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REVIEW ARTICLE

Antimicrobial Resistance: Global Challenges, Resistance Mechanisms and Mitigation Strategies

Arvind Kumar Patel[1,*], Neha Singh[2], Vidhan Chand Bala[3], Pragyandip Parthasarathi Dash[4], Pawan Kumar Goswami[1] and Sandip Chatterjee[1]

[1]Narayan Institute of Pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram, Rohtas, Bihar, 821305, India; [2]Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, 244001, India; [3]School of Pharmaceutical Sciences, IFTM University, Lodhipur Rajput, Moradabad, Uttar Pradesh, 244102, India; [4]Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, 474005, India

Abstract: Antimicrobial resistance (AMR) poses a significant threat to global public health and economic stability, driven by the overuse and misuse of antibiotics in human medicine, veterinary practice, and agriculture. The spread of resistance mechanisms, such as enzymatic degradation, efflux pumps, and horizontal gene transfer, further exacerbates this issue, particularly in low-resource settings.

This review aims to summarize the current understanding of antimicrobial resistance, including its molecular mechanisms, global challenges, economic burden, and innovative mitigation strategies such as antimicrobial stewardship, phage therapy, antimicrobial peptides, and CRISPR-based approaches.

A comprehensive literature review was conducted using scientific databases such as PubMed, Scopus, and Web of Science to gather recent studies, reviews, and guidelines related to AMR. Relevant data on resistance mechanisms, global trends, clinical implications, and mitigation strategies were synthesized to provide an integrated overview of current challenges and solutions.

The review highlights how AMR contributes to increased mortality, prolonged illness, and healthcare costs, while barriers such as limited antibiotic research and diagnostic capacity hinder progress. Integrated approaches, including antimicrobial stewardship, vaccination, phage therapy, and CRISPR-based therapies, are essential to reduce resistance. Additionally, global initiatives like surveillance systems and public awareness campaigns play a vital role in controlling the spread of resistant infections.

Addressing AMR requires coordinated global efforts involving stewardship programs, novel therapeutics, education, and surveillance systems. Sustainable action can reduce antibiotic misuse and delay resistance development, securing effective treatments for future generations.

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*Address correspondence to this author at the Narayan Institute of Pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram, Rohtas, Bihar, 821305, India; E-mail: akpatel4393@gmail.com

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1. INTRODUCTION

1.1. Overview of Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) is a complicated and quickly growing global health concern that is defined by the adaptive capacity of microorganisms, such as bacteria, viruses, fungi, and parasites, to resist and counteract the effects of antimicrobial agents that were once useful in treating infections they caused. AMR occurs when pathogens acquire or evolve mechanisms that enable them to survive and multiply despite the presence of antimicrobial agents [1, 2]. Although the development of resistance is a normal evolutionary process, human activity is mostly responsible for its current rate and scope. The misuse of antibiotics in human health, agriculture, and livestock has accelerated the emergence of resistant strains [3].

Weak regulation, poor infection control, and limited awareness further contribute to the spread of AMR. These factors come together to support a wide distribution of resistant pathogens, which challenge the effectiveness of modern medicine and compromise the success of organ transplants, chemotherapy, surgery, and care for chronic conditions [4, 5]. Without urgent intervention, AMR may render many current treatments ineffective. This could lead to longer durations of illness, higher mortality rates, and steep healthcare costs for nations, as well as loss of gross domestic product worldwide [6].

1.2. Public Health Impact of AMR

AMR represents a grave threat to global health security because of the deep and widespread impact it exerts on public health. AMR threatens the health and well-being of the population and the functions and performance of global public health systems and health care delivery systems. Once-treatable infections become more challenging, if not impossible, to cure as resistance increases, endangering the fundamental basis of contemporary medicine [7].

1.3. AMR in Different Geographical Areas

AMR is a global problem affecting both developed and developing countries, though the contributing factors and consequences vary by region. In developed countries, such as those in Europe, high antibiotic consumption and misuse in healthcare and agriculture have led to significant resistance. According to the ECDC 2014 report, several European nations reported elevated resistance levels and antimicrobial use, resulting in approximately 33,000 deaths annually and an economic burden of €1.5 billion due to healthcare costs and productivity losses [8].

In contrast, developing countries, including parts of Asia, Africa, and Latin America, face challenges such as limited diagnostic facilities, a lack of regulation, and poor infection control. For instance, Sub-Saharan Africa accounted for over 1 million deaths associated with AMR in 2019, while Southeast Asia recorded more than 97,000 deaths, highlighting gaps in treatment access and healthcare infrastructure. Similarly, regions like Latin America and India report high case fatality rates and neonatal deaths linked to resistant infections [9, 10].

In addressing AMR in low-income countries, it is important to also consider the implications of large-scale antibiotic prophylaxis programs. For example, the MORDOR trials evaluated the use of mass azithromycin distribution to reduce child mortality in sub-Saharan Africa. While these programs showed promising reductions in mortality, concerns have been raised about the potential spread of antimicrobial resistance beyond the treated pediatric population [11, 12]. This concern was first emphasized in a commentary related to the MORDOR trial by Poddighe (2019), which highlighted the possible interaction between pediatric and adult populations in the spread of resistance. They state that mass azithromycin use in the MORDOR I trial was associated with increased macrolide resistance, reinforcing the concern that such prophylaxis strategies, although beneficial in reducing child mortality, may accelerate the emergence and dissemination of resistance within and beyond the pediatric population. The overuse of antibiotics in such interventions may lead to resistance in common pathogens, affecting both treated and untreated individuals and posing long-term risks to the effectiveness of antibiotics in these vulnerable communities [13].

1.4. Mortality and Morbidity due to AMR

Global mortality and morbidity are significantly influenced by AMR, which causes longer hospital

stays, more medical complications, and higher death rates. AMR was directly responsible for about 1.27 million deaths globally in 2019, according to current estimates. It was also linked to an additional 4.95 million fatalities through complications, where resistant infections contributed. These numbers put AMR on par with the burden of diseases like HIV/AIDS, TB, and malaria as one of the world's top causes of mortality [14]. Over 2.8 million antimicrobial-resistant illnesses are thought to occur each year in the US alone, leading to tens of thousands of fatalities and making a substantial contribution to the country's overall disease burden. However, not everyone is equally affected by AMR. A disproportionate amount of the burden falls on low- and middle-income countries (LMICs), where issues are made worse by unregulated antibiotic supply, poor diagnostic skills, and restricted access to healthcare services [15, 16].

In these areas, resistant infections frequently go undiagnosed or receive improper treatment, which increases the likelihood of treatment failure, complications, and death. Furthermore, vulnerable groups are particularly in danger, such as young children, the elderly, people with impaired immune systems, and patients undergoing chemotherapy or surgery [17]. In addition to raising the danger of illnesses linked to healthcare, the growing incidence of AMR also jeopardizes the outcome of standard medical operations. Even minor procedures or common diseases could be fatal without adequate antibiotics. The effects go beyond personal health; they put a tremendous burden on hospital infrastructure, raise healthcare costs, and restrict access to safe and efficient treatments [18].

Despite extensive research on antimicrobial resistance (AMR), critical gaps remain in understanding its global spread, contributing factors, and the most effective strategies to mitigate its impact. Existing literature often focuses on localized issues or individual resistance mechanisms without addressing the broader challenges faced across diverse healthcare systems. Therefore, this review aims to provide a comprehensive overview of the global challenges associated with AMR, elucidate the key resistance mechanisms, and explore emerging and integrated mitigation strategies that can be applied across different regions and healthcare contexts. A comprehensive literature review was conducted using scientific databases such as PubMed, Scopus, and Web of Science to gather recent studies, reviews, and guidelines related to AMR.

2. GLOBAL CHALLENGES OF AMR

AMR is a global health emergency of the 21st century, undermining the effectiveness of modern medicine, including the treatment of common infections and standard medical interventions such as surgery and chemotherapy. The World Health Organisation (WHO) considers AMR a major global health challenge, alongside issues such as the COVID-19 pandemic and climate change [6, 18, 19]. This problem has been further exacerbated by the rise of multi-drug resistant (MDR) infections, including resistant tuberculosis and Methicillin-resistant Staphylococcus aureus. Because these microorganisms are resistant to multiple antibiotics, treating the infections they cause can be difficult or even impossible. If no action is taken, growing demands for food and medicines are estimated to drive annual deaths from AMR to 10 million globally by 2050 and trigger an economic disaster, with projected global production losses of $100 trillion (Table **1**) [20].

Regional differences reveal stark disparities in the impact of AMR. While the United States and Europe report significant healthcare costs and mortality figures, low- and middle-income regions such as Sub-Saharan Africa and parts of Asia face dual challenges: inadequate diagnostics and limited access to treatment. Data gaps are particularly concerning in rural and conflict-affected areas, where surveillance infrastructure is weak or absent [21]. Furthermore, emerging resistance patterns, including those associated with novel pathogens and hospital-acquired infections, are insufficiently tracked in many regions. Addressing these gaps through improved data collection and targeted public health interventions is critical to developing equitable and effective global strategies [4].

2.1. Economic burden of AMR

The economic burden of AMR is large and wide-ranging and poses a considerable threat to development and stability throughout the world. World Bank estimates up to $1 trillion could be added to healthcare costs by 2050 as a result of

Table 1. Global impact of antimicrobial resistance.

Region/Category	Mortality Rates	Economic Impact	Refs.
Global	1. 27 million deaths directly due to AMR in 2019	Projected to cause $100 trillion in economic losses by 2050 if no action is taken	[22]
Low- and middle-income countries	Over 4 million deaths are projected in Africa and 4.7 million in Asia by 2050 if AMR is not addressed.	GDP loss of up to 5% in some LMICs; huge strain on under-resourced healthcare systems	[10]
United States	More than 2.8 million AMR infections and 35,000 deaths annually	Estimated to cost up to $1.2 trillion cumulatively by 2050 in healthcare and lost productivity	[23]
India	About 58,000 neonatal deaths/year due to resistant sepsis; rising burden of multi-drug-resistant TB	High public health costs, increased hospital stays, and out-of-pocket expenses	[24]
Europe	About 33,000 deaths annually due to AMR	Estimated €1.5 billion in healthcare costs and productivity loss	[25]
Southeast Asia	Over 97,000 deaths directly attributable to AMR in 2019	Disruption of regional health systems; limited treatment options; cross-border spread of resistant infections	[26, 27]
Latin America	141,000 deaths attributable to AMR in 2019	Increased hospitalization costs and mortality; high case fatality rates associated with multidrug-resistant organisms	[28, 29]
China	600,000 deaths associated with AMR in 2019	Escalating healthcare costs, increased hospital stays, and mortality	[30]
Sub-Saharan Africa	1. 05 million deaths associated with AMR in 2019	Economic loss from reduced labor productivity; substantial burden on healthcare systems	[9, 31]

AMR, due to longer-term illness, longer hospital stays , and the requirement for costlier and more intensive treatments. In addition, AMR is estimated to decrease the global gross domestic product (GDP) by US$1-3.4 trillion annually by 2030, mainly due to reduced labor productivity, disruption in international trade, and health system burden [32, 33].

The economic cost of AMR is not limited to direct medical costs. Industries such as agriculture and food production are also adversely affected, especially where antibiotics are used for livestock. The loss of quality antimicrobials would affect food security, animal health, and the viability of our export industries. Furthermore, "the economic effects are likely to be felt most intensely in low- and middle-income countries (LMICs) where the infrastructure to monitor, prevent and treat resistant infections is often absent" [34]. Without rapid and intensive action worldwide, AMR has the potential to revert millions into abject poverty, disrupt healthcare systems, and reverse decades of progress in global health and economic development [35].

2.2. Impact on Healthcare Systems

The sustainability and performance of health systems throughout the world are under serious threat from antimicrobial resistance (AMR), which undermines the ability of healthcare professionals to treat patients effectively and safely. Curing common maladies becomes infinitely more challenging, costly, and time-consuming when microbes begin to develop resistance to not only first-response medicines but also second and even last-resort antimicrobial treatments. Consequently, this has led to longer hospital stays, increased treatment failure, increased rates of hospital readmission, and increased financial burden on both patients and the health care system [36].

The effectiveness of common, high-risk medical treatments that depend on both preventive and therapeutic antibiotics is threatened by the emergence of AMR. Effective antimicrobial medicines are essential for preventing and treating post-operative infections during surgical procedures such as organ transplants, joint replacement surgery, cesarean sections, and even simple wound

care. These operations become considerably riskier when resistance rises, raising the possibility of complications, prolonged recovery periods, and death [4, 37]. Additionally, hospitals and clinics are being compelled to use more costly, toxic, or ineffective second- or third-line medications, which puts further pressure on healthcare budgets and exacerbates health disparities, especially in low-resource settings where access to more advanced or specialized medications is restricted [38].

2.3. Threat to Modern Medicine

A major setback to contemporary medical development, the emergence of antibiotic resistance poses a threat to undo decades of achievements in the management of chronic diseases, surgical safety, and infectious disease control. What is sometimes called a "post-antibiotic era" could see previously treatable illnesses turn deadly once more, especially in susceptible groups including children, the elderly, and people with impaired immune systems [14].

AMR's potential to jeopardize cancer care is among its most concerning effects. One of the mainstays of cancer treatment, chemotherapy, seriously impairs immune function, making patients more vulnerable to bacterial infections. Therefore, the capacity to prevent and cure infections with efficient antibiotics is crucial to the success of chemotherapy. The risk-benefit ratio of these medicines changes negatively as resistance increases, which may result in fewer treatment options and worse clinical results [19, 37]. Furthermore, AMR has an impact on other crucial care domains that rely on effective antimicrobial treatments, such as newborn intensive care, dialysis, diabetes control, and the treatment of burn and trauma patients. AMR is becoming more widely acknowledged by the international health community as a systemic threat to the basis of contemporary medicine as well as a microbiological problem, necessitating swift and concerted international action [35].

3. MECHANISMS OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) is a serious and growing global health threat that emerges from the ability of bacteria to modify and resist antibiotics. Adaptation takes place *via* several mechanisms, such as efflux pumps, enzymatic degradation, and genetic mutation. The mechanisms frequently act in concert, culminating in exceedingly hard-to-treat bacterial infections. Now, we explain how each of them works, through examples of evidence from recent studies [39, 40].

3.1. Efflux Pumps for the Extrusion of Antibiotics

Efflux pumps reduce antibiotic effectiveness by expelling drugs from bacterial cells. Major families like ABC, MFS, and RND pumps are well described in standard reviews [41]. Recent studies have identified efflux pump inhibitors, such as PAβN, that can restore antibiotic susceptibility in resistant strains [42]. Clinical isolates of Pseudomonas aeruginosa and Acinetobacter baumannii show high resistance linked to pump overexpression, making combination therapies with inhibitors a promising treatment option [43]. Recent studies have also revealed that efflux pump expression can be modulated by environmental stress signals and quorum-sensing pathways, allowing bacteria to transiently upregulate pumps under antibiotic pressure without permanent genetic mutations. Small regulatory RNAs and transcriptional feedback loops have been implicated in fine-tuning pump activity, raising questions about the potential for efflux pump inhibitors to fully reverse resistance (Fig. **1**) [44].

3.1.1. Features of Efflux Pumps

Efflux pumps contribute to multidrug resistance by conferring resistance to a variety of antibiotics, which is a challenge in clinics. For instance, *E. coli* that overexpresses the AcrAB-TolC pump acquires resistance to the antibiotics beta-lactams, fluoroquinolones, and tetracyclines [45]. The expression profiles of these pumps are under fine transcriptional control by transcriptional factors, and mutations in regulatory genes, such as mexR or adeRS, have been demonstrated to generate constitutive over-expression of the pumps that result in an increased MDR phenotype [46, 47]. Furthermore, genes for efflux pumps may be located on plasmids or other mobile genetic units, where they can undergo horizontal transfer between bacterial populations to accelerate the dissemination of resistance [48, 49].

3.1.2. Clinical Implications

In the pathogenic bacteria *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*, drug resistance is

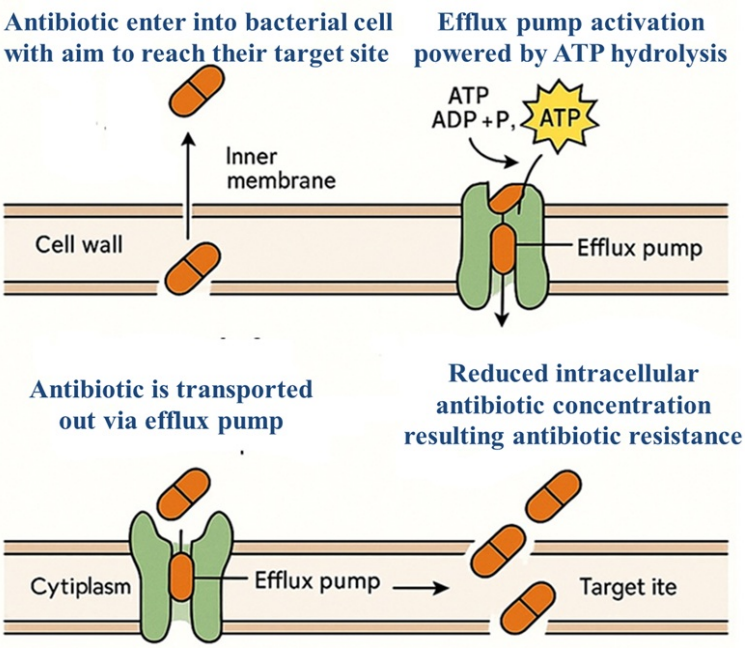

Fig. (1). Mechanism of antibiotic resistance of bacteria using an efflux pump. Membrane transporters actively expel antibiotics, lowering drug concentration inside the cell and contributing to multidrug resistance. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

also the result of efflux pumps. A variety of antibiotics are actively expelled by these membrane transport mechanisms, which lowers intracellular drug buildup. High levels of resistance, especially to tigecycline and fluoroquinolones, have been closely linked to the upregulation of efflux pumps in clinical isolates. This process makes treating infections brought on by these multidrug-resistant organisms more difficult and compromises the effectiveness of available treatments. Furthermore, the clinical utility of efflux pump inhibitors is being actively debated, as compensatory mechanisms and metabolic adjustments may undermine their effectiveness. Current research is focused on identifying specific regulatory pathways that could be targeted without triggering adaptive resistance responses [47, 50].

3.2. Enzymatic inactivation of antibiotics

By generating enzymes that chemically change or degrade the drug molecules, bacteria can withstand antibiotics and counteract their effects. One important resistance mechanism, particularly against beta-lactams, aminoglycosides, and macrolides, is this enzymatic inactivation. Beta-lactamases and aminoglycoside-modifying enzymes are frequent examples that dramatically lower the effectiveness of antibiotics in clinical settings (Fig. **2**) [51, 52].

3.2.1. Key Enzymatic Mechanisms

3.2.1.1. Beta-lactamases

Bacteria manufacture enzymes called beta-lactamases, which hydrolyze the beta-lactam ring, a crucial structural element needed for antibacterial activity, rendering beta-lactam medicines inactive. Antibiotics such as carbapenems, cephalosporins, and penicillins become ineffective as a result. Because they may break down a variety of beta-lactams, including last-resort medications, extended-spectrum beta-lactamases (ESBLs), and carbapenemases are of special concern. These enzymes seriously jeopardize the efficacy of treatment in medical settings and greatly contribute to multidrug resistance in infections [40, 43]. Structural analyses of extended-spectrum beta-lactamases and metallo-beta-lactamases have highlighted the evolutionary flexibility of these enzymes, allowing them to rapidly adapt to new antibiotic classes. Some researchers advocate for the development of allosteric inhibitors that bind distant enzyme sites, but concerns remain about off-target effects and bacterial compensatory evolution [53].

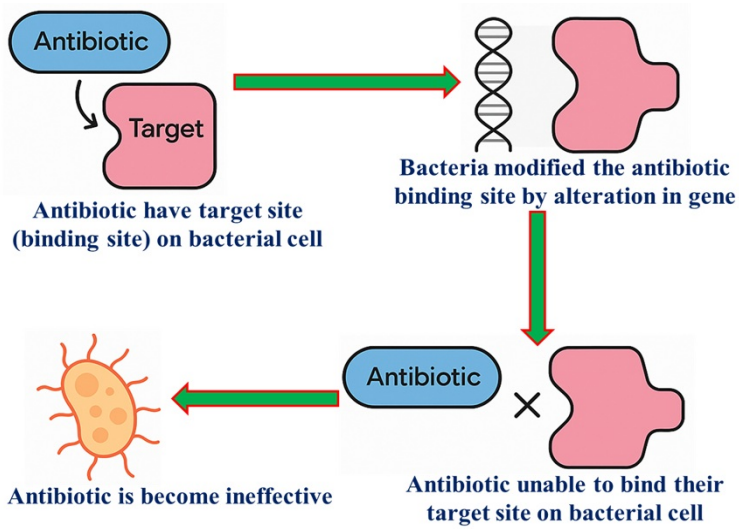

Fig. (2). Mechanism of antibiotic resistance of bacteria by altering the drug target site. Changes in drug target sites or reduced membrane permeability prevent antibiotics from binding effectively, leading to resistance. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3.2.1.2. Aminoglycoside-modifying Enzymes

Aminoglycoside-modifying enzymes add chemical groups to the drug molecule, such as acetyl, adenyl, or phosphate moieties, rendering antibiotics inactive. These changes make it more difficult for the antibiotic to attach to bacterial ribosomes, which inhibits its antibacterial activity and increases resistance, especially in gram-negative bacterial infections. Recent efforts are also exploring gene-editing techniques, such as CRISPR-based approaches, to selectively silence enzyme-coding genes. However, the widespread distribution of mobile genetic elements carrying resistance determinants complicates these strategies, necessitating further investigation into ecological impacts and long-term efficacy. Recent efforts are also exploring gene-editing techniques, such as CRISPR-based approaches, to selectively silence enzyme-coding genes. However, the widespread distribution of mobile genetic elements carrying resistance determinants complicates these strategies, necessitating further investigation into ecological impacts and long-term efficacy [54, 55].

3.2.1.3. Macrolide-modifying Enzymes

Macrolide-modifying enzymes, such as macrolide-streptogramin B (MSB) methyltransferases, methylate the bacterial ribosome's 23S rRNA component to provide resistance. Because of this alteration, macrolides and streptogramins are unable to attach to their target site efficiently, which reduces their antibacterial effectiveness. These antibiotics may also be rendered inactive by other enzymes *via* glycosylation or phosphorylation, which increases bacterial resistance [56].

3.2.2. Clinical Implications

Enzymatic degradation breaks the antibiotics before they can take effect, making it a potent bacterial-resistance strategy. This mechanism tends to spread by horizontal gene transfer, due to resistance to species such as *Klebsiella pneumoniae* that express carbapenemase. The global dissemination of this organism has increased the challenge of managing infection and has intensely diminished available antimicrobial drugs [55].

3.3. Genetic Mutations for Altering Drug Targets and Uptake

The development of antibiotic resistance is largely caused by genetic changes in bacterial genomes. These changes in the site of drug action can cause a reduction in the potency of the antibiotic. Mutations also might increase the capacity of efflux pumps to pump the drug out of the bacterial cell or decrease drug entry. Both within and between bacterial populations, the spread of resistance can be rapid as a result of these transformations, which occur spontaneously or are acquired from other bacteria *via* horizontal gene transfer [52, 57].

3.3.1. Types of Genetic Mutations

3.3.1.1. Target Alterations

When mutations change the structure of bacterial proteins that antibiotics normally bind to, this is referred to as target modification. These changes make the drug less likely to bind and work as intended. For instance, the genes encoding DNA gyrase and topoisomerase IV are modified in *Acinetobacter baumannii* due to mutations in the gyrA and parC. Fluoroquinolones attack these enzymes, and the mutations make it difficult for the drug to bind to the bacteria, rendering them resistant. Emerging research into "hypermutation" suggests that bacteria may temporarily increase mutation rates under stress, accelerating resistance development. The persistence of such mutator phenotypes and their contribution to chronic infections remain active areas of inquiry, with some studies proposing that compensatory mutations stabilize these traits over time [47, 50].

3.3.1.2. Reduced Uptake

Reduced uptake is a resistance strategy in which bacteria modify their cell membrane to restrict antibiotic penetration. Porin channels are microscopic holes in the outer membrane that can become less numerous or less functional due to mutations, which makes it more difficult for medications to enter. Because it stops the antibiotics from getting to their targets and doing their intended function, this reduced permeability is frequently observed in resistance to tetracyclines and fluoroquinolones [55].

3.3.1.3. Efflux Pump Regulation

The genetic modulation of bacterial efflux pump activity is known as efflux pump regulation. Overproduction of efflux pumps can result from the dysfunction of regulating genes such as mexR and adeRS caused by mutations. Particularly in chronic bacterial infections, this enhanced expression enables bacteria to more effectively evade drugs, lowering drug concentration within the cell and fostering antibiotic resistance. The role of regulatory RNAs and epigenetic modifications in controlling efflux pump genes has recently gained attention. These layers of regulation complicate the assumption that targeting single genes will suffice to reverse resistance, prompting calls for combination strategies that account for bacterial adaptability [46, 47].

3.3.2. Clinical Implications

One of the main reasons why clinical bacterial strains are resistant to antibiotics is genetic mutation. Certain mutations in the rpoB gene in Mycobacterium tuberculosis result in resistance to rifampicin, whereas alterations in the katG gene result in resistance to isoniazid. These mutations change the activation pathways or therapeutic targets, which decreases the efficacy of these vital anti-tuberculosis drugs and makes therapy more difficult [58, 59].

3.4. Interplay Between Mechanisms

Treatment is made considerably more difficult by the fact that bacteria usually employ many resistance mechanisms simultaneously. They can withstand even high antibiotic concentrations because of this combination technique. For example, high resistance to fluoroquinolones in Acinetobacter baumannii might result from changes in drug target genes and the development of efflux pumps [50]. Similarly, carbapenem-resistant Enterobacteriaceae frequently exhibit decreased membrane permeability and antibiotic enzymatic degradation, which inhibits drug entrance. The effectiveness of current treatments is limited by these synergistic mechanisms, which increase bacterial survival. There is growing recognition that resistance mechanisms are part of broader stress adaptation networks. For instance, biofilm-associated metabolic shifts and altered gene expression patterns can complement efflux and enzymatic defenses, suggesting that treatment strategies must address both genetic and environmental drivers of resistance. This highlights the urgent requirement for new drugs and strategies to combat infections of drug resistance in clinical practice [55].

3.5. Biofilm Formation and Persistence

The reversible binding of planktonic bacteria to the surfaces using appendages (pili, flagella) forms the initial stage of the biofilm formation process. They consolidate their initial adherence by releasing the extracellular polymeric substances (EPS) and initiate the formation of the biofilm, but now in a permanent stage. Cell proliferation leads to increased thickening of the EPS matrix that can facilitate the recruitment of other microbes and promote the development of elaborate 3D structures. Mature biofilms and metabolic diversity across cells are also driven by chemical gradients,

and water channels enable the exchange of nutrients and waste. Bacteria communicate using signaling molecules, a process known as quorum sensing, which modulates gene expression about resistance, virulence, and biofilm stability. The dispersal phase is eventually triggered by external stimuli such as food scarcity or enzymatic action, in which part of the population detaches and transitions to a motile state, leading to colonization of a new surface. This so-called dynamic even cycle largely contributes to antimicrobial resistance and explains why and how biofilms can persist in extreme environments [60-62].

4. DRIVER OF ANTIMICROBIAL RESISTANCE

One of the main causes of antimicrobial resistance (AMR) is the overuse and abuse of antibiotics in both humans and animals. Self-medication, improper prescription practices by medical professionals, and the use of antibiotics in agriculture are all major contributors to the issue. Furthermore, inadequate infection prevention and control procedures in medical facilities encourage resistance even more. The situation is made worse by restricted new antibiotic development and international travel and trade, which further hasten the cross-border transmission of resistant microorganisms. Particularly in situations with limited resources, poor sanitation and hygiene foster an environment conducive to infection and resistance [63, 64].

AMR increases mortality rates, prolongs hospital stays, and escalates treatment costs. Coordinated international action is needed to combat AMR, which includes stronger antibiotic usage restrictions, funding for novel treatment research, better infection control strategies, and educating the public about appropriate antibiotic use [4]. Among the many drivers, inappropriate human antimicrobial use and weak infection control are the most urgent, with strong evidence. Agricultural use is important but supported by moderate evidence, while environmental and social factors are emerging drivers with weaker evidence. Prioritizing immediate action on well-established drivers alongside further research on uncertain areas ensures a balanced response (Table **2**) [65].

5. STRATEGIES TO MITIGATE ANTIMICROBIAL RESISTANCE

Effective mitigation of antimicrobial resistance requires a layered approach that integrates clinical, public health, and research-based strategies. This section categorizes interventions into stewardship programs, vaccination, therapeutic innovations, next-generation drug development, and global policies. By clearly defining each strategy and illustrating their interdependence, this framework aims to provide healthcare professionals and policymakers with a structured path to combat AMR effectively (Table **3**) [4, 73].

5.1. Antimicrobial Stewardship Programs (ASPs)

Antimicrobial Stewardship Programs (ASPs) form the foundation of AMR mitigation efforts. By ensuring rational use of antibiotics, ASPs help preserve the efficacy of existing treatments while reducing the risk of resistance development. The global perspective of antimicrobial stewardship programs provides a critical and strategic structure in the global fight against the expanding issue of antimicrobial resistance (AMR). ASPs are a critical element of public health efforts to ensure the continued effectiveness of existing antimicrobial medicines. They are diligently prepared to ensure the rational utilization of anti-microbials based on sound evidence and are also patient-centered. The challenge of preserving antimicrobial utility for future generations is combined with the imperative to control effective infection at the levels of ASP, which can achieve therapeutic outcomes while minimizing the risk of resistance development [74]. For instance, studies on antimicrobial consumption in Europe have revealed significant variability in prescription patterns across countries, underscoring the need for standardized stewardship guidelines and region-specific interventions to ensure responsible antibiotic use and curb resistance trends [5].

5.1.1. Implementation of Guidelines and Protocols

The development and broad application of standardized, thoroughly studied treatment protocols that direct the proper choice, dosage, route, and duration of antimicrobial therapy are at the core of ASPs. Current clinical efficacy data, susceptibility patterns, and epidemiological trends all inform these recommendations. ASPs seek to drastically lower the prevalence of empiric, unsuitable, or excessive antibiotic use, the main causes of resistance, by encouraging adherence to these standardized procedures. Additionally, these standards

Table 2. Causes of antimicrobial resistance.

Driver/Challenges	Description	Recent Data	Refs.
Overuse and misuse of antibiotics in human medicine	Antibiotics are often prescribed unnecessarily for viral infections (*e.g.*, common cold, flu) or without microbial confirmation. Self-medication and non-compliance (*e.g.*, incomplete courses) also contribute to resistance.	Global antibiotic consumption increased by 65% from 2000 to 2015. In countries like China and Brazil, per capita use more than doubled during this period. In South Africa, up to 55% of antibiotic prescriptions in primary care were inappropriate.	[5]
Inappropriate antibiotic use in agriculture and livestock	Antibiotics are routinely used in food animals for growth promotion and disease prevention, which encourages the development of resistant bacteria that can be transmitted to humans through the food chain, environment, and direct contact.	Over 70% of medically important antibiotics in some countries are used in animals. Resistant strains like *E. coli* and *Salmonella* have been linked to livestock antibiotic use.	[66, 67]
Limited development of new antibiotics	The pharmaceutical industry has reduced investment in antibiotic R&D due to high costs, lengthy approval processes, and low returns compared to chronic disease drugs.	Only a few new classes of antibiotics have been developed since the 1980s. As of 2023, the WHO reported that the pipeline of truly novel antibiotics is "insufficient" to tackle AMR.	[68, 69]
Poor infection control and sanitation	Lack of proper hygiene, inadequate waste management, and insufficient infection control measures in healthcare settings allow resistant pathogens to spread more easily.	According to the WHO, improving hygiene could reduce the need for antibiotics by up to 60%. AMR is particularly prevalent in hospitals due to persistent exposure to antibiotics and pathogens.	[70]
Global disparities in regulation and surveillance	Many countries lack strong regulatory frameworks, antimicrobial stewardship programs, or effective surveillance systems, making it difficult to track resistance patterns and enforce responsible antibiotic use.	WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) reports large gaps in surveillance capacity, especially in LMICs.	[71]
Lack of public awareness and education	Many individuals do not understand how or when antibiotics should be used. Misinformation and cultural practices can lead to misuse.	Surveys by the WHO found that a significant portion of the population in several countries believes antibiotics can treat viral infections.	[72]

give physicians a solid framework for making decisions, which improves uniformity in prescription procedures across various healthcare environments [75, 76].

5.1.2. Rapid Diagnostic Testing

The use of sophisticated diagnostic tools, such as host-response biomarkers (like procalcitonin) and nucleic acid amplification methods like polymerase chain reaction (PCR), has transformed the clinical ability to quickly and precisely detect infectious etiologies. These developments make it possible to distinguish between bacterial and non-bacterial infections in real-time, which speeds up the start of pathogen-directed treatment and reduces the needless use of broad-spectrum antibiotics. When successfully included in ASPs, rapid diagnostics help close the gap between therapeutic accuracy and clinical ambiguity, which eventually lowers the abuse of antibiotics [77].

5.1.3. Monitoring and Feedback

Within ASPs, a crucial quality assurance mechanism consists of ongoing monitoring of antimicrobial prescribing practices, coupled with rigorous performance audits and personalized feedback [78]. This procedure promotes a culture of accountability, introspection, and iterative learning by pointing out departures from accepted standards and offering prescribers instructive perspectives. Over time, it has been demonstrated that these stewardship-driven feedback loops greatly increase prescriber adherence to stewardship principles and decrease the use of needless antibiotics [79].

5.1.4. Telemedicine-enabled Antimicrobial Stewardship Programs (Tele-ASPs)

The implementation of telemedicine-based ASPs has become a practical and scalable alterna-

tive in healthcare systems when access to infectious disease knowledge is restricted due to geographic, financial, or infrastructure limitations. For frontline healthcare professionals in remote or under-resourced areas, tele-ASPs use digital communication tools to offer remote antimicrobial stewardship support, including consultation, prescription review, and education. These programs ensure that high-quality, evidence-based antimicrobial guidance is available in all care settings, which not only broadens the reach of stewardship treatments but also advances equity in healthcare delivery [80].

The effectiveness of ASPs is established in a variety of healthcare settings, where they can lower antibiotic overuse and enhance therapeutic results. While ASPs are critical for immediate interventions, they must be complemented by vaccination programs, novel therapeutics, and global policies to achieve sustainable AMR control [74].

5.2. Vaccination and Immunotherapy

Vaccination and immunotherapy are key complementary strategies that reduce infection rates and consequently antibiotic usage. Together with ASPs, these approaches lower the overall selection pressure that drives resistance. Vaccines reduce the burden of infections, thereby decreasing the need for antibiotics and slowing the development of resistance [20]. Immunotherapy, which enhances the body's immune response to infections, offers a complementary approach to antibiotics [81]. Vaccines are being developed against priority pathogens, such as Staphylococcus aureus, Klebsiella pneumoniae, and Pseudomonas aeruginosa, to reduce the incidence of infections caused by these organisms [14, 20].

Immunotherapy is the use of monoclonal antibodies, cytokines, and other immune-modulating agents to boost the ability to fight infections. These strategies are especially attractive for combating infections of multidrug-resistant bacteria [20, 81].

5.3. Alternative Therapeutic Approaches

As conventional antibiotics face growing limitations due to resistance, alternative therapeutic approaches offer innovative solutions. These include treatments that specifically target resistant pathogens, modulate host defenses, or bypass existing resistance mechanisms. The exploration of new, non-traditional treatments has emerged as an important new frontier in the management of infectious disease in the modern era when the threat of antimicrobial resistance and its potential continue to reduce the utility of traditional pharmacologic interventions are becoming increasingly recognized. Several of these emerging strategies encompass a spectrum of science-based strategies [82].

5.3.1. Phage Therapy

Bacteriophage therapy is an emerging antibacterial alternative based on the use of phages and viruses that are able to specifically infect and lyse bacteria. Phages are uniquely selective, targeting the harmful bacteria while leaving the host's good bacteria untouched, unlike broad-spectrum antibiotics. This specificity decreases unwanted effects such as dysbiosis. It is of special benefit for combating MDR bacterial strains and presents an alternative to conventional antibiotics in the management of such infections when dealing with MDR bacterial infections [83, 84].

Recent advances, such as the development of phage cocktails that include multiple strains for synergistic therapeutics and genetic modification of phages to broaden host range or for drug delivery, have further increased its clinical outcomes. These advances result in a wider range of feasible treatments, improved effectiveness, and reduced risk of resistance generation. Phage therapy is a potential, personalized, and targeted intervention that is in line with the ideas of precision medicine and microbial stewardship, within the broader strategy to combat AMR [85].

5.3.2. Antimicrobial Peptides

Antimicrobial peptides (AMPs) are a class of natural, evolutionarily conserved compounds that play a crucial role in the innate immune defense of many animals. Broad-spectrum antibacterial efficacy against viruses, fungi, and bacteria is demonstrated by these brief, cationic peptides. Their main mechanism is the fast lysis of pathogens caused by the breakdown of microbial membranes by electrostatic interactions. This membrane-targeted strategy sets AMPs apart from traditional antibiotics by making it intrinsically difficult for bacteria to become resistant. Many AMPs have immunomodulatory qualities that improve host defenses and control inflammatory responses in

addition to their direct antibacterial actions [86, 87]. Due to the growing threat that multidrug-resistant (MDR) microorganisms represent to the world, AMPs have attracted a lot of attention as viable substitutes for conventional antibiotics. They are excellent candidates for the development of innovative therapeutics in the fight against antimicrobial resistance because of their distinct processes and ability to combat resistant species [20, 83].

5.3.3. CRISPR-based Strategies

In the fight against antimicrobial resistance (AMR), CRISPR-Cas systems have quickly become revolutionary biotechnological tools. CRISPR-Cas technologies, which were first discovered to be a prokaryotic adaptive immune system, have recently been repurposed to allow for highly specific, programmable genetic editing in a variety of organisms, including harmful bacteria [88]. The CRISPR-Cas systems can be customized for the targeted cleavage of the antibiotic-resistance genes present in the bacterial genome or plasmid responsible for AMR. CRISPR-based therapies may resensitize resistant bacteria to existing treatments by specifically targeting these resistance elements, and thus restore phenotypic susceptibility to conventional antibiotics. This genome-directed approach represents a frame shift in antibacterial intervention, allowing a level of control and specificity not currently available in that field [89].

In addition, CRISPR-based diagnostics such as the tools Shercek and Detectr provide highly sensitive, rapid, and cost-effective approaches to both identify resistant infections and detect resistance genes at the point of care. They enhance the precision and agility of antimicrobial stewardship efforts by enabling real-time surveillance and rapid treatment decisions. When used in combination, CRISPR-Cas technologies provide a powerful dual-function toolkit that can be used prospectively and specifically to both detect and ameliorate resistance to antibiotics [85].

While these innovative approaches of CRISPR-based therapies and phage therapy offer exciting potential, their clinical application is still limited. Regulatory barriers, high development costs, ethical considerations, and the predominance of early-stage or preclinical evidence pose major challenges. Large-scale trials, standardized regulatory frameworks, and long-term safety data are essential before these therapies can be integrated into routine clinical practice. Thus, although promising, these interventions should be viewed as complementary to, rather than replacements for, established strategies like stewardship programs, vaccination, and rapid diagnostics [90].

5.3.4. CRISPR-Enhanced Phages for Antibiotic-resistant Bacteria

The further emergence of antibiotic-resistant bacterial diseases has required more novel and targeted antimicrobial approaches. The use of bacteriophages themselves as vectors, now as a CRISPR-enhanced bacteriophage, where natural bacteriophage lysis is combined with CRISPR-Cas9-mediated gene modification, is one of the most attractive approaches. Without damage to good microbes, these engineered phages are a less invasive, efficient, and targeted way of eliminating drug-resistant bacteria. Dual mechanism of action phage therapy, in which phages would lyse and infect the bacteria as well as release the CRISPR-Cas elements into the host to target the resistance genes, has the potential to transform the treatment of antimicrobial therapy [90-92].

Those designer phages are derived from wild-type phages, which are chosen for their high infectivity and broad host range, and are genetically improved. The phage genome can be modified by the researchers to allow the phages to specifically target sequences related to resistance, leading to DNA or RNA breakage and cell death *via* the CRISPR-Cas system or its derivatives (Cas12 or Cas13). Moreover, the therapeutic spectrum of the phages is broadened by protein engineering of their tail fibers; this modification enables them to recognize a more diverse array of bacterial strains [93-95]. Central to this approach is an engineered introduction of gene-editing technologies into bacterial cells, which allows the expression of equipment that automatically targets the bacterium's own DNA to eliminate gene(s) for antibiotic resistance (blaNDM, mecA). This minimizes the potential for unexpected disruption to the native microbiota while reviving classic antibiotics. CRISPR-enhanced phages are a potent, next-generation antibacterial approach that can combat diseases resistant to several drugs with unparalleled specificity and accuracy (Fig. **3**) [96, 97].

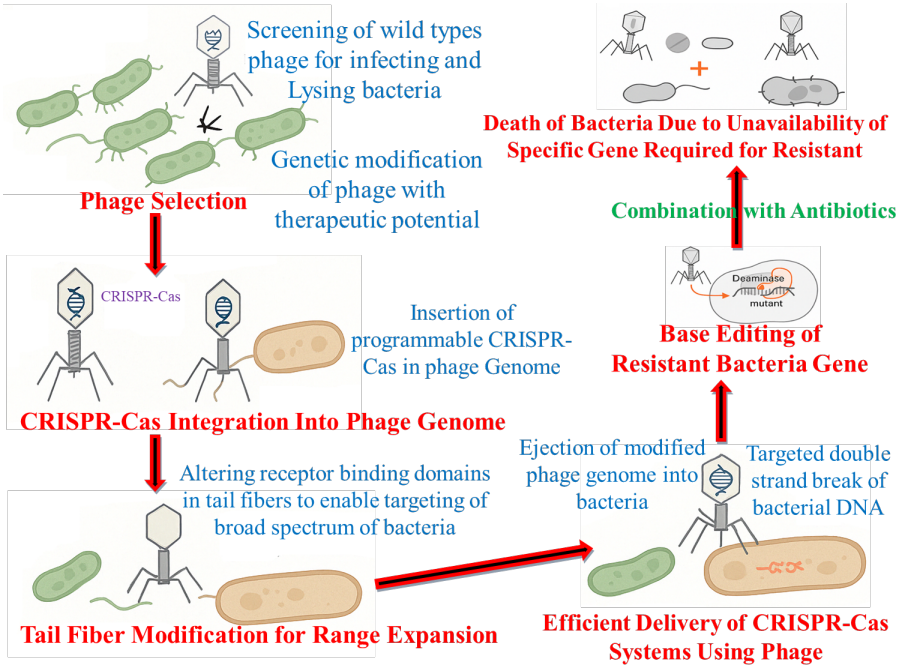

Fig. (3). CRISPR-Enhanced bacteriophage therapy for antibiotic-resistant bacteria. Engineered phages combine natural lytic activity with CRISPR systems to remove resistance genes and restore antibiotic effectiveness.*(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

5.3.5. Other Alternatives

Other new alternative approaches include the use of antimicrobial enzymes, probiotics, and nanomaterials, each of which has unique ways of fighting pathogenic organisms. These treatments either directly combat pathogenic organisms or alter the host microbiota to increase resistance to colonization. When combined, these strategies have the potential to reduce reliance on conventional antibiotics and support the larger endeavor to reduce antimicrobial resistance using creative, multidimensional strategies [83, 84]. Though promising, many of these therapies remain in early research stages. Their integration into routine practice requires further clinical validation, regulatory approvals, and robust safety data.

5.3.6. Development of Next-generation Antibiotics

The decline in effectiveness of existing antibiotics has necessitated the discovery of new drugs with novel mechanisms of action. Next-generation antibiotics aim to address both current resistance patterns and emerging threats. Therefore, the development and use of next-generation antibiotics is an essential component of the global response to the growing AMR challenge [3]. The development of extensively drug-resistant (XDR) and multi-drug-resistant (MDR) pathogens has led to a decline in the effectiveness of current antimicrobial agents, making the search for new therapeutic approaches a key focus of current pharmaceutical and biomedical research [98].

5.3.7. Novel Antibiotic Discovery

Finding completely novel classes of antibiotics with distinct modes of action is the focus of more and more scientific research. This includes the creation of sophisticated beta-lactamase inhibitors, artificial antibacterial substances, and naturally occurring chemicals that can target previously incurable infections and get around known resistance routes [84, 99].

5.3.8. Drug Repurposing

An economical and efficient way to increase the antibacterial repertoire is to strategically reevaluate current pharmaceutical drugs for possible antimicrobial value. Researchers can accelerate the clinical application of these medicines for new infectious indications by utilizing their established pharmacokinetic and safety properties [81].

5.3.9. Combination Therapy

Antimicrobial potency is increased, and resistance evolution may be inhibited when traditional antibiotics are combined with adjunctive medicines, such as membrane permeabilizers, efflux pump inhibitors, or resistance-modifying drugs. Restoring antibiotic activity against resistant organisms and improving therapeutic results are made possible by this synergistic approach [83, 100]. Aside from these developments, there are still many difficult obstacles in the way of sustainable antibiotic innovation. Exorbitant R&D expenses, drawn-out regulatory approval procedures, a lack of financial incentives, and the inherent high danger of resistance developing shortly after market introduction all frequently impede the discovery and clinical development of novel antibiotics. In order to revive antibiotic research and stewardship programs, these multifaceted barriers have led to a diminishing pipeline of really unique antibiotics, highlighting the urgent need for coordinated global legislative reforms, creative funding structures, and public-private collaborations [100, 101].

5.4. Policy, Surveillance, and Global Initiatives

Policies, surveillance networks, and global collaboration create the backbone that allows stewardship programs, vaccination, and therapeutic innovations to be scaled and effectively implemented across regions. A multidisciplinary strategy, which will take environmental, animal, and human health considerations together, is required to address this global issue [102]. Important world programs and policies are as follows.

5.4.1. One Health Approach

In the context of AMR, the One Health approach emphasizes the interdependence of environmental, animal, and human health. Because infections cross species and ecological boundaries, a One Health, multisectoral strategy is essential to effectively tackle resistance. This approach enables integrated actions that are more effective against the multiple determinants of AMR, coordinating efforts across several interlinked domains [28, 103].

5.4.2. Antibiotic Stewardship Programs

The implementation and improvement of ASPs in health systems all over the world is promoted by international campaigns such as the World Health Organization's (WHO) Global Action Plan. These range from efforts to optimize antibiotic use while minimizing their misuse, and promoting stewardship practices to limit the rate of rise of resistance [104].

5.4.3. Surveillance and Monitoring

For the surveillance of the emergence, transmission, and resistance development of diseases, the evolution of a good surveillance infrastructure is indispensable. Robust data collection and surveillance underpin public health responses and policy development, and help to identify resistance hotspots. Surveillance system offers early detection of resistant strains and prevention from emerging and spreading, which guides resource allocation and targeted efforts [3, 103].

5.4.4. Funding and Collaboration

Innovations to develop new antibiotics, tests, and counter-measures, as modern antibiotics replace traditional but less effective antibiotics, anti-infective and diagnostics programs such as the AMR Action Fund and the Global Antibiotic Research and Development Partnership (GARDP) are vital. By encouraging cooperation between both the public and private spheres, these coalitions ensure the sustainability and replenishment of the global antimicrobial pipeline [105].

5.4.5. Public Awareness and Education

Public education and awareness campaigns that directly influence beliefs and behaviors associated with antibiotic use are thus necessary building blocks in the global war against antimicrobial resistance (AMR). Well-organized educational programs are, indeed, able to reduce the inappropriate use of antibiotics, often deriving from misconceptions about their usefulness or effectiveness. Public interventions directed towards patients and the public are necessary to lower the demand for inappropriate prescriptions and the population myths, such as the misconception that antibiotics are effective against viral infections. By encouraging safe health-seeking behavior, these programs encourage people to gain a better understanding of AMR and its long-term implications and usage [103, 106]. The learning of prescribers and teachers (healthcare professionals) is equally important. In professional development programs as well,

Table 3. Key strategies to mitigate AMR and their readiness levels.

Strategy	Evidence Strength	Readiness Level	Limitations
Antimicrobial stewardship programs (ASPs)	Strong (multiple trials, WHO-backed)	High implemented	Requires training and policy support
Rapid diagnostic testing	Strong (clinical validation)	High/Moderate implemented	Cost and access barriers in LMICs
Vaccination	Strong (proven reduction in antibiotic use)	High implemented	Limited availability for some pathogens
Phage therapy	Moderate (case reports, pilot trials)	Low/Moderate implemented	Regulatory challenges, standardization lacking
Antimicrobial peptides (AMPs)	Moderate (preclinical, some clinical trials)	Low implemented	Stability and toxicity concerns
CRISPR-based therapies	Emerging (mainly preclinical)	Very low implementation	Ethical, regulatory, and delivery barriers
Combination therapy	Moderate-Strong (clinical studies for specific pathogens)	Moderate implemented	Risk of increased resistance if misapplied
Immunotherapy (monoclonal antibodies)	Moderate (some clinical approvals)	Moderate implemented	High cost and access issues

adherence to stewardship policies, the targeted use of antibiotics, and the knowledge of resistance patterns are likewise addressed [107, 108]. In addition, working in collaboration with communities on participatory initiatives fosters a sense of shared responsibility for preserving the effectiveness of antibiotics. The community-led interventions promote the correct use of medicines, vaccination, and hygiene, which empower individuals to be able to join the battle against AMR [83, 91].

Among the diverse interventions, current evidence highlights antimicrobial stewardship programs, rapid diagnostic testing, and vaccination as the most immediately impactful strategies, given their proven ability to reduce unnecessary antibiotic use and improve treatment outcomes across healthcare settings. At the same time, innovative approaches such as CRISPR-based therapies and antimicrobial peptides show strong future promise, though they remain largely experimental and require further clinical validation. By prioritizing established strategies with demonstrated effectiveness while continuing to invest in emerging solutions, a balanced and evidence-driven response to antimicrobial resistance can be achieved [103, 109].

CONCLUSION

This review set out to examine current knowledge on antimicrobial resistance (AMR), focusing on global challenges, resistance mechanisms, and mitigation strategies. Our analysis highlights that while antimicrobial stewardship, vaccination, and rapid diagnostics represent the most effective and implementable solutions today, novel approaches such as phage therapy, antimicrobial peptides, and CRISPR-based strategies show promise but remain constrained by limited clinical validation and regulatory barriers. Future efforts should prioritize large-scale trials for emerging therapies, urgent policy reforms to strengthen surveillance and stewardship, and targeted research to address evidence gaps in low-resource settings. Coordinated action is essential to safeguard antimicrobial effectiveness. In addition, this review emphasizes new findings from the literature, including the disproportionate AMR burden in low- and middle-income countries, the unintended risks of large-scale antibiotic prophylaxis programs such as the MORDOR trials, and the promise of emerging strategies like CRISPR-enhanced phages that combine pathogen specificity with programmable versatility. These insights highlight the need for region-specific interventions, clinical validation of novel therapies, and stronger global policy frameworks to ensure equitable access and sustainable impact.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: AKP: study conception and de-

sign, data collection, draft manuscript; NS: draft manuscript; VCB: data collection; PPD: study conception and design, supervision; PKG: Data collection; SC: reviewing and editing. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AMR = Antimicrobial Resistance

ESBLs = Extended-spectrum Beta-lactamases

GDP = Gross Domestic Product

LMICs = Low- and Middle-income Countries

MSB = Macrolide-streptogramin B

WHO = World Health Organisation

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