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REVIEW

Vaccines as Potential Frontliners Against Antimicrobial Resistance (AMR): A Focused Review

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Abstract: Antimicrobial resistance (AMR) poses a formidable global threat, undermining the efficacy of potent antibiotics and complicating the treatment of infectious diseases, which has attracted the attention of scientific communities to revisit vaccines as a potential candidate against these superbugs. Although vaccines dedicated to bacterial infections are substantially reducing antibiotic use and decreasing annual healthcare expenditures for drug-resistant infections. Therefore, the vaccine can potentially prevent bacterial infections, which ultimately reduces the use of antibiotics and limits the opportunity for the development of resistance. Specific vaccines are being developed specifically to target drug-resistant bacteria like multidrug-resistant bacteria of *M. tuberculosis, E. coli*, and *S. aureus*, which not only prevent their spread but also reduce the burden on healthcare systems. However, despite their immense potential, disparate challenges hamper the broader application of vaccines in combating AMR. The most prominent challenge is the restricted accessibility of vaccines for high-priority drug-resistant ESKAPE pathogens. The development of vaccines against these organisms has proven a complicated process due to antigenic variability, immune evasion mechanisms, and a lack of reliable animal models. Furthermore, economic hindrances and logistical barriers, particularly in low- and middle-income countries (LMICs), pose serious hurdles to vaccine access and uptake. In the present review, crucial aspects of the vaccines have been emphasized that are directly correlated with the globalized AMR issues. Therefore, deployment of vaccine development and research against AMR is considered the cornerstone in AMR prevention, promoting balanced use of antibiotics, and ultimately mitigating the dissemination of resistant pathogens.

Keywords: antimicrobial resistance, AMR, antibiotics, drug-resistant pathogens, high priority bacteria, vaccines

Introduction

Antimicrobial resistance (AMR) has developed as one of the predominant, alarming public health threats in the 21st century, with the potential to undermine the era of medical achievements. As per the World Health Organization (WHO), AMR is responsible for millions of deaths annually and is predicted to claim up to 10 million lives per year by 2050 if left uncurbed.[1] According to recent findings, AMR is primarily driven by interconnected factors, including healthcare quality, sanitation infrastructure, economic and climatic conditions, socio-environmental dynamics, weak regulatory framework, anthropogenic, and human behavioral influences.[2,3] Emergence of drug-resistant bacteria is a natural phenomenon; it usually erupts due to the mutations in resistance-related genes or acquisition of horizontal transfer of genes via plasmids that transmit resistance, and may proceed irrespective of the appearance of antimicrobial agents. However, Bacterial vulnerability to conventional antimicrobials invokes the selective pressure for the rise and spread of drug-resistant pathogens, specifically in low and middle-income countries (LMICs) with compromised water, sanitation, and hygiene, healthcare settings, and improper surveillance systems.[4] To date, approximately 70000 million annual deaths have been predicted which resulting in 2% to

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3.5% reduction in global Gross Domestic Product (GDP) by 2050.[3,5] Although AMR is affecting public health majorly in LMICs, on a massive note, which includes longer hospital stays, higher mortality/morbidity rates, complications in treating common infections, declining socio-economic development, enabling the spread of untreatable "superbugs" such as *methicillin-resistant Staphylococcus aureus* (MRSA) and multidrug-resistant *M. tuberculosis*. It has been acknowledged that AMR/ABR cases can prompt a weakening of the effectiveness of routine medical strategies, complicate disease management, impact global health security, and ultimately jeopardize the accomplishment of modern medicine. Additionally, the diagnosis of pathogens exhibiting antimicrobial resistance (AMR) plays a valuable role in epidemiological surveillance research, enabling the estimation of the prevalence of resistant genomes. The evolution of novel antibiotics appears to have reached a dead end. Notwithstanding the immediate need to search for new antimicrobial yields, many pharmaceutical companies have abandoned antimicrobial medicine discovery schemes.[6]

However, various approaches such as antimicrobial stewardship (AMS), proper strategic surveillance systems, development of combinatorial therapy, nano-antibiotics, precision medicines, AI-powered nanobiogram analysis, and vaccines have been inculcated.[7,8] In the present scenario, scientific players are tremendously exploiting the power of vaccines over drug-based therapy, due to their ubiquitous targeted features, which make them a potential candidate for combating resistant pathogens. Moreover, it has been ascertained that vaccines exert their effect prophylactically, slowing AMR development, offer herd immunity, cost cost-effective, provide long-term and population-wide protection, impart selective pressure on resistant pathogens, thus reducing dissemination of infectious diseases.[9] Herein, the present review critically focuses on the efficacy of vaccines as potential frontliners against AMR/ABR, their prospective outlook, regulatory challenges, and clinically approved vaccines. The whole concept has been designed with a view to focus on a combined programmatic approach, aligned with the scheme for primary health care, global health coverage, and health emergency preparedness and response, that covers various levels of the healthcare system as shown in Figure 1.

To date, fragmentary research has existed, which has invoked a comprehensive evaluation of anti-bacterial resistance load across venues that encircle historic landmarks and future forecasts. AMR is a natural phenomenon and a consequence of the quick progression of drug-resistant bacteria. AMR cannot be completely prohibited, so the focus is on restricting, controlling,

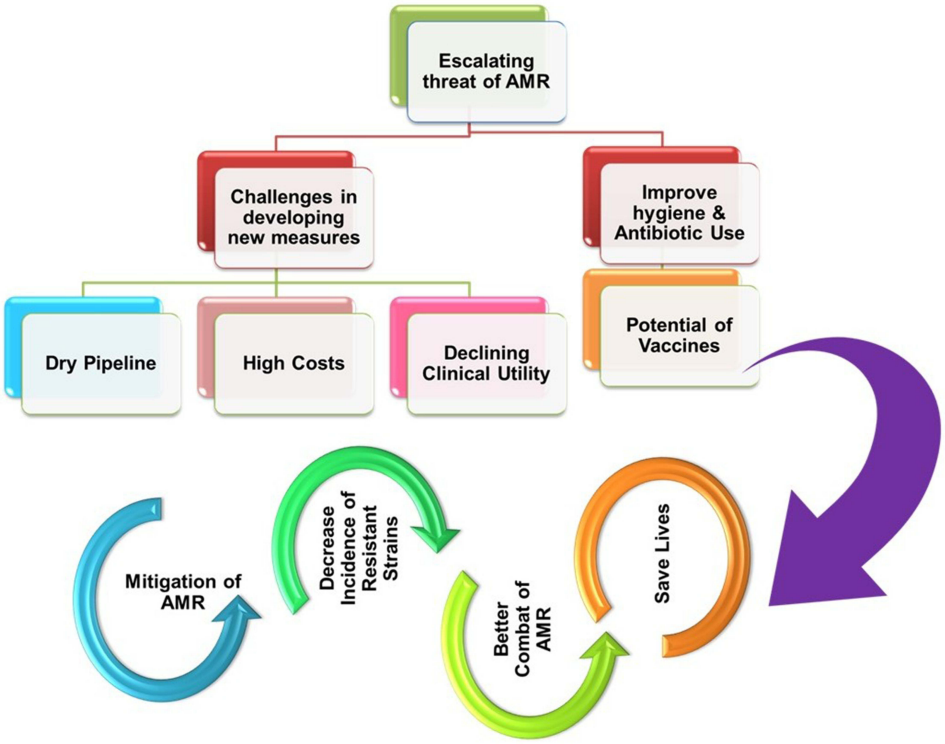

Figure 1 Diagrammatic illustration depicting the steps employed to combat Antimicrobial Resistance (AMR).

and mitigating drug-resistant bacteria.[10] Drug-resistant bacteria are widespread across environmental, human, animal, and food-related ecosystems. During contact with other humans, animals, and the atmosphere, these microorganisms and their resistance labels can be transmitted among different species, affecting the welfare of humans and animals, including associated animals, food-manufacturing animals, and living beings. Beyond intervention, it is determined that worldwide deaths attributable to antibacterial resistance could reach 10 million annually by 2050. Microbes are complicated microorganisms that get and transmit genetic material at an alarming rate with possibly tiny or no cost to themselves; and, contrary to previous dogma, the appearance of an antimicrobial drug has a small impact on the transmission of mobile microbial genetic material but can be picked up for newly acquired resistant tools. In high-income settings, overlong antimicrobial drug excess and unnecessary use have led to the flourishing of 'super-bugs', which are identifiable to many, like methicillin-resistant Staphylococcus aureus.[11] The people-centric strategies for antibacterial resistance summarize the country-level actions required to operationalize the three strategic priorities.

Understanding the Role of Vaccines in Combating AMR

The combined approach involves diagnostic techniques, novel antimicrobial drugs, vaccines, monoclonal antibodies, bacteriophages, and microbiota interventions to counteract the pathogens causing antimicrobial resistance. Vaccines have an unfamiliar effect on health and have been used for decades with less possibility of emergence of resistance, equated with antimicrobial drugs.[12] Innovative approaches and technologies in vaccine research, like structural and reverse vaccinology, polyclonal antibodies attacking multiple targets, nano-adjuvants, smart bioconjugates, polysaccharide-conjugated antigens, nucleic acid vaccines, and rationally modified microbial outer membrane vesicles (OMVs), are promising avenues for future research.[13,14] Usually, vaccines prevent life-threatening diseases by targeting the appropriate population, which reduces healthcare costs, AMR, and resolves sequelae after reinfection. Moreover, the critical angle to develop new vaccine candidates includes the suitable choice of populations for trials, understanding the immunological mechanisms correlated with protection ability, limiting financial incentives for the industries, a lengthy cum expensive process, along with checking the efficacy and biomarkers for characterizing the connection to defense.[15,16] Indeed, the lack of a correlation in defense is a major restriction to characterising a defensive vaccine.[17]

Nevertheless, in reality, no single strategic approach is adequate against AMR. Research and development (R&D) in AMR face global challenges; however, proper addressing is required to ensure the efficacy of novel and efficient antimicrobials to cure drug-resistant infections and prevent the emergence of pan-drug-resistant microbes. Bacterial drug resistance has developed swiftly against nearly every new class of antimicrobials shortly after their introduction into treatment regimens, and the further challenges in producing new antimicrobials indicate that antibiotic research and development alone are insufficient; therefore, a combination of approaches is needed. To upgrade AMR prevention and control, new vaccines have been designed and combined with new antibiotics or other strategies would be a potential solution against AMR.[12] In marked contrast, vaccination can be utilized for decades without creating any resistance. Hence, no linkages have been observed between vaccines and the evolution of drug-resistant microbes. Interestingly, vaccines utilized preventively, when disease-causing microbe populations are comparatively tiny, decrease the likelihood of emerging mutations linked to resistance that will evolve and multiply. Followed by targeting the pathogens in disparate ways, so many mutations are needed to acquire resistance. In a few cases, if vaccine resistance has been observed, it can reduce the disease. Therefore, research on these points may allow the production of an improved vaccine to avoid any future problems.[18]

Microbes (bacteria, viruses, fungi, and parasites) alter the action of available conventional medicines and emerge as drug-resistant microbes, which leads to the AMR situation. Fighting against AMR, vaccines are precise in targeting the microbes' disease, making it less likely to produce drug resistance. Vaccines that counter infectious agents like *Streptococcus* pneumoniae and Haemophilus influenzae have been shown to reduce tolerance to antibiotics. Nevertheless, in-depth research is needed on vaccines against some drug-resistant microbes and diseases such as *Salmonella* typhi, Vibrio cholerae, Escherichia coli, other nosocomial infections, and viruses causing diarrheal and pulmonary disease.[19] Vaccines under clinical development vary from these former vaccines in that they are prepared to address more comprehensively the complicated pathophysiology of *S. aureus* infections by evoking antibodies that mark multiple disease-causing factors. Therefore, the evoked antibody responses are functional and destroy the bacteria or neutralize the factors that cause disease.[20] To provide health benefits to the population, there must be continuous efforts to enhance vaccine coverage via innovative research and

licensing approval to proceed with new vaccines against newer pathogens, as well as drug-resistant microbial and viral pathogens.[20]

Antimicrobial Resistance (AMR) and Related Issues

Drug-resistant microbial evolution can be hammy by infectious diseases, which could severely increase morbidity and mortality to an extent similar to the pre-antibiotic era. This overkilling is due to the emergence of drug-resistant bacteria and their spread. Natural drug resistance depends on the microbes' potential to block the antimicrobial activity as a consequence of inherent structural as well as functional attributes.[21] The emergence of drug resistance is the greatest risk to current chemotherapy, and control measures to combat drug-resistant microbes are urgently required, including the development of novel antimicrobials. Regardless, the unveiling of new molecules with effective antimicrobial activity, pharmacokinetics, drug metabolism, and safety is alarming. However, the drug discovery pipeline also ran dry, which is usually due to the challenges in logistics and the higher price of substantial clinical tests, leading to molecules problematic to make available in the market. The correct clinical utilization of antibiotics can reduce resistance.[22] Enhancing hygiene, precise antimicrobial utilization, and controlled access in underdeveloped and developing countries are significant ways to limit the load of antibacterial resistance; however, these approaches individually are insufficient to minimize the AMR.[23] Antibiotic resistance is usually due to intrinsic mutations and the transfer of mobile genetic elements by HGT. These processes hamper the killing effect of antibiotics and lead to bacterial survival.[24]

Vaccine: A Valuable Weapon to Decrease AMR

Vaccines become a precious and efficient defense that helps in managing AMR, and a list of vaccines is represented in Table 1. Vaccination trains the immune system to identify and establish a quick and strong response against pathogens. An aspect of resistance mechanisms is less in the vaccination strategy. By decreasing the prevalence of drug-resistant serotypes, pneumococcal polysaccharide conjugate vaccines (PCV) have direct protective effects on infants and adults via herd immunity,[25] which reduces antibiotic use and the prevalence of drug-resistant bacterial strains. Perhaps viral vaccines are very efficient in decreasing the prevalence of AMR. The failure of vaccine development against these microbes is due to the targeting of various probable virulence mechanisms and the unavailability of animal models for

Table 1 List of Vaccine Status with Targeted Bacterial Pathogens/Non-Bacterial Pathogens, Which Might Lead to Help in Combating AMR

S. No.	Vaccine	Target (Type)	Impact on AMR	Key Limitations	Status (Till 2025)	Reference
1.	Pneumococcal Conjugate Vaccines (PCV13/15/20)	*Streptococcus pneumoniae*	Reduce incidence of antibiotic-non -susceptible invasive disease; fewer antibiotic courses needed	Serotype replacement; coverage varies by region/ age	Licensed & used globally	[28]
2.	21-Valent Pneumococcal Conjugate Vaccine (PCV 21)	*Streptococcus pneumoniae*	Covering a broad spectrum of antibiotics	Under Investigation	FDA Approved	[29]
3.	Typhoid Conjugate Vaccine (TCV, Vi-TT)	*Salmonella Typhi*	Prevents MDR/XDR typhoid, reducing the need for second-line antibiotics and transmission	No protection against *S. Paratyphi A*; itching and swelling, as well as redness	WHO-prequalified; national introductions ongoing	[30]
4.	MenB (4CMenB) – (with observed cross-protection vs *N. gonorrhoeae*)	*Neisseria meningitidis B*	Observational studies identified a reduced risk of gonorrhoea, and have the potential to curb rising gonococcal resistance	Cross-protection is observational; not licensed for gonorrhoea	Licensed for MenB (adolescents/ young adults)	[31]
5.	Haemophilus influenzae type b (Hib) Conjugate Vaccine –	*Haemophilus influenzae* type b	Dramatically lowers invasive Hib disease and β-lactamase–positive strains → fewer antibiotic exposures	No impact on non-type B strains; requires high coverage	Licensed & widely adopted	[32]

(*Continued*)

Table 1 (Continued).

S. No.	Vaccine	Target (Type)	Impact on AMR	Key Limitations	Status (Till 2025)	Reference
6.	Shigella GMMA Outer-membrane vesicle/GMMA candidate	*S. sonnei* 1790GAHB	Prevents shigellosis, a major driver of empiric antibiotic use; potential to slow resistance emergence	Serotype/strain coverage; durability; LMIC deployment	Phase 2 trials completed; development ongoing	[33]
7.	Extraintestinal Pathogenic *E. coli* (ExPEC) vaccines	*Escherichia coli*	Prevents UTI/BSI in high-risk groups → fewer antibiotic courses and resistant infections	Heterogeneous ExPEC serotypes; mixed late-phase outcomes	Mixed pipeline; maternal GBS6 advancing, ExPEC programs evolving	[34]
8.	Oral Cholera Vaccines (OCV) – *Vibrio cholerae* O1/O139	*Vibrio cholerae* O1/O139	Outbreak prevention reduces mass antibiotic use and inappropriate empiric therapy	Short-term protection; supply constraints; WASH still needed	WHO-prequalified; used in campaigns	[35]
9.	RTS, S/Other Non-bacterial Vaccines	Non-specific	Indirectly reduce inappropriate use of antibiotics for febrile illness misattributed to bacteria	Pathogen-specific; indirect AMR benefit varies by setting	Licensed (malaria, RSV, etc).	[36]
10.	Glycoconjugate vaccine (GBS6)	Group B *Streptococcus*	Preventing large populations of pregnant women and infants from invasive Group B *Streptococcus*	Revealing Serious Adverse Events like puerperium, perinatal conditions, and fetal distress syndrome.	Undergoing Phase 2 Trial	[37]

pre-clinical trials.[26] Clarity in the mechanisms of host-pathogen interactions, like immune evasion, and epidemiology for prevalence and variability of the key antigens, could help in the development of novel and effective vaccines. However, new innovative approaches would be necessary to develop novel vaccines, which would redefine the healthcare system against microbial infections.[27]

Molecular Mechanisms of Vaccines

Vaccines induce protection against microbial infections by training the immune system via various immunological mechanisms.[38] The major immunological mechanisms are the production of specific antibodies by plasma cells (PCs), a specialized class of B-cells, against vaccines containing antigen or toxic components of the pathogen.[39] Vaccine-induced B-cell activation is a very complex process because of the involvement of various kinds of immune cells {B-cells, CD8+ T cells-T_{H1}, T_{H2}, T_{FH}, CD8+T cells, and antigen-presenting cells (APCs) like dendritic cells, macrophages} that occurs in secondary lymphoid organs (SLOs) including the spleen, Peyer's patches and lymph nodes (LN).[40] On injecting the vaccine at the site, it reaches the LN where it is captured by macrophages and delivered to the B-cell zone, which is activated through interaction of the antigen and B-cell receptor (BCR).[41] On activation, the B-cell moves towards the B-cell and T-cell zone border, where the B-cell presents the same antigen to CD4+ T-cells, which also receive secondary signals and assist in their differentiation and proliferation.[42] Activated B-cells cause extra-follicular response or germinal center (GC) response, and extrafollicular response produces short-lived plasma cells (PCs), while GC produces long-lived, high-affinity memory cells and PCs.[43] On the other hand, CD4+ T-cells are activated through integrating with APCs that represent the antigen by major histocompatibility complex-II (MHC-II) class molecules and also provide co-stimulatory signals to CD4+ T-cells.[44] Activated CD4+ T-cells are differentiated into various subtypes, like T_H1, T_H2, and T_{FH}, with different functional profiles.[45,46] IFNγ and IL-4 are the signature cytokines of T_H1 and T_H2, respectively.[47] Effector CD4+ T-cells are differentiated through signals (cytokines and co-stimulatory signals) provided by APCs, specifically dendritic cells (DCs).[44,48] T_{FH} is a special subset of CD4+ T-cells that reside just proximal to B-cell follicles, exhibiting high expression of CD40L and IL-21 and involved in the stimulation of B-cells.[49–51] Mechanisms underlying T_{FH} differentiation are poorly understood. However, T_{FH} differentiation occurs through signals provided by APCs, which are activated by different kinds of adjuvants or antigens found in vaccines.[52,53] T-cell and B-cell interactions in the border zone produce extra-follicular PCs during the early phase of vaccination.[43] With the assistance of T_H1 and T_H2, partially differentiated T_{FH} produces the extra-follicular PCs;[54,55] IFNγ

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produced by T_H1 and T_{FH} stimulates the isotype class switching to IgG2 and IgG3/IgG1 in mice and humans, respectively, while IL-4 produced by T_H2 and T_{FH} stimulates the isotype class switching to IgG1 and IgE in both humans and mice.[54,56] Some vaccines, like live-attenuated vaccines, induce the production of extra-follicular PCs in a thymus-independent manner. However, this response generates only IgM antibodies with low affinity, little isotype switching, and decays rapidly.[57] Long-lived PCs (capable of producing high-affinity antibodies) and memory B-cells are only produced at the GC, a unique structure inside the B-cell follicle.[58,59] The presence of T_{FH} inside GC is essential for the maintenance and formation of GC.[60,61] The B-cells found in the GC undergo somatic hypermutation (SHM) that occurs in the variable region of immunoglobulin genes, which makes immunoglobulin act against distinct antigens.[62–64] B-cells of GC represent the antigen after binding to T_{FH} and compete for their assistance, which is necessary for proliferation and survival of the B-cell, and this selection process undergoes several rounds to develop high-affinity antibodies against antigens found in vaccines.[42] Some of the B-cells of GC undergo terminal differentiation after completing the selection pressure, and this is essential to establish a long-lived immunity triggered by vaccination.[65,66] Studies have observed that the interaction strength between T_{FH} and BCR is the primary mechanism responsible for long-lived immunity.[67–69] Some vaccines, specifically mRNA vaccines acting against AMR, have also been developed to induce CD8+ T-cell immunity.[70] Activation of CD8+ T-cells occurs after interactions with APCs that present antigens of the vaccine via the MHC-I molecule.[45] On activation, naïve CD8+ T-cells proliferate and differentiate into memory and effector cells. Effector cells, CD8+ T-cells, are short-lived and enter into programmed cell death, while memory CD8+ T-cells are long-lived and further proliferate and differentiate into huge waves of effector cells on re-exposure to the same antigen.[71,72] The function of memory CD8+ T-cells is the primary mechanism in aged individuals in case of an insufficient antibody response after influenza vaccination.[73] A novel kind of CD8+ T-cell called T_{RM} (tissue-resident memory T-cell) that resides in non-lymphoid tissue for a long period, which controls re-infections.[74] T_{RM} is the primary candidate to develop vaccines to prevent reinfection, especially in the case of digestive tract and respiratory infections.[74,75]

Epidemiological Level of Vaccine Mechanisms

Vaccines prevent the dissemination and emergence of AMR infections in two ways: direct (vaccination) and indirect (population immunity/herd immunity).[76] Vaccines circumvent bacterial infections and AMR resistance by eliciting rapid immunity that leads to the reduction of the severity of the disease and controls the establishment of AMR infections; consequently, the selective pressure of resistance (Figure 2).[77] Herd immunity protects unvaccinated individuals or ineligible individuals for vaccines, like immunocompromised individuals or cancer patients undergoing chemotherapy, through a process called population immunity.[78] Population immunity protects a large number of individuals from infection compared to individuals undergoing vaccination.[79] Population immunity prevents the spread of AMR infections from an infected population to a susceptible population.[78,80] Conjugate vaccines are the most successful vaccines that protect against both *S. pneumoniae* and *H. influenzae* type b (Hib) infections and are responsible for the rapid establishment of population immunity.[81] Vaccination impedes millions of deaths/year which can be enhanced when the rate of vaccination at the global level is improved such as global vaccination coverage for PCV is around 37% which can be further increased by improvement in global vaccination coverage and this leads to further decrease in spread rate of AMR infections and antibiotic usage.[82,83] Consequently, the reduction in antibiotic use indirectly contributed to a decrease in the emergence of AMR infections.[84] Here, we use *S. pneumoniae* and Hib as examples of how vaccines assist in the fight against AMR infections. *S. pneumoniae* primarily causes community-acquired pneumonia and meningitis, especially in children, and also causes sepsis, specifically in HIV patients.[85] *S. pneumoniae* contributes to being the leading cause of death worldwide among adults and children who are not vaccinated.[86] In 2017, the WHO reported 8 million deaths/year among children under the age of 5 that were caused by *S. pneumoniae*, which made up 15% of all deaths among children under 5 years of age.[87] In 1990, approximately 63000 cases of invasive pneumococcal disease (IPD), either caused by PCV7 or not, were reported each year in the USA before PCV7 was introduced.[88] Nowadays, *S. pneumoniae* becomes resistant to more than three drugs owing to dissemination.[89] PCV contains pneumococcal polysaccharide, which exhibits more than 90% success against IPD, similar to the Hib conjugate vaccine.[90] A report revealed that PCV7 not only prevents *S. pneumoniae*-mediated disease, but it also significantly reduces the colonization and contributes to the establishment of population immunity in individuals who did not receive the vaccine, especially adult populations.[90] Epidemiological studies have shown that approximately 2.1 million cases of IPD, including antibiotic-resistant strains,

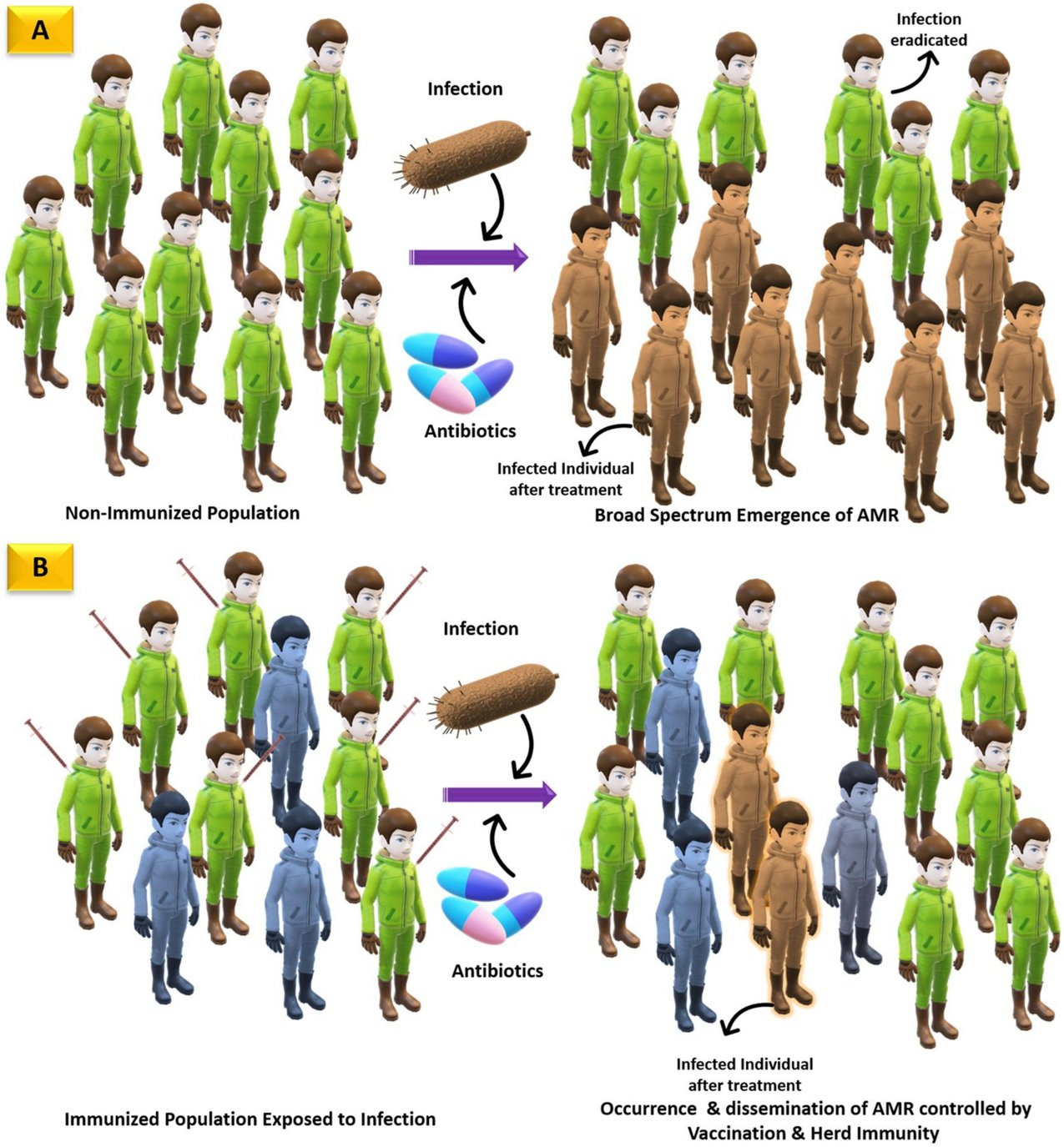

Figure 2 Infographic representation of the impact of vaccines on the prevention of AMR spread and emergence. (**A**) The Population which are not immunized against infectious pathogens the majority of population are susceptible to pathogens, and some of them become infected, which spreads the infection among other susceptible populations. Infected individuals are recommended to take antibiotic treatment to circumvent pathogenic infections. However, excessive antibiotic usage leads to AMR development and its spread to others. (**B**) Populations that are immunized with vaccines decrease AMR spread and emergence.

were controlled in children, as well as adults and older populations by PCV7.[90] Investigations have demonstrated that second-generation PCV (PCV10 and PCV13) covering the 10 and 13 serotypes prevent infections in both a direct and indirect manner with similar efficacy.[91,92] Research revealed that PCV13 decreases antibiotic usage and simultaneously reduces the prevalence of drug-resistant strains.[88,89,91] Another bacterium that causes pneumonia and meningitis is called Hib in children under the age of 5 years.[93] Hib vaccine is the first conjugate vaccine that not only prevents

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disease caused by bacteria with high potency, and protects older children via population immunity; therefore, it also reduces the emergence of antibiotic resistance as it reduces antibiotic use.[77] In 1980, the Hib conjugate vaccine was introduced in the USA, followed by the rest of the world. During that time, the incidence of meningitis and pneumonia caused by Hib was 3.5 to 601 cases/10^6 in different countries.[94] A study has shown β-lactam resistance in Hib bacteria via expression of β-lactamase and penicillin-binding proteins in the early 1970s.[95] According to a global survey report, approximately 16.6% of Hib strains are resistant to β-lactamases that vary among different countries.[96] The development of a Hib conjugate vaccine containing polysaccharide with carrier proteins in the 1960s turned the tide against antibiotic resistance by creating and utilizing effective conjugate vaccines against Hib.[97] One investigation observed a significant decrease in Hib-induced disease cases following the introduction of routine Hib conjugate vaccine use.[98] A significant reduction in nasophageal carriage is also reported in the unvaccinated population in Canada (2.6 cases/10^6 from 1986–1988, while 0.08 cases/10^6 from 2011–2015) due to population immunity, post-Hib conjugate vaccine introduction.[99] Following the introduction of the Hib conjugate vaccine to children under five years of age in the UK, the disease was almost eradicated, and similar outcomes were also observed globally.[100] Studies reported a significant reduction in the Hib strains resistant to β-lactam, and in some countries, such as Japan, a decrease was observed before vaccine introduction.[101,102] Studies have also observed that virus vaccines prevent the spread and emergence of AMR infections in an indirect manner.[76,103,104] Similarly, PCV and other conjugate vaccines also prevent the spread and emergence of penicillin-resistant strains by reducing antibiotic use and establishing rapid population immunity.[105,106]

Current Vaccine Strategies: Preventions and Limitations

Nanotechnology has shown accelerated potential in reverse vaccinology; however, nano-based peptide delivery has multiple challenges, like targeted and safe delivery of vehicles, immunostimulant, antigenic regulation, prolonged controlled release, and evasion of the antigen response.[107] The mRNA-based technology can develop more effective vaccines than other strategies. Generally, conventional antigen-based vaccines showed the rarest side effects. Researchers and vaccine manufacturers must be cautious about escape mutation, re-infection, dosage efficacy, and minimize the unusual events while maintaining the stable or strong efficacy. Investigators collaborating with manufacturers should also focus on research to determine vaccine efficacy when other vaccines (based on similar technology by different manufacturers) are administered in consecutive doses and should check for synergism. Vaccine manufacturers must also consistently modify vaccines with escape mutations.[108,109]

Trials must be performed with mixing or concurrent administration of vaccines to assess the wide variety of cross-protection against emerging variants. Moreover, clinical research should be conducted in other demographic regions, age ranges, identities, and health conditions. Extended funding, research integrity, and thorough analyses are required to manage the emerging pandemic in a short duration.[108–110] Vaccination is a foundation of public health care policy and is considered a cost-effective approach to protect children's health. Most available vaccines have been empirically developed and tested; however, there are lots of challenges to developing novel vaccines against target pathogens, for which there is an urgent need to understand protective immunity. Moreover, vaccination to control disease outbreaks and protect the older population, together with the availability of a range of new technologies, make it the perfect time for immunologists to design the next generation immunogens.[111] Despite the evidence focusing on antibodies being the key mediators of sterilizing and induced immunity by vaccination, most vaccines also prompt T-cell responses. The function of T cells in protection is fragmentary, besides their role in assisting B cell development and antibody production in lymph nodes. Research on individuals with inherited or acquired immune deficiency has shown that antibody inadequacy increases susceptibility to infection, and a lack of T cells results in failure to control a pathogen after infection.[112]

Combinatorial Strategies Combating AMR

A combination of vaccines with other interventions, like antibiotics, phage therapy, microbiome modulators, and phage-antibiotic intervention, offers an excellent approach to preventing AMR emergence and spread. Vaccines combined with phage therapy and monoclonal antibodies exhibit high potency to prevent AMR.[113,114]

Vaccines with Monoclonal Antibodies (MAb)

MAbs and vaccines work in tandem, so their effects are not mutually exclusive. MAbs provide instant protection against infectious pathogens while vaccines take 2 to 3 weeks to establish an immune response. However, vaccines provide a long-term defense by training the immune system, which identifies foreign invaders and neutralizes them.[114] Vaccines provide long-term protection, while MAbs provide short-term protection due to the shorter half-life.[115] Thus, the integration of vaccines with MAbs exhibits synergistic effects because this combination provides immediate and targeted protection (MAbs) and long-term protection (vaccines).[114] This combination is very effective when rapid interventions are required to prevent infection and AMR dissemination.

Antibiotics with Phages

The combination of antibiotic and phage is referred to as phage-antibiotic synergy (PAS), and this interaction leads to synergistic and additive effects.[116–120] Multiple approaches (concurrent or sequential) are used to integrate vaccines with antibiotics, including using phages to increase antibiotic potency and using antibiotics to mitigate the emergence of phage-resistant bacteria.[113] Sequential application of phages and antibiotics exhibited higher potency against bacteria than concurrent application.[121] A study reported that sequential applications of antibiotics and phages clear the biofilm in *P. aeruginosa* than antibiotics or phages.[122] Another set of studies revealed that phages followed by antibiotics inhibited the growth of biofilms more effectively than antibiotics followed by phages alone.[123–125] Delivery of antibiotics using phages reduces the off-target effects and enhances the antibiotic concentrations at the site of infection.[121] Thus, combinations of phages and antibiotics are a promising intervention to prevent AMR.

Vaccines with Phage Therapy

Vaccines decrease the disease burden and antibiotic recommendation pressure, leading to the prevention of AMR spread and emergence.[60] A vaccine that targets a specific surface protein (or virulence factor) further enhances its effectiveness. Phages are employed to target specific bacterial strains and antibiotic resistance, which cannot be controlled with traditional interventions.[126] Thus, the combination of phases and vaccines may offer a promising intervention in preventing AMR. Studies also suggested that phage-based vaccines are more effective in preventing AMR.[127] Various researchers revealed that phage-based vaccines are effective against parasitic diseases, viral diseases, bacterial diseases, and other diseases.[128–139]

Vaccines with Microbiome Modulators

The Microbiota of the human gut plays a crucial role in the establishment of immunity, and modulation of gut microbiota may offer a promising role in preventing AMR.[140] Prebiotics, probiotics, and antibiotics are helpful in the establishment of gut microbiota[141] and can decrease AMR spread and emergence. Vaccines decrease antibiotic usage by evading viral and bacterial pathogens through eliciting immune responses.[4] The combination of microbiome modulators and vaccines is a comprehensive intervention strategy that can reduce the burden of AMR and its spread.

Novel Vaccine Technology

Traditional vaccine approaches have been employed to produce vaccines against various viral and bacterial pathogens. These vaccines become ineffective against looming pathogens with high sequence variability, complex viral pathogenesis, antibiotic resistance, evolving, and persistent infections.[142] Continued scientific effort on the development of novel vaccine technologies, such as virus-vector and nucleic acid vaccines, which revolutionized vaccine development by overcoming the limitations of traditional approaches.[143]

mRNA Vaccines

mRNA vaccines belong to nucleic acid vaccines, overcoming the limitations of DNA vaccines like low immunogenicity owing to low plasmid transfection rate.[144] mRNA vaccines are becoming popular due to their potency, safety, and ability to prevent diseases that are inaccessible to other approaches. It provides long-term protein expression, strong T-cell immunity, and does not interfere with existing immunity or raise immunity to specific pathogens.[142] This approach allows the design of a particular antigen, native-like presentation of antigen, and exposure of specific antigenic sites.[145] Furthermore, multiple

mRNAs can be delivered to the same cell, allowing the design of a single vaccine against multiple targets.[146] mRNA vaccine development is based on a chemically defined, consistent process that shortens the period for vaccine development, simplifies vaccine production and quality control, thus providing sufficient time for human evaluation and antigenic improvement.[147] It is very useful in the case of a disease outbreak because mRNA vaccines can be produced and scaled up through well-established processes and chemicals within weeks without changing the antigen.[142]

Viral Vector-Based Vaccines

The primary issue with mRNA vaccines is cell entry, which can be circumvented by using natural carriers like viruses.[148] Viral vector-based vaccines have shown a strong immune response against pathogens by delivering genetic instructions to specific cell compartments.[142] Desired antigenic genes are inserted into the virus genome by replacing specific viral genes, and this replacement provides (a) formation of a replication-incompetent virus to ensure safety and (b) non-significant alterations in viral genome size.[149] Multiple viruses, including cytomegalovirus (CMV), adenovirus, poxvirus, AAVs (adenovirus-associated viruses), retroviruses, and herpesviruses, are employed in vaccine development and delivery.[142] Viral-vector-based vaccines induce the immune response in the host by activating cellular sensors like TLR9 and strong B and T cell-mediated immunity.[150–155]

Biomaterial-Based Vaccines

The biomaterial approach is the combination of biology, material science, and engineering approaches, which is employed to enhance the efficacy of vaccines.[156] The biomaterial approach offers the opportunity to design promising carriers and explore the understanding of functional aspects of the immune system. Bioengineering-based platforms increased the nature and the magnitude of eliciting an immune response.[157] Infections caused by pathogens induce both adaptive and innate components of the immune system.[158] However, traditional vaccines (protein-based vaccines) elicit a very low immune response while exhibiting an excellent safety profile.[159] Incorporation of adjuvants leads to the increased activation of the innate immune system, which is not possible with protein alone.[160] Delivery of adjuvants without antigen leads to the elicitation of a non-specific immune response, suggesting that adjuvants act as co-stimulators.[161] Thus, co-stimulatory signals are required to generate an innate immune response; however, biomaterials overcome this issue in various ways: (a) entrapment or encapsulation of cargos in lipid carriers or polymer particles, (b) through self-assembly of signals into micro or nano-complexes, virus-like particles (VLPs) or poly-electrolytes, and (c) through attaching cues to the surface of spherical surfaces like AuNPs and polystyrene beads.[161–164] These methods of vaccine development increase the efficacy of the vaccines via (a) the co-delivery of cues to the same cell, (b) the drainage of cues to lymph nodes, and (c) the uptake by APCs while lowering off-target effects.[159,162,165]

Attributes of Vaccine-Induced Protection

Over the past two centuries, vaccines have provided primary protection/immunity in vaccinated individuals through the B-cell and T-cell-dependent mechanisms, which lead to the initiation of a memory response. Vaccines are usually developed to prevent infection. However, some vaccines, in addition to preventing the disease, also work against asymptomatic infection, thereby diminishing the acquisition of a microorganism and establishing herd immunity.[166] Certainly, the initiation of herd immunity is a major characteristic of vaccination programs, which safeguards many more people than those vaccinated. Some vaccines may also initiate transformation in reactivity to future infections with different microorganisms, so-called nonspecific effects through stimulating long-term changes in the activation state of the nonspecific immune system.[166]

Challenges to Vaccination Success

Probably the greatest challenge to vaccination programs is overcoming the solid headwinds against vaccine distribution in underprivileged infrastructure and low-resource settings to address vaccine unwillingness and scale-up, respectively. Fragmentary scientific facts about antigens display a protective effect, and the type of immune response required for protection and further improvement for better vaccines, particularly for older adults are also exists.[167]

Future Vaccine Development

Improved or new vaccines are required for various diseases to decrease the disease burden and mortality. Vaccines for CMV, respiratory syncytial virus (RSV), and group B *Streptococcus* hold market in developed and developing nations. Group B *Streptococcus* vaccines are in phase 2 and 3 trials to induce maternal immunity and passively protect newborns through the placenta.[168] Advanced technologies and platforms that put forward novel ways or adjuvants for antigen delivery. Clinical research on vaccinations has shown that improved antigenicity, knowledge gaps, and challenges need to be discussed.[169] Current developments in immunology, proteomics, genomics, systems biology, and bioinformatics offer great potential to improve knowledge of antigen responses by new or modified vaccines. Vaccination protects vulnerable populations, children, and older adults from diseases. As per the Rights of the Child, every child must be vaccinated for the best health.

Challenges in Vaccine Development Against Drug-Resistant Pathogens

Vaccines are a preventive approach to reduce the spread of infections and emergence of AMR by decreasing antibiotic resistance pressure.[60] A variety of antigenicity and pathogenic factors act as obstacles to vaccine development and AMR reduction.[14] It is difficult to develop vaccines against some pathogens (*C. difficile*, *M. tuberculosis*, and *S. aureus*) due to intracellular persistence of resistance, the lack of specific immune biomarkers, and the high level of antigenic variability (Figure 3).[15]

Clostridium difficile

C. difficile, a bacterium that causes infections in major parts of the large intestine/colon, resulting in diarrhea and sometimes a dreadful condition called colitis.[170] *C. difficile* infections primarily occur owing to the excessive use of antibiotics, resulting in disruption of the natural gut microbiome, which allows *C. difficile* to overgrow.[171] High antigenic variability leads to expression of various kinds of surface proteins and toxin components by different strains of *C. difficile*, which is the primary cause that impedes the development of a universal vaccine.[172] It resides in the gut as spores, which are extremely resistant to immune response and environmental conditions.[173] This leads to intracellular persistence, promoting recurrent infections of *C. difficile* even post-antibiotic treatment. Vaccine efficacy assessment is hindered in clinical trials because *C. difficile* is not protected by universal antibiotics.[174]

Mycobacterium tuberculosis

M. tuberculosis is an adaptable pathogen that causes tuberculosis in the lungs and other organs.[175] An inherent adaptive capacity inside the host, as well as antigenic variability, complicate the recognition of conserved targets, which act as hurdles in the development of a universal vaccine.[176] Evading immune responses by residing inside macrophages leads to intracellular persistence of *M. tuberculosis*, and the unavailability of universal antibiotic protection also acts as a hurdle for the development of a universal vaccine against *M. tuberculosis*.[177]

Staphylococcus aureus

S. aureus is spherical-shaped, non-motile, and a facultative anaerobe; gram-negative bacteria cause sepsis, pneumonia, osteomyelitis, and endocarditis.[178] It is a common infection occurring in hospitals and community-acquired settings. High variability of surface proteins creates a hindrance to effective vaccine development.[179] Unavailability of specific immune biomarkers and biofilm formation hinders the development of a universal vaccine against *S. aureus*.[180]

Economic and Policy Barrier

Vaccines are excellent tools to decrease infections and the dissemination of antibiotic resistance. However, some economic and policy barriers have an impact on its implementation and effectiveness.

Economic Barriers

AMR can be prevented by vaccines, but more evidence is needed to demonstrate vaccines' specific economic value in reducing the development of AMR, which may affect the investment decision and resource allocation. Some studies have evaluated the economic value of PCV in fighting AMR by estimating the cost.[181,182] However, economic evidence

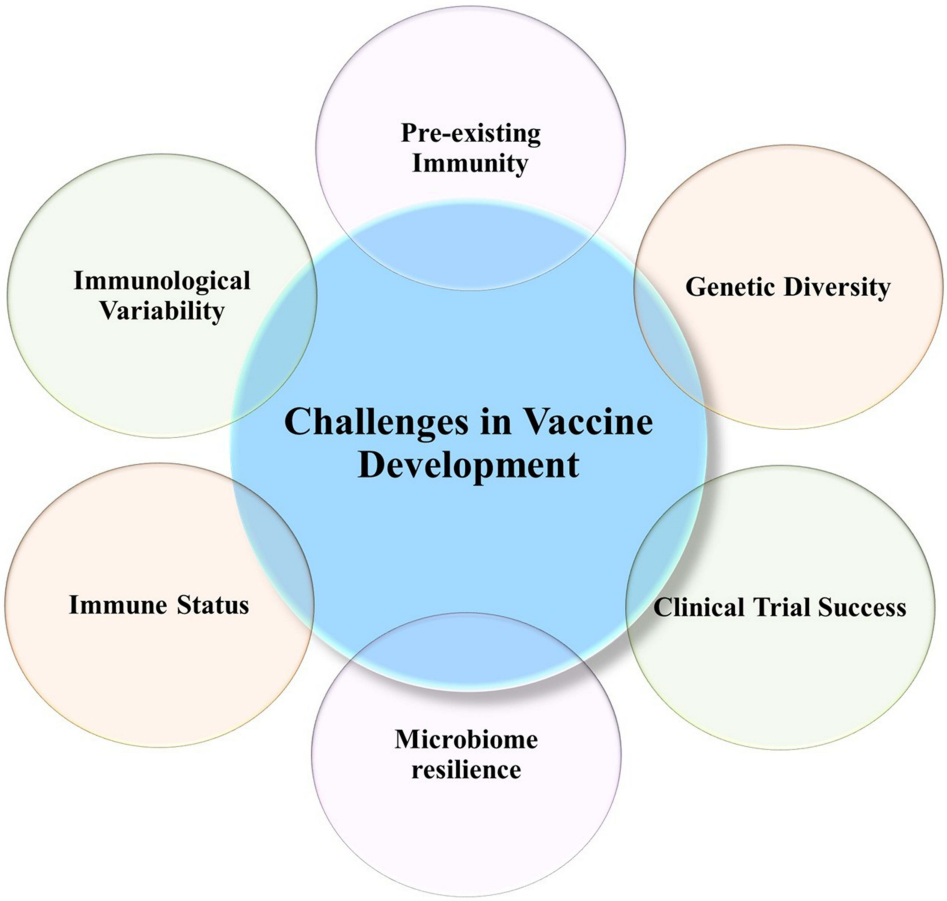

Figure 3 Diagramatic representation of the challenges faced in vaccine development.

regarding vaccines and AMR is limited, like "Antibiotic utilization" and "Longitudinal AMR data" related to vaccine-mediated prevention of the disease. None of the studies examined the effects of serotype replacement and did not account for fitness costs in the AMR model.[183] Limited data are available related to the AMR burden and illness costs in the context of a particular pathogen, which acts as a barrier to evaluating the economic effect of vaccines on AMR. Some countries are unable to afford the vaccine without the support of the government and public organizations, and this acts as a barrier to other interventions like management programmes. Limited studies evaluated the vaccine's cost-effectiveness in instantly slowing AMR development.[183] Research has explored that the PCV7 conjugated vaccine is highly cost-effective for 53 out of 77 countries despite serotype replacement effects.[184]

Policy Barriers

Lack of transportation and knowledge act as a barrier to immunization.[60,185] Hence, an educational programme regarding vaccine safety and effectiveness must be conducted to maximize immunization. Moreover, government organizations, health care sectors and other global agencies must accomplish major initiatives such as incentivising the vaccine research and development (R&D), inculcation of vaccine strategy in Global National Action Plan (NAP), Vaccine rollouts in AMR prone low- and middle-income countries (LMICs), promote AMR vaccine innovation funds at global levels, integrating vaccination drive into antimicrobial stewardship (AMS) programs, ascertain rational use of antibiotics and cases of hospital-acquired infections, monitoring regulatory harmonization, strengthing global surveillance, One Health driven vaccine strategy combating AMR effecaiously. Lack of knowledge about the impact of AMR on health, cost, and society is also acting as a barrier. Thus, policymakers must consider the health, cost, and socio-economic impact of AMR before licensing the vaccine. Clinical trials that examine vaccine effectiveness for AMR must be overseen by regulatory agencies for good risk-benefit analysis and post-vaccine approval.

Conclusion

Vaccines play a pivotal preventive role in reducing the global burden of infectious diseases by preventing infections at an early stage, thereby significantly decreasing the need for antibiotic prescriptions. Partnerships with global consortia like the AMR Action Fund and Global Antibiotic Research & Development Partnership (GARDP) play a crucial role in addressing key challenges in antimicrobial and vaccine innovation, thus aligning with WHO's strategic objectives. In recent years, innovative approaches in vaccine development have been introduced to create advanced vaccine candidates. Interestingly, assessment of antigenic determinants from genomic data allows production of combined vaccines (4CMenB vaccination for meningococcus B). However, the complicated disease development and the lack of suitable animal models for human diseases caused by drug-resistant bacteria, such as *S. aureus* and *C. difficile*, pose a challenge to the development of effective vaccines. For immunization, disparate tactics need to be implemented successfully to screen for any loopholes in the current antibiotic stewardship (ABS) programs. To improve public health outcomes worldwide, it is necessary to investigate and understand the context-specific elements that contribute to ABS programs' efficacy. Combating AMR via combinatorial approaches such as hygiene practices, effective sanitation, infection control/preventive measures, and inculcation of vaccines has become an urgent need in healthcare systems. In the present scenario, vaccines are usually designed as preventive measures along with safety concerns, especially in fragile populations. Though understanding the immune status has been established as a crucial step for successful vaccine development. Moreover, clinical trials and vaccine efficacy must be combined with reactogenicity to raise confidence in health programs. Vaccines are predominantly employed to raise herd immunity against site-specific infection, temporary or chronic human immune deficiency, and an indistinct microbiome. Furthermore, investment in vaccine research and development (R&D) is critically needed to address emerging microbial threats and expand protection against a broader spectrum of diseases. Widespread ensuring and equitable access to vaccines at both local and global levels are equally imperative, which establishes herd immunity and reinforces community health resilience. Thus, vaccines represent a sustainable and cost-effective strategy to promote antimicrobial stewardship efforts and to combat AMR as part of a broader, long-term public health framework.

Future Directions

Vaccines against AMR offer the greatest impact in preventing antibiotic prescription pressure, which leads to a reduction in antibiotic resistance and decreases the spread of resistant bacterial strains. To enhance the vaccine's impact on AMR, global coverage must be spread by educational programs about the effectiveness and safety of vaccines. Rapid approval for novel vaccines against bacterial and viral pathogens for which vaccines do not exist is urgently required. Novel vaccines that are still under development trials against *S. pneumoniae*, *C. difficile*, *S. aureus*, and vaccines against gram-negative bacteria with extended coverage of serotypes, not only prevent diseases caused by these bacterial strains but also prevent the spread of antibiotic resistance. Combined efforts must be employed to develop vaccines against drug-resistant strains (*P. aeruginosa*, Group B *Streptococcus*, *Moraxella catarhalis*, Extra-intestinal *E. coli*, non-typable *H. influenzae*, and carbapenem-resistant *E. coli*) that are still not prevented. Complex basic and clinical science programs require a restricted pool of experienced researcher talent. Novel vaccines may be developed more quickly in the future due to advancements in regulatory sciences. The WHO Bacterial Priorities Pathogen List (BPPL) recognized some pathogens (bacteria from 15 families) like *Neisseria gonorrhea*, *Shigella species*, *M. tuberculosis*, *S. aureus* resistant to methicillin, *K. pneumoniae*, Non-typhoidal *Salmonella*, *E. coli* resistant to fluoroquinolone and cephalosporins, *H. pylori*, *P. aeruginosa*, and others that need urgent attention for the development of vaccines to prevent these life-threatening diseases and AMR.

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Conceptualization, supervision, and project administration: D.S.; Writing-original draft preparation: S.P.; I.S.; J.S.; D.S.; I.K.V.; A.K.; A.R.; and M.S.D.; Writing—review and editing: D.S.; I.S.; J.S.; S.P.; I.K.V.; A.K.; A.R.; and M.S.D.; Analysis and interpretation: S.P.; D.S.; I.S.; J.S.; S.P.; I.K.V.; A.K.; A.R.; and M.S.D.; Visualization: I.S.; and D.S. 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; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; 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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