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Review Article

# Antimicrobial resistance containment in Africa: Moving beyond surveillance

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ABSTRACT

Worldwide, infections caused by drug-resistant pathogens constitute a significant challenge threatening therapeutic efforts. According to the World Health Organization (WHO), antimicrobial resistance (AMR) ranks among the top 10 global public health threats. Organisms with a high rate of multiple host adaptivity, significant genetic diversity (multiple lineages), high virulence factors, and genetic exchange have been isolated from various sources (humans, animals, and the environment) even without exposure to prior antibiotics. Till now, the source of AMR and how resistant clones are selected in the environment remain largely elusive, and potential anthropogenic transmission has been reported in different studies. Various drug-resistant pathogens, lineages, resistant clones, outbreak clusters, plasmid replicates, and genes that play a critical role in resistance dissemination have been identified. Maintenance of certain multidrug-resistant (MDR) determinants has also been shown to enhance or support the propagation of MDR. So far, significant advances have been made in understanding the burden of AMR. However, overcoming AMR requires a holistic approach, as there is no single approach with sufficient precision to curb the threat. While strengthening AMR surveillance efforts is essential, as we have shown, there is also a need to intensify efforts to strengthen therapeutic interventions, especially in priority regions such as Africa. Herein, we discussed the burden of AMR and the dissemination of AMR in humans, animals, and the environment (non-medical drivers). We further delved into the big questions on Africa and discussed how therapeutic interventions involving vaccines and other viable biomaterials could be pivotal in reducing the burden of AMR to the barest minimum.


## 1. Introduction

Antimicrobial resistance (AMR) is an ancient and dynamic global issue threatening public health. Although AMR is a natural occurrence, human interventions and, paradoxically, inaction have contributed to increasing resistance rates. On the one hand, excessive or inappropriate use of antibiotics contributes to the evolution of AMR. Consequently, increasing infections are becoming more and more challenging to treat as currently available antibiotics are losing their effectiveness [1]. The rising tide of AMR is shrinking the pool of treatment options for infections caused by multidrug-resistant bacteria. Unfortunately, the limited progress in developing new antimicrobial agents is a global concern.

Antibiotic-resistant bacteria and their genes are spreading into the environment in various ways, involving both humans and animals [2,3]. Organisms with a high rate of multiple host adaptivity, significant genetic diversity (diverse lineages), high virulence factors, and genetic exchange have been isolated from various sources (humans, animals, and the environment) even without prior exposure to antibiotics [4]. To date, the source of AMR and how resistant clones are selected in the environment remain largely elusive [5], and potential anthropogenic transmission has been reported in several studies [6].

So far, the incidence of AMR bacteria and AMR gene transfer varies between countries and regions. However, the most significant burden is borne by the low- and middle-income countries (LMICs), of which Africa is among the leading affected continents. Currently, the global

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burden of deaths attributed to and associated with bacterial AMR is estimated to be 1.27 and 4.95 million, respectively, in 2019 [7]. In addition, WHO predicts that AMR will cost an additional US $1 trillion in healthcare by 2050 if adequate measures are not implemented [8]. Unfortunately, the burden is projected to be higher in sub-Saharan Africa, and this calls for adequate measures and interventions to curb the threat.

There are several transmission routes of antibiotics, resistance genes, and drug-resistant bacteria (Fig. 1). Both humans and animals are significant sources of resistant dissemination [9,10]. Various drug-resistant lineages, resistant clones, outbreak clusters, plasmid replicons, and genes that play critical roles in resistance dissemination have been identified, and significant advances have been made in understanding the burden of AMR. AMR surveillance is crucial to contain the spread of resistance and to strengthen therapeutic interventions. In this review, the burden and the dissemination of AMR were discussed. A comprehensive insight into non-clinical drives as a significant reservoir and source of AMR dissemination was provided. We

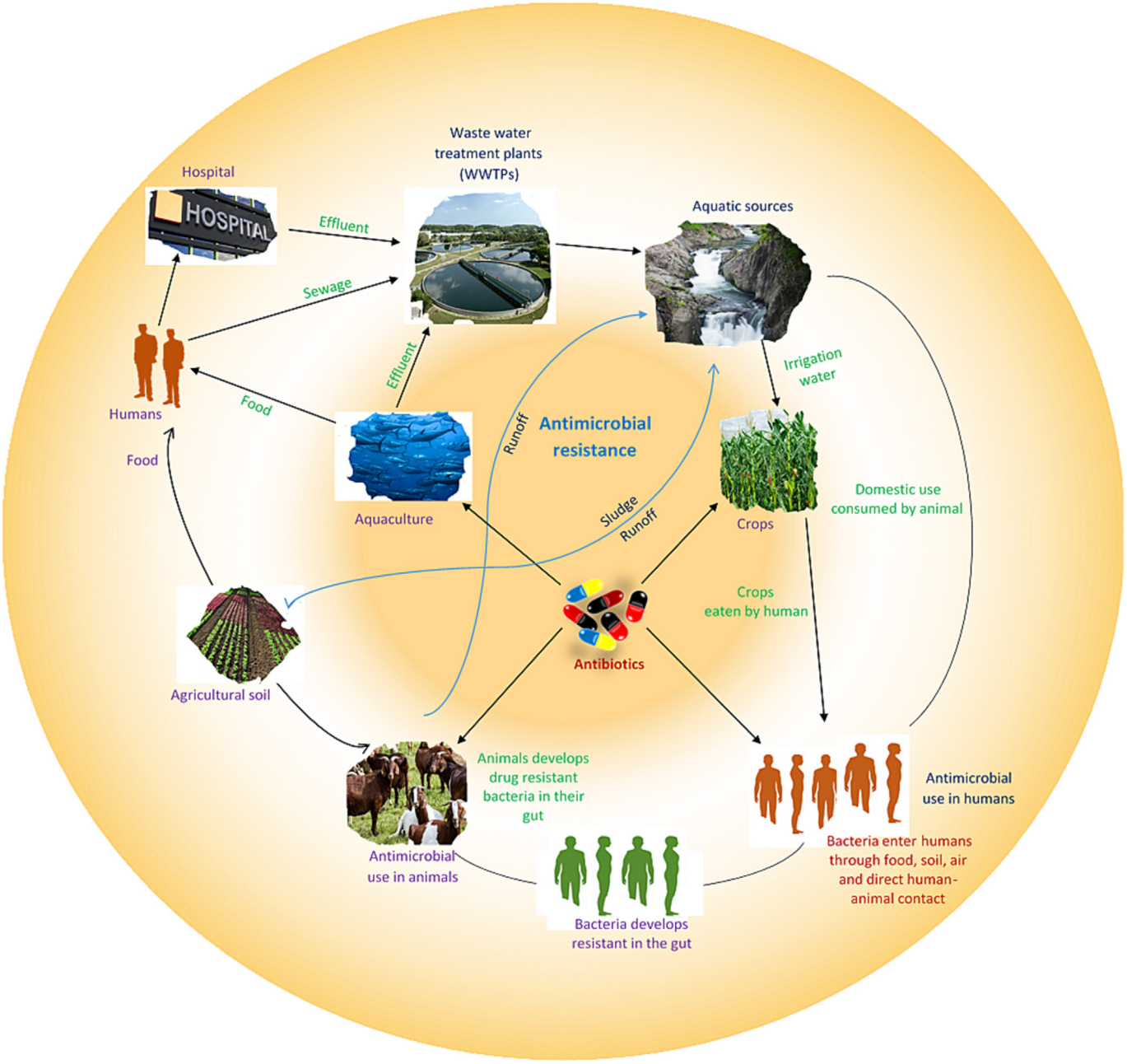


**Fig. 1.** The transmission routes of antibiotics, resistance genes, and drug-resistant bacteria. Antibiotic-resistant bacteria and their associated genes can be transmitted in various ways. Over-prescription, patients not completing treatment, lack of diagnosis, unclean facilities, and poor infection control all contribute to the emergence of resistance. Lack of proper diagnosis can lead to inappropriate or wrong choice of drug for treatment. Antibiotics are also used in aquaculture, crop farming, and even animal husbandry. These drugs are not completely used by animals, as certain levels remain and can be transmitted to humans when consumed. Overall, bacteria enter humans through food, soil, air, and direct human-animal contact. Effluents from aquaculture also contribute to the accumulation of resistant pathogens and bacteria in wastewater treatment plants.

also highlighted how the various therapeutic interventions, with particular emphasis on vaccines, could help to ameliorate the burden of AMR to the barest minimum.

## 2. The big issues: Non-clinical drivers of AMR as a major reservoir and source of AMR dissemination

### *2.1. AMR dissemination in soil*

Multiple routes and linkages allow for the possibility of cross-infection and co-infection and even the transfer of genetic materials. Soil and water are known reservoirs for antimicrobial-resistant bacteria (ARB) and antimicrobial-resistant genes (ARGs) [11] and are significantly affected by agricultural activities. A recent study by Li et al. [12] showed that suppressing the rhizosphere restricts the spread of AMR genes during bacterial invasion. It has been estimated that 90% of bacteria from seawater are resistant to one or more antibiotics, and 20% are resistant to at least five [13]. Antibiotics are neither fully absorbed by animals, nor are they metabolized completely. They are released into the environment as residues through water channels, in soil, and as manure. ARBs and ARGs are introduced into the environment through the use of animal waste as fertilizer, the irrigation of agriculture with effluent from aquaculture or poultry, and the activities of natural processes such as rainfall that carry run-off water from farms. The degradation of these antibiotics in water does not occur immediately and entirely in most cases, and this can trigger the development of selective pressure and repopulation of the resistant clones. Several recent studies have examined the impact of soil on the spread of AMR [12,14–16].

### *2.2. Dissemination of ARB and ARG emergence in the food chain*

Integrated farming, drug residue accumulation, and consumption of contaminated food and food products are the major factors leading to the spread of ABR and ARGs [17–24]. AMR strains could emerge and spread at different stages of the food production chain. The dissemination can occur through direct or indirect human exposure to infected animals and their products or wastes (Table 1). Farmers, abattoir workers, veterinarians, and food handlers are the first group of people at high risk of exposure, and they serve as a perfect source of transmission to the larger population [10,25,26]. Indirect dissemination occurs through the consumption of contaminated food products (e.g., meat, dairy products, and eggs) [27–33].

Furthermore, studies have reported the isolation of antibiotic residues in foods above the maximum residue limit [34]. Thus, human health is directly affected by their interaction cycle with the ecosystem. Absorption, distribution, metabolism, excretion of the drugs, and inappropriate withdrawal times are the risk factors responsible for the development of residues. Several critical resistance genes and organisms with high rates of multiple host adaptivity, high virulence factors, and genetic exchange have been isolated from animals [35]. The incidence of ARB and ARGs transfer varies between countries and regions. Africa is the controlling lead in ARB and ARG transfers through the food chain due to inappropriate or almost non-existent functional implementation strategies and organizations to monitor the non-medical use of antibiotics, especially in livestock and aquaculture.

### *2.3. Spread of AMR pathogens through foods of animal and non-animal origin*

One of the significant sources of AMR is food of animal and non-animal origin (Table 1) [36]. Most animals and their products harbor AMR genes. For example, in previous investigations, the dissemination of drug-resistant *Salmonell*a was associated with contaminated meat, pork, eggs, and turkey [29,37]. Antimicrobial-resistant bacteria and genes have also been recovered from sheep, cattle, goats, swine, and poultry [38–44]. Horizontal gene transfer (HGT) is widespread in aquaculture systems. Thus, seafood is commonly considered to be the “hotspot of AMR” [45]. Even among animals not in close contact with humans, AMR genes previously seen in humans have been reported. Furthermore, *E. coli* resistant to quinolones has been recovered from farm environments and animals in the environment [21,32]. Even in dairy products, AMR genes have been recovered [46]. For non-animal origin, there is limited surveillance data on AMR bacteria. In a report by the EFSA Panel on Biological Hazards [47], about 10% of outbreaks caused by foodborne pathogens were attributed to food of non-animal origin.

### *2.4. Food handlers and contact workers contribute to AMR dissemination*

Poor hygienic practices by food handlers are frequently associated with AMR gene spread, although limited information supports it. However, previous studies have reported drug-resistant *E. coli* from food due to handler contamination (Table 1) [30,48,49]. Although different technologies are in place for processing and preserving food, the potential for the transfer of genetic materials remains. A study by McMahon et al. [50] reported that improper food preservation could alter the phenotypic features of drug-resistant pathogens such as *S. aureus, S. typhimurium*, and *E. coli*. Biocides at sub-lethal concentrations can also induce resistance development [51]. AMR can also be introduced into food as probiotics or even during fermentation.

### *2.5. The risk of co-resistance and cross-resistance associated with antibiotic use in aquaculture*

There is a strong correlation between the increase in antimicrobial-resistant bacteria (AMRB) and aquaculture practice. In aquaculture, the administration of antibiotics in feed and water does not support the control of dosages. It increases the risk of suboptimal levels of antibiotic intake, increasing the possibility of resistance. An estimated 80% of administered antibiotics remained unutilized, incredibly close to application sites, and can be rapidly disseminated to the environment [52]. Cross- and co-selection of antibiotic resistance occurs in the aquatic environment through interaction between zoonotic agents and aquatic sediments, serving as reservoirs for diverse bacterial communities. Fish, for example, are a reservoir for zoonotic pathogens that can be transmitted to humans through direct contact or food contamination [53,54]. These zoonotic pathogens not only infect humans but can also transmit ARGs [55–57].

### *2.6. Wastewater and sewage system as a source of AMR*

Wastewater treatment plants (WWTPs), as a unique interface between humans and the environment, harbor a large microbial genetic diversity and resistance genes, facilitating the exchange of ARGs through horizontal gene transfer [58–60] Several researchers have recently documented the impact of MDR bacteria strains recovered from WWTPs [61–63]. Usually, efficient treatment methods require WWTPs to destroy ARGs while making pathogenic organisms inactive. However, some purification processes in the WWTPs are inefficient as they cannot eliminate the resistant genes of concern. This makes WWTPs hotspots for the spread of antibiotic resistance determinants in the environment, which is a major threat as final effluent is usually discharged into surface waters.

In general, the aquatic environment is constantly affected by anthropogenic events. This makes it a perfect zone for transferring and exchanging mobile elements. While the problem of AMR involving wastewater has been an area of interest for most researchers, there is still a paucity of data in some regions of the world, especially in Africa. Typically, WWTP effluents have reduced ARGs and ARB compared to

**Table 1**
Selected studies on antimicrobial resistance (AMR) bacteria from animals and their products and foods.

| Country of origin | Food sample | Antimicrobial resistance | Reference |
|---|---|---|---|
| Bangladesh, China, India, Philippines | Vegetables, pepper leaves, spinach, stolon of taro, hyacinth bean seeds, sweet potato leaves, etc. | *Staphylococcus aureus (S. aureus), Escherichia coli, (E. coli) Klebsiella pneumoniae, (K, pneumoniae) Enterobacter cloacae, (E. cloacae) Enterobacter aerogenes, (E. aerogenes)* | [18] |
| China, Vietnam, Pakistan | White pepper powder, ginger powder, and Szechuan pepper | *Salmonella* Enteritidis | [19] |
| Egypt, Brazil, Vietnam | Poultry, rabbit meat | *Salmonella Weltevreden; E. coli* | [20] |
| Italy | Venus clam | *E. coli* | [21] |
| Brazil, Argentina | Poultry meat | *Salmonella Heidelberg* | [22] |
| Brazil, China, Poland, Germany | Turkey meat/liver | *K. pneumoniae, E. coli, Citrobacter braakii (C. braakii)* | [23] |
| Vietnam | Shrimp | *Vibrio parahaemolyticus (V. parahaemolyticus)* | [24] |
| Iran | Raw bovine milk | *S. aureus E. coli, Listeria monocytogenes (L. monocytogenes), and Salmonella* spp. | [31] |
| Thailand (different selected areas) | Pigs, broiler, fish, etc. | *ESBL-producing E. coli* | [32] |
| China | Raw milk, cooked food products, and raw meat | *Salmonella, L. monocytogenes, and S. aureus* | [33] |
| Africa | Poultry products | *Campylobacter jejuni (C. jejuni), Campylobacter coli (C. coli), Campylobacter lari (C. lari)* | [38] |
| Sri Lanka | Poultry meat and neck skin | *C. jejuni, C. coli* | [39] |
| Cuba | Meat products, dairy products, etc. | *Salmonella, E. coli, Vibrio cholerae, (V. cholerae) Staphylococcus* | [40] |
| – | Pigs | *Methicillin-resistant S. aureus (MRSA)* | [41] |
| Netherlands (Southern) | Catfish and eel farms (aquaculture) | *Aeromonas* | [42] |
| Ethiopia | Animal-origin food (e.g., egg sandwiches, raw milk, and raw meat) | *Salmonella* spp. | [43] |
| – | ginger root, garlic powder | *Bacillus* spp., *Stenotrophomonas maltophilia Erwinia* spp., *E. cloacae, Ewingella americana, E. americana and Staphylococcus* spp. | [44] |

raw wastewater. However, evidence is emerging that the abundance of ARB and ARGs may increase beyond its basal levels in the receiving river even after treatment [64]. Although it is not yet fully understood how ARGs accumulate in aquatic systems, in some quarters, it has been suggested that there is selective pressure on some populations when antibiotics are present in the aquatic system. Several recent investigations have profiled diverse AMR genes in WWTPs and the downstream water receiving the effluent [65–69].

Available evidence has shown that the purification process in the WWTPs is inefficient, as they cannot eliminate the resistance genes of concern, thus making WWTPs hotspots for the spread of antibiotic resistance determinants in the environment. This is a major concern as the final effluent is usually discharged into surface waters and used for fertilizer production. Thus, the need for intensive wastewater treatment strategies cannot be overemphasized. In addition, hospital wastewater should be adequately treated before discharge into conventional WWTPs. There is also a need for advanced treatment options for the final effluent before being discharged to water bodies. Further studies evaluating the ARB and ARGs in water bodies are urgently needed. These studies should also take note of WWTP effluents and their effects at several distances downstream of the water bodies. These studies will substantially expand our knowledge of antibiotics and ARGs in water and WWTPs.

## 3. The big questions and critical issues for Africa

Some critical questions remain to be answered: What is the exact health and economic burden of AMR in Africa? How many people die from AMR in different regions of Africa? How do we measure the mortality rate attributed to AMR in LMICs, where there is still a significant gap in the availability of surveillance data? Therefore, predicting the impact of new antibiotics over time is a huge and almost impossible task in Africa, mainly due to difficulties in retrieving information on antibiotic use. Any intervention to curb AMR must cut across national/international, hospital, local, and community levels, while taking cues on the questions. Understanding the exact impact of AMR on mortality in Africa is critical, as is improving the capacity to manage, analyze, interpret and share data, and improving diagnostic capacity to inform clinical care. Reducing inappropriate use of antibiotics will also be critical, but how this can work in Africa, where there is still a lack of regulation, remains to be seen.

Africa's primary health issues are enormous, including inadequate human resources, lack of funding for health research and development, and deplorable or unavailability of healthcare infrastructure. Furthermore, political instability, corruption, poor leadership, and poor policies hinder interventions. Poor information management systems or the unavailability of databases for health surveillance purposes are also significant issues. Currently, only a few African countries have established the Global Antimicrobial Resistance partnership (GARP). The establishment of stewardship programs in most settings is also problematic. Lack of well-trained health personnel and poor healthcare services add to the challenges. In addition, antibiotic misuse is rampant due to a lack of regulatory structure and poor pharmacovigilance. Those in rural areas face the greatest burden due to difficult access to primary care and scarce resources.

Moreover, several vaccine issues and challenges still abound in Africa. Measuring the impact of vaccines in combating AMR in an African setting is a gap that needs to be filled and requires a holistic approach [70]. However, to achieve this, there is a need for a robust population-based data system to collect vaccination data and link it to health issues within a region. The population-based data system is critical to monitoring vaccination progress, coverage, and overall population statistics [71]. There is also a need to strengthen water sanitation and hygiene (WASH) and vaccination programs at all levels of Africa. The importance of strengthening WASH infrastructure at different levels has been demonstrated in Zimbabwe, where the typhoid conjugate vaccine (TCV) was successfully used to curb the menace of typhoid in the country (https://www.afro.who.int/countries/zimbabwe/news/zimbabwe-tackles-typhoid-new-vaccination-campaign). To curb this menace, they integrated TCV and WASH into their routine immunization program. In addition to health education and judicious use of antimicrobials, they have reduced the high burden of typhoid to the barest minimum. Therefore, the importance of immunization must be incorporated into routine medical education at all levels. Regional legislation in African countries must be strengthened and fine-tuned to promote health security.

Furthermore, we need to correctly identify the exact natural sources of antibiotics to model resistance emergence and spread appropriately. However, this requires a multi-dynamic approach encompass-

ing experimental research and *in silico* prediction. In Africa, several social, political, and economic issues impede healthcare delivery [72]. However, with one health approach, these challenges can be overcome. The one health approach is essential to increase community engagement and collaboration to improve health security.

## 4. Overcoming AMR requires a holistic approach involving multiple biomaterials, but vaccines are central to achieving the feat

There are several biomaterials (with therapeutic intentions) that have attracted global attention due to their high efficacy and are currently in use against various pathogens [73–76]. However, despite the efficacy of most of these biomaterials, the use of vaccines, in our opinion, remains the most viable alternative [77]. The overuse and misuse of antibiotics in human and veterinary medicine have contributed significantly to the development and spread of drug-resistant pathogens. However, vaccines offer a multifaceted approach to averting antimicrobial resistance [70,78,79]. Vaccines are traditionally viewed as preventive measures against infectious diseases. Vaccines help to reduce the incidence and severity of infectious diseases, thereby reducing the need for antibiotic treatment. For example, the introduction of vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b has led to substantial declines in the number of cases of pneumonia and meningitis, reducing the overall demand for antibiotics [80,81]. Vaccines can prevent infections that frequently lead to secondary bacterial infections. For instance, the influenza vaccine reduces the risk of influenza-related complications, such as bacterial pneumonia, which often require antibiotic therapy [82].

Additionally, vaccination reduces the prevalence of vaccine-targeted pathogens in a population. With fewer pathogens, there is less transmission of these pathogens, resulting in less selection pressure for antibiotic-resistant strains [83]. Furthermore, high vaccine coverage can establish herd immunity, protecting unvaccinated individuals from infection, which indirectly reduces their chances of acquiring drug-resistant infections, as they are less likely to be exposed to infectious agents [84,85]. As a one-health approach, blocking zoonotic infections reduces human diseases. Thus, vaccines must cover both humans and animals.

To date, the remarkable advances in genomics, bioinformatics, structural biology, and immunology have provided researchers with innovative tools to enhance the efficacy of new vaccine formulations against antimicrobial resistance (AMR). These promising strategies include bioconjugation, reverse vaccinology, and novel adjuvants. Some of the vaccine technologies have been pivotal in identifying vaccine candidates. Outer membrane vesicle vaccine (OMV) developed under the umbrella of generalized modules for membrane antigens (GMMA) technology [86], DNA and RNA vaccines [87], and bioconjugates technology [88] are proving to be vital in vaccine design targeting various priority pathogens. Reverse and structural vaccinology [89,90] have also been harnessed to predict conserved surface-exposed factors that could serve as vaccine targets. Other technology platforms for the production of custom-made recombinant glycoconjugate vaccines are also available [77]. Despite all these successes, we still need a continuous pipeline of vaccines with different technologies. The old traditional approach (live attenuated vaccines) has also witnessed some critical and valuable innovations [78]. While we celebrate the success so far, more antigenic components need to be identified by leveraging next-generation technology. For example, Mark Stevens and collaborators have recently used transposon mutagenesis incorporated with sequencing to identify hundreds of candidate genes for vaccine targets.

Different vaccines are being developed against different pathogens, including multi-protective poultry vaccines. CVD1902, a live attenuated vaccine, is also being tested against *Salmonella paratyphi A* [91]. Sequencing technologies integrated with scalable downstream bioinformatic analysis have also been pivotal in identifying bacterial antigens to further mitigate infection due to Salmonella. This approach was recently used to screen the entire *Salmonella* genome and nucleotide identity. Approximately 3,300 conserved *S. enterica* genes were mapped. After subtracting >50 % nucleotide identity from other bacteria, the researchers, through this approach, were able to identify ApeE, a gene belonging to the GDSL lipase family. This gene (required for gall bladder colonization) is conserved in *Salmonella* but absent in other Enterobacteriaceae. Immunization with ApeE (purified protein) protects mice from *Salmonella* and reduces gall bladder colonization. However, the number of conserved *Salmonella* antigens is still limited.

Despite the promise of vaccines, there are still some gaps in the use of vaccination to reduce the burden of AMR. Only a few pathogens are in scope for vaccine development. Currently, we have about 61 vaccines in active clinical development for use against bacteria. Among bacterial pathogens, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis,* and *Shigella* have the highest number of vaccine candidates, and unfortunately for most pathogens, there are no licensed vaccines, although candidates are in clinical trials. Another major challenge can be explained using the pneumococcal conjugate vaccine (PCV) as an example. The pneumococcal conjugate vaccines have proven effective across different geographical regions despite the high diversity in serotypes across borders. Differences in geographical burden have not been a deterrent for wide application. However, in practical terms, the vaccine targets about seven capsular serotypes. Unfortunately, there are more than 100 known pneumococcal capsular serotypes. Therefore, in practical terms, vaccines targeting this pathogen can only protect against a few serotypes. However, recent vaccine formulations have increased coverage of up to 13 and 20 serotypes. This increase in diversities cannot be ignored and can be attributed to the expansion of existing genetic lineages, the import of genetic lineages, and even the evolution of existing genetic lineages in different regions.

Several African studies have reported high clonal diversity [92–95]. This area is critical because most bacterial pathogens have acquired transferable resistance genes on their plasmids, leading to new sub-lineages with more resistant and well-fortified virulent determinants. In Sudan, for example, the expanding nature of ST131 of *E. coli* with a wide distribution of resistance genes was reported [96]. Thus, only heightened surveillance efforts could help to understand circulating bacterial clones of importance, curtail the spread of high-risk clones, and identify potential outbreak clusters in African regions – this is an area where we suggest integrating scalable genomics into routine surveillance programs because vaccines covering key serotypes could be helpful in different regions of Africa and LMICs generally.

It is pertinent to state that vaccines are valuable in Africa, but commercial incentives are limited. The coronavirus pandemic helped us to understand that more than 99% of vaccines rolled out in Africa are imported. It is a pathetic situation that an entire continent relies on imported vaccines due to the unavailability of vaccine production plants. It portrays that Africa is still at the back of the queue in terms of research and development. This issue is also one of the main reasons for vaccine hesitancy due to paranormal beliefs and a lack of trust in the safety of foreign vaccines. Therefore, scaling up vaccine production in Africa is critical to improving health security and should be given adequate attention. Although this comes with several challenges [97], they are not insurmountable.

Another therapeutic intervention proving effective is antibody therapy. Antibody therapy is a viable therapeutic approach because antibodies can trigger bacteria killing via immune modulation, while complement can also enhance the phagocytosis of bacteria. For example, *Shigella* monoclonal antibodies (ShimAbs) have proven effective against *Shigella sonnei* and *flexneri*. Thus, GMMA and monoclonal antibodies are complementary platforms to fight shigellosis. However, to fully exploit their potential, it is necessary to understand the interplay

between antibiotic-resistant bacterial infections and the innate immune system. This understanding is very critical to the proper design of an effective vaccine candidate.

## 5. Impact of vaccine in overcoming AMR: Africa as a case

In 2016, a significant discovery was made in Pakistan's Sindh province. Researchers identified an extensively drug-resistant clone of *S. Typhi* with the potential to trigger a global public health crisis [98]. This clone resisted first- and second-line antibiotics and third-generation cephalosporins, causing heightened concern within the medical community [99]. Subsequently, this clone sparked a major typhoid outbreak, affecting over 5,200 individuals in the Sindh region [100]. Pakistani authorities launched an emergency typhoid vaccination campaign in the most affected areas in response to the outbreak and the limited treatment options available. They utilized the WHO-prequalified conjugate vaccine. This vaccine was approved for use in children and infants under two years of age [101]. The vaccination campaign was critical in reducing *Salmonella* infection. This example showed the impact of vaccines in curtailing drug-resistant bacterial pathogens. Other examples of the impact of vaccines in different regions of the world are available and were recently reviewed by [102].

In Africa, the typhoid outbreak in Zimbabwe was particularly challenging due to the high levels of multidrug resistance and reduced susceptibility to fluoroquinolones observed in the *S. Typhi* isolates [103]. A few months after the vaccination campaign commenced, the vaccination campaign had a significant impact. No cases of typhoid were detected among the 24 children aged 6 months to 15 years who underwent blood culture tests, which starkly contrasted to the previous study conducted just before the vaccination campaign, which found 23 out of 109 (21%) positive blood cultures indicating typhoid cases. Notably, this endeavor marked the first attempt to control a typhoid outbreak in Africa through vaccination and the inaugural use of the Vi-conjugate typhoid vaccine on the continent [104]. Many lessons can be drawn from the Zimbabwe case, including that vaccination's importance must be incorporated into routine medical education at all levels. Also, a recent study examined data from national household surveys conducted in 77 countries between 2006 and 2018, covering 944,173 children. This study focused on estimating the protection provided by selected vaccines against antibiotic-treated episodes of acute respiratory infection [105]. According to their findings, current global coverage levels of rotavirus vaccines prevent 13.6 million cases of antibiotic-treated diarrhea illness in children under two years of age, while pneumococcal vaccines prevent 23.8 million cases of antibiotic-treated respiratory illness among children under five years of age in LMICs each year.

In curtaining drug-resistant infectious diseases, several issues about the African region still need to be addressed. However, in just one generation, the African Region has made remarkable strides in enhancing immunization access and reducing child mortality rates. Notably, several diseases, such as polio and maternal and neonatal tetanus, are on the verge of being eradicated or eliminated. However, despite these notable accomplishments, national and subnational immunization coverage rates have plateaued in numerous countries, causing the African Region to still trail behind other global regions regarding vaccine accessibility. Alarmingly, approximately one in five African children do not receive all the essential and fundamental vaccines required. Consequently, more than 30 million children under the age of five continue to suffer from vaccine-preventable diseases (VPDs) every year in Africa. Tragically, over half a million children succumb to VPDs annually, accounting for around 58% of global VPD-related fatalities [106,107].

Strategic investments are imperative to fortify healthcare systems to address these critical issues. There is a need for robust immunization programs that can reach every individual in Africa, especially those most vulnerable. Expanding vaccine accessibility is essential for improving child health and survival and establishing the groundwork for countries to deliver essential health services to every person, fostering their well-being and prosperity. Thus, more innovative approaches that could potentially be applied to address other AMR issues in the future are needed.

## 6. Conclusion and prospects

Antimicrobial resistance is a global problem that has so far resisted modern therapeutic interventions. Infections caused by multidrug-resistant (MDR) pathogens are a severe threat to public health worldwide, especially in Africa, and require serious attention and proper monitoring, particularly in our setting. The trend and evolution of resistance to several drugs remain elusive to date. In addition, AMR dynamics and patterns among different pathogens remain unclear. So far, clinical data are under-exploited, and there is a paucity of surveillance data in Africa. How MDR bacterial clones are selected in an environment free of antibiotics raises several questions yet to be answered.

Therefore, there is a need to correctly identify the exact natural sources of antibiotics to model resistance emergence and spread appropriately. There is a need to critically model and track resistance evolution and dissemination. We also think that for adequate AMR surveillance and to properly track and monitor resistance rise, a multi-dynamic approach encompassing experimental (phenotypic) research and *in silico* analysis involving whole genome sequencing (WGS) and bioinformatics analysis is indispensable. We also infer that integrating scalable genomics into routine surveillance programs is a critical and indispensable approach to AMR surveillance. There is a need to strengthen surveillance programs crucial in generating data that could aid in precision health care, developing better treatment approaches and vaccines for specific pathogens, and strengthening baseline public health systems. Overall, overcoming AMR requires a holistic approach, as there is no single approach with enough precision to curb the AMR menace. While strengthening AMR surveillance efforts is essential, there is also a need to intensify efforts in developing newer biomaterials and vaccines with broad coverage.

## Conflict of interest statement

The authors declare that there are no conflicts of interest.

## Author contributions

**Zikora Kizito Glory Anyaegbunam:** Resources, Writing – review & editing. **Ifeanyi Elibe Mba:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing. **Yandev Doowuese:** Writing – review & editing. **Ngozi J. Anyaegbunam:** Writing – review & editing. **Toluwalase Mba:** Writing – review & editing, Resources. **Fetuata Aminat Aina:** Resources, Writing – review & editing. **Vincent Nnamdigadi Chigor:** Supervision. **Emeka Innocent Nweze:** Supervision. **Emmanuel A. Eze:** Supervision.

## References

[1] T. Matsumoto, O. Darlington, R. Miller, et al., Estimating the economic and clinical value of reducing antimicrobial resistance to three gram-negative pathogens in Japan, JHEOR. 8 (2) (2021) 64–75, https://doi.org/10.36469/001c.28327.
[2] D.G.J. Larsson, C.F. Flach, Antibiotic resistance in the environment, Nat. Rev. Microbiol. 20 (2022) 257–269, https://doi.org/10.1038/s41579-021-00649-x.
[3] W. Mukuna, T. Aniume, B. Pokharel, C. Khwatenge, A. Basnet, A. Kilonzo-Nthenge, Antimicrobial susceptibility profile of pathogenic and commensal bacteria recovered from Cattle and Goat farms, Antibiotics (Basel) 12 (2) (2023) 420, https://doi.org/10.3390/antibiotics12020420.
[4] X. Liu, G. Zhang, Y. Liu, S. Lu, P. Qin, X. Guo, B. Bi, L. Wang, B. Xi, F. Wu, et al., Occurrence and fate of antibiotics and antibiotic resistance genes in typical urban

water of Beijing, China, Environ. Pollut. 246 (2019) 163–173, https://doi.org/10.1016/j.envpol.2018.12.005.
[5] S.A Baron, O. Mediannikov, R. Abdallah, E. Kuete Yimagou, H. Medkour, G. Dubourg, Y. Elamire, P. Afouda, I.I. Ngom, E. Angelakis, et al., Multidrug-resistant Klebsiella pneumoniae clones from wild Chimpanzees and Termites in Senegal, Antimicrob. Agents Chemother. 65(9) (2021) e0255720, http://doi.org/10.1128/AAC.02557-20.
[6] S.L. Bager, I. Kakaala, E. Kudirkiene, D.K. Byarugaba, J.E. Olsen, Genomic characterisation of multidrug-resistant extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae from chimpanzees (pan troglodytes) from wild and sanctuary locations in Uganda, J. Wildl. Dis. 58 (2) (2022) 269–278, https://doi.org/10.7589/JWD-D-21-00068.
[7] Antimicrobial Resistance Collaborators, Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, Lancet 399 (10325) (2022) 629–655, https://doi.org/10.1136/ebnurs-2022-103540.
[8] European Antimicrobial Resistance Collaborators, The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis, Lancet Public Health (11) (2022) e897–e913, http://doi.org/10.1016/S2468-2667(22)00225-0.
[9] C.G. van der Westhuizen, F.J. Burt, N. van Heerden, W. van Zyl, T. Anthonissen, J. Musoke. Prevalence and occupational exposure to zoonotic diseases in high-risk populations in the Free State Province, South Africa. Front. Microbiol. 14 (2023) 1196044, http://doi.org/10.3389/fmicb.2023.1196044.
[10] A. Caneschi, A. Bardhi, A. Barbarossa, A. Zaghini, The use of antibiotics and antimicrobial resistance in veterinary medicine, a complex phenomenon: A narrative review, Antibiotics (Basel) 12 (3) (2023) 487, https://doi.org/10.3390/antibiotics12030487.
[11] Y.G. Zhu, Y. Zhao, D. Zhu, M. Gillings, J. Penuelas, Y.S. Ok, A. Capon, S. Banwart, Soil biota, antimicrobial resistance and planetary health, Environ. Int. 131 (2019) 105059, https://doi.org/10.1016/j.envint.2019.105059.
[12] Y. Li, X. Deng, N. Zhang, Z. Shen, R. Li, Q. Shen, J.F. Salles, Rhizosphere suppression hinders antibiotic resistance gene (ARG) spread under bacterial invasion, One Health 2 (16) (2023) 100481, https://doi.org/10.1016/j.onehlt.2023.100481.
[13] M. Pepi, S. Focardi, Antibiotic-resistant bacteria in aquaculture and climate change: A challenge for health in the Mediterranean area, Int. J. Environ. Res. Public Health 18 (11) (2021) 5723, https://doi.org/10.3390/ijerph18115723.
[14] Z.Z. Yan, Q.L. Chen, C.Y. Li, B.A. Thi Nguyen, Y.G. Zhu, J.Z. He, H.W. Hu, Biotic and abiotic factors distinctly drive contrasting biogeographic patterns between phyllosphere and soil resistomes in natural ecosystems, ISME Commun. 1 (1) (2021) 13, https://doi.org/10.1038/s43705-021-00012-4.
[15] L. Zhang, J. Bai, Y. Zhai, K. Zhang, Z. Wei, Y. Wang, H. Liu, R. Xiao, M.A. Jorquera, Antibiotics affected the bacterial community structure and diversity in pore water and sediments with cultivated Phragmites australis in a typical Chinese shallow lake, Front. Microbiol. 14 (14) (2023) 1155526, https://doi.org/10.3389/fmicb.2023.1155526.
[16] Y.R. Liu, M.G.A. van der Heijden, J. Riedo, C. Sanz-Lazaro, D.J. Eldridge, F. Bastida, E. Moreno-Jiménez, X.Q. Zhou, H.W. Hu, J.Z. He, et al., Soil contamination in nearby natural areas mirrors that in urban greenspaces worldwide, Nat. Commun. 14 (1) (2023) 1706, https://doi.org/10.1038/s41467-023-37428-6.
[17] M. Samtiya, K.R. Matthews, T. Dhewa, A.K. Puniya, Antimicrobial resistance in the food chain: trends, mechanisms, pathways, and possible regulation strategies, Foods 11 (19) (2022) 2966, https://doi.org/10.3390/foods11192966.
[18] D. Jung, J.E. Rubin, Identification of antimicrobial resistant bacteria from plant-based food products imported into Canada, Int. J. Food Microbiol. 319 (2020) 108509, https://doi.org/10.1016/j.ijfoodmicro.2020.108509.
[19] D. Bae, O. Kweon, A.A. Khan, Isolation and characterization of antimicrobial-resistant nontyphoidal *Salmonella enterica* serovars from imported food products, J. Food Prot. 79 (8) (2016) 1348–1354, https://doi.org/10.4315/0362-028X.JFP-15-564.
[20] A. Muller, W. Jansen, N.T. Grabowski, C. Kehrenberg, Characterization of *Salmonella enterica* serovars recovered from meat products legally and illegally imported into the EU reveals the presence of multiresistant and AmpC-producing isolates, Gut Pathog. 10 (1) (2018) 40, https://doi.org/10.1186/s13099-018-0268-3.
[21] N. Roschanski, S. Guenther, T.T.T. Vu, J. Fischer, T. Semmler, S. Huehn, et al., VIM-1 carbapenemase-producing *Escherichia coli* isolated from retail seafood, Germany 2016, Euro Surveill. 22 (43) (2017) 17, https://doi.org/10.2807/1560-7917.ES.2017.22.43.17-00032.
[22] R.R. van den Berg, S. Dissel, M.L.B.A. Rapallini, C.C. van der Weijden, B. Wit, R. Heymans, Characterization and whole genome sequencing of closely related multidrug-resistant *Salmonella enterica* serovar Heidelberg isolates from imported poultry meat in the Netherlands, PLoS One 14 (7) (2019) e0219795, https://doi.org/10.1371/journal.pone.0219795.
[23] T. Gelbícová, I. Kolackova, M. Krutova, R. Karpiskova, The emergence of mcr-1-mediated colistin-resistant *Escherichia coli* and *Klebsiella pneumoniae* in domestic and imported turkey meat in the Czech Republic 2017–2018, Folia Microbiol. 65 (1) (2020) 211–216, https://doi.org/10.1007/s12223-019-00709-z.
[24] A. Briet, N. Helsens, S. Delannoy, S. Debuiche, A. Brisabois, G. Midelet, S.A. Granier, NDM-1-producing Vibrio parahaemolyticus isolated from imported seafood, J. Antimicrob. Chemother. 73 (9) (2018) 2578–2579, https://doi.org/10.1093/jac/dky200.
[25] V. Kasimanickam, M. Kasimanickam, R. Kasimanickam, Antibiotics use in food animal production: escalation of antimicrobial resistance: where are we now in combating AMR?, Med Sci. (Basel) 9 (1) (2021) 14, https://doi.org/10.3390/medsci9010014.
[26] W. Sirichokchatchawan, P. Apiwatsiri, P. Pupa, I. Saenkankam, N.O. Khine, A. Lekagul, K. Lugsomya, D.J. Hampson, N. Prapasarakul, Reducing the risk of transmission of critical antimicrobial resistance determinants from contaminated pork products to humans in South-East Asia, Front. Microbiol. 27 (12) (2021) 689015, https://doi.org/10.3389/fmicb.2021.689015.
[27] D. Stępień-Pyśniak, T. Hauschild, M. Dec, A. Marek, M. Brzeski, U. Kosikowska, Antimicrobial resistance and genetic diversity of *Enterococcus faecalis* from yolk sac infections in broiler chicks, Poult. Sci. 100 (12) (2021) 10149, https://doi.org/10.1016/j.psj.2021.101491.
[28] L. Hu, G. Cao, E.W. Brown, M.W. Allard, L.M. Ma, A.A. Khan, G. Zhang, Antimicrobial resistance and related gene analysis of Salmonella from egg and chicken sources by whole-genome sequencing, Poult. Sci. 99 (12) (2020) 7076–7083, https://doi.org/10.1016/j.psj.2020.10.011.
[29] K.Y. Lee, E.R. Atwill, M. Pitesky, A. Huang, K. Lavelle, M. Rickard, M. Shafii, M. Hung-Fan, X. Li, Antimicrobial resistance profiles of non-typhoidal Salmonella from retail meat products in California, 2018, Front. Microbiol. 3 (2022) 835699, https://doi.org/10.3389/fmicb.2022.835699.
[30] K.Y. Lee, K. Lavelle, A. Huang, E.R. Atwill, M. Pitesky, X. Li, Assessment of prevalence and diversity of antimicrobial resistant Escherichia coli from retail meats in Southern California, Antibiotics (Basel) 12 (4) (2023) 782, https://doi.org/10.3390/antibiotics12040782.
[31] S. Hassani, M.H. Moosavy, S.N. Gharajalar, S.A. Khatibi, A. Hajibemani, Z. Barabadi, High prevalence of antibiotic resistance in pathogenic foodborne bacteria isolated from bovine milk, Sci. Rep. 12 (2022) 3878, https://doi.org/10.1038/s41598-022-07845-6.
[32] A. Boonyasiri, T. Tangkoskul, C. Seenama, J. Saiyarin, S. Tiengrim, V. Thamlikitkul, Prevalence of antibiotic resistant bacteria in healthy adults, foods, food animals, and the environment in selected areas in Thailand, Pathog. Glob. Health 108 (2014) 235–245, https://doi.org/10.1179/2047773214Y.0000000148.
[33] G. Chao, X. Zhou, X. Jiao, X. Qian, L. Xu, Prevalence and antimicrobial resistance of foodborne pathogens isolated from food products in China, Foodborne Pathog. Dis. 4 (2007) 277–284, https://doi.org/10.1089/fpd.2007.0088.
[34] M.M.J. Arsène, A.K.L. Davares, P.I. Viktorovna, S.L. Andreevna, S. Sarra, I. Khelifi, D.M. Sergueïevna, The public health issue of antibiotic residues in food and feed: Causes, consequences, and potential solutions, Vet World. 15 (3) (2022) 662–671, https://doi.org/10.14202/vetworld.2022.662-671.
[35] R. Wang, L. van Dorp, L.P. Shaw, P. Bradley, Q. Wang, X. Wang, L. Jin, Q. Zhang, Y. Liu, A. Rieux, et al., The global distribution and spread of the mobilized colistin resistance gene mcr-1, Nat. Commun. 9 (2018) 1179, https://doi.org/10.1038/s41467-018-03205-z.
[36] V. Silva, S. Araújo, A. Monteiro, J. Eira, J.E. Pereira, L. Maltez, G. Igrejas, T.S. Lemsaddek, P. Poeta, Staphylococcus aureus and MRSA in livestock: antimicrobial resistance and genetic lineages, Microorganisms 11 (1) (2023) 124, https://doi.org/10.3390/microorganisms11010124.
[37] European Food Safety Authority (EFSA). Foodborne antimicrobial resistance as a biological hazard-scientific opinion of the panel on biological hazards. EFSA J. 6 (2008) 765, https://doi.org/10.2903/j.efsa.2008.765.
[38] B.K. Akosua, O.D. Kwasi, H.F. Enoch, A.K. Karen, Multidrug resistant Campylobacter in faecal and carcasses of commercially produced poultry, Afr. J. Microbiol. Res. 11 (2017) 271–277, https://doi.org/10.5897/AJMR2015.8329.
[39] K.S.A. Kottawatta, M.A.P. Van Bergen, P. Abeynayake, J.A. Wagenaar, K.T. Veldman, R.S. Kalupahana, Campylobacter in broiler chicken and broiler meat in Sri Lanka: influence of semi-automated vs. wet market processing on Campylobacter contamination of broiler neck skin samples, Foods 6 (2017) 105, https://doi.org/10.3390/foods6120105.
[40] Y. Puig-Peña, V. Leyva-Castillo, R. Tejedor-Arias, M.T. Illnait-Zaragozí, N. Aportela-López, A. Camejo-Jardines, J. RamírezAreces, Antimicrobial resistance in bacteria isolated from foods in Cuba, MEDICC Rev. 22 (2022) 40–45, https://doi.org/10.37757/MR2020.V22.N3.9.
[41] T.S. Frana, A.R. Beahm, B.M. Hanson, J.M. Kinyon, L.L. Layman, L.A. Karriker, A. Ramirez, T.C. Smith, Isolation and characterization of methicillin-resistant Staphylococcus aureus from pork farms and visiting veterinary students, PLoS One 8 (2013) e53738, https://doi.org/10.1371/journal.pone.0053738.
[42] J. Penders, E. Stobberingh, Antibiotic resistance of motile aeromonads in indoor catfish and eel farms in the southern part of The Netherlands, Int. J. Antimicrob. Agents 31 (2008) 261–265, https://doi.org/10.1016/j.ijantimicag.2007.10.002.
[43] M. Ejo, L. Garedew, Z. Alebachew, W. Worku, Prevalence and antimicrobial resistance of Salmonella isolated from animal origin food items in Gondar, Ethiopia, Biomed. Res. Int. 2016 (2016) 1–8, https://doi.org/10.1155/2016/4290506.
[44] J.C. Brown, X. Jiang, Prevalence of antibiotic-resistant bacteria in herbal products, J. Food Prot. 71 (7) (2008) 1486–1490, https://doi.org/10.4315/0362-028x-71.7.1486.
[45] H. Tate, S. Ayers, E. Nyirabahizi, C. Li, S. Borenstein, S. Young, C. Rice-Trujillo, S. Saint Fleurant, S. Bodeis-Jones, X. Li, et al., Prevalence of antimicrobial resistance in select bacteria from retail seafood—United States, 2019, Front Microbiol 13 (2022) 928509, https://doi.org/10.3389/fmicb.2022.928509.
[46] B. Catry, J. Dewulf, D. Maes, B. Pardon, B. Callens, M. Vanrobaeys, G. Opsomer, A. De Kruif, F. Haesebrouck, Effect of antimicrobial consumption and production type on antibacterial resistance in the bovine respiratory and digestive tract, PLoS One 11 (2016) e0146488, https://doi.org/10.1371/journal.pone.0146488.

[47] EFSA Panel on Biological Hazards (BIOHAZ), Scientific opinion on the risk posed by pathogens in food of non-animal origin. Part 1 (outbreak data analysis and risk ranking of food/pathogen combinations), EFSA J. 11 (2013) 3025, https://doi.org/10.2903/j.efsa.2013.3025.
[48] S. Kim, H. Kim, Y. Kim, M. Kim, H. Kwak, S. Ryu, Antimicrobial resistance of *Escherichia coli* from retail poultry meats in Korea, J Food Prot 83 (10) (2020) 1673–1678, https://doi.org/10.4315/JFP-20-150.
[49] N. Byrne, L. O'Neill, J.A.C. Díaz, E.G. Manzanilla, A.P. Vale, F.C. Leonard, Antimicrobial resistance in *Escherichia coli* isolated from on-farm and conventional hatching broiler farms in Ireland, Ir. Vet. J. 75 (1) (2022) 7, https://doi.org/10.1186/s13620-022-00214-9.
[50] M.A.S. McMahon, J. Xu, J.E. Moore, I.S. Blair, D.A. McDowell, Environmental stress and antibiotic resistance in food-related pathogens 73 (1) (2007) 211–217, https://doi.org/10.1128/AEM.00578-06.
[51] R.N. Whitehead, T.W. Overton, C.L. Kemp. Webber, M.A. Exposure of *Salmonella enterica* Serovar Typhimurium to high level pathogens, Appl. Environ. Microbiol. 73 (2007) 211–217, https://doi.org/10.3389/fmicb.2020.01613.
[52] S.I. Polianciuc, A.E. Gurzău, B. Kiss, M.G. Ştefan, F. Loghin, Antibiotics in the environment: causes and consequences, Med. Pharm. Rep. 93 (3) (2020) 231–240, https://doi.org/10.15386/mpr-1742.
[53] X. He, M. Deng, Q. Wang, Y. Yang, Y. Yang, X. Nie, Residues and health risk assessment of quinolones and sulfonamides in cultured fish from Pearl River Delta, China, Aquaculture 458 (2016) 38–46, https://doi.org/10.1016/j.aquaculture.2016.02.006.
[54] G. Ferri, C. Lauteri, M. Scattolini, A. Vergara, Antibiotic resistance profiles and ARG detection from isolated bacteria in a culture-dependent study at the codfish industry Level, Foods 12 (8) (2023) 1699, https://doi.org/10.3390/foods12081699.
[55] M. Pepi, S. Focardi, Antibiotic-resistant bacteria in aquaculture and climate change: a challenge for health in the Mediterranean area, Int. J. Environ. Res. Public Health 18 (11) (2021) 5723, https://doi.org/10.3390/ijerph18115723.
[56] D. Schar, C. Zhao, Y. Wang, D.G.J. Larsson, M. Gilbert, T.P. Van Boeckel, Twenty-year trends in antimicrobial resistance from aquaculture and fisheries in Asia, Nat. Commun. 12 (1) (2021) 5384, https://doi.org/10.1038/s41467-021-25655-8.
[57] A. Hossain, M. Habibullah-Al-Mamun, I. Nagano, S. Masunaga, D. Kitazawa, H. Matsuda, Antibiotics, antibiotic-resistant bacteria, and resistance genes in aquaculture: risks, current concern, and future thinking, Environ. Sci. Pollut. Res. Int. 29 (8) (2022) 11054–11075, https://doi.org/10.1007/s11356-021-17825-4.
[58] J. Guo, J. Li, H. Chen, P.L. Bond, Z. Yuan, Metagenomic analysis reveals wastewater treatment plants as hotspots of antibiotic resistance genes and mobile genetic elements, Water Res. 123 (2017) 468–478, https://doi.org/10.1016/j.watres.2017.07.002.
[59] S. Gholipour, Z. Shamsizadeh, D. Halabowski, W. Gwenzi, M. Nikaeen, Combating antibiotic resistance using wastewater surveillance: Significance, applications, challenges, and future directions, Sci. Total Environ. (2023) 168056, https://doi.org/10.1016/j.scitotenv.2023.168056.
[60] F. Berglund, S. Ebmeyer, E. Kristiansson, D.G.J. Larsson. Evidence for wastewaters as environments where mobile antibiotic resistance genes emerge. Commun. Biol. 6 (2023) 321, https://doi.org/10.1038/s42003-023-04676-7.
[61] P. Magdalena, R. Magda, S. Stefan, P.B. Krzysztof, P. Stepnowski, J. Kumirsk, D. Wolecki, E. Mulkiewicz, Identification of selected antibiotic resistance genes in two different wastewater treatment plant systems in Poland: a preliminary study, Molecules 25 (12) (2020) 2851, https://doi.org/10.3390/molecules25122851.
[62] J. Alexander, N. Hembach, T. Schwartz, Evaluation of antibiotic resistance dissemination by wastewater treatment plant effluents with different catchment areas in Germany, Rep. Nat. Res. 10 (2020) 8952, https://doi.org/10.1038/s41598-020-65635-4.
[63] H. Liu, X. Zhou, H. Huang, J. Zhang, Prevalence of antibiotic resistance genes and their association with antibiotics in a wastewater treatment plant: process distribution and analysis, Water 11 (2019) 2495, https://doi.org/10.3390/w11122495.
[64] T. Jäger, N. Hembach, C. Elpers, A. Wieland, J. Alexander, C. Hiller, Reduction of antibiotic resistant bacteria during conventional and advanced wastewater treatment, and the disseminated loads released to the environment, Front. Microbiol. 9 (2018) 2599, https://doi.org/10.3389/fmicb.2018.02599.
[65] W. Shen, Y. Chen, N. Wang, P. Wan, Z. Peng, H. Zhao, W. Wang, L. Xiong, S. Zhang, R. Liu, Seasonal variability of the correlation network of antibiotics, antibiotic resistance determinants, and bacteria in a wastewater treatment plant and receiving water, J. Environ. Manage. 1 (317) (2022) 115362, https://doi.org/10.1016/j.jenvman.2022.115362.
[66] S. Perveen, C. Pablos, K. Reynolds, S. Stanley, J. Marugán, Growth and prevalence of antibiotic-resistant bacteria in microplastic biofilm from wastewater treatment plant effluents, Sci. Total Environ. 856 (Pt 2) (2023) 159024, https://doi.org/10.1016/j.scitotenv.2022.159024.
[67] S. Bonetta, A. Di Cesare, C. Pignata, R. Sabatino, M. MacrÙ, G. Corno, M. Panizzolo, S. Bonetta, E. Carraro, Occurrence of antibiotic-resistant bacteria and resistance genes in the urban water cycle, Environ. Sci. Pollut. Res. Int. 30 (12) (2023) 35294–35306, https://doi.org/10.1007/s11356-022-24650-w.
[68] P. Deng, X. Hu, W. Cai, Z. Zhang, Y. Zhang, Y. Huang, Y. Yang, C. Li, S. Ai, Profiling of intracellular and extracellular antibiotic resistance genes in municipal wastewater treatment plant and their effluent-receiving river, Environ. Sci. Pollut. Res. Int. 30 (12) (2023) 33516–33523, https://doi.org/10.1007/s11356-022-24545-w.
[69] Q. Lu, R. Zhao, Q. Li, Y. Ma, J. Chen, Q. Yu, D. Zhao, S. An, Elemental composition and microbial community differences between wastewater treatment plant effluent and local natural surface water: a Zhengzhou city study, J. Environ. Manage. 325 (2023) 116398, https://doi.org/10.1016/j.jenvman.2022.116398.
[70] M. Holm, R.M. Zellweger, N. Poudyal, K.H.T. Smith, H.S. Joh, F. Marks, Measuring the link between vaccines and antimicrobial resistance in low resources settings – limitations and opportunities in direct and indirect assessments and implications for impact studies, Front. Trop. Dis. 3 (2022) 805833, https://doi.org/10.3389/fitd.2022.805833.
[71] C.L. Ventola, Immunization in the United States: recommendations, barriers, and measures to improve compliance: part 1: childhood vaccinations, Pharmacol. Ther. 41 (7) (2016) 426–436.
[72] O.O. Oleribe, J. Momoh, B.S. Uzochukwu, F. Mbofana, A. Adebiyi, T. Barbera, R. Williams, S.D. Taylor-Robinson, Identifying key challenges facing healthcare systems in Africa and potential solutions, Int. J. Gen. Med. 12 (2019) 395–403, https://doi.org/10.2147/IJGM.S223882.
[73] A.C. Rios, C.G. Moutinho, F.C. Pinto, F.S. Del Fiol, A. Jozala, M.V. Chaud, M.M. Vila, J.A. Teixeira, V.M. Balcão, Alternatives to overcoming bacterial resistances: state-of-the-art, Microbiol. Res. 191 (2016) 51–80, https://doi.org/10.1016/j.micres.2016.04.008.
[74] I.E. Mba, E.I. Nweze, Nanoparticles as therapeutic options for treating multidrug-resistant bacteria: research progress, challenges, and prospects, World J. Microbiol. Biotechnol. 37 (6) (2021) 108, https://doi.org/10.1007/s11274-021-03070-x.
[75] I.E. Mba, E.I. Nweze, Antimicrobial peptides therapy: an emerging alternative for treating drug-resistant bacteria, Yale J. Biol. Med. 95 (4) (2022) 445–463.
[76] N.J. Anyaegbunam, C.C. Anekpo, Z.K.G. Anyaegbunam, Y. Doowuese, C.B. Chinaka, O.J. Odo, et al., The resurgence of phage-based therapy in the era of increasing antibiotic resistance: from research progress to challenges and prospects, Microbiol. Res. 264 (2022) 127155, https://doi.org/10.1016/j.micres.2022.127155.
[77] I.E. Mba, H.C. Sharndama, Z.K.G. Anyaegbunam, C.C. Anekpo, B.C. Amadi, D. Morumda, Y. Doowuese, U.J. Ihezuo, J.U. Chukwukelu, O.P. Okeke, Vaccine development for bacterial pathogens: advances, challenges and prospects, Trop. Med. Int. Health 28 (4) (2023) 275–299, https://doi.org/10.1111/tmi.13865.
[78] F. Micoli, L. Del Bino, R. Alfini, F. Carboni, M.R. Romano, R. Adamo, Glycoconjugate vaccines: current approaches towards faster vaccine design, Expert Rev. Vaccines 18 (9) (2019) 881–895, https://doi.org/10.1080/14760584.2019.1657012.
[79] I. Frost, H. Sati, P. Garcia-Vello, M. Hasso-Agopsowicz, C. Lienhardt, V. Gigante, P. Beyer, The role of bacterial vaccines in the fight against antimicrobial resistance: an analysis of the preclinical and clinical development pipeline, Lancet Microbe 4 (2) (2023) e113–e125, https://doi.org/10.1016/S2666-5247(22)00303-2.
[80] S. Alghamdi, The role of vaccines in combating antimicrobial resistance (AMR) bacteria, Saudi J. Biol. Sci. 28 (12) (2021) 7505–7510, https://doi.org/10.1016/j.sjbs.2021.08.054.
[81] B. Wahl, K.L. O'Brien, A. Greenbaum, A. Majumder, L. Liu, Y. Chu, I. Lukšić, H. Nair, D.A. McAllister, H. Campbell, I. Rudan, R. Black, M.D. Knoll, Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15, Lancet Glob. Health. 6 (7) (2018) e744–e757, https://doi.org/10.1016/S2214-109X(18)30247-X.
[82] M.A. Rolfes, B. Flannery, J.R. Chung, A. O'Halloran, S. Garg, E.A. Belongia, M. Gaglani, R.K. Zimmerman, M.L. Jackson, A.S. Monto, et al., Effects of influenza vaccination in the United States during the 2017-2018 Influenza season, Clin. Infect. Dis. 69 (11) (2019) 1845–1853, https://doi.org/10.1093/cid/ciz075.
[83] M. Lipsitch, G.R. Siber, How can vaccines contribute to solving the antimicrobial resistance problem?, mBio 7 (3) (2016) e00428–16, https://doiorg/10.1128/mBio.00428-16.
[84] P. Fine, K. Eames, D.L. Heymann, "Herd immunity": a rough guide, Clin. Infect. Dis. 52 (7) (2011) 911–916, https://doi.org/10.1093/cid/cir007.
[85] A. Sharma, S.N. Menon, V. Sasidevan, S. Sinha, Epidemic prevalence information on social networks can mediate emergent collective outcomes in voluntary vaccine schemes, PLoS Comput. Biol. 15 (5) (2019) e1006977, https://doi.org/10.1371/journal.pcbi.1006977.
[86] L. Van Der Pol, M. Stork, P. Van Der Ley, Outer membrane vesicles as platform for vaccine technology, Biotechnol. J. 10 (11) (2015) 1689–1706, https://doi.org/10.1002/biot.201400395.
[87] Z. Matic, ˇ M. Santak. Current view on novel vaccine technologies to combat human infectious diseases. Appl. Microbiol. Biotechnol. 106(1) (2021) 25–56, https://doi.org/10.1007/s00253-021-11713-0.
[88] M. Cloutier, K. Muru, G. Ravicoularamin, C. Gauthier, Polysaccharides from Burkholderia species as targets for vaccine development, immunomodulation and chemical synthesis, Nat. Prod. Rep. 35 (12) (2018) 1251–1293, https://doi.org/10.1039/c8np00046h.
[89] A. Sette, R. Rappuoli, Reverse vaccinology: developing vaccines in the era of genomics, Immunity 33 (2010) 530–541, https://doi.org/10.1016/j.immuni.2010.09.017.
[90] M.I. Anasir, C.L. Poh, Structural vaccinology for viral vaccine design, Front. Microbiol. 10 (2019) 738, https://doi.org/10.3389/fmicb.2019.00738.

[91] C.A. MacLennan, J. Stanaway, S. Grow, K. Vannice, A.D. Steele, Salmonella combination vaccines: moving beyond Typhoid, Open Forum Infect. Dis. 10 (Suppl 1) (2023) S58–S66, https://doi.org/10.1093/ofid/ofad041.
[92] E.A. Osman, M. Yokoyama, H.N. Altayb, D. Cantillon, J. Wille, H. Seifert, P.G. Higgins, L. Al-Hassan, Klebsiella pneumonia in Sudan: multidrug resistance, polyclonal dissemination, and virulence, Antibiotics (Basel) 12 (2) (2023) 233, https://doi.org/10.3390/antibiotics12020233.
[93] A.O. Afolayan, A.O. Oaikhena, A.O. Aboderin, O.F. Olabisi, A.A. Amupitan, O.V. Abiri, V.O. Ogunleye, E.E. Odih, A.T. Adeyemo, A.T. Adeyemo, et al., Clones and clusters of antimicrobial-resistant Klebsiella From southwestern Nigeria, Clin. Infect. Dis. 73 (Suppl_4) (2021) S308–S315, https://doi.org/10.1093/cid/ciab769.
[94] A.O. Afolayan, A.O. Aboderin, A.O. Oaikhena, E.E. Odih, V.O. Ogunleye, A.T. Adeyemo, O.S. Adeyemo, A. Bejide, S. Underwood, M. Argimón, et al., An ST131 clade and a phylogroup A clade bearing an O101-like O-antigen cluster predominate among bloodstream *Escherichia coli* isolates from Southwest Nigeria hospitals, Microb. Genomics 8 (12) (2022) mgen000863, https://doi.org/10.1099/mgen.0.000863.
[95] S. Mahazu, W. Sato, A. Ayibieke, I. Prah, T. Hayashi, T. Suzuki, S. Iwanaga, A. Ablordey, R. Saito, Insights and genetic features of extended-spectrum beta-lactamase producing *Escherichia coli* isolates from two hospitals in Ghana, Sci. Rep. 12 (1) (2022) 1843, https://doi.org/10.1038/s41598-022-05869-6.
[96] G. Tegha, E.J. Ciccone, R. Krysiak, J. Kaphatika, T. Chikaonda, I. Ndhlovu, D. van Duin, I. Hoffman, J.J. Juliano, J. Wang, Genomic epidemiology of *Escherichia coli* isolates from a tertiary referral center in Lilongwe, Malawi, Microb. Genomics 7 (1) (2021) mgen000490, https://doi.org/10.1099/mgen.0.000490.
[97] P.M. Heaton, Challenges of developing novel vaccines with particularglobal health importance, Front. Immunol. 11 (2020) 517290, https://doi.org/10.3389/fimmu.2020.517290.
[98] E.J. Klemm, S. Shakoor, A.J. Page, F.N. Qamar, K. Judge, D.K. Saeed, D.K. Wong, V.K. Dallman, T.J. Nair, S. Baker, et al., Emergence of an extensively drug-resistant *Salmonella enterica* Serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins, mBio 9 (1) (2018) e00105–e00118, https://doi.org/10.1128/mBio.00105-18.
[99] J.R. Andrews, S. Baker, F. Marks, M. Alsan, D. Garrett, B.G. Gellin, S.K. Saha, F.N. Qamar, M.T. Yousafzai, I.I. Bogoch, et al., Typhoid conjugate vaccines: a new tool in the fight against antimicrobial resistance, Lancet Infect. Dis. 19 (1) (2019) e26–e30, https://doi.org/10.1016/S1473-3099(18)30350-5.
[100] F.N. Qamar, M.T. Yousafzai, M. Khalid, A.M. Kazi, H. Lohana, S. Karim, A. Khan, A. Hotwani, S. Qureshi, F. Kabir, F. Aziz, N.M. Memon, M.H. Domki, R. Hasan, Outbreak investigation of ceftriaxone-resistant *Salmonella enterica* serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study, Lancet Infect. Dis. 18 (12) (2018) 1368–1376, https://doi.org/10.1016/S1473-3099(18)30483-3.
[101] A. Bhatti, C. Carias, F. Corsi Mendez, Y. Choi, A. Skolnik, A comprehensive assessment of child care vaccination laws across the US, Health Affairs (Project Hope) 41 (4) (2022) 589–597, https://doi.org/10.1377/hlthaff.2021.01205.
[102] V. Costanzo, G.N. Roviello, The potential role of vaccines in preventing antimicrobial resistance (AMR): An update and future perspectives, Vaccines (Basel) 11 (2) (2023) 333, https://doi.org/10.3390/vaccines11020333.
[103] H.S. N'cho, K.P. Masunda, I. Mukeredzi, et al., Notes from the Field: Typhoid Fever Outbreak — Harare, Zimbabwe, October 2017–February 2018, Morb. Mortal. Wkly Rep. 68 (2019) 44–45, https://doi.org/10.15585/mmwr.mm6802a5.
[104] I.D. Olaru, R.M.S. Chingono, C. Bottomley, F.R. Kandiye, F. Mhino, C.A. Nyamayaro, S. Manyau, M. Vere, P. Chitando, P. Chonzi, T.C. Darton, J. Dixon, K. Kranzer, The effect of a comprehensive typhoid conjugate vaccine campaign on antimicrobial prescribing in children in Harare, Zimbabwe: a mixed methods study, Lancet Global Health 11 (9) (2023) e1422–e1431, https://doi.org/10.1016/S2214-109X(23)00319-4.
[105] J.A. Lewnard, E.T. Rogawski McQuade, J.A. Platts-Mills, K.L. Kotloff, R. Laxminarayan, Incidence and etiology of clinically-attended, antibiotic-treated diarrhea among children under five years of age in low- and middle-income countries: Evidence from the Global Enteric Multicenter Study, PLoS Negl. Trop. Dis. 14 (8) (2020) e0008520, https://doi.org/10.1371/journal.pntd.0008520.
[106] S. Ozawa, S. Clark, A. Portnoy, S. Grewal, L. Brenzel, D.G. Walker, Return on investment from childhood immunization in Low- and Middle-Income Countries, 2011–20, Health Affairs (project Hope) 35 (2) (2016) 199–207, https://doi.org/10.1377/hlthaff.2015.1086.
[107] M.P. Shah, J.E. Tate, J.M. Mwenda, A.D. Steele, U.D. Parashar, Estimated reductions in hospitalizations and deaths from childhood diarrhea following implementation of rotavirus vaccination in Africa, Expert Rev. Vaccines 16 (10) (2017) 987–995, https://doi.org/10.1080/14760584.2017.1371595.