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The role of vaccines in reducing antimicrobial resistance: A review of potential impact of vaccines on AMR and insights across 16 vaccines and pathogens

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ABSTRACT

In 2019, an estimated 4.95 million deaths were linked to antimicrobial resistance (AMR). Vaccines can prevent many of these deaths by averting both drug-sensitive and resistant infections, reducing antibiotic usage, and lowering the likelihood of developing resistance genes. However, their role in mitigating AMR is currently underutilized.

This article builds upon previous research that utilizes Vaccine Value Profiles—tools that assess the health, socioeconomic, and societal impact of pathogens—to inform vaccine development. We analyze the effects of 16 pathogens, covered by Vaccine Value Profiles, on AMR, and explore how vaccines could reduce AMR. The article also provides insights into vaccine development and usage.

Vaccines are crucial in lessening the impact of infectious diseases and curbing the development of AMR. To fully realize their potential, vaccines must be more prominently featured in the overall strategy to combat AMR. This requires ongoing investment in research and development of new vaccines and the implementation of additional prevention and control measures to address this global threat effectively.

1. Introduction

Antimicrobial resistance (AMR) poses a significant global burden, with estimates indicating that approximately 4.95 million deaths globally were associated with bacterial AMR in 2019 [1]. The majority of these deaths occurred in low- and middle-income countries, which are particularly vulnerable to the spread of AMR due to factors such as poor water and sanitation infrastructure, limited access to healthcare including diagnostics and effective treatments, and misuse and overuse of antibiotics. To prevent the spread of AMR, it is crucial to adopt measures such as promoting access to, and appropriate use of, antimicrobials as well as diagnostics; enhancing infection prevention and control, and investing in the development of new antimicrobial agents [2]. Often underappreciated, another effective way to prevent AMR is through the development and use of vaccines.

Vaccines work by stimulating the body's immune system to recognize and attack specific pathogens, such as bacteria and viruses, and can prevent AMR through several mechanisms. Firstly, vaccines reduce the incidence of infections with drug-susceptible and drug-resistant pathogens, leading to a reduction in cases and deaths, but also economic costs associated with treating infections. Secondly, vaccines can prevent secondary infections, for example as with *Streptococcus pneumoniae* after an initial infection with influenza. Thirdly, if enough people are vaccinated, vaccines not only protect individuals from getting infected with

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drug resistant pathogens, but also protect those who are not immunised via herd immunity. Fourthly, when infections are prevented by vaccines, the use of antibiotics decreases, thus reducing a key driver of developing resistance [3]. The use of typhoid conjugate vaccine (TCV) to prevent the spread of *Salmonella* Typhi, both resistant and susceptible, in Pakistan and Zimbabwe, is an excellent example that demonstrates how vaccination campaigns were used successfully as part of the outbreak response and can impact AMR across all the mentioned pathways [4].

Despite the clear mechanisms by which vaccines can impact AMR, vaccines are too often overlooked in the medical and popular literature as powerful tools to reduce AMR, especially in concert with other interventions such as effective sanitation, hygiene and infection prevention measures, antibiotic access and stewardship measures to optimize use; and continued efforts to develop new antimicrobial agents To overcome this challenge, the World Health Organization (WHO) has published an Action Framework to leverage vaccines to reduce AMR and antibiotic use. The Framework includes actions for AMR and vaccine stakeholders to advocate for vaccines to be developed and optimally used to reduce AMR alongside other interventions. The actions are centred around three strategic goals: 1) Expand use of licensed vaccines to maximize impact on AMR, 2) Develop new vaccines that contribute to prevention and control of AMR, and 3) Expand and share knowledge of vaccine impact on AMR to help advocate for further investment [3]. In addition, to better understand vaccines that will become available to reduce AMR, WHO has analysed the clinical pipeline of vaccines against AMR priority pathogens, *Mycobacterium tuberculosis* and *Clostridium difficile*. The analysis found 61 vaccines in clinical development, mostly for *Streptococcus pneumoniae* and *M. tuberculosis*. Worryingly, there were no vaccines in clinical development against critical priority pathogens such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii* [5]. The report recommends accelerating the development of vaccines in late-stage development and, for remaining pathogens, conducting research to better understand the effects of vaccines on AMR.

The burden of AMR across some pathogens with vaccines in development, and the potential impact of these vaccines, has been described in Vaccine Value Profiles (VVPs), a set of publications that are intended to provide a high-level, holistic assessment of available data on the health, economic, and societal burden of a pathogen [6]. The profiles are being developed for pipeline vaccines and vaccine-like products against 16 pathogens, focused on those vaccines that are approaching pivotal licensure studies within the next three years, and may be considered for investment decision-making. The VVPs were developed by working groups of subject matter experts from academia, non-profit organizations, public private partnerships and multilateral organizations in collaboration with stakeholders from the WHO regions of AFR, AMR, EUR, WPR. All contributors have extensive expertise on various elements across the vaccine development continuum, including basic research, clinical development, regulatory and policy decision, country introduction and uptake. A template used to develop the VVPs is included in the supplementary material. The VVPs are published in a three-part series of a Special Issue and will be updated periodically as new information becomes available. The goal of this cross-cutting article is to highlight AMR patterns of these 16 pathogens with vaccines in development, as well as pathways and evidence of potential vaccine impact in reducing AMR to inform decisions such as vaccine funding, research and development.

2. Results and discussion

a. Bacteria

i. *Mycobacterium tuberculosis*

Drug-resistant tuberculosis (DR-TB) is a major contributor to antimicrobial resistance and a threat to global health security [7]. The four categories of drug-resistant TB that are well characterized are: Rifampicin-resistant TB (RR-TB), Multi-drug resistant TB (MDR-TB), Pre-extensively drug-resistant TB (pre-XDR-TB), and Extensively drug-resistant TB (XDR-TB) [8]. In 2021, there were around 450,000 incident cases (95 % uncertainty interval [UI]: 399 000–501 000) of MDR/RR-TB. The countries with the largest share of incident cases of MDR/RR-TB in 2021 were India (26 % of global cases), the Russian Federation (8.5 % of global cases) and Pakistan (7.9 % of global cases) [9]. In 2021, approximately 191,000 (95 % uncertainty interval (UI) 119,000–264,000) deaths and 7.9 million DALYs were caused by MDR/RR-TB globally [9]. In addition, RR-TB was responsible for 6.93 million (95 % UI 5.52–8.53) disability-adjusted life years (DALYs) in 2020, most of which (5.96 million DALYs, 95 % UI: 4.63—7.42) were in the 30 high MDR/RR-TB burden countries [10]. While the majority of DALYs may be attributed to morbidity and mortality that occurs during treatment, TB often leads to long-term morbidity among survivors [9].

The BCG vaccine has been shown to protect children against TB, but its efficacy in adults and adolescents is limited [11]. There is a need for improved TB vaccines. In the report to evaluate the pipeline of bacterial vaccines against WHO priority AMR pathogens the WHO calls for acceleration of the development of new TB vaccines, and for AMR endpoints to be measured in clinical trials to inform future policy decision and country uptake [5]. Pipeline analyses have identified 20 vaccines in preclinical development (in 2021) [5], and 16 vaccines in clinical development (in 2022), including five candidates in phase 3 [9]. Developing effective TB vaccines is challenging due to the complexity of the disease, lack of known correlates of protection, and the cost and long-time frame required for clinical trials. Despite this, an initial efficacy trial has shown that the M72/AS01E vaccine candidate reduces the risk of progression to active TB disease in previously exposed adults and adolescents by around 50 % [12], and modelling studies show that such a vaccine could avert 119,000 (7.3 %) RR-TB deaths within the 30 countries that account for 90 % of the RR-TB incidence worldwide, between 2020 and 2035 [13].

ii. *Escherichia coli* [14]

Escherichia coli (*E. coli*) is a common bacterium found in the gut, but some strains can cause intestinal and extraintestinal infections, leading to serious health issues. One of the problems with *E. coli* is the development of resistance to antibiotics, which makes it harder to treat infections. Enterotoxigenic *E. coli* (ETEC) and extraintestinal pathogenic *E. coli* (ExPEC) are two pathotypes that have different recommended antibiotic regimens, reflecting local resistance patterns, and requiring development of distinct vaccines. Reports of polymyxin resistance in enteric *E. coli* isolates have raised concerns. While fluoroquinolones and azithromycin are still useful treatment options in many settings, resistance to first-line antibiotics has been reported in post-marketing and cohort studies [15]. Additionally, studies have described the existence of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) strains of *E. coli*, the latter resistant to almost all classes of antibiotics [16,17]. Carbapenem-resistant *E. coli* isolates, mostly associated with urinary tract infections (UTIs) and blood stream infections (BSIs) tend to be XDR, which is a concern since carbapenems are last resort antibiotics. Carbapenem-resistant *E. coli* has thus been identified as a critical priority AMR pathogen by the WHO [17]. The prevalence of MDR and XDR *E. coli* varies geographically, with a higher prevalence reported in low- and middle-income countries [1].

As of 2021, there were six vaccines in clinical development against ETEC [5]. However, the NCT03548064 trial was terminated due to the Covid-19 pandemic [18], and a trial for the Shigella-ETEC candidate from EMERGENT BioSolutions is mentioned on the sponsor's website, however, not registered [19]. The B-subunit/whole-cell cholera vaccine has been shown to provide partial protection against some strains of ETEC for up to 3 months, and infection with wild-type ETEC in human challenge studies provides nearly complete protection from reinfection. A vaccine targeting labile-toxin (LT) toxoid and colonization factor antigen (CFAs) could cover up to 80 % of enteric disease-causing strains,

but correlates of protection have not been established. Both oral B-subunit/whole-cell cholera vaccines and an early inactivated ETEC whole cell vaccine candidate targeting LT enterotoxin and common colonization factors have shown field efficacy in travellers but were not fully effective in LMIC infants and children [20]. An improved inactivated whole-cell ETEC vaccine, containing higher amounts of colonization antigens as well as the dmLT adjuvant, is rapidly moving toward Phase 3 studies in LMICs as well as in travellers. Earlier cholera and ETEC vaccine studies, and the more recent clinical studies with the most advanced ETEC vaccine candidate ETVAX suggest that vaccine protection may extend beyond ETEC illness and include other diarrheagenic *E. coli* [21–23].

These observations in travellers and in LMIC infant population warrant further investigation but, if confirmed, could have a significant impact on antibiotic use in both groups.

There are multiple potential markets for an ETEC vaccine, including infants in LMICs, travellers, and the military, and the development of a vaccine that covers ETEC in combination to other pathogens may further increase its value [24]. Evidence from both CHIMs and field trials suggests that effective ETEC vaccine will likely lower the need for antibiotic intervention [25,26]. A modelling analysis suggests that an ETEC vaccine given to 6 month old infants could avert 2,779 (95 % uncertainty intervals 2,043—4,136) deaths associated with resistance [27].

ExPEC is a major etiological agent responsible for community acquired UTIs, hospital acquired BSIs and sepsis. Its low incidence in hospitals makes recruitment for vaccine clinical trials challenging, especially given that high-risk populations do not overlap with each other and require different recruitment strategies. The target population for a vaccine needs to be clearly defined and would likely include those at high risk of UTIs in clinical settings. Prevention of UTI caused by *E. coli* could reduce antibiotic consumption. Overall, a better understanding of the impact of a vaccine targeting *E. coli* is necessary as it is an integral component of the human microbiome.

Based on genomic and proteomic analysis, vaccine development for ExPEC may be facilitated by the observation that a number of candidate vaccine antigens are shared across diarrheagenic *E.coli* and ExPEC pathotypes [20]. Modelling estimates that an ExPEC vaccine given to 6 week old infants and elderly could avert 15,316 (11,794—19,992) deaths due to bloodstream infections associated with resistance, and avert 6,727 (5,659—7,934) deaths due to urinary tract infections associated with resistance [27].

In 2021, there were four vaccine candidates in active clinical development against ExPEC [5]. The WHO recommends that the development of ETEC vaccines be accelerated, and that AMR endpoints be measured in clinical trials to inform future policy decision and country uptake [5]. For ExPEC vaccines, there is a need to better understand vaccine development feasibility, delivery and impact on drug sensitive and drug resistant infections against major syndromes such as UTIs, BSIs and sepsis.

iii. *Klebsiella pneumoniae*

Klebsiella pneumoniae, a Gram-negative bacterium, is a prominent cause of healthcare-associated infections that are often resistant to multiple antibiotics, making treatment challenging [28]. According to the Global Burden of Diseases study, in 2019, *K. pneumoniae* infections caused an estimated 642,000 deaths and 27.4 million DALYs across all ages, including 124,000 neonatal deaths, all associated with AMR [1]. *K. pneumoniae* poses a particular threat in low and middle-income countries, which bear the brunt of mortality burden. The pathogen was the leading cause of neonatal sepsis in seven LMICs in Africa and South Asia [29], and it was in the casual chain of 18 % of all neonatal deaths in high mortality settings [30]. Recognized as a critical priority by the WHO and an urgent threat by the CDC, carbapenem-resistant *K. pneumoniae* warrants urgent attention in the ongoing battle against antimicrobial resistance [17,31].

Given the high burden and resistance of *K. pneumoniae,* development and introduction of an effective vaccine could be an important approach to help reduce disease burden.

As of 2021, one vaccine candidate for *K. pneumoniae* was in clinical development [5]. Key vaccine indications would include prevention of neonatal sepsis through maternal immunization, and prevention of healthcare associated infections. However, vaccine development for *K. pneumoniae* is challenging for many reasons, including multiplicity of serotypes, lack of clarity whether antibody mediated immunity against capsular antigens is protective against disease, and lack of correlates of protection against invasive disease. Additional challenges include the difficulty of conducting clinical trials in pregnant women, and the lack of a readily identifiable target population for prevention of healthcare associated infections in adults, which affects trial design and recruitment, the cost-effectiveness case for the vaccine [5] and its commercial attractiveness.

Nevertheless, a vaccine against *K. pneumoniae* could play a significant role in preventing a proportion of the health and economic burden associated with drug-sensitive and drug-resistant infections, antibiotic use, and further development of resistance. In low-income countries, where *K. pneumoniae* is associated with a significant burden of neonatal sepsis, maternal vaccination of pregnant women with a vaccine of 70 % efficacy could potentially avert 80,258 neonatal deaths and 399,015 neonatal sepsis cases annually worldwide, representing over 3.40 % of all neonatal deaths [32].

The WHO encourages research to better understand the feasibility of developing and delivering a vaccine against *Klebsiella pneumoniae*, especially for the prevention of neonatal sepsis and highlights the need for data collection to estimate the potential impact of a vaccine on AMR [5].

iv. Group B *Streptococcus* [33]

Group B *Streptococcus* (GBS) is a bacterium commonly found in the gastrointestinal tract. Invasive GBS infections occur in pregnant women and neonates as well as older adults and immunocompromised populations, especially those with underlying conditions [34]. GBS is the most common cause of neonatal meningitis globally, although infant disease can also present non-specifically as sepsis, pneumonia, meningitis, or in bones and joints. Among adults, GBS infection can present as bacteraemia, endocarditis, osteomyelitis, septic arthritis, pneumonia, skin and soft tissue infection, and urinary tract infections. It is estimated that up to 40 % of pregnant women in HIC will receive intrapartum antibiotic prophylaxis (IAP) with penicillin for the prevention of mother to child transmission of GBS, and obstetric care is one of the drivers of antimicrobial use. Penicillin remains the mainstay of treatment in infant and adult disease due to GBS often in combination with gentamicin. Although resistance to penicillin is low, reduced susceptibility has been reported in several countries, mostly associated with mutation of the penicillin-binding-protein 2x [35]. Erythromycin and clindamycin are alternative IAP for patients with penicillin allergies, but resistance rates to these antibiotics in many countries have accordingly changes in the recommendations to vancomycin as second line IAP, although vancomycin use is extremely problematic in LMIC. Additionally, resistance to other classes of antibiotics, such as aminoglycosides and fluoroquinolones, is on the rise [36]. The US CDC has expressed concern about AMR in GBS given that, according to IHME estimates, globally, there were around 69,000 AMR-associated GBS neonatal and postnatal deaths in 2019 [1]. The administration of IAP during childbirth may have further unintended consequences, such as increasing antibiotic resistance in GBS and other carriage strains and altering infant microbiota. However, the evidence on this issue remains unclear [37].

As of 2023, there are several GBS vaccine candidates in various stages of clinical development, including late phase trials. However, because a major use would be maternal immunization, developing an effective GBS vaccine has proven to be challenging due to the need to

consider the relative immunosuppression of pregnancy. Such vaccines must be sufficiently immunogenic for the antibodies to cross the placenta at levels that will provide protection to the infant in the first months of life. Additional challenges include the low incidence of invasive GBS disease in infancy (worldwide estimates range from 0.1 to 1/1000 livebirths) [38], which limits the feasibility of undertaking a field efficacy trial to support regulatory approval. The vaccine must be safe for pregnant women, their foetuses and newborns, as well as the elderly, the populations intended to benefit from the vaccines in development. Other challenges include ensuring appropriate length of protection and determining frequency of vaccination during pregnancy, the strength of the maternal immunization platform for vaccine delivery, how to ensure sufficient vaccine efficacy in elderly populations given the existence of immunosenescence, as well as ensuring the vaccine is cost-effective and widely accessible to those who need it most [39]. Despite these obstacles, the potential benefits of a GBS vaccine are significant. WHO has published a full assessment of value of GBS vaccines and found that GBS vaccination could result in substantial declines in global morbidity and mortality due to GBS. A maternal vaccine is likely to be a cost-effective intervention, with a positive global net monetary benefit under most assumptions if the vaccine is affordably priced [40]. A GBS vaccine could avert a proportion of drug-sensitive and resistant infections and deaths, antibiotic use, and significant economic costs associated with treating GBS infections, however, evidence is missing. The data on impact of a GBS vaccine on all cause AMR infections should be collected during trials and other research to validate these hypotheses.

v. *Neisseria gonorrhoeae*

Gonorrhoea is a sexually transmitted bacterial infection caused by *Neisseria gonorrhoeae* that can cause pelvic inflammatory disease, infertility, adverse pregnancy outcomes, increased HIV acquisition risk, and neonatal conjunctivitis, in addition to genital symptoms of cervicitis and urethritis. An estimated 82 million new gonococcal infections occurred globally in 2020 [41]. Antimicrobial agents like sulphonamides, penicillin, tetracycline, spectinomycin, fluoroquinolones, macrolides, and cephalosporins have all been recommended for the treatment of gonorrhoea at different times in history. However, the bacterium has sequentially developed resistance to each of these antibiotics over time, with many strains now resistant to multiple drugs. Extended-spectrum cephalosporins like ceftriaxone and cefixime are currently the only recommended first-line treatments for gonorrhoea; however, the inappropriate use of these drugs in the late 1990 s and early 2000 s is thought to have facilitated the selection of drug-resistant strains [42–44]. This has made treatment decisions for gonorrhoea increasingly challenging and raises concerns about the development of extensively drug-resistant strains that may not be treatable with currently available antibiotics. The first extensively drug-resistant gonococcal strain displaying high-level resistance to ceftriaxone and almost all antibiotics previously used against gonorrhoea was reported in 2011 [42–44]. The continuing emergence and spread of antibiotic-resistant gonococcal strains highlight the need for the development of vaccines, new treatment strategies, and enhanced surveillance to monitor the spread of resistance, in addition to ongoing efforts to promote condom use, raise awareness in at-risk populations, and expand healthcare access.

Biological challenges to gonococcal vaccine development include the lack of known correlates of protection, lack of immunity from natural exposure, poor understanding of immunity and the existence of multiple pathogenic strains [45]. Nonetheless, in a number of observational studies, outer membrane vesicle (OMV)-based group B meningococcal vaccines, including 4CMenB, have shown moderate effectiveness (~30–40 %) against gonorrhoea, likely due to genetic similarities between *Neisseria meningitidis* and *Neisseria gonorrhoeae* [46]. 4CMenB is now being evaluated for prevention of gonorrhoea in several phase II-IV studies. In addition, a new gonococcal-specific vaccine candidate is now in Phase I/II studies [5,47].

Mathematical modelling studies have shown that even partially efficacious vaccines for gonorrhoea can have a marked impact in reducing *N. gonorrhoeae* infections[48,49]. In the current context, when truly untreatable gonococcal infections are rare, estimates suggest that a vaccine against *Neisseria gonorrhoeae* infection given to 70 % of adolescents with 10 years efficacy of 70 % could avert around 8 917 (6 929–11 667) DALYs associated with AMR [27]. The AMR-associated DALYs averted could rise substantially if the increasing threat of untreatable infections is realized. Additionally, a vaccine is expected to reduce antibiotic use and slow down the emergence of resistant strains. One model of gonorrhoea transmission among men who have sex with men has predicted that a gonococcal vaccine with 30 % efficacy can delay AMR development by several years and a 90 % efficacious vaccine with 40 % uptake could prevent emergence of AMR altogether [50]. However, empirical data are needed to confirm this. WHO recommends that the development of gonorrhoea vaccines be accelerated, with AMR endpoints measured in clinical trials to inform future policy decisions and country uptake [5].

vi. *Salmonella* paratyphi A [51], non-typhi.

Salmonella species, including Typhi, Paratyphi A, and non-typhoidal serovars, have developed resistance to multiple antibiotics, posing a significant public health threat globally. As mentioned earlier, the licensed typhoid conjugated vaccine (TCV) against *Salmonella* Typhi has already been documented to have a significant impact on AMR, and is not discussed further in this article.

Invasive diseases caused by non-typhoidal *Salmonella* (iNTS) is a serious global health threat and NTS serovars are included in the WHO Global Priority List of antibiotic-resistant bacteria, with fluoroquinolone-resistant *Salmonella* spp. and third-generation cephalosporin resistant NTS being high [17]. According to 2019 IHME estimates, there were 2,772 (1,449–4,754) deaths globally associated with an infection with NTS. High levels of antibiotic resistance are widespread in sub-Saharan Africa, where syndrome-associated antibiotic use is high, and *Salmonella* spp. often have higher antibiotic minimal inhibitory concentration values than other bacterial species [1].

Salmonella Paratyphi A (SPA), a cause of typhoid fever clinically indistinguishable from that caused by Typhi, is included in the WHO Global Priority List of antibiotic-resistant bacteria as a high priority and SPA is classified as a serious threat for MDR by the CDC [31]. According to the global burden of disease study 20,000 antimicrobial resistance deaths and 1,420,000 DALY were attributed to SPA in 2019 [1]. The prevalence of MDR SPA is low, but the prevalence of fluoroquinolone non-susceptibility is high in South Asia, particularly in China, India, Nepal, and Bangladesh. Asian SPA isolates exhibit differing AMR phenotypes, with MDR prevalence varying geographically, and XDR SPA is considered a potential threat due to the emergence of azithromycin resistance [52]. However, culture-confirmed SPA antimicrobial susceptibility patterns in returning travelers show a 97 % prevalence of resistance to ciprofloxacin and largely susceptibility to other drugs [53].

In 2021, there was one vaccine in clinical development for NTS and 4 vaccines against SPA [5]. Despite a success in developing a vaccine against *Salmonella* Typhi, challenges to develop a vaccine against other *Salmonella* spp. remain and include poorly defined disease burden, requirement for a large efficacy trial or regulatory clarity on how to use a human infection model to inform vaccine policy, and lack of correlates of protection. One analysis found that a vaccine against non-typhi *Salmonella* infection given to 70 % of infants with 5 years efficacy of 80 % could avert 1,820 (1,412—–2,624) deaths associated with resistance, while a vaccine against *Salmonella* Paratyphi infection given to 70 % of infants, with 5 years efficacy of 70 % could avert 1,463 (853—–2,793) deaths associated with resistance [27]. A combination vaccine against multiple *Salmonella* serovars could offer a better value and uptake than

stand-alone vaccines against individual *Salmonella* serovars.

The WHO recommends that the development of SPA vaccines should be accelerated, and that AMR endpoints are measured in clinical trials to inform future policy decision and country uptake [5]. WHO also recommends continuing the development of iNTS vaccines while we collect data and expand knowledge on the impact of iNTS vaccines on AMR [5]. The impressive effectiveness of the TCV vaccine on XDR and documented impact on AMR suggest that similar outcomes could be achieved for other *Salmonella* vaccines [54].

vii. *Shigella*

Shigella is a major bacterial cause of moderate to severe diarrhea, including dysentery, and has shown increasing resistance to multiple antibiotics. Major outbreaks of resistant Shigella were reported in key populations such as men who have sex with men (MSM) [55]. Globally, an estimated 1.65 million DALYs and 29,000 deaths were associated with antibiotic-resistant *Shigella* infection [1]. In a large case-controlled study, *Shigella* was identified as a leading driver of antibiotic use by infants and children [56].

The WHO identified fluoroquinolone resistant *Shigella* spp. as a medium AMR threat and the CDC considers drug-resistant *Shigella* as a serious threat requiring prompt and sustained action [17,31]. *Shigella* is also included as a medium priority pathogen in the Indian priority pathogen list, intended to prioritize vaccine for discovery, research and development of new antibiotics in India [57]. In the US, a non-trivial percentage of *Shigella* species has emerged resistant to important antibiotics, including ciprofloxacin (6 % resistant, 17 % with decreased susceptibility), azithromycin (14 % with decreased susceptibility), and both drugs (3 % resistance) [31].

Shigella has 4 primary species, *S. dysenteriae, S. flexneri, S. sonnei, and S. boydii*, that are responsible for causing shigellosis with varying degree of severity, with more severe cases, including dysentery, being common in low- and middle-income countries (LMICs) due to poor sanitation, malnutrition and limited access to healthcare. In high-income countries (HICs), milder forms of the disease (often due to *S. sonnei)* are more prevalent due to better hygiene and healthcare infrastructure. The burden of severe shigellosis is disproportionately higher in LMICs, contributing to childhood mortality.

There were 9 vaccine candidates in clinical development against *Shigella* spp. in 2023, with three candidates in phase 2, and one in phase 3. The largest target population is in lower-resourced settings, limiting the commercial attractiveness to develop a vaccine; however, other populations in high-income countries exist, including travellers, men who have sex with men, and military personnel. A combination vaccine with other vaccines against diarrhoea could improve the value proposition and likelihood of Shigella vaccine uptake [58].

A modelling analysis suggest that a vaccine against moderate to severe *Shigella* infection given to 70 % of infants with 5 years efficacy of 60 % could avert 4,133 (2,765—6,132) deaths and 369,238 (242,138–552,960) DALYs associated with resistance [27]. Additionally, a vaccine is expected to reduce antibiotic use, and slow down the development of resistant genes, however, evidence must be collected during clinical trials and other research. The WHO recommends continuing the development of *Shigella* vaccines as an important tool to combat the AMR threat [5].

b. Viruses

Prescribing antibiotics to treat viral infections is unnecessary and ineffectual; nonetheless, viral infections are one of the leading causes of antibiotic use. Viral vaccines thus have the potential to reduce the misuse of antibiotics in treating viral infections, thereby reducing the development of AMR. Finding alternative ways to detect and prevent viral infections is essential in reducing the use of antibiotics and the development of AMR.

Respiratory infections caused by respiratory syncytial virus (RSV) and influenza are presumptively treated (i.e., in the absence of an etiological diagnosis) with antibiotics, and conditions caused by other viruses such as cytomegalovirus (CMV) [59], herpes simplex virus (HSV), norovirus [60], and chikungunya virus (CHIKV) can also trigger inappropriate antibiotic use. Increasing awareness about pathogen transmission and outbreaks patterns, as well as developing and accessing new diagnostics are essential in reducing the high use of antibiotics that are inappropriately prescribed. The use of vaccines to avert viral infections could also reduce antibiotic use, and consequently reducing AMR in bacterial pathogens.

RSV is the main cause of bronchiolitis and pneumonia in young children and is often inappropriately treated with antibiotics because of a lack of diagnostic certainty about its involvement in those infections, especially where laboratory facilities are limited. A study from Finland reported that over 50 % of children younger than 14 years with confirmed RSV infections received antibiotic treatment [61]. A recent study of a maternal RSV vaccine found a 12.9 % reduction in antibiotic prescribing among infants in the first three months of life [62]. Pivotal studies of a long-acting RSV monoclonal antibody recently reported a reduction of 23.6 % in antibiotic prescribing in infants receiving the monoclonal antibody [63].

Vaccines against influenza were not included in the vaccine value profiles; however, a *meta*-analysis found high-certainty evidence that influenza vaccine can reduce days of antibiotic use among healthy adults by 28.1 %, and moderate evidence that it can reduce antibiotic use in children [64].

Vaccines against RSV and influenza show promise in reducing the need for antibiotics, and their use should be encouraged to prevent the development of AMR. Additionally, increasing awareness about the appropriate use of antibiotics for viral infections, and developing and using improved diagnostics are crucial in preventing the development of AMR.

c. Parasites

i. Malaria (*Plasmodium vivax* and *Plasmodium falciparum*)

In 2021 there were estimated 247 million cases and 625,000 malaria deaths, majority of them on the African continent. Almost 98 % of malaria cases are attributed to parasite *Plasmodium falciparum* which has developed resistance to several antimalarial drugs over time. Only 2 % of cases are attributed to *P. vivax*, and a handful to *P. knowlesi* [65]. Currently, the first line treatment for uncomplicated malaria is the highly efficacious WHO-recommended artemisinin-based combination therapy (ACT) which has been an integral contributor to the remarkable successes in global malaria control seen over the last 20 years [66]. While protecting the efficacy of these medicines is a global public health priority, ACT resistance has emerged in southeast Asia, and more recently partial resistance, with slowed parasite clearance time, has been identified in some areas of Africa, where transmission malaria burden is high, and where the consequences of spreading ACT resistance could be devastating [67]. There is a lack of next-generation treatment drugs for *P. falciparum*.

There are currently two vaccines against P. falciparum malaria recommended for use by the WHO: RTS,S and R21/Matrix-M. Both vaccines are safe and effective and once widely used, expect to have high impact on the reduction of malaria incidence. Other vaccines are in early development, including those against *P. vivax*. Monoclonal antibodies against malaria, also in early clinical development, may offer a promising new approach to prevent malaria.

Modelling analyses suggest that a vaccine against *P. falciparum* malaria with an initial efficacy of 80 % and waning by 20 percentage points over four years, when provided to children under 5 months of age could avert 313.9 (Uncertainty Interval [UI] 249.8–406.6) clinical malaria cases per 1,000 children vaccinated, 0.9 (UI 0.6–1.3) resistant cases per 1,000 children vaccinated, and 0.9 (UI 0.6–1.2) deaths per 1,000

children vaccinated in the WHO African region between 2021–2030. However, if resistance to ACT was to increase, as observed with previous malaria treatments, the impact of such vaccine could be much higher, averting up to 10.4 (7.3–15.8) resistant cases per 1,000 children over the same period [68].

ii. Leishmaniasis [69]

Leishmaniasis, a parasitic disease transmitted by sandflies, is a significant public health problem in many parts of the world. The available drugs for treatment include several antileishmanial drugs, but the increasing prevalence of AMR in Leishmania parasites has become a concern. Resistance to the antimonial drug sodium stibogluconate, once the mainstay of treatment, has been reported in Southeast Asia and may be related to environmental antimony pollution. Resistance to miltefosine, the only oral drug for visceral leishmaniasis, has also been reported. Factors contributing to treatment failure include host and environmental factors, non-compliance due to high treatment costs, and the use of "human" drugs for zoonotic reservoirs. Strategies to combat AMR in Leishmania parasites include combination therapy, allometric dosing, clinical trials of new chemical entities, and host-directed therapies [69]. There is currently one vaccine in phase II clinical development, ChAd63-KH, however vaccine impact on resistance is yet to be evaluated.

3. Conclusions

AMR is an established public health threat fuelled in part by the overuse and misuse of antimicrobials, often obtained without a prescription and easily purchased outside of health centres. Bacterial, parasitic and fungal vaccines can play a significant role in averting drug-sensitive and drug-resistant infections, reducing the overall use of antimicrobials, and reducing the development and transmission of resistance genes. Viral vaccines can also reduce the number of infections that may be inappropriately treated with antibiotics or lead to secondary bacterial infections, thereby indirectly reducing AMR.

In addition to expanding use of current vaccines targeting AMR pathogens, accelerating the development of vaccines for pathogens with high potential for impact on AMR is crucial to effectively control the transmission of some of the deadliest pathogens that also result in significant health and economic burden. These include priority pathogens such as *Mycobacterium tuberculosis*, extraintestinal pathogenic *Escherichia coli* (ExPEC), *Salmonella enterica* serovar Paratyphi A, *Neisseria gonorrhoeae*, Group B *Streptococcus* (GBS), Enterotoxigenic *Escherichia coli* (ETEC), non-typhoidal *Salmonella*, and *Shigella* spp, influenza viruses, respiratory syncytial virus (RSV), and malaria. These vaccines can not only prevent disease but also reduce the need for antibiotics and other antimicrobials, thereby reducing the risk of AMR. Furthermore, vaccines will likely provide protection against a pathogen with a broad range of resistance and can also offer long-lasting immunity.

Despite their potential impact, the development of vaccines faces several challenges, including diversity of vaccine-targeted populations, the complexity of vaccine biology and the high degree of genetic diversity among pathogen strains, as well as the lack of clarity about their impact, which can be measured across criteria such as health burden, economic burden, AMR, short and long-term morbidity, and other, collectively known as the Full Value of Vaccines [70]. The impact of vaccines on AMR can be an important component when evaluating the full value of vaccines with predominant use in LMICs, to inform vaccine development, introduction and use. An evaluation of a value proposition for a vaccine against *Shigella* found that the impact on AMR significantly increases the likelihood of vaccine introduction and use in countries [71]. It is therefore essential to expand our knowledge of the potential impact of vaccines and other tools to combat AMR and to continue investing in their development alongside new antimicrobial agents, diagnostics and other prevention and control tools. Combining vaccines with other prevention and control strategies such as improved sanitation and hygiene, as well as optimizing the use of antimicrobial medicines, control of disease transmission through vector control and behavioural changes is required to effectively curb the spread of AMR.

The escalating prevalence of multiple antimicrobial-resistant pathogens would necessitate the development and deployment of multiple novel vaccines in order to significantly impact AMR and reduce antibiotic consumption. Although several of these pathogens are significant contributors to the disease burden, their significance may be considered relatively moderate compared to previous vaccine targets such as *Shigella*, or paratyphoid and non-typhoidal *Salmonella*. Integrating one or more additional vaccine doses into already densely populated immunization schedules requiring multiple visits poses a formidable hurdle for healthcare systems. This is where multi-pathogen combination vaccines may play a role, as they enable the administration of several vaccines against pathogens with moderate burden in a single administration. Furthermore, combination vaccines have the potential to specifically target the primary pathogens responsible for distinct clinical syndromes, like combining vaccines against enteric pathogens to prevent diarrhoea or vaccines against respiratory infections to prevent otitis media or pneumonia. This approach not only aligns with user preferences but also holds the promise of delivering additive or synergistic benefits in reducing antimicrobial utilization. Nevertheless, realizing the full potential of combination vaccines necessitates innovative strategies, regulatory guidance, and incentives to expedite their development and availability.

In conclusion, vaccines are an essential tool to reducing the burden of infectious diseases and the development of AMR. By reducing the need for antibiotics and other antimicrobials, vaccines have the potential to make a significant impact in the fight against AMR. However, to optimize their contribution, their role needs to become more visible as part of the overall toolbox for combatting AMR. Continued investment in research and development including new vaccines, along with the implementation of other prevention and control strategies, is imperative to combat this global threat.

Author agreement

The authors declare that this is original work which has not been published before, and that all authors have agreed to the submitted paper.

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Author contribution

MHA conceptualized the article, curated and analysed data and wrote the original draft. All remaining authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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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.

Data availability

All data is published and referenced

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Appendix A. Supplementary material

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