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Antimicrobial Resistance Mechanisms of Drug-resistant Bacterial Pathogens: A Narrative Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author GS designed the review, collected the literature and prepared the first draft. Authors MM and AL contributed critical analysis, review and editing of the manuscript. Author SS supervised the work and approved the final version of the manuscript. All authors read and approved the final manuscript.

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Review Article

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Abstract

Many antibiotics and other antimicrobial medicines become ineffective due to antimicrobial resistance, which is a serious danger to global health. Numerous bacterial survival tactics, such as the enzymatic breakdown of antibiotics, target site changes, efflux pumps, decreased membrane permeability, and biofilm development, are responsible for this phenomenon. The spread of resistance is accelerated by genetic elements that facilitate horizontal gene transfer, such as

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integrins, transposons, and plasmids. The overuse and abuse of antibiotics in agricultural and human health, inadequate infection control procedures, environmental contamination, and international travel are major causes of antimicrobial resistance. AMR has serious repercussions, including longer illness duration, higher mortality, and a large financial strain on healthcare systems. To combat this crisis, a multifaceted approach is necessary, incorporating novel antimicrobial development, antibiotic stewardship programs, infection prevention strategies, global surveillance, and regulatory interventions. Alternative therapies such as phage therapy, antimicrobial peptides, and microbiome-based treatments offer promising solutions. Additionally, public awareness campaigns and responsible antibiotic use are critical for slowing resistance progression. Governments, medical professionals, researchers, and the general public must work together to combat AMR globally. Designing successful ways to lessen the effects of AMR requires an understanding of its molecular mechanics and causes. AMR poses an existential threat to contemporary medicine since it may usher in a post-antibiotic age in which common infections are incurable without immediate intervention.

Keywords: Antimicrobial resistance; biofilm formation; Efflux pumps; horizontal gene transfer; infection control; multidrug resistance.

1. Introduction

Antimicrobial resistance is a serious hazard to global public health and threatens the effectiveness of contemporary medicine. Morbidity, mortality, and healthcare expenses have gone up as a result of the growth in infections that are extensively and multidrug-resistant. According to recent estimates, bacterial AMR directly caused 1.27 million of the 4.95 million fatalities that occurred globally in 2019 (Gashaw et al., 2025). If effective interventions are not enacted, AMR is projected to lead to as many as 10 million deaths annually by the year 2050. Microorganisms exhibit a variety of complex mechanisms to develop resistance. Major strategies involve the enzymatic breakdown or alteration of antibiotics, changes to target sites, activation of efflux pumps, decreased membrane permeability, and the formation of biofilms. β-lactamases, for example, are produced by bacteria and hydrolyse β-lactam antibiotics, making them useless. Biofilms, which are protective microbial communities, further enhance resistance by providing a physical barrier against antimicrobials and facilitating genetic exchange among bacteria (Wu et al., 2020).

AMR develops and spreads due to a number of causes. The main causes include overuse and abuse of antimicrobials in plants, animals, and people. The selection of resistant strains is encouraged in healthcare settings by improper prescribing practices and patient noncompliance with treatment plans. Antibiotics are used in agriculture to promote cattle growth and prevent sickness, which leads to the development of resistance that can be passed on to people through the food chain. Environmental factors are also important, including the discharge of resistant bacteria and antibiotic residues into water systems from pharmaceutical manufacturing and insufficient wastewater treatment. Addressing the AMR conundrum requires a multifaceted approach (Laxminarayan et al., 2013). The development of new antibiotics and alternative treatments, the establishment of strong antimicrobial stewardship initiatives to guarantee the prudent use of currently marketed medications, and the bolstering of infection prevention and control protocols in public areas and hospitals are some of the tactics. Global monitoring systems are required to monitor resistance patterns and inform policy decisions. In order to implement laws governing the use of antibiotics in agriculture and to further the research and development of novel antimicrobial agents, international cooperation is required. Campaigns to raise public awareness are also essential for teaching communities about the correct use of antibiotics and the need for good hygiene in preventing infections.

Mechanisms of Antimicrobial Resistance: AMR develops through various molecular pathways that enable bacteria to evade the action of antimicrobial agents.

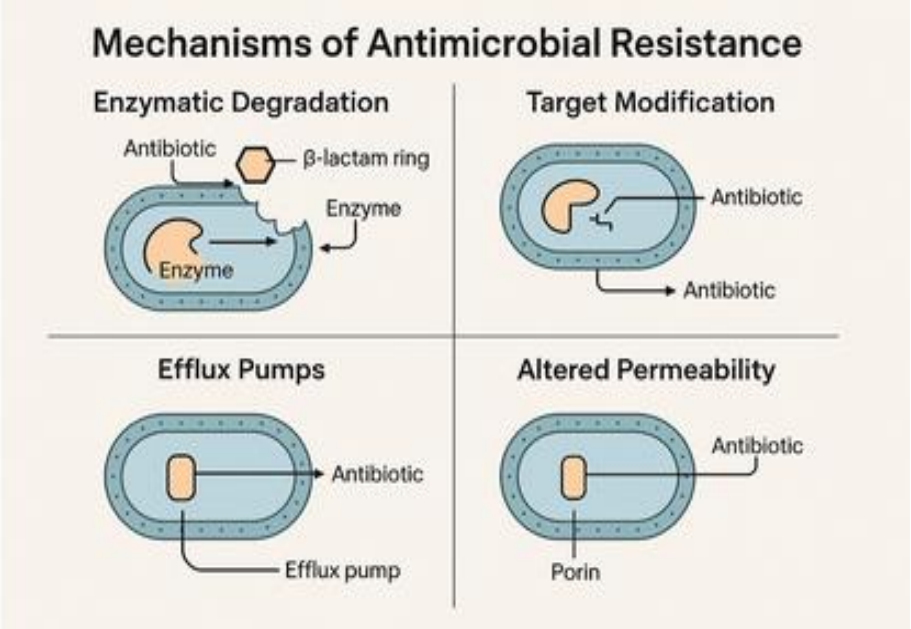

Fig. 1. Overview of antimicrobial resistance mechanisms
(Source: Belay et al., 2024)

Enzymatic Degradation: Bacteria can render antibiotics ineffective by enzymatically degrading them, mainly through the production of β-lactamases that hydrolyse the β-lactam ring. Recent studies have explored innovative approaches to counteract this resistance mechanism, and it could be noted that the zinc-based metal–organic framework (MOF) mimics β-lactamase activity (Raju et al., 2024). This MOF effectively hydrolysed β-lactam antibiotics such as amoxicillin and ceftriaxone, offering insights into potential biomimetic catalysts for antibiotic degradation. An extensive review of β-lactamase enzymes and their inhibitors discussing the structural elements, mutations, and kinetics that contribute to the enzymes' ability to hydrolyse β-lactam antibiotics (Huang & Zhou, 2025; Kang et al., 2024; Zhanel et al., 2024). This thorough examination contributes to our comprehension of the progression of β-lactamase-mediated resistance and guides the creation of potent inhibitors. Such research deepens our insight into the mechanisms of enzymatic degradation and shapes approaches to address antibiotic resistance (Balasubramanian et al., 2021).

Target Modification: Mutations that change penicillin-binding proteins (PBPs) are frequently the cause of bacterial resistance to β-lactam antibiotics, such as methicillin, which decreases the effectiveness of the medications. While *Staphylococcus aureus* acquires the mecA gene, it produces PBP2a, a PBP variation that has a low affinity for β-lactam antibiotics. This allows the bacteria to continue synthesising cell walls even while these antibiotics are present.

Recent studies have further elucidated the mechanisms behind this resistance:

- **Molecular Determinants of β-Lactam Resistance in MRSA**: This study emphasises that high-level β-lactam resistance in Methicillin-resistant *Staphylococcus aureus* (MRSA) depends on a number of genetic variables, including PBP2a, that control cell wall formation, cell signalling pathways, and metabolism (Malar et al., 2020). Comprehending these factors is crucial for creating innovative approaches to fight MRSA infections.
- **Proteomic Changes in MRSA Under Methicillin Stress**: Research indicates that exposure to methicillin leads to increased production of PBP2, suggesting that MRSA can upregulate certain PBPs in response to antibiotic pressure, thereby enhancing its resistance capabilities (Ribeiro et al., 2021). These revelations highlight the intricacy of bacterial antibiotic resistance processes and the necessity of all-encompassing strategies to tackle this worldwide health issue.

Efflux Pumps: Efflux pumps contribute to bacterial pathogenicity, biofilm formation, and

stress-induced survival in addition to providing antibiotic resistance. Techniques to stop these pumps are being researched to improve the efficacy of already available antibiotics. To increase the effectiveness of already available antibiotics, methods to block these pumps are being investigated (Gaurav et al., 2023).

- **ATP-Binding Cassette Superfamily**: Utilises ATP hydrolysis to transport substrates across membranes.
- **Major Facilitator Superfamily**: Transports substrates in response to chemiosmotic ion gradients.
- **Extrusion Family of Multidrug and Toxic Compounds:** Exports drugs using proton or sodium gradients.
- **Cell Division, Nodulation, and Resistance Superfamily:** These pumps, which are mostly present in Gram-negative bacteria, release a variety of antibiotics.
- **Small Multidrug Resistance Family**: Transports lipophilic drugs and quaternary ammonium compounds.
- **Proteobacterial Antimicrobial Compound Efflux Family**: Recently identified, involved in exporting antimicrobial compounds.

Altered Permeability: Bacteria can decrease antibiotic uptake by modifying the expression or function of porin channels in their outer membranes, leading to reduced permeability. For instance, in *Pseudomonas aeruginosa*, downregulation of OprD porin is a crucial outer membrane channel in *P. aeruginosa* and is associated with carbapenem resistance. Understanding the regulatory networks controlling porin expression is crucial for developing therapeutic strategies against multidrug-resistant strains (Wu et al., 2024).

Horizontal Gene Transfer of Drug-Resistance genes: By means of transformation, transduction, and conjugation, Horizontal Gene Transfer **(**HGT) allows bacteria to obtain resistance genes from other bacteria. Resistance characteristics can spread quickly among many species and settings thanks to this approach. Mobile genetic elements like integrons, transposons, and plasmids facilitate gene transfer, contributing to the spread of drug-resistant diseases (Seukep et al., 2022). A crucial process by which bacteria obtain genetic material from other organisms without going via the conventional parent-to-offspring inheritance chain is called horizontal gene transfer. Both the quick spread of antibiotic resistance genes and bacterial adaptability are greatly aided by this process. HGT is facilitated by three main mobile genetic elements: integrons, transposons, and plasmids.

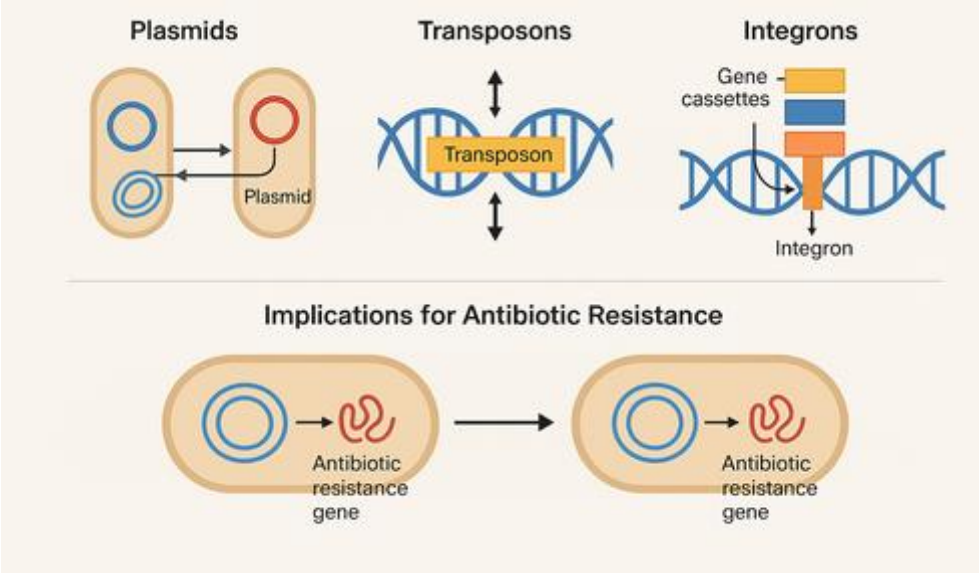

Fig. 2. Horizontal gene transfer (HGT)
(Source: Wang et al., 2024)

Overuse and Misuse of Antibiotics: The unrestricted or misuse of antibiotics induces antibiotic resistance among microorganisms.

Clinical Misuse: Antibiotic resistance in clinical settings is mostly caused by self-medication, improper prescribing practices, and noncompliance with prescribed antibiotic courses. When antibiotics don't work for viral diseases like the common cold, doctors will sometimes prescribe them. In addition to not helping the patient, this overuse encourages the growth of bacterial strains that are resistant. Additionally, patients who do not adhere to the prescribed antibiotic regimen may inadvertently encourage the survival of partially resistant bacteria, further exacerbating the problem.

Agricultural Use: The use of antibiotics in cattle to encourage growth and prevent disease is primarily responsible for the emergence of antibiotic-resistant bacteria. In some countries, antibiotics are administered to animals in sub-therapeutic concentrations without a diagnosis of disease, aiming to stimulate growth. This practice can eliminate susceptible bacteria, leaving behind those that are naturally resistant. These resistant bacteria can then spread to humans through various pathways, including environmental exposure and the consumption of animal products, thereby diminishing the effectiveness of antibiotics in human medicine (Wang et al., 2024).

Plasmids: Plasmids are autonomous, circular DNA molecules distinct from the bacterial chromosome. They often carry genes beneficial for bacterial survival under selective pressures, such as antibiotic resistance genes. Through conjugation—a process where two bacteria form a direct connection—plasmids can transfer between cells, spreading resistance traits across diverse bacterial populations. This mechanism has been implicated in the emergence of multidrug-resistant strains, particularly within the Enterobacteriaceae family. The global dissemination of multidrug-resistant plasmids is exacerbated by the selective pressure exerted by widespread antibiotic use in both clinical and agricultural settings (Zhou et al., 2024).

Transposons: Transposons, or "jumping genes," are DNA sequences capable of moving from one genomic location to another, either within the same organism or between different organisms. They can carry antibiotic resistance genes and integrate into plasmids or chromosomal DNA, facilitating their spread. A notable example is the Tn7 transposon, which has evolved to utilise minimal CRISPR systems for RNA-guided transposition. These CRISPR-associated transposons (CASTs) lack traditional interference mechanisms but possess specialised machinery that complexes with CRISPR RNA and associated Cas proteins to mediate transposition. CASTs have been identified across various bacterial species and are implicated in the horizontal transfer of antibiotic resistance genes, thereby enhancing bacterial adaptability (Rybarski et al., 2021).

Integrons: Integrons are genetic platforms that capture and express gene cassettes, which are mobile genetic elements containing genes, often for antibiotic resistance. An integron comprises an integrase gene (intI), a recombination site (attI), and a promoter (Pc) that drives the expression of integrated gene cassettes. Through site-specific recombination, integrons incorporate gene cassettes, enabling bacteria to rapidly adapt to environmental challenges, including antibiotic exposure. Integrons are commonly associated with plasmids and transposons, facilitating the horizontal transfer of resistance genes among bacterial populations (Mazel 2006). Their ability to capture and express diverse gene cassettes underscores their role in the rapid evolution of antibiotic resistance.

Implications for Antibiotic Resistance: The interplay between plasmids, transposons, and integrons accelerates the spread of antibiotic resistance among bacterial communities. For instance, integrons can capture resistance genes and, when located on plasmids or transposons, can disseminate these genes across different bacterial species through HGT. This genetic exchange leads to the emergence of multidrug-resistant pathogens, complicating treatment strategies and posing significant public health challenges. Understanding the mechanisms underlying HGT and the roles of these mobile genetic elements is crucial for developing interventions to curb the spread of antibiotic resistance (Partridge et al., 2018).

Recent Advances and Future Directions: Recent studies have shed light on the structural and functional dynamics of these mobile genetic elements. For example, the discovery of CRISPR-associated transposons has opened new avenues for understanding bacterial genome evolution and developing novel genetic

engineering tools. Ongoing research aims to elucidate the regulatory mechanisms governing integron activity and the environmental factors influencing HGT. Such insights are essential for devising strategies to mitigate the dissemination of antibiotic resistance genes and combat the global threat of antibiotic-resistant infections (Faure et al., 2019).

Environmental and Socioeconomic Factors: Environmental and socioeconomic factors play pivotal roles in the proliferation of antibiotic-resistant bacteria. Two significant contributors are:

Wastewater and Pharmaceutical Pollution: Effluents from healthcare facilities and pharmaceutical industries often contain antibiotics and other pharmaceutical compounds that are not entirely removed by conventional wastewater treatment processes. Recent studies have highlighted the presence of various pharmaceuticals, including antibiotics, in rivers within national parks, indicating that even seemingly pristine environments are affected by such pollution. This contamination poses risks to aquatic ecosystems and human health, particularly by fostering antimicrobial resistance (AMR) (European Union, 2024).

In response to this issue, regulatory measures have been implemented to mitigate pharmaceutical pollution. This "quaternary treatment" process aims to eliminate micropollutants, such as pharmaceutical residues, from wastewater before it is discharged into the environment. However, this directive has faced opposition from the affected industries, leading to potential legal challenges (Vijayaraghavan et al., 2021; Biji et al., 2016; Wu et al., 2020; Farraj et al., 2024; Rajaselvam et al., 2024).

Global Travel and Trade: The rapid movement of people and goods across the globe facilitates the spread of antibiotic-resistant pathogens. Earlier studies have revealed that pathogenic microbes, including those resistant to antibiotics, can travel vast distances through atmospheric pathways. For example, studies have shown that dust storms can carry viable bacteria and fungi over thousands of miles, potentially introducing resistant strains into new environments. This airborne transmission underscores the complexity of controlling the spread of antimicrobial resistance in the context of globalisation (Wilcox et al., 2024). A study highlighted that extensive antibiotic use in animal laboratories, often without proper oversight, likely contributes to human drug resistance. This finding emphasises the need for stringent antibiotic regulation and responsible use across all sectors to combat the global threat of antimicrobial resistance.

New Drug Classes: Innovative Antimicrobial Agents Targeting Novel Bacterial Pathways:

- **Teixobactin**: Teixobactin, identified through advanced soil culturing methods, is a novel class of antibiotics that specifically targets lipid precursors crucial for the synthesis of bacterial cell walls. Its unique mechanism offers hope against resistant strains (Ling et al., 2015).
- **Nacubactam**: This investigational β-lactamase inhibitor exhibits a dual mechanism by inhibiting both β-lactamases and penicillin-binding proteins, enhancing its efficacy against carbapenem-resistant Enterobacteriaceae (Widodo et al., 2023).
- **Zosurabalpin (RG6006)**: Developed through a collaboration between Roche and Harvard University, zosurabalpin targets the lipopolysaccharide transporter in *Acinetobacter baumannii*, offering a novel approach to treating infections caused by this challenging pathogen (Yao et al., 2021).
- **Brilacidin**: Brilacidin, a synthetic analogue of host defence peptides, shows promise in combating methicillin-resistant Staphylococcus aureus (MRSA) and various other bacteria by compromising their cell membranes (Mone et al., 2023).
- **CRISPR-Enhanced Phages**: Locus Biosciences is pioneering therapies using bacteriophages enhanced with CRISPR technology to target antibiotic-resistant bacterial infections, such as *Escherichia coli* in urinary tract infections (Citorik et al., 2014).

Phage Therapy and Antimicrobial Peptides:

Alternative Strategies to Combat Resistant Infections which involve:

- **Phage Therapy**: In phage therapy, viruses are used to kill bacteria or weaken their defenses. Clinical trials and compassionate use cases have demonstrated phage therapy's potential in

treating multidrug-resistant infections (Lin et al., 2017).

- **Antimicrobial Peptides (AMPs)**: The innate immune response includes antimicrobial peptides (AMPs), which have broad-spectrum antibacterial properties (Mookherjee et al., 2020).
- **Cathelicidin Antimicrobial Peptide**: LL-37 is a human antimicrobial peptide with broad-spectrum activity. Studies have shown its potential in combating infections and modulating immune responses (Dürr et al., 2006).
- **Enzybiotics**: These are enzyme-based antibacterials derived from bacteriophages, offering a targeted approach to lysing bacterial cells (Fischetti, 2018).
- **Oyster-Derived Proteins**: Researchers have identified a protein in the blood of Sydney rock oysters capable of killing bacteria and enhancing the efficacy of conventional antibiotics (Green et al., 2014). This discovery holds potential in combating antimicrobial resistance.

Infection Prevention and Control:

Infection Prevention and Control (IPC) encompasses strategies essential for reducing the incidence of infections and mitigating antimicrobial resistance. Two pivotal components of IPC are:

Improved Hygiene Practices: Hand Hygiene, Sterilisation Protocols, and Hospital Sanitation:

- **Hand Hygiene**: Maintaining good hand hygiene is essential to avoiding illnesses linked to healthcare. The World Health Organisation (WHO) emphasises that proper handwashing by healthcare workers significantly reduces the transmission of pathogens (WHO, 2009).
- **Sterilisation Protocols**: Adherence to stringent sterilisation protocols for medical instruments and environments is vital. Implementing advanced sterilisation techniques, such as hydrogen peroxide vapour and ultraviolet cleaning devices, has been shown to reduce infection rates (Kundrapu et al., 2012).
- **Hospital Sanitation**: It is essential to keep the hospital environment clean. Infection hazards can be reduced in large part by routinely cleaning and disinfecting surfaces and managing waste properly (Rutala& Weber, 2019).
- **Hand-washing Devices and Hygiene**: To improve access to hygiene, especially in resource-limited settings, devices like the Sato Tap have been developed. These devices function without plumbing, making hand hygiene more accessible (Ishiyama, 2024). Encouraging patients to practice hand hygiene can reduce infection rates. Providing sanitising gels or wipes within reach and educating patients on proper handwashing techniques are effective strategies (Haverstick et al., 2017).

Vaccination Programs: Preventing Infections to Reduce Antibiotic Use:

- **Pneumococcal Vaccination**: Vaccines against *Streptococcus pneumoniae* have significantly reduced the incidence of pneumococcal diseases (Song et al., 2013).
- **Influenza Vaccination**: Annual flu vaccinations are recommended for individuals aged six months and older. Immunising healthcare workers also decreases the risk of viral pneumonia among patients (Moghadami, 2017).
- **UTI Vaccines**: Vaccines like Uromune (MV-140) have been developed to prevent recurrent urinary tract infections (UTIs). Clinical studies have shown that Uromune reduces the total number of UTIs by about 70% and increases UTI-free rates from around 25% to 57% (Aziminia et al., 2019).
- **RSV Vaccination**: Vaccines providing protection against Respiratory Syncytial Virus (RSV) have been developed, offering 86% protection against this serious lung infection. In the UK, eligible groups include adults aged 75-79 and pregnant women at least 28 weeks along (Singh & Chibale, 2021).
- **Advancements in Vaccine Delivery**: Needle-free vaccines, such as nasal sprays, are being developed to improve vaccine acceptance and coverage. This method not only facilitates administration but also offers potential for more effective immunity by targeting the entry points of pathogens (Catalano et al., 2022).

Global Policy and Surveillance: Antimicrobial resistance poses a significant threat to global health, necessitating comprehensive strategies

that encompass regulatory measures and international collaboration.

Regulatory Measures: Banning Non-Therapeutic Antibiotic Use in Agriculture:

The excessive use of antibiotics in agriculture, especially for non-medical reasons like enhancing growth in livestock, has been recognised as a significant factor in the emergence of antimicrobial resistance. In 2024, several countries implemented stringent regulations to curb this practice:

- **European Union (EU)**: The European Union implemented a thorough prohibition on the use of antibiotics for promoting growth in livestock, underscoring its dedication to addressing antimicrobial resistance (EU,2024) (Parmanik et al., 2022).
- **United States**: The U.S. Food and Drug Administration has established final guidelines that limit the use of medically significant antibiotics in livestock, allowing their application exclusively for therapeutic reasons under the oversight of a veterinarian (Duan et al., 2023).
- **China**: The Ministry of Agriculture and Rural Affairs in China has declared a countrywide prohibition on the use of colistin as a feed additive, in response to growing concerns regarding increasing colistin resistance (Bharadwaj et al., 2022).
- **India**: The Food Safety and Standards Authority of India issued regulations prohibiting the use of antibiotics for non-therapeutic purposes in animal husbandry, aiming to reduce AMR risks (Kunz Coyne et al., 2022).
- **Brazil**: The Brazilian Health Regulatory Agency implemented policies restricting the prophylactic use of antibiotics in livestock, aligning with global efforts to combat (Alara & Alara, 2024).

International Collaboration: Coordinated Global Efforts to Monitor and Combat AMR:

Addressing AMR requires unified global action. In 2024, several initiatives underscored the importance of international collaboration:

- **United Nations High-Level Meeting on AMR**: In September 2024, world leaders convened at the UN General Assembly, committing to a 10% reduction in AMR-related deaths by 2030 and emphasising the need for multisectoral approaches (Terreni et al., 2021).
- **Global Leaders Group on Antimicrobial Resistance**: This group continued its advocacy in 2024, promoting policies to mitigate AMR across human, animal, and environmental health sectors (Liu et al., 2021).
- **CARB-X Funding Expansion**: The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator received additional funding from international partners in 2024 to support the development of innovative antimicrobial products (Jubair et al., 2021).
- **One Health Global Antimicrobial Resistance Partnership**: This initiative facilitated collaboration among nations to integrate human, animal, and environmental health strategies against AMR (Kebede et al., 2021).
- **World Health Organisation (WHO) Surveillance Programs**: The WHO expanded its Global Antimicrobial Resistance and Use Surveillance System in 2024, enhancing data collection and sharing among member states (Wang et al., 2022).

2. Conclusion

A major threat to global health is antimicrobial resistance, which jeopardises the efficacy of antibiotics and other antimicrobial treatments. The emergence of extensively drug-resistant and multidrug-resistant infections is fueled by microbial survival strategies like biofilm development, efflux pump activation, target site alterations, and enzymatic antibiotic degradation. The issue is made worse by the overuse and abuse of antibiotics in agriculture and human medicine, as well as by inadequate infection control, environmental contamination, and international travel, all of which call for immediate international action. Once-treatable infections are becoming life-threatening, while medical procedures such as surgeries and chemotherapy face heightened risks of complications due to drug-resistant infections. Rising healthcare costs and productivity losses further affect economies. Among the several tactics required to fight AMR are the creation of novel antibiotics and complementary therapies like phage therapy and antimicrobial peptides. Strengthening antimicrobial stewardship, improving infection prevention through hygiene and vaccination, and enhancing global surveillance systems are

crucial. Public awareness programs encouraging ethical antibiotic usage must be implemented in conjunction with regulatory measures, such as prohibiting the use of non-therapeutic antibiotics in agriculture. Governments, researchers, medical professionals, and the general public must work together globally to lessen the effects of antibiotic resistance.

Consent

This study did not involve human participants, and therefore, informed consent was not required.

Ethical Approval

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of this manuscript.

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Competing Interests

Authors have declared that no competing interests exist.

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