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Progress and Challenges in Antimicrobial Resistance and Bacterial Vaccines

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Abstract: In recent decades, pathogens have continued to strike humans in the form of newly emerging or re-emerging infectious diseases, opportunistic infectious diseases, and infections caused by drug-resistant microbes. In response, humans have developed modern platform technologies that can produce effective vaccines to prevent pathogens from causing infectious diseases. Vaccines against antimicrobial-resistant organisms could prevent or minimize life-threatening infections, thus lowering healthcare costs. These pharmaceutical products could also reduce antibiotic use, lowering the risk of antimicrobial resistance (AMR) emergence. Furthermore, once a population has received enough vaccines, indirect protection via herd immunity can help to prevent the spread of resistant strains. In this sense, antibiotics would be unnecessary once the burden of pathogen-associated illnesses is reduced. Based on such a notion, bacterial vaccines would be an excellent and applicable solution to fight AMR. In this review, we highlight our current understanding of AMR, the role of bacterial vaccines in preventing AMR, and discuss the potential of bacterial vaccines and their pitfalls in managing infectious diseases.

Keywords: antimicrobial resistance; bacteria; infectious disease; antibiotics; vaccination.

1. Introduction

Infants born in high-income countries today can expect to live longer than the ones in less-developed countries [1]. Our success in combating various infectious diseases, which used to kill 50 percent of individuals before the age of 20 in the past, is largely responsible for the

additional 35 years of life we acquired during the last century [1]. Furthermore, with the advancement of medical and pharmaceutical technologies, certain viral diseases such as smallpox, rabies, measles, rubella, and mumps, and several bacterial diseases such as diphtheria, tetanus, typhoid fever, and cholera, can now be anticipated for better outcomes [1]. This achievement was accomplished mostly via improved hygiene and antibiotic treatment of infectious disorders.

Following the discovery of penicillin, the antibiotic age began. With numerous antibiotics discovered from microbes, humans were able to claim a victory in the battle against pathogenic bacteria temporarily. However, as we can see now, antibiotics are starting to be clinically ineffective due to bacterial resistance to antibiotics [2,3], endangering millions of lives yearly. Even common medical or surgical procedures like joint replacements, chemotherapy [4], or catheter insertions [5] will be significantly perilous if antibiotics are no longer useful [6]. Furthermore, as the worldwide antimicrobial resistance (AMR) issue worsens, putting more lives at risk, and given the limitations of current and future medicines, there is an urgent need for new antibiotics [7,8]. However, finding new antibiotics has been scientifically challenging [9,10]. Thus, to face this life-threatening problem, we need to find alternative solutions.

Antimicrobial-resistant bacterial pathogens can infect people and cause serious, potentially fatal diseases [11]. Antibiotics currently available for first-line treatment are ineffective against resistant infections, and second-line antibiotics may be necessary to clear the illness [11,12]. On the other hand, administering a second-line antibiotic may encourage the formation of new antimicrobial-resistant isolates resistant to second-line antibiotics. As a result of the emergence and spread of AMR at the community level, treating sick people becomes more challenging [11]. Antimicrobial-resistant pathogens inflict significant harm, morbidity, and death [11,13].

As the curative effort started to be unsuccessful, scientists and clinicians are now considering preventing bacterial infections through vaccinations [11]. Kennedy and Read illustrate that vaccines can be used for a long time with little or no resistance [14]. Vaccines can thus manage infections for a long time before becoming useless. This happens because vaccinations function prophylactically to prevent infections from starting, whereas medications treat an ongoing infection in which bacteria grow and mutate, allowing the drug to pick resistant versions. On the other hand, vaccines stimulate a protective immune response against several antigenic targets, whereas medicines target only a few metabolic pathways on bacteria. Selection having less opportunities, it can be suggested that vaccination is more likely to have an effect than antibiotic treatment.

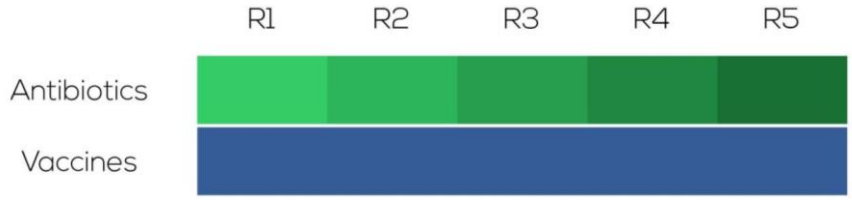

Figure 1. Schematic representation showing the use of antibiotics selects for resistance (R), making the antibiotic obsolete, while vaccines can offer long-term benefits against pathogenic bacteria (modified from [15]).

Antibiotic research and development (R&D) are facing high-level obstacles as new and effective antibiotics to treat illnesses resistant to all previous treatments are difficult to discover [15,16]. Antibiotic R&D is plainly insufficient, given how quickly resistance has arisen to each

new class of antibiotics introduced historically and the hurdles in generating new antibiotics. A multifaceted and globally coordinated strategy is required [15]. Therefore, a continual pipeline of new antibiotics is needed for effective treatment. In contrast, vaccines can offer a very long-time usage without generating significant resistance, as illustrated in Figure 1.

Vaccination is a remarkable medical-pharmaceutical solution to prevent the rise of infectious diseases, yet it has been persistently underappreciated. Increased vaccine coverage and the development of novel vaccines targeting antibiotic-resistant pathogens can help turn the tide of the never-ending battle against pathogenic bacteria [17,18]. Vaccination has the advantage of being long-lasting and can be used for decades without causing significant resistance. Vaccines have so far proven successful in preventing the emergence of resistant strains of pathogens [17,19]. This behavior can be attributed to two important factors. First, vaccines are employed as a preventative measure when pathogen populations are small, reducing the possibility of resistance-inducing mutations appearing and spreading. Second, many vaccines attack organisms from different angles, necessitating numerous changes to develop resistance [4,20,21].

The use of vaccines to combat AMR is promising but also not without challenges. While the technology that can help us produce effective vaccines is available, identifying broadly protective bacterial antigens is a critical hurdle in the vaccine development process. In antigen identification, genomic and immunological techniques have dominated the field [22-24]. However, other emerging technologies, such as rationally designed Outer Membrane Vesicles (OMVs) of Gram-negative bacteria, RNA- and DNA-based vaccines, improved antigens engineered through synthetic and structural biology, and novel adjuvants with increased potency, provide additional opportunities to develop vaccines against the AMR threat [17,25,26]. With its encouraging use against AMR, bacterial vaccines shall be a subject of intense R&D to harness their full potential. In this review, we discuss the emergence and the mechanisms of AMR as well as the impact of existing bacterial vaccines on AMR. In addition, we also summarize the status of bacterial vaccine development for selected pathogens and discuss challenges and possible approaches that can support the use of bacterial vaccines to target antimicrobial-resistant pathogenic bacteria.

2. Bacterial Infection, Host Immune Responses, and Antimicrobials

Although the immunomodulatory methods employed by viruses and bacteria appear to be rather distinct at first appearance, there are surprising parallels and shared basic mechanisms. Both infections must overcome the same host defensive processes, and the comparable techniques they have developed to eliminate host immunity are instructive. Furthermore, viral and bacterial infections are frequently related, with one pathogen exploiting vulnerabilities in the host's defenses induced by another disease [27,28].

The exposed surface of viral and bacterial pathogens is the major interface between the host and pathogen, and immune systems recognize the exposed surface as a crucial characteristic for initiating microbial clearance. It also gives the pathogen many options for presenting immune modulator mimics, altering (or avoiding) host immune responses, expressing adhesins or receptor ligands to bind the virus to host surfaces, and presenting invasins or fusion proteins to promote absorption into host cells. Other compounds on the surface, such as protective capsules or even captured host proteins, can help the host survive. Keeping this complex surface of proteins and carbohydrates hidden from immune surveillance and Toll-like receptor (TLR) identification while exposing important components like adhesins

and invasins is a huge challenge for bacterial infections. The expression of a carbohydrate capsule is a frequent technique for disguising bacterial surfaces. To escape opsonization and phagocytic clearance, the pneumococcus (*Streptococcus pneumoniae*) relies heavily on its capsule to inhibit antibody and complement deposition on its surface. Capsules are also used extensively by bacteria that cause meningitis (*Haemophilus influenzae*, *Escherichia coli* K1, and *Neisseria meningitidis*) to support their extracellular lifestyle within the host by inhibiting antibody and complement deposition and insertion [29-31].

Lipid A, the main core component of lipopolysaccharide (LPS), is largely conserved throughout most Gram-negative bacteria and hence plays a key role in TLR activation, particularly TLR4. Because of differences in O antigen, different species can commonly reinfect the same host. Although LPS is surface-exposed and a complement target, membrane insertion by the membrane attack complex does not occur in the cellular membrane because it protrudes from the surface [32-34]. Gram-negative bacteria change TLR4 responses by modifying lipid A. Salmonella, for example, has a two-component sensor (PhoP/PhoQ) that perceives the host environment and controls several virulence genes. Some of these genes code for enzymes that modify lipid A, such as a 3-O-deacetylase (PagL) and a lipid A palmitoyltransferase (PagP). TLR4 activation and NF-κB synthesis are up to 100 times less active with these modified versions of lipid A [27].

Bacterial pathogens have devised strategies to circumvent peptidoglycan processing and identification [32,35]. Virulence factors have been identified as genes involved in peptidoglycan synthesis, turnover, and recycling. *Listeria monocytogenes*, for example, can be found in the cytoplasm of macrophages and other host cells. Peptidoglycan hydrolases, found on the surface and secreted, have been identified as virulence factors [36]. These mechanisms typically involve one of three approaches: (1) having multiple but distinct copies of a molecule, each with its own on/off control; (2) possessing one expression locus and numerous silent copies of the gene, and continuously switching which gene is expressed [27,37]; or (3) possessing a highly variable region in a molecule that is continuously transforming [27].

One or more innate immune cell types are selectively activated and attracted to the injection site depending on the pathogen infecting the host. Neutrophils, for example, are recruited preferentially in response to bacterial and viral illnesses, but eosinophils are successful in responding to parasitic diseases. Immune activation is triggered by the interaction of pattern recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs) expressed by immune cells and pathogens, respectively [36,38]. Inflammasomes are known to be activated by flagellin, which is produced by numerous Gram-negative bacteria like Salmonella, Francisella, and Legionella. Cell pyroptosis, an inherently inflammatory process that leads to programmed cell death, occurs as a result of this. Other viral cytoplasmic sensors, such as the cytosolic double-stranded (ds) DNA sensor DAI (DNA-dependent activator of IFN), may also play a role in virus and bacterial pathogen detection. Pentraxins, complement proteins, natural antibodies, and various cytokines are other components of the innate immune system involved in pathogen defense. C-reactive pentraxin is one of the most common antimicrobial pentraxins. One of the common pentraxins with antimicrobial activity is C-reactive protein (CRP) which can promote agglutination [39-41].

In vertebrates, including humans, two immune responses are available to respond to bacteria: innate and adaptive immune responses. The key difference between these two immune responses lies in what sensors are used in antigen recognition and how much antigen is recognized. In innate immunity, the antigens are recognized by different sets of PRRs,

germline-encoded sensors with broad specificities for conserved and invariant characteristics of microbes. Antigen receptors, on the other hand, mediate adaptive immunological recognition: the genes encoding these receptors are constructed from germline gene segments, and somatic recombination of these segments allows the formation of a broad repertoire of receptors with random but restricted specificities. On T and B cells, antigen receptors are clonally dispersed, allowing for clonal selection of pathogen-specific receptors and providing the foundation for immunological memory [32,42].

3. Antimicrobial Resistance: Causes and Mechanisms

The discovery of penicillin by Alexander Fleming in 1928 became a huge breakthrough in modern medicine, saving millions of lives. Soon, AMR—a phenomenon in which microorganisms grow despite being exposed to antimicrobials—followed [7,43]. It is natural for a microorganism to evolve resistance mechanisms to survive, at least as a self-defense mechanism against the antibiotics it produces [44-46]. The first AMR documentation by Abraham and Cain dates back to 1942, a year before the widespread use of Penicillin [43,47,48]. Resistance occurs through a series of biochemical processes in the bacteria, in which bacteria can exhibit one or more resistance actions [49]. Resistance occurs not at any cost; this process can reduce the fitness of bacteria (such as growth rate) during the process [49-51]. Therefore, only in the presence of antibiotics resistance takes place [49].

Although considered an ancient natural phenomenon, the rapid increase in AMR cases and the slow progress in antibiotic discovery turn AMR into a significant threat [16,52,53]. The genetic plasticity of bacteria accelerates the generation of AMR in bacteria, in which resistance occurs at any time by microorganisms through spontaneous mutations, gene evolution, and passing of resistance genes through horizontal gene transfer (HGT) [49,54,55]. Any parts of genetic elements in bacteria can gain resistance genes and facilitate their transmission; the type of element involved in the process differs within the genus of the bacteria [56-59]. In 1942, only four resistant strains from hospitalized patient samples were reported [60]; now, more than 2.8 million AMR cases occur annually in the United States alone [61].

Understanding the resistance mechanism in the fight against AMR will be very beneficial in searching for novel antimicrobials since bacteria have developed escape mechanisms against the previous therapeutic targets. The following section will discuss the mechanism of AMR as the main target of antimicrobial therapy.

3.1. Resistance versus persistence.

Before further discussing the mechanism of AMR, one should understand the difference between resistance and persistence. Resistant cells survive and replicate in the presence of antimicrobials [62-65]. These cells will pass this trait to the daughter cells through the HGT of the antibiotic resistance gene [62,63]. Therefore, measuring minimum inhibitory concentration (MIC)—the lowest concentration needed to inhibit the growth of microorganisms—is the way to observe the resistance level, as resistance happens when a higher MIC is needed [63,66].

In contrast, persister cells do not possess any resistance genes though they do not respond to antimicrobials [62]. These cells are present in 1% of stationary cultures or biofilms and can cause chronic, recurrent infection [62,67-71]. The inactive state of persister cells causes their ability to survive antimicrobial therapy as most antimicrobials do not target this phase [62,63,72,73]. Once regrown, persister cells are still sensitive to antimicrobials with

standard MIC [63,74]. There is an implication of how persister cells might evolve resistant mechanisms through HGT and mutagenesis promoted by the stress response, as reviewed in several pieces of literature [68,71,72].

3.2. Molecular aspects of antimicrobial resistance.

Generally, AMR may originate from intrinsic and acquired mechanisms [75,76]. Intrinsic resistance is an innate mechanism (in the form of a distinctive structure or function) possessed by a bacterial species to resist certain antibiotics; this is not related to HGT [62,75,77,78]. The cell wall of Gram-negative bacteria is composed of lipopolysaccharide (LPS), which is an excellent example of this intrinsic resistance mechanism. This structure limits the entry of certain antibiotics, such as vancomycin, and hinders their efficacy against Gram-positive bacteria [37,55,75,79,80]. Another well-known intrinsic AMR mechanism is mediated by bacterial efflux pumps [62,81]. In contrast, the acquired resistance mechanism involves passing genetic elements through the HGT process from resistant bacteria to bacteria that previously owned no resistance genes; this phenomenon can temporarily or permanently affect bacteria [49,62].

Mobile genetics elements (MGEs) are DNA elements primarily involved in acquired resistance since these elements may uptake and mobilize genes within the genome (intracellular mobility) or cells-to-cells (intracellular mobility) [49,82,83]. Variations in MGEs—such as Insertion sequences (IS), transposons (Tn), and integrons—predominantly rule the diversification of resistant traits among bacteria [56,82]. IS is a small DNA element that carries the transposase (*tnp*) gene and can move randomly on the same DNA or other DNA in one cell. At the same time, transposons are more prominent elements with similar capabilities to IS [82]. *Klebsiella pneumoniae* can develop resistance to ertapenem through an IS modification of *omp*K36, the gene that regulates the action of porin—an antibiotic transfer protein—as reported by Lee *et al*. [84].

Integrons are versatile genetic elements that allow the acquisition and expression of genes inserted within gene cassettes [85]. Integrons consist of gene encoding integrase (*intI*) that catalyzes the insertion and excision of gene cassettes which are embedded in the recombination site of integron (*attI*) [86,87]. The gene cassette of integrons can carry over 40 resistance genes, including broad-spectrum β-lactams (ESBL) ($bla_{OXA.101}$-*aac*(6')–*Ib*), and plays a massive role in the dissemination of AMR in various microorganisms [88]. Recently, Böhm *et al*. discovered a novel integron-based resistance gene *gar* that encodes a kinase-like modifying enzyme against glucosamine-contains aminoglycoside from clinical isolates [89]. This gene does not match the formerly known aminoglycoside modifying enzyme (AME) genes [89].

Another MGE, plasmids—a circular-shaped self-replicating DNA—is the most well-known transfer system for resistant genes in Gram-positive and Gram-negative bacteria [62,82]. Though not primarily responsible for the mobilization of resistance genes within the DNA, plasmid remains essential for transferring the AMR genes [90]. Plasmid-mediated resistance is the most common route for AMR gen acquisition in bacteria and is responsible for the emergence of AMR in hospitals [49,62]. Plasmids contain abundant IS and other resistance MGEs and assist the movement of these materials, intra- and interspecies [90]. Conjugative plasmids move from one cell to another through the conjugation process—in which two bacteria perform physical contacts followed by the formation of bridges that enable the transfer of plasmids [49,91]. In addition, conjugative plasmids can also transfer non-

conjugative plasmids [90]. Cafini *et al*. reported the ability of a clinical isolate of *Staphylococcus epidermidis* from a Spanish hospital to transmit the linezolid *cfr* resistance gene to MRSA clinical isolates from Japan through conjugation and transduction pathways [92]. In another review, Luo *et al*. discussed the role of plasmids in disseminating the mobilized colistin resistance (*mcr*) gene in humans and animals, implying how easily resistance traits move from one microorganism to another [93].

Resistance acquisition can occur through transformation—incorporation of cell-free DNA [62]. When a bacterial cell is damaged or dies, it releases the naked DNA into the environment, which can cross the membrane cells of other bacteria, followed by DNA expression [94]. Although transformation is the simplest model of HGT, not all microorganisms can accept this naked DNA since the cells carrying out this process must be competent [49,94]. In addition to that, such study of the ability of non-antibiotic drugs (e.g., ibuprofen, gemfibrozil, and propranolol) to facilitate the dissemination of resistance genes, raises a new concern, mainly due to the widespread of drug residues as well as the transformable strains in the environment [94].

The ability of phages as carriers of resistant genes through the transduction process has been demonstrated in various studies. For example, Haaber *et al*. demonstrated the ability of phage ϕ11 to transmit resistance-coding genes to *S. aureus in vitro* and *in vivo* models [95]. Various studies have widely reported infectious phage particles in food products [96]. This route cannot be underestimated, especially since it can significantly contribute to the spread of resistance genes among the normal digestive flora [97].

3.3. Primary mechanism of antimicrobial resistance.

Resistance mechanism in bacteria falls into four major biochemical pathways: (1) modification/inactivation of antibiotics, (2) drug-uptake limitation, (3) alteration of the target site, (4) other mechanisms (biofilm and intracellular survival) [49,62,90].

3.3.1. Modification/inactivation of antibiotics

The most common mechanism of AMR happens through the production of enzymes that inactivate or destroy antibiotic molecules [49,98]. Modifying enzyme works by catalyzing chemical alteration (through acetylation, adenylation, or phosphorylation) of the main structure of antibiotics, thus hindering the interaction of the drugs and their targets [49,90,99,100]. This action is often observed in antibiotics that inhibit ribosomal protein synthesis. As an illustration, AME catalyzes the covalent changes of hydroxyl or amino groups in specific parts of aminoglycoside, leading to poor binding of the molecule to the ribosome [49]. Jouybari *et al*. demonstrated the importance of gene encoding these enzymes in the *A. baumannii* clinical isolates; hence, they suggested controlling its spreading to maintain effective therapy [101].

The β-lactamase enzyme is the oldest and most diverse AMR mechanism [102]. Several studies have reported more than 2500 diverse -lactamase responsible for AMR to one or more -lactam antibiotics [90]. As is well known, β-lactam antibiotics target penicillin-binding protein (PBP). This transpeptidase plays a role in the polymerization process and cross-linking of glucan bonds in bacterial cell walls [102]. Inactivation of -lactams by -lactamase enzymes occurs by breaking the amide bond in the -lactam ring, leading to the inactivation of the drugs [49]. Mutations of β-lactamase enzymes (e.g., TEM-3 from TEM-1 Penicillin) give rise to the presence of Extended-spectrum β-lactamase to be one of the significant problems in infection

therapy because this enzyme is not only able to hydrolyze one type of β-lactam antibiotics (e.g., penicillin), but are also active against first to third-generation cephalosporins, and monobactams [49,102].

3.3.2. Limitation of antibiotic uptake.

Several antibiotics administered in clinical settings target intracellular processes in bacterial or structural parts of bacteria located in cytoplasmic [103]; therefore, the drug must penetrate the cell walls and membrane of bacteria to exert its effect [49]. However, not all drugs can cross this barrier easily; for example, some hydrophilic compounds (e.g., tetracyclines) rely on porins to enter bacterial cells [49,90]. Modifying the type, the number of expressions, or porins' functions will inhibit porin-dependent antibiotics' action [49,90]. *Pseudomonas aeruginosa* exhibits the typical example of this mechanism. Carbapenem resistance in *P. aeruginosa* is associated with the gene mutation of the *oprD* gene that regulates the expression of OprD porin protein, which facilitates the translocation of carbapenems in the cells. Another porin gene mutation—*oprH*—is also linked to the resistance of gentamicin in some strains of *P. aeruginosa* [104].

The ability of bacteria to eject antimicrobial compounds out of the cells was first reported in the 1980s and is still one of the significant contributors to AMR incidents in clinics [49]. Till now, there are five categories of bacterial efflux pumps: (1) the major facilitator adenosine triphosphate binding cassette (ABC), multidrug and toxic compound extrusion family (MATE), major facilitator superfamily (MFS), resistance nodulation-cell division family (RND), and small MDR family (SMR) [104]. Tetracycline resistance is the classical model of this mechanism [49]. Recently, Beheshti *et al*. unveiled the role of tet(A) and tet(B) genes in regulating the tetracycline efflux mechanism in *A. baumannii* from hospital patients [105]. Another efflux pump—AdeABC—also becomes a critical AMR determinant in *A. baumanii* resistance towards carbapenems [106].

3.3.3. Alteration of antimicrobial target sites.

To escape antibiotics, bacteria develop several mechanisms to modify the antibiotic target site, including enzymatic modification and point mutations, and completely replace or 'bypass' the target site [49]. Fluoroquinolones target the DNA gyrase enzyme by forming complexes that interfere with the DNA replication [104,107]. Microorganisms that survive the pressure of this antibiotic had a mutation in the quinolone resistance-determining region (QRDR) region of the *gyrA* DNA sequence [107]. For example, *Pseudomonas aeruginosa* had a point mutation of the amino acid at position 83 of *gyrA*, while *E. coli* with mutation Tyr-122 and Ser-83 to alter the binding target of ciprofloxacin (CPX), leading to an increase in the MIC of CPX [104,107]. The critical mechanism of macrolide resistance occurs through the insertion of a methyl group on the ribosome by an enzyme encoded by the erm gene (erythromycin ribosomal methylation). The target for enzymatic changes in this mechanism is domain V of DNA 23rRNA (specifically, nucleotide A2058) on the 50S ribosomal subunit, and as a result, macrolides cannot bind to their target [49,90].

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria replaced the target site by producing PBP2, penicillin-binding protein-2 [90]. MRSA uses the *mecA* gene to express the production of PBP2 with a lower affinity for β-lactams resulting in decreased or total inhibition of β-lactam antibiotic binding [49,62,90]. As shown in the cotrimoxazole resistance,

overproducing the target of antibiotics is an example of a target bypass mechanism [49,90,108]. Cotrimoxazole is an analog of a natural substrate for enzymes that play a role in folate biosynthesis; overproduction of the target enzyme causes a lack of antimicrobial that can bind to the target so that bacteria can escape the effect of antimicrobial therapy [49,90].

3.3.4. Other mechanisms.

Bacteria can form biofilms—bacteria colonization in the extracellular matrix—as a defense mechanism against antimicrobial attack [62,71]. Biofilms can protect bacteria from the host immune system and are difficult to penetrate by antimicrobials [62,90]. In addition, the bacteria in the biofilm are mainly inactive, which is rarely targeted by antimicrobials. In addition, the HGT process can also occur in biofilms; this mechanism is often a concern in clinical settings [62]. Finally, microbes can also form specific structures, such as intracellular compartments, that allow microbes to survive even after being engulfed by macrophages—as observed in *K. pneumoniae* [90,109].

4. Types of Bacterial Vaccines

There is a global crisis brewing in the world regarding antibiotic resistance. Antimicrobial-resistant pathogens have the potential to endanger the health of 700,000 people each year [100,110-113]. The fight against this type of pathogen necessitates fulfilling two critical requirements. First, funds should be allocated to research and development to discover and modify new antibiotics. However, the majority of antibiotics currently on the market have only one mechanism of action for killing bacteria, such as cell walls [114] or the translation machinery [115], drug efflux [116], drug target change or reconfiguration [117]. Even antibiotic inactivation [117], are all examples of adaptive systems and intrinsic defenses that bacteria have developed. Consequently, the use of antibiotics has ceased to be beneficial. In addition, antibiotic selectivity can play a role in developing clone resistance to antibiotics.

In contrast to antibiotics, vaccines could be used to prevent the spread of diseases, including bacterial pathogens. It has the potential to aid in the prevention and treatment of life-threatening diseases, as well as the reduction of healthcare costs and the use of antibiotics in primary and secondary therapies. This has the potential to slow the spread of antibiotic resistance cases. The use of vaccines, which target multiple antigens or epitopes in the same antigen (polyclonal antibodies), helps to reduce the number of resistant clones [118]. If people are properly vaccinated, and resistant strains are avoided, indirect protection, also known as herd immunity, can be increased in a population.

4.1. Live bacterial vaccine.

A vaccine method that uses live bacteria to trigger an immune response to itself or to a transported vaccine component appears appealing. Live bacterial vaccines provide several advantages, including the ability to replicate a natural infection, inherent adjuvant qualities, and the easiness of being administered orally. Live vaccines derived from pathogenic and non-pathogenic food-related microbes are now being tested. Pathogenic bacteria, on the other hand, require attenuation to reduce their virulence. The utilization of bacteria as vaccine delivery vehicles necessitates the creation of recombinant strains containing the antigen-coding gene cassette. Live vaccination vehicles are gaining fresh interest as more is learned about mucosal

immunity and genetic techniques for heterologous gene expression become available [119,120].

Live bacterial vaccines are relatively easy-applied and cheaper to produce than other types of vaccines [121]. Several strategies for live bacterial vaccines have been developed, such as *in vitro* attenuation, chemical mutagenesis, recombinant bacteria, and recombinant bacterial vectors. The only vaccine licensed to prevent tuberculosis is an example of *in vitro* attenuation technique which consists of Bacille Calmette-Guérin (BCG), a *Mycobacterium bovis* strain that was occasionally causing tuberculosis in humans [122].

4.2. Recombinant vaccines.

VPM1002 is a recombinant BCG (rBCG) with the listeriolysin O (LLO) encoding gene (hly) from *Listeria monocytogenes* in place of the *urease C* gene. Antigens and bacterial DNA are released into the cytosol as a result of its expression in VPM1002, prompting autophagy, inflammasome activation, and pathogens' death. In preclinical tests, VPM1002 showed significantly higher immunogenicity, efficacy, and safety [123].

4.3. Killed bacterial vaccines.

Vaccines targeting intracellular bacterial and protozoal pathogens that have been killed or inactivated are famously unsuccessful at generating protective immunity. Infection with live *Listeria monocytogenes* elicits long-lasting CD8 Tcell–mediated immunity, whereas immunization with heat-killed *L. monocytogenes* (HKLM) is not protective. The authors demonstrated that immunization with HKLM primes memory CD8 T lymphocyte populations that, despite their magnitude, are ineffective in protecting against future *L. monocytogenes* infection. HKLM vaccination primes T lymphocytes that do not gain effector functions, in contrast to live infection, which evokes huge numbers of effector CD8 T cells, T cells that do not gain effector activities are primed by HKLM vaccination. Our findings suggest that Tcell–dependent protective immunity can be distinguished from memory T cell growth and that the production of effector T cells may be required for long-term protective immunity [124].

4.4. Subunit/inactivated vaccines.

This type of vaccine uses a mixture of proteins, peptides, polysaccharides, purified proteins, or inactivated bacteria as immunogens that cannot replicate in the host. Instead of whole pathogens, the subunit vaccine uses selected fragments as antigens. On the other hand, bacteria or pathogens in inactivated vaccines are wholly inactivated by heat, radiation, or chemicals to destroy their ability to replicate and cause illness while maintaining their immunogenicity, which the immune system has to recognize [125]. Generally, the subunit/inactivated vaccines can be categorized as whole bacteria, protein-based, peptide-based, and polysaccharide-based. Subunit vaccine causes fewer side effects than live or inactivated vaccine. Still, it might be less immunogenic since they contain fewer antigens than the former, and the elimination process might eliminate the component triggering innate immunity [126]. *Bordetella pertussis* is an example of whole bacteria inactivated vaccine whose reactogenicity, when given parenterally, is more significant than most other types of vaccines [127].

4.5. DNA vaccines.

DNA vaccines incorporate a DNA plasmid containing a transgene encoding sequences of the selected protein from the pathogen with the eukaryotic promoter as a control that is directly introduced or encapsulated with lipids through host cells [122]. Several benefits of the DNA vaccine are the absence of pre-existing immunity and its high stability [128]. Also, the DNA vaccine might be particularly effective in stimulating the cell-mediated Th1-type immune response in which protective immunity from *Mycobacterium tuberculosis* infections is suspected. Thus, it is the potential to use and has indicated the promise in animal studies [129]. However, drawbacks include reduced expression efficiency due to the requirement for nuclear import before transcription and nuclear export before antigen translation [128].

4. Current State of Bacterial Vaccines

Currently, only a few bacterial vaccines are available to combat bacterial resistance. Thus, bacteria are becoming more antibiotic-resistant. Certain bacteria, including *E. coli, K. pneumoniae,* MRSA, *Neisseria gonorrhoeae, M. tuberculosis, Clostridioides difficile, Shigella, Salmonella, Campylobacter, and Pseudomonas aeruginosa* are classified as critical pathogens by the World Health Organization and CDC. Therefore, some researchers have attempted to develop vaccines to prevent them from infecting the human population. However, most of them failed to complete the clinical trial phases (Table 1).

Table 1. Completed clinical trials related to antibacterial resistance pathogens (ClinicalTrials.gov).

Bacterial target	Clinical Trials Number	Age Target	Location	Manufacturer	Final Phase
Clostridioides difficile	NCT01896830	40 - 75 years	Japan	Sanofi Pasteur	2
	NCT03918629	≥ 50 years	USA	Pfizer	3
	NCT03579459	65 - 85 years	USA	Pfizer	3
	NCT02117570	50 - 85 years	USA	Pfizer	3
	NCT02561195	65 - 85 years	USA	Pfizer	2
	NCT01706367	50 - 85 years	USA	Pfizer	1
	NCT02052726	50 - 85 years	USA	Pfizer	1
	NCT00772343	18 - 85 Years	USA	Sanofi Pasteur	2
	NCT00350298	≥ 18 years	USA	MassBiologics	2
	NCT01296386	≥ 65 years	Austria and Hungary	Valneva Austria GmbH	1
Pseudomonas aeruginosa	NCT00778388	18 -65 Years	Austria and Germany	Valneva Austria GmbH	1
	NCT01563263	18 - 80 Years	Austria	Valneva Austria GmbH	3
Klebsiella pneumoniae	NCT04959344*	18 -to 70 Years	Germany	GlaxoSmithKline	2
Staphylococcus aureus	18 - 85 Years		USA	Pfizer	2
	NCT01011335	18 - 55 Years	USA	Nabi Biopharmaceuticals	2
Escherichia coli	NCT02289794	18- 70 years	Switzerland	GlycoVaxyn AG	1
	NCT01147445	18 - 45 Years	USA	National Institute of Allergy and Infectious Diseases (NIAID)	1
Neisseria gonorrhoeae	NCT04094883	18 - 25 Years	USA	University of North Carolina	4 (Bexsero™)
	NCT04415424*	18 - 40 Years	Australia	Kirby Institute	3
	NCT04722003*	18 - 40 Years	USA	NIAID	2
Salmonella	NCT01129453	18 - 45 Years	USA	University of Maryland	1
	NCT01608815	≥ 2 years	Japan	Sanofi Pasteur	3
	NCT00131833	5 - 60 Years	China	International Vaccine Institute	4
	NCT00125008	≥ 2 years	India	International Vaccine Institute	4

	NCT00131820	5 – 18 Years	Vietnam	International Vaccine Institute	4
Shigella	NCT01531530	18 - 45 Years	USA	University of Maryland,	1
	NCT02017899	18 - 45 Years	USA	GSK Vaccines Institute For Global Health S.r.l.	1
	NCT02676895	18 - 45 Years	Kenya	GlaxoSmithKline	2
	NCT00368316	1 - 4 Years	Israel	National Institutes of Health Clinical Center (CC) (Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD))	3
Campylobacter	NCT02067676	18 - 50 Years	USA	U.S. Army Medical Research and Development Comman	1

*Recruiting

Only a few vaccines have successfully completed clinical trials and are now available on the market. Vaccines against *Bacillus anthracis*, *Vibrio cholerae*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Salmonella typhi* are among them. As a result, none of them are resistant to antimicrobials, with the exception of tuberculosis-causing bacteria and meningococcal species, including *N. gonorrhoeae* (Table 2).

Table 2. FDA approved bacterial vaccines (FDA.gov).

Bacterial vaccine	Type	Function	Route	Trade Name	Abbrev.	Manufacturer	Dose in routine series	Approved Ages
Anthrax	Inactivated (Adj.)	Prevention of disease caused by *Bacillus anthracis*	i.m	BioThrax	AVA	Emergent BioDefense Operations Lansing LLC	3	18-65 years
Cholera	Live Attenuated	Prevention of disease by *Vibrio cholerae* serogroup O1.	Oral (liquid)	Vaxchora	-	Emergent Travel Health, Inc.	1	18-64 years
Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP)	Inactivated (Adj.)	Prevention of disease caused by *Clostridium tetani*, *Bordetella pertussis*, and *Corynebacterium diphtheriae*	i.m	Daptacel	DTaP	Sanofi Pasteur, Ltd.	5	6 weeks - 6 years
				Infanrix		Glaxo Smith Kline Biologicals		
				Adacel	Tdap	Sanofi Pasteur, Ltd	1	10 – 64 years
				Boostrix	Tdap	Glaxo Smith Kline Biologicals	1	≥ 10 years
Diphtheria and Tetanus Toxoid Adsorbed (DT)	Inactivated (Adj.)	Prevention disease by *C. diphtheriae* and *C. tetani*	i.m	Generic	Td	Sanofi Pasteur, Inc	5	6 weeks - 6 years
				Tenivac	Td	Sanofi Pasteur, Ltd	1 (every 10 years)	≥ 7 years
				TDVAX	Td	Mass Biologics	3	≥7 years
Haemophilus influenzae type B	Inactivated (Adj.); Tetanus toxoid conjugate	Prevention disease by *Haemophilus influenzae* type B	i.m	ActHIB	Hib (PRP-T)	Sanofi Pasteur, SA	4	2 months-5 years
	Inactivated (Adj.); Tetanus toxoid conjugate			Hiberix	Hib (PRP-T)	Glaxo Smith Kline Biologicals	4	6 weeks-4 years

Bacterial vaccine	Type	Function	Route	Trade Name	Abbrev.	Manufacturer	Dose in routine series	Approved Ages
	Inactivated (Adj.); Meningococcal conjugate			Liquid Pedvax-HIB	Hib (PRP-OMP)	Merck Sharp & Dohme Corp.	3	2-71 months
Meningococcal (Groups A, C, Y, and W-135)	Inactivated (Diphtheria CRM197 Conjugate)	Prevention disease by *Neisseria meningitidis* serogroup A, C, Y, and W-135	i.m	Menveo	MCV4-MenACWY-CRM	Glaxo Smith Kline Biologicals SA	2	2 months – 55 years
	Inactive (Diphtheria Toxoid Conjugate)			Menactra	MCV4-MenACWY-D	Sanofi Pasteur Inc	2	9 months – 55 years
	Inactivated (polysaccharide conjugate)			MenQuadfi	MenACWY-TT	Sanofi Pasteur, Inc.	1	≥ 1 years
	Inactivated			Menomune-A/C/Y/W-135	-	Sanofi Pasteur Inc	1	≥ 2 years
Meningococcal Group B	Recombinant (Adj.)	Prevention disease by *N. meningitidis* serogroup B	i.m	Bexsero	MenB-4C	Novartis Vaccines and Diagnostics, Inc	2	10-25 years
				Trumenba	MenB-FHbp	Wyeth Pharmaceutical, Inc.	2 or 3	
Pneumococcal	Inactivated (polysaccharide polyvalent)	Prevention pneumonia by *Streptococcus pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F	i.m	Pneumovax 23	PPSV23	Merck Sharp & Dohme Corp	1	≥ 2 years
	Inactivated (13-valent conjugate/CRM$_{197}$ Protein)	Prevention pneumonia by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F		Prevnar 13	PCV13	Wyeth Pharmaceutical, Inc	4	≥ 6 weeks
	Inactivated (15-valent conjugate	Prevention pneumonia by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F		Vaxneuvance		Merck Sharp & Dohme Corp.	1	≥ 18 years
	Inactivated (20-valent conjugate)	Prevention pneumonia by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F,14, 15B, 18C, 19A, 19F, 22F, 23F and 33F		Prevnar 20	PCV20	Wyeth Pharmaceutical, LLC	1	≥ 18 years
Tuberculosis	Live Attenuated	Prevention of tuberculosis by *Mycobacterium tuberculosis*	i.m	BCG Vaccine U.S.P.		Organon Teknika Corp., LLC	1	Infants and children with negative tuberculin skin tests

Bacterial vaccine	Type	Function	Route	Trade Name	Abbrev.	Manufacturer	Dose in routine series	Approved Ages
Typhoid	Inactivated (polysaccharide)	Prevention typhoid fever caused by *Salmonella enterica* serovar Typhi	i.m	Typhim Vi		Sanofi Pasteur SA	1	≥ 2 years
	Live Attenuated		Oral (capsul)	Vivotif		Berna Biotech,	4	≥ 6 years

Note: i.m, intramuscular

5. Perspectives and Future Directions

While bacterial vaccines offer numerous advantages in the fight against life-threatening bacterial diseases, several drawbacks appear to limit their use. To overcome these, some strategies have been devised. The development of some RNA-based bacterial vaccines, with multiple Phases I–III clinical studies currently underway [17]. Non-replicating and self-amplification RNA vaccines have been used to combat pathogenic diseases. Non-replicating RNA vaccines are easier to make and less expensive to produce, but their lifespan and expression level may be limited. Sequences and ideas adopted from single-positive strand RNA viruses, such as alphaviruses, can be used to build self-amplifying RNA systems (Alphavax). These vectors encode the non-structural genes and the immunogen but not the structural genes, allowing for a single replication cycle without the risk of producing an infectious virus. As a result of intracellular amplification of the antigen-encoding RNA, a modest dose of vaccine can create a huge amount of antigen. Several clinical trials for infectious pathogens such as HIV, rabies, and Zika have been conducted using RNA-based vaccination [164].

The hypodermic needle has been recognized as the mainstay of vaccine delivery technology due to its direct low-cost means of administration and remarkable efficacy profile determined over decades of usage. A quick validation can be made to ensure that the dose has been properly administered. However, the numerous disadvantages and restrictions of needle and syringe distribution are beginning to make it appear to be an out-of-date method. One of the most significant of these drawbacks is the impact of pain and needle phobia on patient compliance and, as a result, vaccination rates [165].

Novel ways have been proposed to overcome these restrictions, such as conjugating Vi polysaccharide to an appropriate carrier protein. This allows the T cell-independent Vi polysaccharide antigen to be converted into a T cell-dependent antigen. Despite the fact that a phase III investigation of a *Salmonella typhi* Vi composite vaccine showed over 90% effectiveness in children aged 2 to 5. The lack of a clear financial motivation for developing *Salmonella typhi* vaccines hampered the vaccines' entrance to the market. Due to the expanding network of vaccine makers in emerging nations, Vi glycoconjugate vaccines were just recently licensed in India and China [166].

Another strategy to support the use of bacterial vaccines is by encouraging antimicrobial drug repurposing. This effort refers to utilizing a formerly approved drug with established indications in treatment for bacterial diseases — either as monotherapy or as an adjuvant [7,130]. The concept of drug repurposing is not in the pharmacy field; for example, sildenafil—an anti-hypertension, turns a cure for erectile dysfunction [130]. Drug repurposing can offer an efficient and economical way to produce antimicrobial therapy with well-known drug characteristics, cutting the time of new drug discovery [131]. When employing this strategy, toxicity and side effects of the repurposed drug become a significant concern since antimicrobial therapy is generally given in higher doses than non-antibiotic drugs [130,131]. However, considering the benefits and potential of drug-repurposing, this strategy may become

a fast, efficient way to fill the lack of antimicrobial therapy, notably when supported by the pharmaceutical industries [130,132].

Another interesting approach to consider is the involvement of commensal microbes in maintaining host immune responses and host physiological homeostasis. Microbial colonization influences host fitness differently depending on the microbial adaption method. These impacts can be beneficial, as seen by the numerous gut microorganisms that provide a variety of advantages to the host. However, in some situations, microbial colonization can be harmful to the host, and the bacteria that colonize are known as pathogens. The purpose of virulence factors is to allow for adaptation to specific settings in host niches while promoting transfer to another host. Some common motifs of virulence-factor activity (and thus pathogenicity) can be recognized in this way. Bacterial pathogens have virulence factors that allow them to do a variety of things (depending on the niche they colonize): penetrating surface epithelia, attaching to cell surfaces and/or the extracellular matrix, invading intracellular compartments, acquiring iron, evading host defense mechanisms, and transmitting to another host [32]. By studying the role of commensal microbes in maintaining host immune responses, there will be heaps of chance in the future to harness its potential in the fight against AMR bacteria.

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Conflicts of Interest

The authors declare no conflict of interest.

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