Review

The role of vaccines in combating antimicrobial resistance (AMR) bacteria

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ABSTRACT

Most pathogens have developed an intrinsic capacity to thrive by developing resistance to antimicrobial compounds utilized in treatment. Antimicrobial resistance arises when microbial agents such as bacteria, viruses, fungi, and parasites alter their behaviour to make current conventional medicines inefficient. Vaccination is one of the most effective strategies to fight antimicrobial resistance. Vaccines, unlike drugs, are less likely to produce resistance since they are precise to their target illnesses. Vaccines against infectious agents such as *Streptococcus pneumoniae* and *Haemophilus influenzae* have already been shown to reduce tolerance to antimicrobial medications; however, vaccines against some antimicrobial-resistant pathogens such as *Vibrio cholerae, Salmonella typhi, Escherichia coli,* nosocomial infections, and pulmonary and diarrheal disease viruses require more research and development. This paper describes vaccine roles in combatting antimicrobial resistance, quantifies the overall advantages of vaccination as an anti-antimicrobial resistance approach, analyzes existing antimicrobial vaccines and those currently under development, and emphasizes some of the obstacles and prospects of vaccine research and development.
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Contents

1. Introduction

In 1998, the infectious diseases were one of the main causes of mortality globally, accounting for 25% of all deaths (World Health Organization, 1999). In 2019, non-communicable diseases were the biggest global health burden, but infectious diseases still account for 9% of all deaths worldwide ("Infectious diseases preva-

lence by country 2019 | Statista", 2021). This significant decrease in the impact of infectious diseases can largely be attributed to the successful use of antimicrobials.

Antibiotic discovery in 1928 and their subsequent worldwide use was vital in transforming medicine from a merely diagnostic science to one with a more therapeutic orientation (Infectious Diseases Society of America, 2011). Since sulfonamides, penicillin and streptomycin were first used in the 1940s, the next four decades became a golden period of antimicrobial agents (Thakare et al, 2020). Numerous antibacterials, antifungals, antivirals, and antiparasitics have since been developed and used to fight infectious illnesses (Davey, 2021). Pathogenic microbes, however, are always evolving and acquiring new characteristics at an astounding rate.

Most microbes have developed over time an intrinsic capacity to thrive by developing resistance to antimicrobial chemicals that are employed in treatment. AMR, also known as drug resistance, arises when microbial agents such as bacteria, viruses, fungi, and parasites alter their behavior in order to make current conventional medicines inefficient (Asokan & Kasimanickam, 2013). Several studies have linked higher rates of AMR to unregulated use of drugs (Hofer, 2019; Rogues et al., 2017; Tran et al., 2017).

AMR illnesses are already widespread, culminating in longer hospital stays, greater medical expenditures, and higher fatality rates. Micoli et al. (2021) reported that the global yearly death toll from AMR infections is projected to reach 700,000, and the rise in infections with AMR agents may represent a health risk, with the number of fatalities overtaking those caused by cancer by 2050. AMR reduction will need national and global coordination of technical, behavioral, economic, and political actions (Ghosh et al., 2019).

There's no denying that combating a danger as large and complicated as AMR necessitates a diverse set of treatments, including novel antimicrobials, improved diagnostics, and improved management (Jansen, 2021; Jit & Cooper, 2020). It also necessitates a greater focus on a variety of strategies to prevent illness and minimize antibiotic usage, such as enhanced cleanliness and increased vaccination use. Clift & Salisbury (2017) postulated that vaccines may be the best or only approach to save lives in illnesses where AMR has grown widespread such as gonorrhea.

The creation and use of vaccines against infectious illnesses is a significant strategy that offers distinct benefits in fighting AMR transmission. According to Rosini et al. (2020), vaccination's potential as an anti-AMR strategy has long been acknowledged, but it has lately gained considerable attention. Wahl et al. (2018) observed that following the advent of vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenzae*, there was a decrease in antibiotic use and bacterial resistance. Vaccines have been recognized as an essential tool to decrease demand for antimicrobial drugs and thereby combat AMR in assessments commissioned publicly in the UK, the EU, and the US (European Commission, 2020; "March 2015 – vaccines and global health: ethics and policy", 2015; O'Neill, 2016). However, as they only evaluate a portion of the mechanisms through which vaccinations might impact antibiotic usage and tolerance, these studies understate the possible value of vaccines. Multiple interacting ecological, epidemiological, and health-systems mechanisms via which vaccinations impact AMR have recently been described in a number of new reviews (Buchy et al., 2020; Sevilla et al., 2018).

This paper summarizes the roles of vaccines in combating AMR, quantitates the overall benefits of vaccination as an anti-AMR strategy, reviews existing anti-AMR vaccines and those under development and highlights some of the challenges and future prospects of vaccine research and development (R&D) as well.

Although the significance of vaccinations in combating AMR has been addressed or discussed in previous articles and strategies on
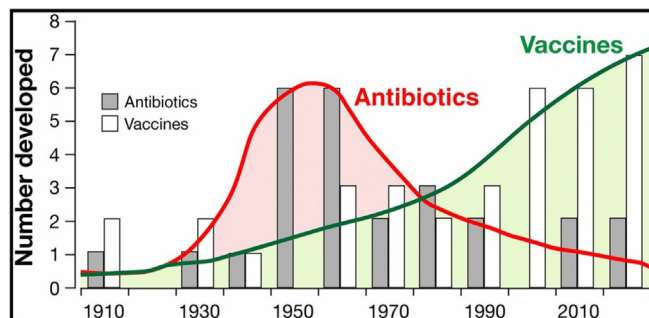

Fig. 1. An illustration of the antibiotics and vaccines that have been licensed for use in humans. the data shows the golden age of antibiotics in the 1940s and 1950s and the current golden age of vaccines (Bloom et al., 2018).

AMR, there has been considerably less work made into promoting the increased use of current vaccines and the design of new to prevent AMR (Mendelson et al., 2016). A 2016 review, however, claimed that vaccines as a means of combating AMR were underresearched and required more funding (O'Neill, 2016). According to the research, vaccine R&D investment lags behind most of new medications, and in the present worldwide health model, therapy receives significantly more time and incentive than prevention. Fig. 1 is a diagrammatic illustration of how more effort is being transferred from antibiotic R&D to vaccine R&D.

2. Discussion

2.1. What makes vaccines more effective

Vaccines contain a variety of features that make them highly successful in the fight against AMR. First, aside from the targeted strains, vaccination typically has minimal impact on the development of microbes. This is due to the fact that vaccines function by allowing the immune system to detect antigens that are very specific to the diseases being vaccinated against (Jit et al., 2020). Antimicrobials, on the other hand, can cause both targeted and non-targeted bacteria to acquire resistance. Broad-spectrum antibiotics in particular, interfere with the human microbiome, especially in children, thus affecting the general health (Relman & Lipsitch, 2018). Besides, they have also been shown to enhance selection of resistance in bystander bacterial species of the normal flora (Tedijanto et al., 2018). According to Kennedy and Read (2018), vaccine resistance is considerably less likely to emerge than drug resistance. Still, it is more difficult to establish when it occurs, and the molecular basis is less well known. Nonetheless, in the instances studied, the significant health advantages linked with immunization were substantially maintained. Vaccine resistance, it is argued, is less of a worry than medication resistance since it is less likely to emerge and, when it does, is less damaging to human and animal health and well-being. Such cases of vaccine resistance have been reported for *S. pneumoniae, B. pertussis, Yersinia ruckeri,* among others (Kennedy & Read, 2018). Fig. 2 shows how antibiotics tend towards being completely obsolete as the microbes develop more resistance unlike viruses which will remain effective against the strain for a very long time.

Secondly, due to the particular character of vaccination, vaccines targeting certain strains of a disease that are more harmful or inclined to developing resistance can be created (Jit et al., 2020). This was the case with *S. pneumoniae* vaccines which were developed using virulence factors that were most likely to trigger aggressive illness (Feldman & Anderson, 2014). Thirdly, vaccines and antimicrobial agents can act in tandem, according to Rynkiewicz et al. (2016) — vaccines can lower the rate at which
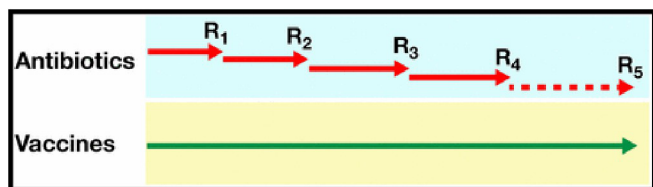
Fig. 2. The usage of antibiotics selects for resistance (R), rendering the antibiotic useless. As a result, successful therapy necessitates a constant supply of new antibiotics. Vaccines, on the other hand, can be used for a long period without causing considerable resistance (Kennedy & Read, 2018).

Fig. 3. Earlier vaccine development relied solely on live attenuated or killed vaccines. With advances in molecular techniques, vaccine development is now embracing reverse vaccinology, monoclonal antibodies and RNA vaccines more (Rosini et al., 2020).

people become infected, therefore extending the time it takes for a disease to develop tolerance to a medication.

Finally, vaccinations can be given merely a few times and have a long-term influence on the entire community by avoiding disease. This is accomplished in part through vaccines' near-lifetime effects (Blok et al., 2015) and in part through the establishment of herd immunity, which prevents the transmission of an infectious agent (Mallory et al., 2018; Rasmussen, 2020). Antimicrobial agents, on the other hand, must be provided on a regular basis in response to each attack. They have limited capacity to halt the forward spread of drug resistant bacteria since there is often a gap between the onset of virulence and receiving treatment (Hobson et al., 2021).

2.2. Vaccine research & development

Vaccination is now considered one of the most revolutionary and cost-effective discoveries in medical science, in a public health perspective. Currently, a productivity gap exists in vaccine development, describing a scenario in which the expected turn-over does not match the invested resources (Halliday, 2017; Ozawa et al., 2017). Although the risk profiles for novel bioactive molecules have been released, there is scant data on vaccine R&D. Findings from a 2013 study that evaluated all vaccine projects from 1998 to 2009 from basic studies all the way to market registration indicated that on average, developing a vaccine takes 10.71 years and there is only a market entry probability of 6% (Pronker et al., 2013).

Several design strategies are currently employed in developing all vaccines at large and those targeted at AMR in particular (Rosini et al., 2020). Live attenuated (LAV) and subunit vaccines utilize Pasteur's "isolate, inactivate and inject" principle. LAVs such as the BCG vaccine that prevents tuberculosis, therefore, are incapable of causing disease but retain their immunogenicity which provides recurrent antigenic stimulation allowing memory B cells to develop (Minor, 2015). Safer LAVs such as *Bordetella pertussis* vaccine have been produced with the advent of recombinant DNA technology, a technique that allows genetic detoxification of microbial toxins (Pizza et al., 2012; van den Ende et al., 2017). According to Rappuoli (2018), polysaccharide-based vaccines against *N. meningitis, S. pneumoniae* and *H. influenzae* type b have been produced in the recent decades, in the form of glycoconjugates. Glycoconjugation is, however, unsuitable for complex vaccines and this drawback is overcome by bioconjugation (Harding & Feldman, 2019; Xu & Moyle et al., 2017). Adjuvants that enhance the immune system's response to vaccines are also being used to boost the speed, potency and persistence of immunization (Dowaider, 2021; Pifferi, 2021). Other emerging technologies in vaccine R&D include reverse vaccinology, monoclonal antibodies and RNA vaccines. These techniques are being utilized in developing vaccines against *N. meningitis, Clostridium difficile* and *Streptococcus pyogenes* (Moxon et al., 2019; Tsumoto et al., 2019; Bloom et al., 2020).
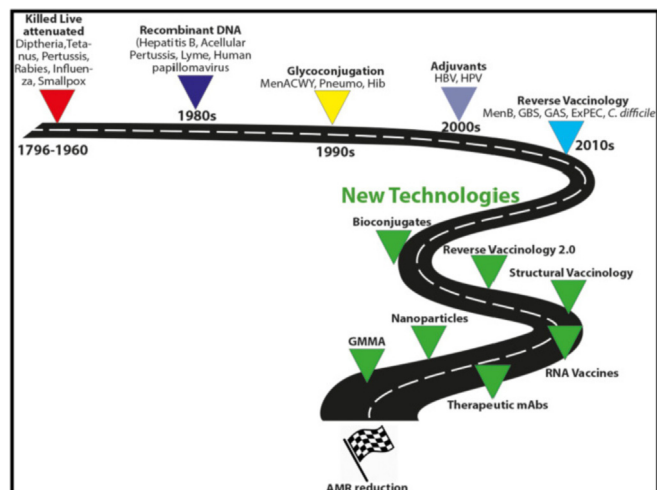
Vaccination lowers the incidence of infections, mortality rates and eliminates the need for further drugs as a result of resistance. New technologies in vaccine design and monoclonal antibodies are therefore vital in combating AMR. Fig. 3 illustrates the evolution of vaccine development.

2.3. New antimicrobial vaccines under development

Although effective vaccines against some AMR microorganisms such as *N. meningitis, S. pneumoniae* and *H. influenzae* have been developed and are already in use, there is still a plethora of other AMR pathogens that are yet to be tackled. Table 1 showing highly pathogenic AMR microbes that have prioritized by the WHO and the US CDC. Most of them are resistant against multiple drugs including aminoglycosides, β-lactams, tetracyclins, sulfonamides, chloramphenicol, etc (CDC, 2019; Sabino et al., 2020; Shristava et al., 2018)

Currently, there are no vaccines in use for *C. difficules,* extraintestinal *E. coli* (except for whole-cell-based Solco-Urac and Uro-Vaxom which are not widely used), *S. aureus, N. gonorrheae, P. auregenosa, K. pneumoniae, Salmonella spp,* among others (Brodie et al., 2020; Moussa et al., 2020; Wade et al., 2019). Fig. 4 outlines the various vaccines that are currently under development for these pathogens.

Vaccines for *C. difficile* that are currently being developed target toxin A and toxin B, which are the primary virulence factors (Seeberger, 2021). Pfizer's TcdA and TcdB toxoid vaccine and Valneva's VLA84 already in their phase III trials, are both very immunogenic and have proved to be effective (de Bruyn et al., 2021; Stevens et al., 2021). ExPEC, a vaccine based on adhesion

Table 1
Highly pathogenic AMR microbes that have prioritized by the WHO and the US CDC.

Pathogen	CDC Priority	WHO Priority
C. difficiles	Urgent	Not Ranked
Tissue *E. coli*	Urgent	Critical
S. aureus	Top	Top
N. gonorrheae	Top	Top
P. aeruginosa	Urgent	Critical
K. pneumoniae	Top	Top
S. enterica	Top	Top
Shigella spp	Top	Medium

Fig. 4. Vaccine candidates that are currently in various phases of development are displayed. To discover and produce such vaccines, several vaccine methods (protein vaccine, glycoconjugate, synthetic conjugate, bioconjugate, outer membrane vesicles (OMVs), and LAVs) are being used (Micoli et al., 2021).

protein FimH and an adjuvant (Kowarik et al., 2021; Palmioli et al., 2021) and ExPEC4V, a vaccine based on O antigens (Jiang et al., 2021; Verboom et al., 2021), are in their phase I trials against the AMR pathogenic extra intestinal *E. coli.* StaphVAX, V710 and SA4ag, developed against *S. aureus* have been analyzed for efficacy in clinical trials (Fernandez et al., 2021; Scully et al., 2021). Developing a vaccine against *N. gonorrheae* has proven to be a daunting and complicated task because the pathogen's surface proteins are subject to "antigenic diversity and phase variation" (Lin et al., 2021). The human specificity of the pathogen is also a major drawback to studying it. An *N. meningitidis B* OMV-based vaccine has been evaluated against *N. gonorrheae B* in clinical trials and found to be only 31% effective (Bernet et al., 2021). Several other vaccines against *K. pneumoniae, P. aureginosa, S. enterica,* and *Shigella sp,* are also being developed as already illustrated in Fig. 4. *Mycobacterium tuberculosis,* the causative agent of tuberculosis (TB), also poses a global health challenge, as it exhibits severe multi-drug resistance (MDR) and extensive drug resistance (XDR) (Seung et al., 2015). In high prevalence countries, the Bacille Calmette-Guérin (BCG) vaccine is used to immunize against the disease and is often included in the immunization schedule. However, the BCG vaccine does not always protect against TB (Okafor & Momodu, 2019). Consequently, efforts the WHO has taken steps to advocate for TB vaccine research and development. Recently, the WHO'S <u>Product Development for Vaccines Advisory Committee (PDVAC)</u> called for the development of a WHO Preferred Product Characteristics (PPC) for new TB vaccines, a step geared towards enhancing efficacy and quality control ("New TB Vaccine Research", 2021). Results from recent Phase IIb clinical trials of the M72/AS01E TB candidate vaccine conducted in Kenya, South Africa and Zambia showed significant efficacy (90% CI, 12–71) after three years of follow-up.

2.4. Quantifying the benefits of vaccines in fighting AMR

The European Policies (2021) report highlights that the easiest method to approximate the value of AMR vaccination is to calculate the reduced probability of getting an AMR infection in vaccinated persons by the medical and economic costs of infection with such a pathogen. This method, nonetheless, may be overly restricted for a number of reasons. To begin with, the value of immunization must be assessed in light of the many ways by which vaccines prevent infections, such as providing herd immunity, selective targeting, interspecific effects, and many others (Watts et al., 2021; Banerjee et al., 2021). This is almost impossible. Second, a number of studies have shown that the broader advantages that immunization confers to households are sometimes

ignored (Splitorff, 2021; Fenta et al., 2021; Wahl et al., 2021). Gotham et al. (2021) hypothesized that the economic implications of funding antimicrobial R&D are huge when you perceive of labor costs, time factors and inability to perform surgical procedures due to untreatable post-operative infections. Finally, it is critical to examine the worldwide character of the advantages of AMR pathogen vaccines. AMR affects HICs and LMICs alike, according to the "GLASS" report by the World Health Organization (2021). This externality is rarely considered in valuation analysis, which may deter companies from producing vaccines (Cox et al., 2021). Strategies like advanced market guarantees and market entrance benefits, which Gavi and others have successfully used for pneumococcal vaccinations, might be able to solve such failures (Debellut et al., 2021, Luthra et al., 2021; Ochalek et al., 2020).

2.5. Challenges and future prospects

Despite the significant progress that vaccination has brought in solving the problem of infectious diseases, the process of developing vaccines is painstakingly complex and slower that we would wish (Bailey et al., 2019). Vaccine development is often hampered by: (1) inadequate knowledge of immune responses to infection; (2) poorly understood virulence factors for some pathogens; (3) absence of authorized adjuvants and delivery methods to generate the requisite responses; and (4) antigenic diversity and phase variations in some organisms, such as *N. gonorrheae* (Idris et al., 2021; Ramstad et al., 2007; Voss et al., 2018). Some microorganisms have several virulent serotypes, and researchers always have to develop vaccines that can act against a wide range of serotypes. For example, most cases of meningococcal disease worldwide are caused by six serogroups (A, B, C, Y, W-135 and X) of *N. meningitidis,* and the quadrivalent vaccine had to include all of them (Rouphael & Stephens, 2012). Moreover, the funding required to develop, test and license new vaccines is substantial, while the most profitable markets are frequently not the most in need, as a study by Gouglas et al. (2018) suggested. A combination of several of the above factors has hindered the development of vaccines against some AMR bacteria such as *E. coli* and *N. gonorrheae,* as already observed.

Immunization with vaccines can only protect individuals from being infected with a particular microorganism. Vaccines are not usually helpful to individuals who are already infected. Consequently, they cannot be utilized to combat MDR and XDR in such contexts. Potentially useful anti-infectious treatments against MDR and persistent bacteria include; antimicrobial peptides (AMPs), anti-virulence compunds, and phage therapy alone or in combination with antibiotics (Pacios et al., 2020). While many AMPs are naturally produced by microorganisms, they can also be chemically synthesized in the laboratory. The synergistic interactions of AMPs and antibiotics comined with the anti-biofilm activity of AMPs are of significant interest to researchers currently (Magana et al., 2020; Mahlapuu et al., 2020). Anti-virulence compounds mask the virulence factors of bacteria, preventing attachment and tissue invasion. BF8 discovered in 2013 for example, is a QS inhibitor of *E. coli.* It disrupts the bacteria's biofilms and makes associated cells highly sensitive to ofloxacin (Wang, 2020). Phage therapy involves tapping into bacteriophages ability to infect and lyse bacterial cells, without attacking eukaryotic cells (Pires et al., 2020). One of the benefits of phage treatment over broad-spectrum antibiotics is its high selectivity for target bacterial pathogens, with minimal harmful effects on the host or the host commensal microbiome, resulting in a low number of secondary effects. The synergistic interactions between phages and the host immune system are a fascinating feature of phage treatment. Indeed, because it is not advantageous for phages to kill all of the host bacteria at the infection site (otherwise, they would

be unable to replicate), they can be expected to control bacterial pathogens and significantly reduce the population, allowing the patient's immune system to eliminate the remaining pathogens (Gorski et al., 2020; Luong et al., 2020).

However, the emergence of new vaccine R&D technologies (Fig. 3) such as bioconjugation, reverse vaccinology 2.0, structural vaccinology, nanoparticles among others, is revolutionizing the way vaccines are currently being developed. The contribution of molecular biology to vaccine design and understanding of concepts can also not be overstated (Afrough et al., 2019). Molecular techniques such as recombinant DNA technology and cloning have enhanced our understanding of virulence and host immune response mechanisms, cutting the development time to as short as less than a year as in the case of the Covid-19 vaccines against SARS-Cov2: Pfizer, Moderna, Astrazeneca, etc. (Lurie et al., 2020). These techniques are also being utilized in developing vaccines against AMR pathogens.

3. Conclusion

One of the most efficient ways to combat drug resistance is vaccination. Vaccines, unlike antimicrobials, are less prone to cause resistance since they are incredibly precise to their target diseases. Vaccines against infectious agents like *S. pneumoniae* and *H. influenzae* have already been shown to reduce tolerance to antimicrobial medications, but vaccines against AMR pathogens like *V. cholerae, S. typhi, E. coli,* nosocomial infections, and pulmonary and diarrheal disease viruses require more focus in terms of R&D. New vaccine development technologies such as bioconjugation, reverse vaccinology, structural vaccinology, and nanoparticles significantly impact vaccine development time, packaging, and efficacy. Revolutionary molecular techniques such as recombinant DNA technology technologies effectively enhance immunological studies and are expected to cut the development time to less than a year.

Vaccines against AMR infectious agents have the potential to prevent or minimize life-threatening illnesses, therefore lowering health-care expenditures, as well as reduce the usage of medications, slowing the rise of AMR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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