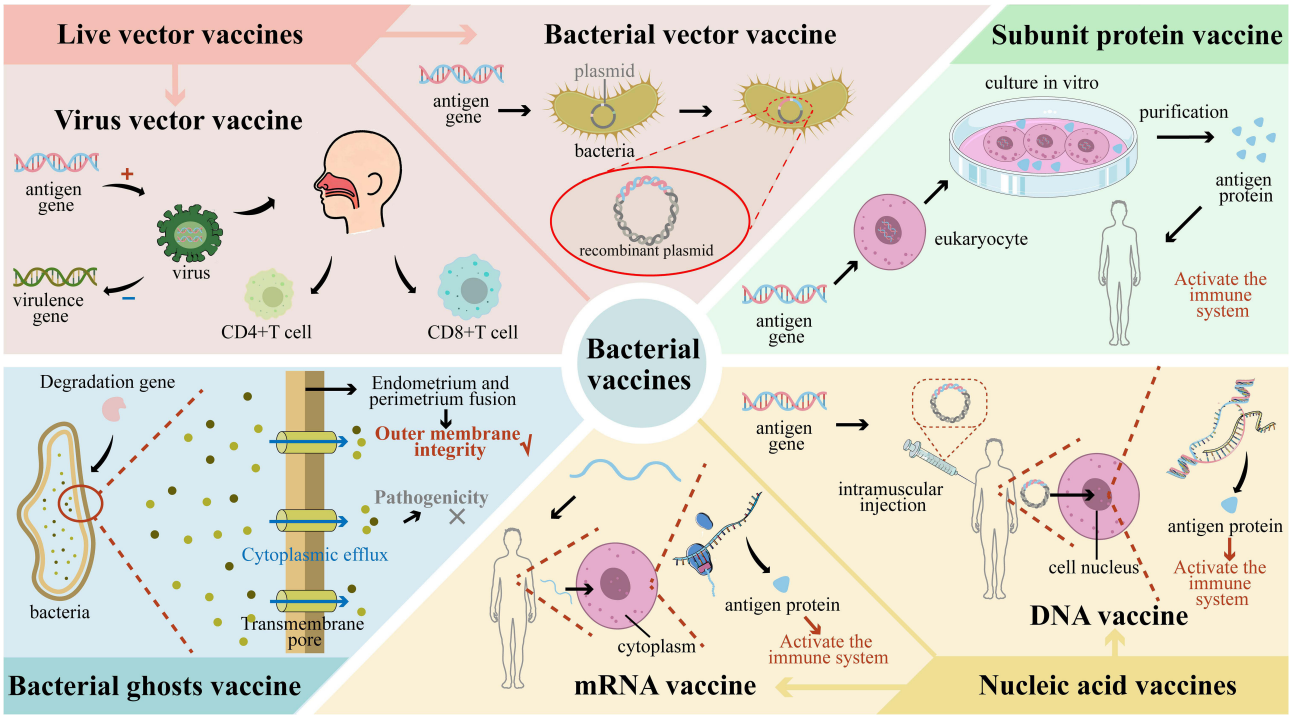

Figure 2 Classification and characteristics of new bacterial vaccines. Black arrows indicate procedural flow. Red arrows denote activation events. A red "+" signifies up-regulation or enhancement; a blue "−" indicates selective removal. Blue arrows illustrate efflux through the trans-membrane pore. Red circles highlight regions emphasized in the main text. A red check-mark (√) marks retention of activity, whereas a grey cross (×) indicates reduction (toxicity attenuation).

introduced through molecular biology techniques. Live vector vaccines can induce humoral immunity, cellular immunity, and mucosal immunity in the body.

Bacterial Vector Vaccine

A bacterial live vector vaccine involves inserting specific antigen genes from a pathogen into the bacterial genome or its plasmids. During bacterial proliferation, it directly expresses foreign antigens or presents the foreign DNA to host cells as a type of recombinant bacteria. Common bacterial vectors include Salmonella, Listeria monocytogenes, Lactobacillus, Bordetella pertussis (B. pertussis), and Bacillus subtilis. Salmonella, a Gram-negative bacterium, can undergo attenuation through chemical mutation or genetic engineering, making it one of the most widely studied bacterial vectors. When attenuated Salmonella is used as a live vector, it is typically administered orally or nasally, delivering target antigen proteins or antigen plasmids to host cells through a natural infection route, thereby inducing an immune response.[62,63] For example, Corthésy et al used attenuated Salmonella typhimurium (S typhimurium) as a vector, introducing genes encoding Helicobacter pylori (H. pylori) urease subunits A and B, and immunized mice nasally, the results showed that 60% of the mice developed resistance to H. pylori, triggering both Th1 and Th2 immune responses.[64] Lactobacillus is considered one of the safest bacterial vectors available, studies have shown that Lactococcus lactis can deliver DNA plasmids into host cells. For instance, Adachi et al developed a vector vaccine using *Lactobacillus casei* to express human papillomavirus (HPV) E7 protein, and administered it to mice through oral, intradermal, and intramuscular routes, effectively inducing a mucosal immune response.[65]

Despite certain progress in bacterial live vector vaccines, they still face two major challenges: first, how to improve the stability of live vectors to ensure immune efficacy while inducing more durable and effective immune protection; second, the safety concerns in clinical applications, as reversion to virulence may pose serious health risks to the host.

Virus Vector Vaccine

Through genetic engineering modifications, viral vectors retain their cell-infecting capability while deleting virulence genes, enabling them to deliver antigen genes to the host body without causing disease. This process generates antigens

Table 1 Comparative Summary of New Bacterial Vaccines

Classification	CoreTechnology/Principle	Key Advantages	Major Challenges/Limitations
Live Vector Vaccines	Use attenuated bacteria or viruses, MVA as vectors to deliver and express target antigen genes.	• Induce broad immune responses (humoral, cellular, mucosal). • Mimic natural infection, promoting durable immunity. • Suitable for intracellular pathogens.	• Risk of virulence reversion (bacterial vectors). • Preexisting immunity can limit efficacy (viral vectors). • Potential safety concerns in immunocompromised hosts.
Bacterial Ghost Vaccines	Gram-negative bacterial envelopes emptied of cytoplasmic content via controlled expression of phage lysis gene E, retaining native outer membrane structure.	• Retain native antigen conformation and immunogenicity. • Non-living, improved safety profile. • Self-adjuvating; no need for external adjuvants.	• Primarily applicable to Gram-negative bacteria. • Complex production and scale-up. • Potential antigen loss during "ghosting" process.
Nucleic Acid Vaccines	Delivery of plasmid DNA or mRNA encoding antigen(s) into host cells, which then produce the antigen and stimulate immunity.	• Rapid design and manufacturing. • Flexible for multi-antigen or broad-spectrum design. • DNA vaccines induce strong T-cell responses; mRNA vaccines avoid genome integration.	• Low in vivo transfection efficiency (DNA). • Stability and cold-chain requirements (mRNA). • Bacterial mRNA vaccines are still in pre-clinical stages. • Potential safety issues (eg, autoimmunity).
Subunit Protein Vaccines	Recombinant expression and purification of pathogen-specific proteins, administered with adjuvants.	• High safety (no live components). • Well-defined composition, scalable production. • Can target conserved, essential virulence factors.	• Often weak immunogenicity, requiring potent adjuvants. • May not cover all protective epitopes. • Limited efficacy against intracellular bacteria.

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that induce CD4+ and CD8+ T cell-mediated immune responses.[66] Common viral vectors in bacterial vaccines include adenovirus (AdV) and modified vaccinia virus (MVA).[67] AdV have shown promising developments in tuberculosis prevention, these vaccines deliver *Mycobacterium tuberculosis* (*M. tuberculosis*) antigen genes into the human body, inducing specific immune responses against tuberculosis. Currently, three primary vaccines are advancing in development: AdAg85A based on human adenovirus type 5 (Ad5), AERAS-402 based on type 35, and ChAdOx1.85A based on a chimpanzee adenovirus vector (ChAd).[68]

Using guinea pigs as models, Xing et al assessed AdAg85A's efficacy, demonstrating a significantly higher survival rate in guinea pigs vaccinated with BCG/AdAg85A by nasal or intramuscular routes compared to controls.[69] Notably, guinea pigs vaccinated via the nasal mucosal route saw survival rates increase from 10% to 60% upon reinfection with *M. tuberculosis*. This vaccine has undergone extensive testing across multiple animal models and Phase I to IIb clinical trials, showing that nasal immunization can induce CD4+ and CD8+ T cell responses, providing protection against *M. tuberculosis* infection.

The AERAS-402, based on the Ad35 vector, expresses Ag85A, Ag85B, and TB10.4, and research shows it induces robust T cell immune responses and protection against *M. tuberculosis* in murine models.[70] Its safety and immunogenicity have been validated in healthy adults, and it is currently in Phase II clinical trials.[68]

To counteract the impact of pre-existing anti-adenovirus antibodies in humans, researchers developed the recombinant vaccine ChAdOx1.85A based on chimpanzee adenovirus. This vaccine expresses Ag85A and induces high levels of cellular immune responses and protection against *M. tuberculosis* infection. ChAdOx1.85A is currently undergoing Phase II clinical trials.[68,71]

Poxviruses are double-stranded DNA viruses classified into two subfamilies and twelve genera. Different species of poxviruses infect various animals, causing related diseases. For safety, most studies employ replication-deficient poxviruses. These viruses can activate humoral and cellular immunity, particularly T-cell responses, which aid in controlling intracellular pathogens—a crucial feature for preventing and treating infections by intracellular pathogens like *M. tuberculosis*. Representative poxvirus vectors include four types of replication-deficient poxviruses: modified vaccinia virus Ankara (MVA), NYVAC derived from the Copenhagen strain, ALVAC derived from canarypox virus, and TROVAC derived from avipoxvirus.[72,73] Poxvirus vectors are currently used in developing vaccines for bacterial infections like tuberculosis and anthrax, with some already in clinical trials. One example is the tuberculosis vaccine MVA85A, which uses MVA as a vector. Although clinical trials have shown that MVA85A has good immunogenicity, its protective efficacy still requires improvement.

In summary, live vector vaccines can induce multiple immune responses; however, genome integration may lead to uncontrolled gene expression, and attenuated live vectors carry the potential risk of virulence reversion. Future research should focus on further refining immunization pathways and conducting long-term monitoring of the safety and immunogenicity of live vector vaccines to better understand and optimize their performance.

Bacterial Ghost Vaccine

A bacterial ghost is the outer shell structure of Gram-negative bacteria that lacks cytoplasmic components such as nucleic acids and ribosomes. Through the expression of the lytic gene E from bacteriophage PhiX174, the inner and outer membranes of the bacterium fuse, creating transmembrane pores with diameters ranging from 40 to 200 nm. The cytoplasmic contents are then expelled through these pores by osmotic pressure. Bacterial ghosts retain a complete outer membrane structure similar to that of natural bacteria but lack the pathogenicity of live bacteria. As a result, they can serve as vaccines, inducing both humoral and cellular immune responses without the need for adjuvants.

Eko et al conducted oral immunization experiments on rabbits using bacterial ghosts derived from *Vibrio cholerae* (*V. cholerae*) O1 or O139, the results showed that this bacterial ghost vaccine could induce high-titer antibodies against *V. cholerae*, with rabbits exhibiting complement-dependent killing activity against both homologous and heterologous strains.[74] Chen et al developed a novel vaccine based on S typhimurium bacterial ghosts (SL7207-BG) and performed oral immunization on mice infected with H. pylori, and the results indicated that this vaccine could induce strong humoral and cellular immune responses in mice.[75] Recombinant bacterial ghost vaccines have now been successfully

developed against *E. coli*,[76] Flavobacterium columnare,[77] Haemophilus parasuis,[78] and streptococcal diseases.[79] As a safe and highly immunogenic inactivated vaccine candidate, bacterial ghosts show broad application potential.

Nucleic Acid Vaccines

Nucleic acid vaccines function by introducing a vector containing the exogenous gene sequence (DNA or mRNA) encoding the antigenic protein into the host. This approach relies on the host cell's expression system to synthesize the antigenic protein, thereby inducing an immune response against the antigen in the host to prevent or treat diseases.

DNA Vaccine

DNA vaccines utilize plasmids as vectors to deliver gene fragments encoding antigens into the host. Host cells then synthesize the target antigen protein through transcription and translation, presenting it to the immune system and thereby inducing a strong humoral and cellular immune response. DNA vaccines can be administered through various routes, including intramuscular injection, subcutaneous injection, mucosal delivery, in vivo electroporation, and even cupping.[80–82] In one study, Jiang et al cloned the ESAT-6 T-cell epitope gene of *M. tuberculosis* along with the FMS-like tyrosine kinase 3 ligand gene into the pIRES plasmid and administered it to mice via intramuscular injection, significantly inducing CD4+ Th1 and CD8+ T-cell immune responses.[83] Additionally, a *V. cholerae* DNA vaccine constructed with the cholera toxin B subunit (CTB) or Omp genes enabled antigen expression in the host and elicited a robust antibody response, thus providing strong scientific support for the development of DNA vaccines to prevent cholera infection.[84]

mRNA Vaccine

mRNA vaccines are recognized for their effectiveness in preventing viral infections, and their application in bacterial infections is gradually gaining attention. Bacterial RNA vaccines are under investigation as potential tools for addressing bacterial infections, particularly those caused by multidrug-resistant strains. By designing RNA vaccines that target multiple antigens of bacteria, it is possible to develop broad-spectrum vaccines that can combat various drug-resistant strains. This approach is especially promising in the context of hospital-acquired infections (HAIs) and in combating highly resistant bacteria such as MRSA or pan-drug-resistant (PDR) A. baumannii.

RNA vaccines deliver mRNA that encodes pathogen antigens, enabling human cells to express the corresponding antigen proteins. The immune system then recognizes and attacks these antigens, leading to a protective immune response against the pathogen. This approach bypasses the traditional processes of culturing or producing antigen proteins in vaccines, significantly accelerating the vaccine development process. Although no RNA vaccines targeting bacterial infections have yet entered clinical use, preliminary studies have shown their potential feasibility. For example, RNA vaccines targeting pathogenic bacteria such as *M. tuberculosis* and *K. pneumoniae* are currently being tested in animal models. RNA-based vaccines against bacterial pathogens are still at the pre-clinical stage; no bacterial mRNA vaccines have yet entered human clinical trials. In the future, RNA vaccines are expected to be used for the prevention or treatment of a range of bacterial infections that are difficult to control with traditional antibiotics.

Subunit Protein Vaccine

Subunit protein vaccines are developed by inserting genes encoding pathogen-specific proteins into appropriate expression systems, such as prokaryotic expression systems like *E. coli*, or eukaryotic expression systems like yeast, insect cells, and mammalian cells. The pathogen proteins are then cultured in large quantities in vitro and subsequently purified. Subunit vaccines typically require the use of adjuvants to enhance the immunogenicity of the vaccine and maintain a lasting immune response. For example, Monaci et al evaluated the effect of the MF59 adjuvant on the immunogenicity and efficacy of the 4c-Staphylococcus aureus vaccine in mice, the findings demonstrated that intraperitoneal injection of the MF59/4c-Staphylococcus aureus vaccine could induce a durable protective immune response and significantly improve the survival rate of mice in a Staphylococcus aureus peritonitis model.[85]

Currently, available subunit protein vaccines for human use include the hepatitis B vaccine, influenza vaccine, shingles vaccine, cholera vaccine, and group B meningococcal vaccine. The recombinant subunit vaccine platform has

technical advantages such as safety, efficacy, mature industrialization, and good stability. Selecting appropriate adjuvants and optimizing the immunization route are crucial for enhancing the protective efficacy of these vaccines.

Innovative Technologies for Enhancing Bacterial Vaccine Development

Advancements in new technologies offer potential breakthroughs for the development of highly effective vaccines. For example, optimizing the use of adjuvants can significantly enhance the immunogenicity of vaccines; bacterial outer membrane vesicles (OMVs) serve as effective immunostimulants to induce host immune responses; and the introduction of nanomaterials provides more precise and efficient pathways for vaccine delivery and antigen presentation (Figure 3).

Adjuvant Technology

Vaccines typically consist of three components: immunogen, adjuvant, and carrier. The immunogen determines the specificity and targeting of the induced immune response; the adjuvant influences the intensity of the immune response; and the carrier determines the type of response elicited. Adjuvants exert their effects through various mechanisms, including stimulating the release of cytokines and chemokines, enhancing antigen presentation, activating inflammasomes, and delaying antigen degradation. Clinical studies have shown that adjuvants play a crucial role in vaccines by rapidly triggering immune responses, promoting the recruitment and activation of immune cells, and effectively inducing

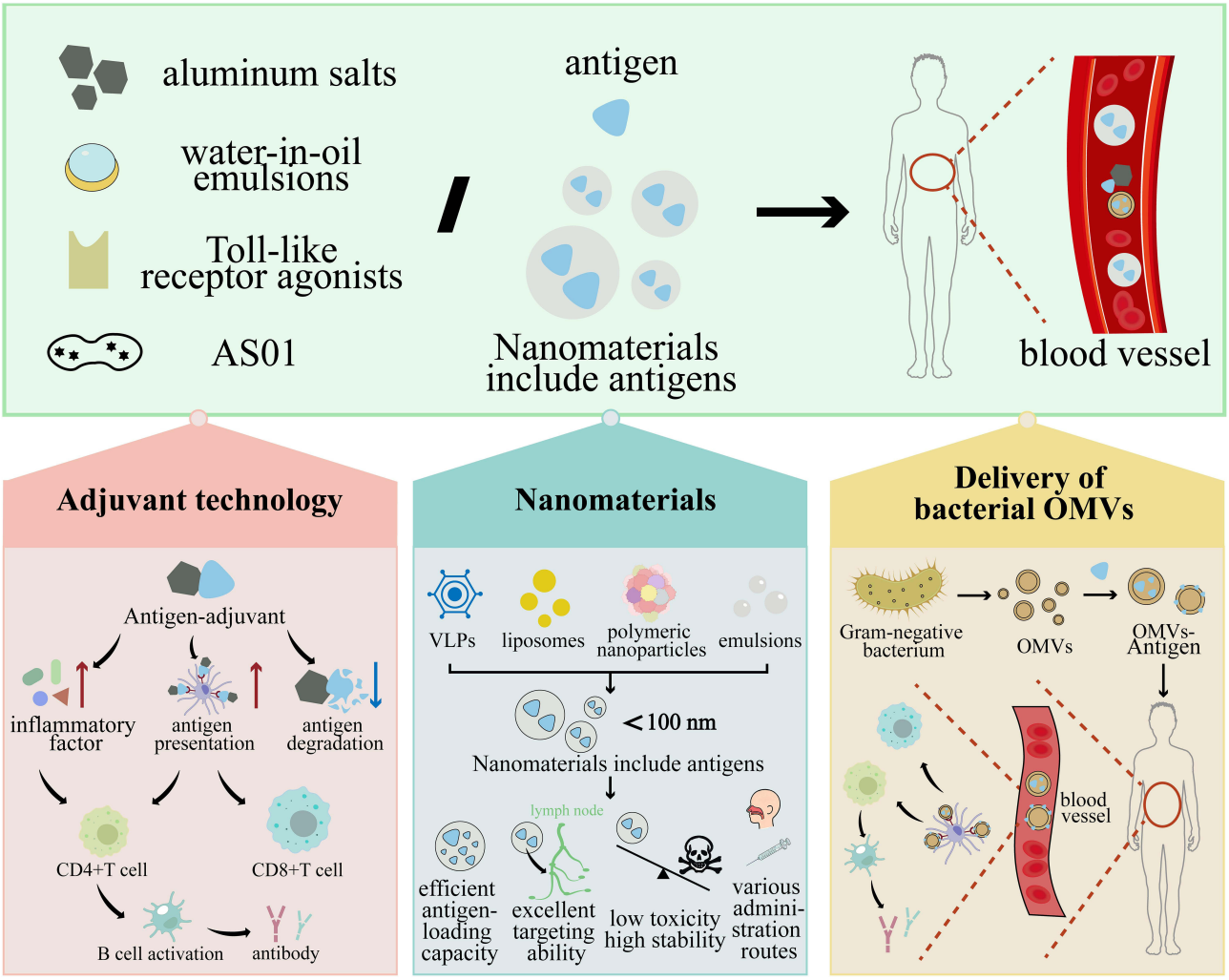

Figure 3 Innovative technologies for enhancing bacterial vaccine development. Black arrows trace the experimental workflow. Red arrows represent increases in target yield; blue arrows depict decreases. Red circles delineate the anatomical areas selected for detailed display.

antigen-specific T cell production by targeting antigen-presenting cells.[86] For example, polylactic acid (PLA) nanoparticles used as adjuvants for pneumococcal polysaccharide vaccines can enhance the stability and immunogenicity of the antigens;[87] Freund's complete Adjuvant used in anthrax vaccine preparation can create a durable antigen reservoir at the injection site, thus enhancing the immune response. Currently, the FDA in the United States has approved various adjuvants for use in human vaccines, including aluminum salts, water-in-oil emulsions, Toll-like receptor agonists, and AS01 (Table 2).

Application of Nanomaterials in Antibacterial Vaccine Design

Nanomaterials, defined as particles with a diameter at the nanoscale (<100 nm), serve as delivery carriers for vaccine antigens. Compared with traditional vaccines, nano-vaccines based on nanomaterials and technology offer significant advantages, including efficient antigen-loading capacity, excellent targeting ability, low toxicity, high stability, and various administration routes. Nanomaterials have diverse functions in vaccine applications, with nearly all nano-vaccines utilizing nanomaterials as transport carriers. Some nanomaterials also possess intrinsic immunogenicity, enabling them to act as adjuvants. Common nanomaterials used in vaccines include virus-like particles (VLPs), liposomes, polymeric nanoparticles, and emulsions (Table 3).

In the design and application of bacterial vaccines, nanomaterials show immense potential. Wei et al reported a multi-antigen nano-toxoid vaccine based on poly lactic-co-glycolic acid nanoparticles coated with macrophage membranes, this vaccine significantly enhanced mice's resistance to pathogenic *P. aeruginosa* without triggering hemolysis or other toxin-related responses.[88] Studies have shown that, whether administered subcutaneously or intranasally, this vaccine induces

Table 2 The Functions and Types of Human Vaccine Adjuvants

Adjuvant Name	Time to Market	Explanation	Function	Disease Type	Vaccine Type
Alum	1926	Insoluble particulates of hydroxide, phosphate, hydroxy phosphate sulfate salts	Stimulate antibody production, enhance antigen immunogenicity	Diphtheria, tetanus, pertussis, inactivated poliomyelitis vaccine, hepatitis A and B, human papilloma virus, meningococcal, pneumococcal	Inactivated vaccines, protein vaccines
MF59	1997	Oil in water emulsion of squalene, span 85, tween 80	Enhances recruitment of APCs and their activation, promotes antigen uptake and migration of immune cells to lymph nodes, modulates humoral and cell immune responses	Influenza	Flu vaccine
AS04	2005	Alum-adsorbed TLR4 agonist	Stimulates TLR.4, increasing APC maturation, imparts the Th1 type of immune response. improves humoral and cellular immune responses.	Human papilloma virus and hepatitis B virus	Subunit vaccine
AS03	2009	Oil-in-water emulsion	Induces the production of cytokines and recruitment of immune cells. modulates humoral and cellular immunity	Infectious diseases	Flu vaccine
AS01	2017	Liposome	Recruit monocytes and neutrophils, promote monocyte differentiation into dendritic cells, enhance the antigen presentation ability of dendritic cells	Malaria and herpes	Shingles Vaccine
OMV	2015	Outer Membrane Vesicle	Activate the intrinsic immune signaling pathway	Meningitis	B-type meningococcal vaccine
Virosome	2000	Liposome	Promotes uptake of vaccine antigen by APCs interacts with B cells leading to T-cell activation.	Hepatitis A, influenza	Influenza vaccine and hepatitis A vaccine
CpG 1018	2017	Soluble TLR9 ligand (oligonucleotide) co-administered with HBV vaccine, 22-mer oligonucleotide sequence containing CpG motifs	Boosts the humoral immune response, Th1-type immunity, CD8+ T-cell-mediated immunity	Hepatitis B	Influenza vaccine and hepatitis A vaccine

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Table 3 Nanomaterials Commonly Used in Vaccines and Their Characteristics

Types of Nanomaterials	Purpose and Application	Characteristics and Advantages	Application Instructions
Lipid nanoparticles	Delivering bacterial antigens or DNA vaccines	Effectively package antigens or DNA to protect them from degradation	*Mycobacterium tuberculosis* vaccine
Polymeric nanoparticle	Antigen and adjuvant carriers	Controlled antigen release, good biodegradability	Chitosan or PLGA nanoparticles
Gold Nanoparticles	Enhance immune response	High stability, easy surface modification of antigens, improved antigen delivery and immune response	Anti Helicobacter pylori vaccine
Iron oxide nanoparticles	Adjuvants and antigen carriers	Magnetic targeted delivery while enhancing antigen presentation	Salmonella vaccine
Nano emulsion	Stable antigen carrier	Enhance immunogenicity, great biocompatibility and stability	Anti anthrax vaccine
Protein nanoparticles	Antigen carrier and adjuvant	Improve antigen delivery efficiency and promote immune cell recognition	VLP used for tetanus

specific memory antibodies against *P. aeruginosa*, effectively preventing lethal infections caused by carbapenem-resistant *K. pneumoniae* (CRKP). Additionally, Wu et al developed a core-shell structured vaccine comprising CRKP outer membrane vesicles encapsulating bovine serum albumin nanoparticles, which significantly promoted the accumulation of CRKP-specific antibodies in mice, thereby protecting them from *K. pneumoniae* infection.[89] Despite the broad application of nanomaterials in vaccine development, there are limitations and challenges. For example, some nanoparticle-based vaccines may induce systemic or localized inflammatory reactions,[90] and certain nanomaterials with prolonged residence in the body could lead to thrombus formation.[91] Moreover, the production and storage costs of nanomaterial-based vaccines are relatively high.[92]

Application of OMVs in Antibacterial Vaccine Design

OMVs are spherical structures with diameters ranging from 10 to 250 nanometers, secreted by Gram-negative bacteria. OMVs are increasingly recognized as a novel secretion system capable of transporting various substances, including lipids, proteins, nucleic acids, cytotoxins, and signaling molecules, and they exhibit a range of biological functions.[93,94] OMVs can encapsulate target antigens within the vesicle lumen or embed them on the outer membrane, presenting them to host cells. The potent immunogenicity of OMVs stems from their unique composition and structure.[95] As natural nanoparticles, OMVs display pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS) and lipoproteins, which are recognized by pattern recognition receptors on antigen-presenting cells (APCs).[96] This interaction triggers innate immune signaling, leading to APC activation, cytokine production, and upregulation of costimulatory molecules—a process that provides built-in adjuvant activity.[97] Furthermore, their particulate nature enhances uptake by APCs.[98] Once internalized, OMVs can facilitate both MHC class II presentation of surface antigens and, through membrane fusion or disruption, cross-presentation of lumenal antigens on MHC class I, thereby stimulating robust $CD4^+$ and $CD8^+$ T-cell responses alongside antibody production.[99] This combination of intrinsic adjuvanticity and efficient antigen delivery underpins their efficacy as vaccine platforms. Once recognized by host cells, OMVs can trigger immune responses, thus achieving effective antigen presentation. Additionally, OMVs inherently contain multiple antigens, such as outer membrane proteins, lipoproteins, and endotoxins.[100]

Muralinath et al utilized OMVs from modified S. Typhimurium vaccine strains to present the model antigen PspA from *S. pneumoniae* within the vesicle lumen, after nasal immunization in mice, this OMV-based vaccine provided protection against lethal *S. pneumoniae* infection in mice.[101] Researchers also stabilized OMVs by reinforcing their structure with size-controlled bovine serum albumin nanoparticles, resulting in a structurally stable and uniform bovine serum albumin-OMV vaccine, immunization with this vaccine improved survival rates in mice infected with CRKP.[89] Moreover, an OMV vaccine derived from Neisseria meningitidis (N. meningitidis) has been shown to be immunogenic and safe in clinical trials and has received clinical approval.[102]

The Resistance Mechanism of Antibiotics

Before the advent of antibiotics, bacterial infectious diseases were a major challenge in global public health. With the development of bacterial vaccines, many infectious diseases have been effectively controlled. For instance, vaccines

against *S. pneumoniae*, *B. pertussis*, and *N. meningitidis* have significantly reduced the incidence and mortality rates of these diseases.[103] The impact of bacterial vaccines is evident not only in decreasing infection rates but also in reducing pathogen transmission through herd immunity.

However, current bacterial vaccines also face several limitations. For example, many vaccines do not provide comprehensive protection against all pathogenic strains, and effective vaccines for certain bacterial diseases are still unavailable. Additionally, high development costs and lengthy production timelines further limit the accessibility and widespread adoption of new vaccines.

Challenges Faced by Bacterial Vaccines

The diversity and rapid evolution of bacterial antigens present a key challenge in vaccine development. Many bacteria possess highly diverse surface antigens, which are the main targets for vaccine-induced immune responses. However, due to the ease of mutation and recombination in bacterial genomes, the targeted antigens often change over time, leading to a gradual decrease or loss of vaccine efficacy. For instance, *S. pneumoniae* has over 90 distinct serotypes, yet current pneumococcal vaccines only cover a subset of these, meaning that some unaddressed serotypes can still cause disease, complicating the development of broad-spectrum vaccines.[104] The rapid evolutionary rate of bacteria allows them to adapt swiftly to environmental pressures. Common pathogens such as *Escherichia coli* can generate diverse antigenic phenotypes through frequent gene exchange, increasing the difficulty of vaccine development.[105] Additionally, certain bacteria utilize complex biological structures to evade immune attacks. For example, *M. tuberculosis* and *P. aeruginosa* have complex cell wall structures that serve as strong antigen barriers, making it challenging for the immune system to recognize and target them effectively.

To address the challenges of antigen diversity and rapid bacterial evolution, researchers are exploring innovative vaccine development strategies. One cutting-edge approach is reverse vaccinology, which leverages genomic techniques to identify conserved bacterial antigens—those that vary minimally across strains and can elicit an immune response, this strategy enables the development of broad-spectrum vaccines that target common antigens across various bacterial strains, thereby reducing the issue of vaccine failure due to antigenic diversity.[106] Additionally, research on broad-spectrum vaccines is advancing, aiming to focus on critical antigen regions shared among different strains to overcome the disadvantages brought by rapid bacterial evolution. However, despite the new pathways offered by these technologies, ensuring that broad-spectrum vaccines remain effective over time remains an unresolved challenge. Bacterial evolution is not limited to antigens; bacteria may employ other mechanisms, such as altering metabolic pathways, regulating gene expression, or forming biofilms, to further evade the immune system.[107,108] Thus, effective vaccine design must account not only for antigen diversity but also for the biological complexity of bacteria to provide reliable, long-term immune protection.

The complexity of antibiotic-resistant bacteria adds significant challenges to bacterial vaccine development. Firstly, the emergence of multidrug resistance is a multifaceted problem. Bacteria can develop resistance not only through gene mutations but also via horizontal gene transfer—such as through plasmids, transposons, and bacteriophages—which enables rapid dissemination of resistance genes within bacterial populations. Some resistance genes even confer resistance to multiple antibiotics simultaneously. For example, MRSA displays resistance to several commonly used antibiotics, making treatment of these infections extremely difficult.[109] The complex antigenicity and high resistance levels of these bacteria require vaccine designs that not only elicit an immune response but also target strains with high antibiotic resistance. Secondly, certain resistant bacteria demonstrate enhanced adaptability, rapidly evolving under immune pressure. Pathogens like PRA not only develop resistance to nearly all available antibiotics but also evade the host immune system by altering antigenic characteristics.[110] Given the rapid mutation rates of these bacteria, vaccines that cannot be updated quickly may lose their efficacy. To address this, researchers are exploring more conserved antigen targets, which tend to vary less among bacterial strains and resistant variants, providing a promising direction for vaccine development against antibiotic-resistant bacteria.

Future Prospects of Bacterial Vaccines

With the continuous advancements in biomedical sciences and technology, the future of bacterial vaccines presents boundless possibilities. Emerging scientific and technological innovations are transforming vaccine research, production, and distribution, offering broader and more effective protective measures for humanity. The future directions for bacterial vaccine development primarily focus on several key areas: the application of emerging technologies, the development of broad-spectrum vaccines, personalized vaccines, and solutions to challenges in vaccine distribution and accessibility.

Reverse Vaccinology, which identifies potential vaccine targets through bacterial genome analysis, offers a powerful tool for tackling multidrug-resistant bacteria and emerging infectious diseases in the future.[106] Synthetic biology, by designing and constructing novel microbial systems, enables the creation of antigens or delivery systems with specific functions, optimizing the immunogenic efficacy of vaccines.[111] The diversity and rapid evolution of bacteria make broad-spectrum vaccines a key objective for future development.

The rational design of broad-spectrum vaccines hinges on the identification of antigens that fulfill stringent mechanistic criteria to ensure cross-strain and cross-species protection.[112] These criteria are derived from the functional and evolutionary constraints on the pathogen. First, ideal antigens are evolutionarily conserved, encoded by genes under high negative (purifying) selection, often involved in essential cellular processes, which minimizes sequence variation and provides a stable target.[113] Second, the antigen must be constitutively expressed and accessible on the bacterial surface or during infection to ensure engagement by the immune system.[114] Third, it should play a critical role in pathogenesis or general fitness, so that immune pressure imposes a high fitness cost on escape variants.[115] Fourth, the antigen must be inherently immunogenic, capable of eliciting a potent protective response targeting conserved epitopes.[116] Finally, candidates with low potential for phase variation or functional redundancy are preferred to prevent immune evasion.[117] Integrated bioinformatic pipelines, leveraging comparative genomics and in silico epitope prediction, are employed to screen for antigens meeting these criteria, followed by validation in preclinical models.

Such vaccines aim to provide long-lasting and wide-ranging protection against multiple strains or even different pathogenic species by targeting conserved bacterial antigens or essential metabolic pathways that are less prone to mutation. Broad-spectrum vaccines are also expected to play a critical role in combating superbugs and emerging infectious diseases. By focusing on shared characteristics of these pathogens, broad-spectrum vaccines could serve as potent tools against these complex infections.[118]

Traditional vaccines are typically administered through injections and often require strict cold-chain transport, limiting their accessibility in developing countries and remote areas. In the future, the development of novel vaccine delivery systems will revolutionize the global accessibility of vaccines. For example, nanotechnology is already playing a vital role in vaccine delivery, nanoparticles can encapsulate antigens and deliver them to specific immune cells, significantly enhancing vaccine immunogenicity and efficacy, additionally, nanoparticle-based delivery systems offer high stability, reducing the need for cold-chain transport, and can therefore be effective in resource-limited regions.[119,120] Another promising approach is needle-free injections and mucosal vaccines, needle-free technology minimizes pain and the risk of cross-infection during vaccination, while mucosal vaccines, delivered through the mouth or nasal cavity, trigger both local and systemic immune responses, particularly suited for preventing respiratory and gastrointestinal infections.[121,122] Mucosal vaccines reduce reliance on medical facilities and simplify vaccine use, greatly enhancing convenience. Thus, leveraging the latest advancements in nanomedicine, structural biology, and materials science—such as liposomes, self-assembling nanoparticles, VLPs, polymeric nanomaterials, cytokine-complex adjuvants, and mucosal adjuvants—is essential. Research into these next-generation adjuvants and delivery systems forms the foundation for developing novel bacterial vaccines, aiming to strengthen immune response intensity and diversify immune response types.

The accessibility and global equity of vaccines remain critical issues that must be addressed in future vaccine promotion efforts.[123] Many new vaccines are costly to develop and produce, making it challenging for low-income countries and remote areas to obtain timely vaccine protection. In the future, ensuring fair distribution of vaccines globally through international collaboration and innovative economic models will be a significant challenge in vaccine

promotion. Organizations such as public-private partnerships and the Global Alliance for Vaccines and Immunization (GAVI) are working to reduce inequalities in global vaccine distribution.[124] Establishing a more equitable vaccine supply chain is crucial, especially in response to emerging infectious diseases and pandemics.

Conclusion

The strategic development of next-generation bacterial vaccines is increasingly informed by the need to directly counteract specific antimicrobial resistance AMR mechanisms. As reviewed herein, the rational design of vaccine platforms aligns with overcoming distinct resistance challenges: the threat of enzymatic antibiotic inactivation and efflux pump-mediated resistance is met by vaccines inducing high-titer neutralizing or opsonizing antibodies; the challenge posed by target modification and intracellular persistence necessitates robust cellular immunity, effectively elicited by live vector and some nucleic acid platforms; and the rapid antigenic variation of pathogens is addressed through broad-spectrum antigens identified via reverse vaccinology. This paradigm underscores that modern vaccinology is evolving into a precision tool against AMR, targeting the biological vulnerabilities of bacteria that antibiotics alone cannot address.

Bacterial vaccines operate through multiple mechanisms to reduce the development of antibiotic resistance. Vaccines targeting bacterial pathogens not only decrease infections caused by antibiotic-resistant or antibiotic-sensitive pathogens but also help protect the health of unvaccinated populations while maintaining sufficient immune levels. With the application of emerging technologies and continuous breakthroughs in vaccine research and development, the emergence of broad-spectrum vaccines, personalized vaccines, and novel delivery systems will significantly enhance vaccine effectiveness and accessibility. At the same time, global collaboration will promote solutions to vaccine accessibility issues, allowing more populations to receive effective vaccine protection. Although the diversity and rapid evolution of bacteria present certain challenges, the future development of bacterial vaccines will undoubtedly play an indispensable role in the field of global health.

Abbreviations

Kp, *Klebsiella pneumoniae*; cKp, classical *Klebsiella pneumoniae*; CRKp, carbapenem-resistant *Klebsiella pneumoniae*; AAC, Aminoglycoside Acetyltransferases; ABC, ATP-binding Cassette; AdV, Adenovirus; AMR, Antimicrobial Resistance; ANT, Aminoglycoside Adenylyltransferases; APCs, antigen-presenting cells; APH, Aminoglycoside Phosphotransferases; AR, Antibiotic Resistance; BCG, Bacillus Calmette-Guérin; ChAd, Chimpanzee Adenovirus; CRKP, Carbapenem-Resistant *Klebsiella pneumoniae*; CTB, Cholera Toxin B Subunit; DNA, Deoxyribonucleic Acid; ESBL, Extended-Spectrum Beta-Lactamase; FDA, Food and Drug Administration; GAVI, Global Alliance for Vaccines and Immunization; HAI, Hospital-Acquired Infection; HPV, Human Papillomavirus; LAV, Live Attenuated Vaccine; LPS-OM, Lipopolysaccharide Outer Membrane; MATE, Multidrug and Toxic Compound Extrusion; MFS, Major Facilitator Superfamily; MVA, Modified Vaccinia Virus Ankara; mRNA, Messenger RNA; MRSA, Methicillin-Resistant Staphylococcus aureus; Omp, Outer Membrane Porin; OMV, Outer Membrane Vesicle; PAMPs, pathogen-associated molecular patterns; PBP, Penicillin-Binding Protein; PLA, Polylactic Acid; PLGA, Poly Lactic-co-Glycolic Acid; PDR, pan-drug-resistant; RND, Resistance-Nodulation-Division; RNA, Ribonucleic Acid; SMR, Small Multidrug Resistance; TLR, Toll-like Receptor; VLP, Virus-like Particle; WCV, Whole-Cell Vaccine; WHO, World Health Organization.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; All authors took part in drafting, revising or critically reviewing the article; All authors gave final approval of the version to be published; All authors have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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