Antimicrobial Resistance: Interplay of Animal, Environment, Human and Coordinated Mitigation Strategies

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ABSTRACT

Bacteria, viruses, fungi, and parasites are examples of microorganisms that exhibit resistance; in contrast, antibiotic resistance is exclusive to bacterial resistance. Antimicrobial resistance poses an escalating global threat to human health. The emergence of multidrug-resistant pathogens, resulting in compromised treatment efficacy and increased mortality rates poses a significant problem to global health. The transmission of antimicrobial resistant strains between humans and animals, particularly in close contact settings, underscores the necessity of a unified approach to one health and further blurs the boundaries between human and animal health. This article aims to highlight microbial resistance which are of significant clinical and epidemiologic importance. Environmental reservoirs, including water bodies and soil, serve as critical conduits for the transmission of antimicrobial resistant genes. Antimicrobial resistance is a complex dynamic within the interconnected realms of human, animal, and environmental health necessitating a comprehensive understanding of the subject matter. It is important to review the intricate interplay of these factors, as current evidence suggests, emphasising the urgent need for coordinated mitigation strategies to address the multifaceted challenges posed by antimicrobial resistance. This review provides insight on fostering interdisciplinary research which is critical for elucidating the intricate pathways of resistance transmission and for developing innovative interventions against antimicrobial resistance. The urgency of implementing coordinated and holistic mitigation strategies cannot be overstated, as the consequences of inaction extend beyond individual health sectors to encompass the broader fabric of global health security.

Keywords: antimicrobial resistance; antimicrobials; global health; multi-drug resistant pathogens; one health; resistant genes.

Highlights

1. Antimicrobial resistance is an escalating global health threat.

2. Water and soil are key in spreading antimicrobial resistant genes.

3. Antibiotic-resistant genes underscore the importance of a unified 'One Health' approach.

4. Understanding the links between human, animal, and environmental health is crucial in tackling antimicrobial resistance.

5. Interdisciplinary research is key for developing effective interventions.

INTRODUCTION

Antimicrobial resistance (AMR) is the process by which a microbe evolves and acquires increased or complete resistance to an antimicrobial agent to which it was formerly sensitive to (Fletcher 2015). Antimicrobial-resistant infections, sometimes known as "superbugs," which include virulent pathogen species that have developed resistance to antibiotics, antifungals, antivirals, antimalarials, and anthelmintics limit the effectiveness of antimicrobials for treating infectious diseases in human populations (Ukuhor 2021). The indiscriminate use of antimicrobials in clinical fields of human and veterinary medicine for treatment, prophylaxis and to improve productivity (livestock industry) have been implicated as the drivers of AMR emergence (Samreen *et al*. 2021). These resistant bacteria strains such as *Campylobacter*, *Salmonella*, *Escherichia coli*, can be transmitted between humans, animal and the environment for example, in wild animal-human setting as well as between livestock-environment setting such as in aquaculture (Lepper *et al*. 2022). AMR which is particularly relevant in the clinical field (Salam *et al*. 2023), has been observed in the cases of nosocomial infections (Healthcare-Associated Infections or HAIs), where there have been reports of transmission of infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) among hospital patients admitted for the treatment of other ailments (Huang *et al*. 2019), with the current resistance to first-line antibiotics being approximately 26% for bacterial infections affecting humans (Rhouma *et al*. 2022). Treating diseases like Human Immunodeficiency Virus (HIV)/acquired immunodeficiency syndrome (AIDS), bacillary dysentery, acute respiratory infections, tuberculosis, malaria, and sexually transmitted infections is becoming more expensive and difficult as they become resistant. Furthermore, AMR pose a threat to life-saving medical procedures like organ transplants that depend on antibiotics to avoid surgical site infections (Ukuhor 2021). Antimicrobial resistance patterns have also been observed in nonbacterial infections such as in fungal infections where *Candida glabrata*, *C. krusei*, and *C. lusitanae* have intrinsic resistance to some antifungal drugs, whereas *C. auris*, an emerging pathogen, has the potential to be resistant to multiple drugs (Morrison & Zembower 2020). The problem of resistant viruses is also reported and a well-documented phenomenon among people living with HIV (Morrison & Zembower 2020).

Bacterial resistance develops naturally, either through mutation or the acquisition of new resistant genes via genetic exchange mechanisms (Samreen *et al*. 2021). Mobile genetic elements such as plasmids, integrases, and transposases inherent in the resistant bacteria facilitates horizontal gene transfer (HGT) between different bacterial species therefore, HGT plays a significant role in the spread of AMR (Ma *et al*. 2021). Antibiotic-resistant microorganisms can spread to humans through the food chain, direct contact with animals, and wastewater discharge from farms, hospitals, and pharmaceutical facilities (Samreen *et al*. 2021). Gastrointestinal endoscopic procedures involving the use of duodenoscopes occasionally serve as portal of entry of microbes with reports of antimicrobial resistant pathogens including bacteria such as *Helicobacter pylori*, *Methylobacterium mesophilicum*; viruses including both hepatitis B, hepatitis C; the fungi, *Trichosporon asahii*; and the parasite, *Strongyloides stercoralis* among patients undergoing duodenoscopy (Morrison & Zembower 2020). Antimicrobial resistance is a multifaceted, intricately linked problem with many elements (Prestinaci *et* *al*. 2015).

Recent advances in research studies have highlighted the critical role of the environment, humans, and animals in the development of AMR. Livestock have been recognised as a major contributor to the spread of resistant bacteria to humans and the environment although data from recent studies indicates their contribution may be lower than initially estimated (Rhouma *et al*. 2022). Livestock faecal matter used as organic manure in agricultural systems are source of antimicrobial resistant genes (ARGs) as they may contain AMR pathogens including bacteria, fungi that can contaminate food and water, leading to foodborne and waterborne illnesses (Graham *et al*. 2019). The use of antibiotics in animal production over a period of time results in the development of drug-resistant strains in the animal (Manyi-Loh *et al*. 2018). Wildlife ecosystems possess considerable potential as repositories of anti-microbial resistant organisms (AROs) and ARGs (Samreen *et al*. 2021). Some species, such as *Escherichia coli* are drug-resistant, with several isolates demonstrating plasmid-mediated resistance in wildlife (van den Honert *et al*. 2021). Such resistance may have evolved from the environmental dissemination of antibiotics used by livestock and humans (Furness *et al*. 2017). Zoonotic diseases also aid in the transmission of resistant bacteria between animals and human (Lepper *et al*. 2022).

The contribution of the environment to the emergence of AMR has been highlighted by various studies through possible transmission routes of resistant pathogens from human and agricultural waste effluents into natural water bodies and soil (Lepper *et al*. 2022). Although antibiotic misuse and overuse are the primary causes of antimicrobial resistance (AMR), there is strong evidence that other non-use variables such as pollution and inadequate local sanitation, with the natural environment acting as a large conduit, also contribute to the rising worldwide issue of AMR (Prestinaci *et al*. 2015). Mitigation strategies at the human-animal-environment interface requires implementation of the One Health approach as an effective tool for the management of AMR and its impact on the global healthcare system (Rhouma *et al*. 2022). Guidelines regarding the use of antibiotics in humans and food animals are critical aspects of a One Health strategy to tackle AMR, there is a need for a more comprehensive approach that incorporates wildlife, aquaculture, and the environment in particular (Velazquez-Meza *et al*. 2022). The objective of this review is to highlight the seemingly unending global threat of AMR, environmental drivers involving the interaction of man, animal, environment and the role of One Health approach for the better understanding and bridging the gap between the menace caused by AMR with public health.

Antimicrobial resistance and its significance in global health

There is an increasing concern about AMR as it significantly impacts global economy and healthcare owing to easy purchase of unprescribed antimicrobials over the counter in developing and developed countries, heightened demand for food from animals due to the growing human populations, increased trade and globalisation (Samreen *et al*. 2021). AMR is a severe threat to global health security (Prestinaci *et al*. 2015). The rise in fungal resistance to last-resort antimicrobial drugs such the echinocandins (caspofungin, anidulafungin, and micafungin) is becoming a concerning issue globally (Sekyere & Asante 2018). Excessive and inappropriate use of antimicrobials in food production and human medicine leads to an annual global mortality toll of over 700,000 due to resistant infections; if action is not taken to curb AMR, there could be as many as 10 million deaths by 2050, surpassing the death toll from cancer (Samreen *et al*. 2021; Adebisi & Ogunkola 2023). The threat caused by the escalation of antibiotic-resistant infections speculates about 10 million lives being lost, costing a total of $100 trillion globally in economic output if this trend continues until 2050 (Nwobodo *et al*. 2022). Millions of lives are lost to AMR every year, and it is predicted that this will result in an exponential rise in patient sickness and death worldwide (Dadgostar 2019). There has also been a correlation shown between bacterial resistance coinfections and severe acute respiratory syndrome coronavirus 1 (SARS), middle east respiratory syndrome (MERS), and severe acute respiratory syndrome coronavirus 2 (COVID-19) as studies have reported that mortality from these infections is due to secondary bacterial and fungal infections some of which are resistant to antibiotics and antifungals respectively (Ukuhor 2021).

Genetic mutations that offer resistance to pathogens can potentially spread into very fatal pandemics in an increasingly interconnected and globalised world (Salam *et al*. 2023). AMR continues to be one of the world's most pressing, deadly, and complicated health concerns due to its growing pandemic potential, huge costs to people and the economy, and complex nature (Prestinaci *et al*. 2015). Over the past century, antimicrobials have been instrumental in achieving major progress in global health; nevertheless, the advent of antimicrobial resistance (AMR) demands the adoption of global health legislation to ensure this progress is maintained (Coque *et al*. 2023). Although each antimicrobial drug is beneficial to the treatment of specific infections, it is paradoxical that their use has the potential to deplete the global stock of potent antimicrobial agents resulting in antibiotic resistance (Li *et al*. 2017). High levels of antibiotic use, critically ill patients, and a continuous invasion by pathogenic microbes in the healthcare setting facilitates the spread of resistant pathogens and the horizontal transfer of resistance genes, which in turn promotes antimicrobial resistance development (Ukuhor 2021). The global aim of ensuring that everyone has access to efficient antimicrobial treatments is jeopardised by the declining efficacy of present antimicrobials as a result of AMR (Dadgostar 2019). To attain this common objective, wherein antimicrobials remain effective for everyone (non-excludable) and their effectiveness is largely unaffected by individual usage (not highly competitive), it is imperative to safeguard the existing antimicrobial supply, increase its accessibility through creative approaches, and guarantee equitable access to antimicrobials for individuals in all areas and nations (Prestinaci *et al*. 2015; Li *et al*. 2017; Serwecińska 2020). The proliferation of AMR, which impacts humans, animals, agriculture, and the environment, has necessitated a unified "One Health" approach that demand international cooperation and coordination (White & Hughes 2019).

The One Health approach

The Food and Agriculture Organisation of the United Nations (FAO), the World Organisation for Animal Health (formerly OIE), the World Health Organisation (WHO), and the United Nations Environment Programme (UNEP) (tripartite and UNEP) have recently defined the One Health approach as "an integrated, unifying approach that aims to sustainably balance and optimise the health of people, animals, and ecosystems" (Rhouma *et al*. 2022). One Health is a theoretical framework and methodological approach that fosters cooperation among diverse stakeholders in the development and execution of programs, regulations, legislation, and studies with the goal of enhancing public health outcomes via improved cooperation and communication (Mackenzie & Jeggo 2019). The concept of One Health approach is well suited to tackle the problems of antibiotic resistance, food safety, and zoonotic diseases (Velazquez-Meza *et al*. 2022). One Health necessitates the coordinated efforts of multiple health science professions working at the local, national, and international levels in conjunction with their related fields and institutions in order to achieve effective health outcomes for people, domestic animals, wildlife, plants, and the environment (Prata *et al*. 2022). One Health approach has been recognised by the FAO, OIE and WHO as an essential component of disease control and prevention (Mackenzie & Jeggo 2019). The One Health concept has received support from national organisations and professional groups in numerous fields across various nations (Rabinowitz *et al*. 2013).

The increasing implications of AMR impede attempts to achieve sustainable development, so it is necessary that global communities unite in a determined effort to maintain ongoing access to antimicrobial drugs in order to increase their effectiveness for the benefit of the world population (Jasovský *et al*. 2016). National action plans (NAPs) involving multisectoral regional and international programmes and policy initiatives, in line with a One Health approach and the global action plan on antimicrobial resistance, with the goal of implementing national measures for strengthening appropriate use of antibiotics in humans and animals have been implemented in approximately 178 countries worldwide (WHO 2023). currently, One Health approach to tackle AMR is to reduce antibiotic usage in livestock as growth promoters and use antimicrobials only for treatment, and rarely for prophylaxis (Velazquez-Meza *et al*. 2022), preventing the transmission of resistant bacteria and preserve the efficiency of antibiotics (Rhouma *et al*. 2022).

Antimicrobial resistance transmission across species

AMR transmission across species is a serious concern in the fields of public health and veterinary medicine (Prestinaci *et al*. 2015). Approximately 75% of antimicrobials administered to farm animals are excreted through faeces or urine, potentially contaminating the surrounding farm environment, agricultural lands, and runoff following manure application as fertiliser for growing agricultural crops (Rhouma *et al*. 2022). Furthermore, the transmission of resistant bacteria between species occurs through various pathways, including direct contact between human and animals, manure application in soil, wastewater and the use of antimicrobial agents in agriculture (Graham *et al*. 2019). Primary and secondary antifungal drug resistance mechanisms might be innate or acquired, lowering intracellular drug levels or interfering with drug activity at drug target locations. For instance, target-site changes brought about by point mutations mediate yeast resistance to echinocandins

(Sekyere & Asante 2018). Antibiotic-resistant bacteria can also be transmissible between animals, humans, and the environment as livestock may serve as reservoirs (Serwecińska 2020). People can be exposed to diverse fungal airborne spores known as bioaerosols, which are produced by opportunistic pathogenic fungi that are frequently found in our close environment (Fisher *et al*. 2022).

The interconnectedness of human, animal, and environmental health highlights the transmission of AMR across species, emphasising the intricate relationships between these domains and the need for joint efforts to combat AMR (Singh *et al*. 2021). ARGs results from either gene mutations or gene recombination (Chen *et al*. 2023). Recent studies have shown that non-antibiotic compounds such as prescription drugs, over the counter drugs, feed additives, artificial sweeteners, pharmaceuticals and other environmental pollutants can also facilitate the transfer of ARGs through conjugation using self-transmissible plasmids which are shared amongst bacteria (Alav & Buckner 2023). HGT plays a significant role in the transfer of resistant bacteria such as in the exchange of tetracycline resistance genes between human MRSA and canine methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), indicating cross-species antimicrobial resistance gene transfer (Frosini *et al*. 2020). ARGs poses a serious threat to public health as there are now limited treatment options due to reports of bacteria carrying transmissible plasmids such as *mcr* variants, $bla_{\text{NDM-1}}$, *tet*(X4), which confer resistance to a wide variety of antibiotics (Alav & Buckner 2023). ARGs which are widely present in soil following environmental contamination can be transmitted to leaves and roots of plants either as endogenous or exogenous ARGs, allowing these plant microbiomes especially rhizosphere microorganisms to spread in the ecosystem and enter the food chain posing a threat to human health after these bacteria gain entry to the human body (Chen *et al*. 2023). According to Mboowa *et al*. (2021), AMR acquisition and transmission occurs primarily in human-human interface than in human-environment interface most especially within and outside health care settings where index patients admitted into a hospital ward in Uganda acquired antimicrobial resistant bacteria (ARB) within 24 hours of admission and other in-contact individuals with the index patients tested positive for ARB within 72 hours at most. To reduce AMR transmission across species, there is a growing consensus on the significance of reducing the transmission of resistant bacteria via the environment to humans (Lepper *et al*. 2022), prudent use of antimicrobials in both human and veterinary medicine (Samreen *et al*. 2021). This involves promoting responsible antibiotic prescribing practices, boosting surveillance of antibiotic usage and resistance, and strengthening biosecurity measures in agricultural settings (Manyi-Loh *et al*. 2018). Furthermore, fostering interdisciplinary collaboration among healthcare professionals, veterinarians, environmental scientists, and policymakers is essential in developing and implementing comprehensive strategies that address the complex dynamics of AMR transmission across species (Mudenda *et al*. 2023).

Environmental reservoirs and drivers of AMR

The emergence and dissemination of antimicrobial resistance are significantly influenced by environmental factors (Fletcher 2015). One significant mechanism is the natural selection of antibiotic-resistant microorganisms in environmental reservoirs such as soil and water (Munita & Arias 2016). Antibiotics are released into the environment through a variety of channels, such as pharmaceutical waste, agricultural runoff, or inappropriate waste disposal, creating a selection pressure which helps resistant microorganisms survive. (Manyi-Loh *et al*. 2018; Samreen *et al*. 2021). These resistant strains have the ability to persist in the environment, transferring resistance genes to other microorganisms, and possibly even pass these genes on to diseases that can infect people and animals (Larsson & Flach 2022). Additionally, resistant bacteria can spread between various ecosystems and species through the environment (Djordjevic *et al*. 2013). Water bodies can carry antibiotic-resistant bacteria over great distances (Kusi *et al*. 2022). AMR can spread to new geographical areas, for instance, when migratory birds, fish, or even the wind carry resistant bacteria from contaminated water (Manyi-Loh *et al*. 2018; Kusi *et al*. 2022). Fungal AMR is rapidly increasing due to widespread use of fungicides in agriculture e.g., azole-resistant *Aspergillus fumigatus*, with some of these effects being clinically significant (Fisher *et al*. 2022).

Pharmaceutical, agricultural, and human waste all have a substantial impact on environmental contamination (Malmqvist *et al*. 2023). Pharmaceutical waste results from the improper disposal of expired or unused drugs, heavy metals and other chemical compounds including their residues, which can contaminate water supplies or when disposed in landfills (Karungamye *et al*. 2022; Waleng & Nomngong 2022). The environmental persistence of these medications may result in unanticipated ecological effects, such as the emergence of bacteria resistant to antibiotics and the disruption of aquatic environments (Felis *et al*. 2020).

Pesticides, fertilisers, and antibiotics are used in agriculture, which contributes significantly to environmental contamination (Manyi-Loh *et al*. 2018). Fertilisers and pesticides that leak from fields into bodies of water can pollute water bodies and disturb the soil biota (Bashir *et al*. 2020). Applying manure as fertiliser can cause antibiotic-resistant bacteria to arise as a result of overuse of antibiotics in agriculture (Manyi-Loh *et a*l. 2018). These resistant bacteria have the ability to remain in water and soil, which could be dangerous for human and environmental health (Samreen *et al*. 2021). Untreated human waste can also contaminate water sources, causing a public health hazard (Lin *et al*. 2022). As a result, the combined effects of human, agricultural, and pharmaceutical waste highlight the urgent need for better waste management techniques and long-term strategies to reduce environmental pollution (Rayan 2023). This interrelation between environmental compartments underscores the importance of a One Health approach that recognises the interplay between human health, animal health, and the environment in addressing the complex challenge of AMR (Mackenzie & Jeggo 2019). Mitigating AMR requires efforts to reduce environmental contamination with antibiotics, enhance surveillance of resistant bacteria in natural settings, and promote responsible practices in agriculture, healthcare, and waste management to limit the environmental drivers of resistant genes (Manyi-Loh *et al*. 2018; Samreen *et al*. 2021).

AMR surveillance and data sharing

AMR surveillance provides valuable data to guide public health policies and interventions (Prestinaci *et al*. 2015). In order to promptly adjust treatment and control measures, surveillance is necessary for the early detection of growing resistance patterns in the veterinary and healthcare systems (Tambo *et al*. 2014). This early warning system is critical for ensuring that effective antibiotics are available to treat bacterial illnesses, therefore maintaining public health (Salam *et al*. 2023). Additionally, Authorities can make decisions on the use of antibiotics, antibiotic stewardship programs, and infection control measures with the help of monitoring trends in resistance among different bacterial species across different geographical regions (Johnson 2015). Surveillance in animal husbandry helps ensure that antibiotics are used responsibly in veterinary care and agriculture, lowering the possibility that humans will come into contact with resistant bacteria through the food chain (Ma *et al*. 2021).

The goal of addressing antibiotic resistance holistically is facilitated by AMR surveillance, which encourages cooperation between the animal and human health sectors (Prestinaci *et al*. 2015). Since many antibiotics are used in both animal husbandry and human healthcare, a coordinated strategy is essential to preventing the emergence and spread of resistant bacterial strains in these interrelated fields (Cella *et al*. 2023). Through the development of innovative treatment options to lower the risk of AMR, surveillance data can support research into the underlying causes of AMR (Ashley *et al*. 2019). Maintaining an edge on resistance trends and modifying tactics appropriately need regular data collecting and analysis (Giamarellou *et al*. 2023). According to Velazquez-mela *et al*. (2022), addressing AMR problems requires coordinated data sharing amongst environmental, veterinary, and healthcare organisations. Despite challenges like data privacy, compatibility, legal barriers, and resource allocation, the benefits are significant (Brous *et al*. 2020). Early detection and response to AMR trends (Iskandar *et al*. 2021), advancements in AMR research, comprehensive models for understanding various AMR sources and transmission pathways are informed decision-making tools for policymakers and healthcare providers (Samreen *et al*. 2021). Overall, overcoming these challenges and establishing secure, standardised data-sharing mechanisms is crucial for effectively combating AMR on a global scale (Pokharel *et al*. 2019).

According to (WHO 2021), the Centre for Disease Control and Prevention (CDC) in the United States' Antibiotic Resistance (AR) lab network is one of the successful surveillance programs that has shown the value of tracking and combating AMR. A pilot *Candida* monitoring program was initiated in 2018 by the WHO to collect historical data on antifungal resistance in isolates of invasive *Candida* isolates (Fisher *et al*. 2022). In order to monitor and track trends in resistance, a network of reference labs and regional and state public health labs gathers and examines clinical specimens (Iskandar *et al*. 2021). This programme has helped identify growing resistance trends, guide treatment options, and implement effective control measures. (Uddin *et al*. 2021). These successful surveillance programmes such as The World Health Organisation Global Antimicrobial Resistance Surveillance System (GLASS), Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP), The Antimicrobial Resistance Surveillance in Animals Program (ARSAP) - Australia demonstrate the necessity

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of gathering and sharing data in combating AMR successfully. (WHO 2021).

Advancements in AMR research

Collaborative research efforts to combat AMR have gained significant momentum in recent years, as the rise of drug-resistant pathogen poses a growing threat to global public health (Salam *et al*. 2023). One crucial aspect of these efforts involves the development of novel therapeutic agents and other therapeutic alternatives (Dutescu & Hillier 2021). Real-world studies involving the use of therapeutic drug monitoring to explore the pharmacokinetics of antifungal drugs is necessary to minimize side effects while decreasing the development of antifungal resistance and to balance therapeutic potential and dosage optimization (Fisher *et al*. 2022). Certain plant-derived compounds including alkaloids, polyphenolics, anti-virulence drugs, bacteriocins, typically Nisin which is produced by certain species of *Lactococcus* and *Streptococcus* have all been found by researchers as promising alternatives to antibiotics with great potential of combating AMR (Salam *et al*. 2023). Novel research which involves the introduction of new vaccines may help to prevent infections thus minimising antibiotic use, for example, pneumococcal conjugate vaccines have played a vital role in reducing resistant *Streptococcus pneumoniae* infection (Prestinaci *et al*. 2015). Many pharmaceutical companies, academic institutions, and governmental organisations are coming together to invest in the discovery and development of novel antibiotics that can effectively treat infections caused by resistant pathogens (Bradley *et al*. 2007). These collaborations often include interdisciplinary teams of microbiologists, chemists, and bioinformaticians who work together to identify promising drug candidates and study their mechanisms of action (Madhu *et al*. 2022). In addition to new antibiotics, researchers are exploring alternative treatments to address AMR (Gupta & Sharma 2022). Recent advancements in investigating the potential of phage therapy, which utilises bacteriophages to target and kill specific bacterial strains is a viable alternative in treating infections caused by antibiotic-resistant bacterial strains (Lin *et al*. 2017). Moreover, there is growing interest in harnessing the power of the human immune system to combat infections, with collaborative studies between immunologists, geneticists, and clinicians to develop innovative immunotherapies and vaccines (Pulendran & Davis 2020). Non-peptide organic molecules, probiotics, prebiotics, antimicrobial peptides, nanoparticles, organic acids, essential oils, faecal microbial transplant, use of quorum sensing/antivirulence inhibitors have been employed in various research studies and are considered as part of novel strategies which are effective against multi-drug resistant bacteria (Helmy *et al*. 2023). Additionally, the use of artificial intelligence (AI) and machine learning in AMR research has revolutionised the ability to predict resistance patterns and aid novel antibiotics discovery (Melo *et al*. 2021). These technologies, are useful to data scientists and biologists to enable both professionals in the analysis of vast data sets to uncover insights that were previously challenging to obtain (Aldoseri *et al*. 2023). The use of AI and machine learning enhances diagnostic tools giving rapid and reliable diagnosis, identification of various resistant bacteria trends and optimising the best treatment approach in order to strengthen traditional antibiotic stewardship, thus addressing the crisis caused by AMR (Ahmed *et al*. 2024).

Furthermore, innovative solutions to combat AMR extend beyond just the development of new treatments (Salam *et al*. 2023). Collaborative efforts are also focused on improving antimicrobial stewardship practices and raising awareness about responsible antibiotic use among healthcare providers and the general public (Khadse *et al*. 2023). Recent advances in research involving AMR hold significant promise for coordinated mitigation strategies (Majumder *et al*. 2020) One major breakthrough is the development of new diagnostics that enable rapid and precise identification of drug-resistant pathogens such as technologies which apply nucleic acid amplification, whole genome sequencing, hybridisation, immunodiagnostic and mass spectrometry-based methods and biosensor-based antibiotic susceptibility testing (Vasala *et al*. 2020). These diagnostics, often based on genomics and metagenomics, provide healthcare practitioners with essential information to make informed treatment decisions (Gaston 2023). Such advancements can help prevent unnecessary antibiotic use and limit the spread of resistance (Lee *et al*. 2013). Innovations in areas of biomedical science allows for rapid laboratory AMR surveillance and epidemiology aiding a clear understanding of novel antibiotic resistance mechanisms through whole genome sequencing (Tang *et al*. 2023).

Another promising area of research involves the repurposing of existing drugs to combat resistant infections (Liu *et al*. 2021). This approach often relies on interdisciplinary collaborations between pharmacologists, clinicians, and computational biologists to identify existing compounds with the potential to overcome drug-resistant mechanisms (Farha & Brown 2019). By leveraging the extensive knowledge of drug libraries and combining it with cutting-edge computational methods, researchers are exploring novel treatment options (Vora *et al.* 2023). This not only offers an efficient way to address AMR but also has the potential to reduce the time and resources required for drug development, enabling more rapid responses to emerging resistance threats (Salam *et al*. 2023). By understanding resistance mechanisms at a molecular level, researchers can design more effective drugs and develop strategies to prolong the efficacy of existing antibiotics (Muteeb *et al*. 2023). These technological advancements are vital for creating coordinated mitigation strategies that can adapt to the evolving landscape of AMR (Prestinaci *et al*. 2015; Joshi *et al*. 2021). Ultimately, the potential impact of these recent advances in research lies in our ability to develop more targeted, efficient, and sustainable approaches to combat antimicrobial resistance on a global scale (Samreen *et al*. 2021; Uddin *et al*. 2021).

Antimicrobial stewardship and responsible use

Antibiotic stewardship is a comprehensive collection of methods and techniques used to encourage the prudent and responsible use of antibiotics in medical settings (Ha *et al*. 2019). The primary goal is to decrease the emergence and spread of antibiotic resistance while simultaneously improving patient outcomes (Khadse *et al*. 2023). Antibiotic stewardship programmes involve guidelines, education, and monitoring which are implemented in healthcare settings to ensure that antibiotics are only prescribed when clinically indicated (Chukwu *et al*. 2021). A multidisciplinary approach invoving collaboration is used by healthcare professionals in order to make well-informed judgments regarding prescribing antibiotics (MacDougall & Polk 2005). Additionally, in order to guarantee that antibiotic therapy remains necessary, they also promote periodic reviews (Khadse *et al*. 2023). Healthcare professionals should also adopt antifungal stewardship programmes including improved diagnosis of antifungal resistance such that only novel antifungal drugs meant for clinical use are used in treating at-risk individuals in order to limit future emergence of antifungal resistance (Fisher *et al*. 2022). Healthcare practitioners are also educated by stewardship programmes about the dangers of AMR and the significance of using antibiotics responsibly (Adebisi 2023).

Healthcare workers play a critical role in ethical antibiotic prescribing practices (Jimmy & Jose 2011). This entails following established rules and prudently prescribing antibiotics based on reliable diagnoses (Calvo-Villamañán *et al*. 2023). As a result, while prescribing antibiotics, medical professionals need to use caution and take into account the patient's medical history, the particular pathogen, and the possibility of side effects (Llor & Bjerrum 2014). Promoting antimicrobial stewardship initiatives within healthcare facilities is greatly facilitated by healthcare personnel (Chukwu *et al*. 2021). These initiatives are focused on maximising the use of antibiotics to enhance patient outcomes and reduce resistance (Khadse *et al*. 2023). By actively taking part in these initiatives, medical professionals can work with interdisciplinary teams to create and enforce guidelines for the responsible use of antibiotics, monitor prescription practices, and inform colleagues on how antimicrobial resistance is changing. (Chukwu *et al*. 2021). By implementing these concerted efforts, medical practitioners prescribe with caution and based on evidence, significantly extending the longevity of antimicrobial effectiveness and protecting healthcare from the threat of antimicrobial resistance in the future (Majumder *et al*. 2020).

Antibiotic stewardship programmes address the overuse and misuse of antibiotics (Llor & Bjerrum 2014). This misuse creates selective pressure, which results in the development of antibiotic-resistant bacteria (Uddin *et al*. 2021). Programmes for antibiotic stewardship also encourage the use of narrow-spectrum antibiotics and the use of the right medication for the right infection (Hand 2013). Healthcare practitioners can lessen antibiotic resistance by choosing the antibiotic that is most effective for a given infection (Lee *et al*. 2013). Additionally, stewardship programmes emphasise the appropriate course of treatment to avoid unnecessarily using antibiotics (Srinivasan 2017). Additionally, these programmes support AMR surveillance and monitoring (Khadse *et al*. 2023). They monitor and track resistance patterns to identify emerging problems and adjust treatment regimens accordingly (Ha *et al*. 2019).

Due to the substantial effect of antibiotics on food safety, the environment, and public health, it is crucial to use it responsibly in human healthcare and agriculture (Manyi-Loh *et al*. 2018). Appropriate diagnosis, prescription of the right antibiotic for the particular infection, and maintenance of appropriate dosage and length of therapy are all components of responsible antibiotic usage in healthcare. (Ha *et al*. 2019). It also includes improving hygiene and infection control techniques to reduce the transmission of infections, hence minimising the need for antibiotics (Manyi-Loh *et al*. 2018). Antimicrobials are used in livestock production for varying purposes including therapeutic (to treat sick animals), prophylaxis (to prevent infection), metaphylaxis (treat infected animals within the same group as healthy animals) and as feed additives (growth promoter) of which some of these antimicrobials are categorised as medically important for human medicine (Rhouma *et al*. 2022). Adhering to withdrawal periods to avoid antibiotic residues in food products and using antibiotics sparingly are key components of responsible antibiotic use in agriculture (Manyi-Loh *et al*. 2018). This practice guarantees food safety by preventing the transmission of antibiotic-resistant bacteria to humans through the food chain when these animal products are consumed (Endale *et al*. 2023). Other essential components of appropriate antibiotic usage for varied agricultural purposes are sustainable farming techniques that prioritise animal health and welfare while minimising antibiotic use (Manyi-Loh *et al*. 2018). It is essential to employ a multifaceted approach that incorporates public education, healthcare practices, and regulatory actions to encourage the prudent use of antibiotics (Alam *et al*. 2023). These measures work together to reduce antibiotic overuse, lessen bacterial selection pressure, and boost the potency of these life-saving medications (Uddin *et al*. 2021).

Public education and awareness

A crucial component of raising public knowledge is teaching people how to take antibiotics appropriately (Matthew *et al*. 2019). Public education regarding the safe use of antibiotics is essential to the prevention of AMR since it influences behavior and encourages responsible use of antibiotics (Chukwu *et al*. 2020). Many individuals especially in areas where antibiotics are easily accessible in the open market are unaware of the consequences of overusing or misusing antibiotics, including the development of drug-resistant bacteria (Llor & Bjerrum 2014). Public education enlightens people and advocates for greater support in the fight against AMR (Matthew *et al*. 2019). Campaigns for public health can educate people on the difference between viral and bacterial infections, highlighting the fact that antibiotics are not effective against the latter (Khoshgoftar *et al*. 2021). Furthermore, public awareness campaigns can educate people to understand the importance of hand hygiene, vaccination, and other preventive measures, which can help prevent the spread of diseases, thus reducing the overall demand for antibiotics (Leal *et al*. 2022).

Raising public awareness is a crucial component of a multi-faceted strategy to mitigate AMR, as it empowers individuals to make informed decisions about their health and contributes to the collective effort to preserve antibiotics efficacy for future generations (Matthew *et al*. 2019; Majumder *et al*. 2020). Patients can also be encouraged to complete their antibiotic treatment as recommended and to never share or save medications for later use (Chukwu *et al*. 2020). Additionally, public awareness can foster support for policy changes and increased research funding to address AMR comprehensively (Majumder *et al*. 2020). Healthcare professionals play a crucial role in patient education regarding the responsible use of antimicrobial resistant drugs (Prestinaci *et al*. 2015). As frontline health workers, they are responsible for conveying essential information about the nature of antibiotics, the importance of completing prescribed treatment, and the potential consequences of antibiotic misuse or abuse (Adebisi 2023). By fostering a patient-centered approach, healthcare professionals can empower individuals to make informed decisions about their general well-being and public health (Muteeb *et al*. 2023). Effective communication between healthcare providers and patients is key to ensuring that patients understand the necessity of following prescribed regimens, abstaining from self-medication, and appreciating the consequences of antibiotic resistance (Rather *et al*. 2017).

Public awareness campaigns such as "World Antibiotic Awareness Week" organised by the WHO on AMR have been adopted globally to address the growing problem of antibiotic abuse and the development of antibiotic resistance (WHO 2023). AMR has also been addressed in large part through educational programs, with academic institutions and medical colleges incorporating AMR into their curricula to guarantee that future healthcare professionals are knowledgeable enough and prepared to handle the global health threat caused by AMR (Fuller *et al*. 2023). Various organisations and health agencies have developed educational programmes and trainings targeting healthcare practitioners, students, and the general public (Alderwick *et al*. 2021). These programmes frequently concentrate on raising awareness of the negative effects of antibiotic abuse, appropriate prescription procedures, and the roles that individuals can play in preventing the spread of microorganisms that are resistant to antibiotics (WHO 2023). Collaboration between governments, pharmaceutical firms, healthcare providers, and non-governmental organizations has been crucial to the accomplishment of numerous campaigns and action plan against AMR (Alderwick *et al*. 2021). Sustaining success and reducing the long-term effects of antibiotic resistance on public health will require a persistent commitment to public education and awareness (Majumder *et al*. 2020; Chukwu *et al*. 2021).

Regulatory policies and incentives

Governments can encourage the prudent use of antibiotics by enacting laws and providing incentives (Rogers Van Katwyk *et al*. 2019). This includes instituting prescription-only practices, limiting the amount of antibiotics sold over-the-counter, and creating standards for healthcare professionals (Al-Jedai *et al*. 2022). Additionally, these regulations might encourage pharmaceutical industry to concentrate on tackling the AMR problem by fostering research and development of novel antibiotics and alternatives to already existing drugs (Muteeb *et al*. 2023). Investment in creative solutions can also be encouraged by monetary rewards and market-based strategies like prizes and awards for antibiotic development (Dutescu & Hillier 2021).

Global cooperation and policy initiatives

AMR has no geographical borders as resistant bacteria and genes can spread throughout the world due to globalisation, travel and trade (Prestinaci *et al*. 2015; Samreen *et al*. 2021). Consequently, in order to effectively monitor and control the development of resistant diseases, international collaboration is essential in order to stay ahead of any evolving threat due to AMR through data sharing on resistance patterns, best strategies in antimicrobial stewardship programmes and combined surveillance efforts (Cella *et al*. 2023). In addition, international collaboration is also vital in the development of new antibiotics and alternative treatments (Muteeb *et al*. 2023). The process of developing new drugs is costly and time-consuming, and would require combined efforts (Padhy & Gupta 2011). Collaboration among governments, educational institutions, pharmaceutical firms, and funding bodies can help to share information, pool resources, and hasten the development of new treatments for infections resistant to drugs (Miethke *et al*. 2021).

Additionally, global alliances can guarantee fair access to novel antibiotic-resistant therapies, enabling individuals in any area, irrespective of their financial status, to obtain them (Bhatt & Bathija 2018). The creation and execution of coordinated initiatives to lessen the effects of AMR are made possible by international collaboration, which provides a united front against this global public health issue. (Hoffman & Behdinan 2015). Policymakers and regulatory bodies have acknowledged the pressing need to combat AMR at both the national and international levels (Prestinaci *et al*. 2015; WHO 2023). Various strategies have been put in place by national governments to address AMR locally (WHO 2023). These strategies frequently include creation and implementation of laws to encourage the prudent use of antibiotics in medical care and agriculture, improving surveillance systems to track trends in resistance, and supporting public awareness campaigns (Prestinaci *et al*. 2015). For instance, antibiotic stewardship programmes are implemented in many nations' healthcare establishments to ensure antibiotics are used sparingly and only when necessary (Chukwu *et al*. 2021; Khadse *et al*. 2023).

At the international level, organisations like WHO, FAO, OIE have been engaged in several activities to combat AMR. These organisations have developed global action plans and recommendations to help member nations fight antimicrobial resistance (AMR) in a comprehensive manner (WHO 2023). The WHO's global leadership and experience are crucial in raising awareness and encouraging cooperation among governments to solve this critical public health issue (Bornman & Louw 2023). Moreover, antibiotics and other antimicrobial drugs' accessibility may be impacted by international agreements on pharmaceutical trade and restrictions, thereby reducing indiscriminate usage (Dadgostar 2019). Maintaining the efficacy of these life-saving medications requires prudent and uniform regulation at the national and international levels to prevent the emergence and spread of drug resistance (Cella *et al*. 2023).

CONCLUSION

The interplay between human, animal, and environmental health within the context of AMR development necessitates a comprehensive and coordinated approach to mitigate the looming threat. Among other causes, the overuse and misuse of antimicrobials in human healthcare, livestock production, and environmental contamination converge to create a perfect storm, where resistant microbes can proliferate and compromise the effectiveness of crucial medical interventions. Models designed to understudy the interaction of the environment, animals and humans are novel techniques designed to solve the problem of AMR which are also useful in research studies.

In conclusion, the imperative for coordinated mitigation strategies is clear. Urgent international cooperation is necessary to address the transnational threats presented by AMR, adjust to the obstacles it presents, and preserve the common global supply of efficacious antibiotics. This will further pave the way for a more sustainable and resilient future. The collaboration of diverse stakeholders and novel strategies in research is essential to implement effective measures that preserve the efficacy of antimicrobials, protect public health, and ensure the well-being of our planet for generations to come.

Data availability statement

All relevant data are included in the paper.

Conflict of interest

The authors declare that they have no competing interests regarding the authorship, research, and publishing of this review paper.

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Authors' contribution

All authors contributed to the manuscript and gave their consent for the work to be published. Uzoka UH conceptualised the idea of the work. Uzoka UH and Mgbenwelu FC wrote the first draft. Edward IG revised the work. Isiaka AB, Ani NV and Ugwor EI reviewed the work.

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