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Review Paper

Antibiotic Resistance: Current Challenges and Future Directions

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ABSTRACT

Antibiotic resistance constitutes a significant global health challenge, jeopardising the efficacy of therapeutic interventions for severe infections. The emergence of resistant pathogens has imposed considerable pressure on healthcare systems globally, intensifying health disparities and economic burdens. This review presents a thorough analysis of antibiotic resistance, delving into its historical evolution, fundamental mechanisms, and current global crisis. It elaborates on resistance mechanisms such as efflux pumps, enzymatic degradation, and genetic mutations. Clinical cases exemplifying the challenges of managing drug-resistant infections include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant tuberculosis (MDR-TB), underscoring the complexities and risks associated with these conditions. Furthermore, the review highlights pressing global issues, including the overuse and misuse of antibiotics, insufficient new drug development, inequities in healthcare access, and the substantial economic ramifications of resistance. It critically evaluates existing strategies aimed at mitigating resistance, such as antimicrobial stewardship programs, comprehensive surveillance systems, infection control protocols, and initiatives to increase public awareness. The exploration of future strategies to combat antibiotic resistance reveals promising advancements, including the development of novel antibiotics, the utilisation of CRISPR technology, innovations in vaccines, and the formation of public-private partnerships. These strategies present potential solutions to the escalating crisis of resistance. The review concludes with policy recommendations that stress the necessity for international collaboration, improved global surveillance, and financial incentives to encourage pharmaceutical research and development. Antibiotic resistance constitutes a critical global health challenge, necessitating immediate and collaborative initiatives to maintain the effectiveness of essential therapeutic interventions and safeguard public health.

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INTRODUCTION

Antibiotic resistance is increasingly acknowledged as a paramount threat to global public health. This review examines the contemporary challenges posed by antibiotic resistance and explores potential strategies to address this pressing issue. By analysing resistance mechanisms, evaluating current interventions, and identifying gaps in research and policy, this review seeks to offer a comprehensive understanding of the situation. Furthermore, antibiotic resistance is not only a significant concern for affluent nations but also poses substantial risks for developing economies, where emerging diseases exacerbate public health challenges. It is estimated that nearly all infections acquired annually are attributable to multidrug-resistant organisms, which are becoming progressively difficult to manage with existing antibiotics. The World Health Organization (WHO) projects that by 2050, antimicrobial resistance could result in approximately 10 million fatalities each year, surpassing cancer as the leading cause of death globally[1,2]. The overuse and misuse of antibiotics in both the healthcare and agricultural sectors are significant contributors to the development of antibiotic resistance. This phenomenon is a critical factor leading to the emergence of drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacteriaceae (CRE)[3,4]. The diminishing efficacy of existing antibiotics poses a significant public health challenge globally, particularly in areas with constrained healthcare resources. This review further examines the worldwide economic ramifications of antibiotic resistance, which may increase to trillions of dollars as a result of factors such as heightened healthcare expenditures, extended hospitalizations, and diminished workforce productivity[5,6]. The advent of antibiotics revolutionized medical practice, marking a significant turning point initiated by Alexander Fleming's discovery of penicillin in 1928. Consequently, antibiotics rapidly became integral to contemporary healthcare, enabling the effective treatment of bacterial infections that were previously considered fatal. However, Fleming underscored the importance of appropriate antibiotic usage and foresaw the emergence of antibiotic-resistant bacteria if their application was not judiciously managed[7,8]. The emergence of antibiotic resistance was observed shortly after the widespread introduction of antibiotics in the 1940s, with the identification of penicillin-resistant strains of *Staphylococcus aureus* occurring within a few years of their initial use[9]. Despite the introduction of numerous antibiotics to the market, bacterial populations have continued to evolve, resulting in diminished efficacy of these treatments. The emergence of antibiotic-resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), has significantly complicated the management of common infections, posing a substantial challenge to public health and clinical practice[10,11]. Multidrug-resistant organisms have emerged as a predominant factor contributing to healthcare-associated infections, resulting in increased rates of complications, prolonged hospitalizations, and elevated mortality rates. On a global scale, antibiotic resistance is recognized as a critical threat to public health and economic stability. According to reports from the World Health Organization (WHO), if no interventions are implemented, antibiotic resistance may lead to the deaths of up to 10 million individuals annually by the year 2050[12]. The issue of antibiotic resistance is exacerbated in developing nations, where access to healthcare services is limited and the regulation of antibiotic usage is inadequate. Additionally, the excessive reliance of the agribusiness industry on antibiotics in livestock production contributes

significantly to the increase in resistance, primarily through environmental contamination[13]. Despite the significant challenges posed by antibiotic resistance, the development of new antibiotics has markedly diminished in recent years. This stagnation in antibiotic innovation is largely attributed to pharmaceutical companies' reluctance to invest in research and development, stemming from the limited financial returns associated with these medications. Consequently, this trend not only hampers the advancement of effective treatments but also contributes to the growing diversity of antibiotic-resistant pathogens, thereby complicating global efforts to combat antibiotic resistance[14]. The global healthcare landscape is at risk of regressing to a pre-antibiotic era, wherein even minor infections could pose significant life-threatening risks. This scenario underscores the urgent need for the development of novel antimicrobial agents and the prudent application of current antibiotics to mitigate this impending crisis.

Overview of Antibiotic Resistance Mechanisms

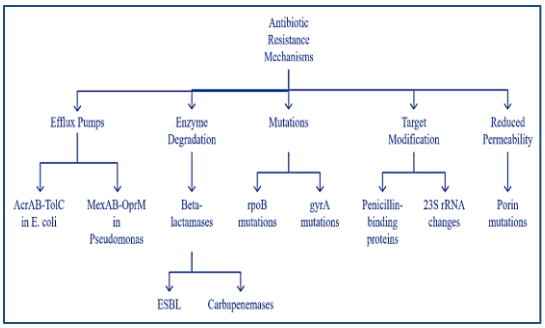

Figure 1 Flow Diagram showing Antibiotic Resistance Mechanisms / Examples

Transport proteins/Efflux Pumps

Efflux pumps are integral membrane proteins utilized by bacteria to expel harmful compounds, including antibiotics, from their intracellular environment. These transport mechanisms are capable of discharging a diverse array of antibiotics, thereby contributing to multidrug resistance in bacterial populations. The upregulation of efflux pump expression in organisms such as *Pseudomonas aeruginosa* and *Escherichia coli* poses a significant challenge to the effectiveness of antibiotic therapies, leading to diminished therapeutic outcomes[15]. The AcrAB–TolC efflux pump in *Escherichia coli* and the MexAB–OprM system in *Pseudomonas aeruginosa* exemplify mechanisms that confer multidrug resistance (MDR) to bacterial species, enabling them to endure elevated levels of antibiotic exposure [16]. Efflux pumps represent a fundamental mechanism underlying antibiotic resistance in both gram-positive and gram-negative bacterial species. These transport proteins actively expel antimicrobial agents from the bacterial cell, thereby reducing the intracellular concentration of the drugs and diminishing their efficacy. This phenomenon poses significant challenges in the treatment of bacterial infections, necessitating a deeper understanding of efflux pump mechanisms to develop more effective therapeutic strategies [17,18].

The action of enzymes that degrade antibiotics

A prevalent mechanism of antibiotic resistance involves the synthesis of enzymes that either degrade or alter antibiotics, thereby neutralizing their efficacy. For example, beta-lactamase enzymes can hydrolyse the beta-lactam ring present in penicillins and cephalosporins, leading to the inactivation of these pharmacological agents. Among the most concerning types of beta-lactamases are extended-spectrum beta-lactamases (ESBLs) and carbapenemases, which are resistant to more than ten beta-lactam antibiotics, including

critical therapeutic options such as carbapenems[19]. The proliferation of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae within clinical environments has escalated into a significant public health concern. Consequently, patients are increasingly confronted with a limited array of effective antimicrobial options for the management of these resistant pathogens[20].

Mutations

Bacterial mutations in their genetic material can lead to alterations in the target sites of antibiotics, resulting in a diminished binding affinity and subsequent resistance to these pharmacological agents. For example, mutations in the rpoB gene, which encodes an RNA polymerase, have been identified as significant contributors to the development of resistance to rifampicin, an essential medication in the treatment of tuberculosis[21]. The mutations observed in the gyrA gene significantly influence the functionality of the DNA polymerase protein, leading to the development of fluoroquinolone resistance in bacteria. Fluoroquinolones represent a widely utilized class of antibiotics that are particularly effective in treating respiratory and urinary tract infections[22]. Mutations in bacterial populations can proliferate rapidly, particularly in environments characterized by elevated antibiotic pressure.

Target Modification

Bacteria can develop resistance through various mechanisms, including alterations in antibiotic target sites. This phenomenon can result in the failure of drugs to bind effectively to their intended targets. A notable example is the modification of penicillin-binding proteins (PBPs) in *Staphylococcus aureus*, which confers resistance to methicillin, a member of the beta-lactam antibiotic class. Additionally, mutations in the mecA gene have been identified, leading to the production of a modified PBP (PBP2a) that has significantly reduced affinity for beta-lactams. Consequently, this adaptation enables methicillin-resistant *Staphylococcus aureus* (MRSA) to survive in the presence of these antibiotics[23]. Alterations in the 23S rRNA component of the bacterial ribosome have been identified as a fundamental mechanism underlying resistance to macrolide antibiotics and other inhibitors of protein synthesis[24].

Permeability is reduced

Certain bacteria increase the impermeability of their outer membrane to waste and antibiotics, thereby preventing these substances from entering the cell. Gram-negative bacteria, exemplified by *Pseudomonas aeruginosa*, possess an outer membrane that is intrinsically less permeable than that of gram-positive bacteria. Additionally, mutations in porins—proteins that facilitate the passage of antibiotics and other molecules—can lead to a reduced flow of these agents through the outer membrane. This phenomenon of decreased permeability significantly contributes to the ineffectiveness of antibiotics, highlighting a critical challenge in combating bacterial infections[25].

Clinical Examples

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant antibiotic-resistant pathogen associated with various clinical infections, including skin and soft tissue infections, sepsis, and pneumonia. The resistance of MRSA to methicillin is attributed primarily to the mecA gene, which, upon activation, modifies penicillin-binding proteins (PBPs). This alteration ultimately enables bacteria to evade the effects of antibiotics, contributing to their survival and persistence in clinical settings[9]. The acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) in both inpatient and outpatient environments presents significant challenges, primarily due to the resistance of the organism to

conventional antibiotics. In such cases, clinicians may resort to the use of last-resort antibiotics, including vancomycin, as well as newer agents such as linezolid, to effectively manage infections[26].

***Vancomycin-Resistant Enterococcus* (VRE)**

Vancomycin-resistant enterococci (VREs) are a significant concern in the context of healthcare-associated infections, particularly among immunocompromised patients. Enterococci, which are typically found in the gastrointestinal tract, can develop resistance to vancomycin, one of the last-resort antibiotics available. This resistance leads to challenging clinical scenarios, resulting in infections that are difficult to manage, including bacteraemia, endocarditis, and urinary tract infections[27]. Vancomycin-resistant enterococci (VREs) exhibit a mechanism of resistance that involves the modification of cell wall precursors, rendering vancomycin ineffective in binding to and inhibiting cell wall synthesis. Consequently, the therapeutic options for VRE infections are restricted to alternative antibiotics, including linezolid and daptomycin. However, these alternatives frequently present a greater toxicity profile and reduced efficacy than vancomycin does.[28,29].

Multidrug-Resistant *Mycobacterium tuberculosis* (MDR-TB)

Tuberculosis (TB), caused by strains of *Mycobacterium tuberculosis* that exhibit drug resistance, represents a significant public health challenge, particularly in regions with elevated incidence rates of the disease.[30]. Multidrug-resistant tuberculosis (MDR-TB) is characterized by resistance to the two most potent first-line antitubercular agents, isoniazid and rifampicin. This condition represents a significant challenge in tuberculosis management. In cases where MDR-TB is diagnosed, the treatment options may include second-line drugs, which, while not substantially more effective, often exhibit increased toxicity. The use of these second-line agents in conjunction with MDR-TB treatment remains a critical consideration in clinical practice[31]. In contrast to drug-susceptible tuberculosis (TB), which can be effectively managed with shorter and safer treatment regimens, drug-resistant TB presents a significant challenge because of its resistance to two or more second-line medications. This necessitates the implementation of comprehensive drug combination strategies to enhance antimicrobial efficacy. The dynamics of antimicrobial resistance in this context require increased scrutiny from both researchers and healthcare providers to develop more effective treatment protocols[32,33].

Carbapenem-Resistant *Enterobacteriaceae* (CRE)

Carbapenem-resistant *Enterobacteriaceae* (CRE), which include strains of *Klebsiella pneumoniae* and *Escherichia coli*, are resistant to carbapenems, which are regarded as the most effective last-line antibiotics for treating gram-negative infections[34]. The resistance mechanisms to carbapenems in certain pathogens, particularly in the context of resistant strains, are predominantly attributed to the production of carbapenemase enzymes. Notably, *Klebsiella pneumoniae* carbapenemase (KPC) is a significant enzyme that facilitates the hydrolysis of a wide range of carbapenems. This enzymatic activity undermines the efficacy of these critical beta-lactam antibiotics, posing a substantial challenge in clinical settings[35]. Therapeutic approaches for infections caused by carbapenem-resistant Enterobacteriaceae (CRE) are associated with significantly elevated mortality rates. The treatment landscape is characterized by a scarcity of effective drug combinations, often necessitating the use of older, more toxic agents such as polymyxins[36].

Current Global Challenges in Antibiotic Resistance

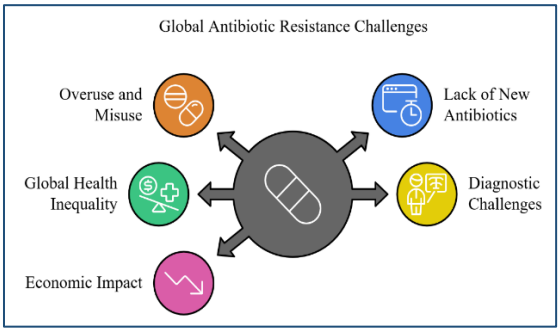

Figure 2-Current Global Challenges in Antibiotic Resistance

Overuse and Misuse of Antibiotics

One of the primary contributors to the global rise in antibiotic resistance is the excessive and inappropriate utilization of antibiotics. In clinical settings, antibiotics are frequently prescribed for viral infections, including common colds, despite the absence of effective treatments for these conditions. Research indicates that nearly 30–50% of antibiotics dispensed in outpatient clinics are prescribed inappropriately, often for ailments such as respiratory tract infections[37]. In developing countries, over-the-counter sales of medications often lead to self-medication practices among consumers, which can result in dosing errors that compromise the effectiveness of treatments. Notably, a study conducted in Bangladesh revealed that 44% of antibiotics were dispensed without a prescription, underscoring the significant public health implications of unregulated pharmaceutical sales[38,39]. The inappropriate application of antibacterial agents in the health sector is compounded by the improper prescription of these drugs in livestock, which represents a significant concern. The utilization of antimicrobials in animal agriculture is essential for maintaining productivity levels. This practice is particularly pronounced in the United States and China, where the volume of antibiotics administered to cattle surpasses that used in human populations. The emergence of antibiotic-resistant bacteria in animals poses a significant threat to public health, as these new strains can disseminate throughout the environment, ultimately exacerbating antibiotic resistance in both animals and humans. In 2017, the World Health Organization (WHO) recommended the cessation of routine antibiotic use in healthy animals. However, this recommendation has seen limited implementation, particularly in low-income countries where regulatory oversight is often insufficient [40–42].

Lack of new antibiotics

The development of novel antibiotics has lagged significantly behind the increasing prevalence of antibiotic-resistant bacteria. In recent years, there has been a notable decline in the availability of new antibiotics on the market. Over the past four decades, the introduction of new antibiotic classes has been limited, with the majority being modifications of existing drugs rather than entirely new entities[14]. Pharmaceutical companies are increasingly apprehensive about investing in antibiotic development owing to the substantial costs and limited profitability associated with these medications. In contrast to treatments for chronic conditions, antibiotics are typically prescribed for brief durations, and the rapid emergence of resistance can render them ineffective within a few years. To combat this challenge, initiatives such as the Global Antibiotic Research and Development Partnership (GARDP) have been established to enhance antibiotic research and development through collaborative efforts between the public and private sectors. However, the drug development pipeline remains critically under resourced, and changes in policy

may result in scenarios where even common and mild infections become untreatable[43–45].

Global Health Inequality

Antibiotic resistance presents a significantly greater challenge in low- and middle-income countries (LMICs) than in developed nations. This disparity is largely attributed to the prevalence of infectious diseases and the inadequacy of healthcare resources in these regions. In LMICs, antibiotics are often utilized as substitutes for essential hygiene, sanitation, and infection control practices. The absence of regulatory oversight and limited access to affordable healthcare further exacerbate the situation, resulting in the widespread availability of antibiotics without prescriptions, which contributes to their misuse.[46]. In India, more than 70% of antibiotics are purchased without a medical prescription, contributing to the proliferation of antibiotic-resistant bacteria. Notably, multidrug-resistant *Mycobacterium tuberculosis* has serious public health implications associated with this trend, highlighting the urgent need for regulatory measures to control antibiotic sales and usage[47]. The disparities in the distribution of essential medications result in a significant imbalance, where certain populations experience an oversaturation of resources while others are deprived of access to life-saving treatments. This inequality exacerbates public health challenges, as untreated infections can lead to increased mortality rates and facilitate the rapid transmission of diseases. The World Health Organization has emphasized the critical need for a global response to address these inequities; however, progress in many regions remains sluggish[48,49].

Diagnostic challenges

The development of antibiotic resistance is significantly influenced by the inadequacy of affordable, rapid, and precise diagnostic methods, particularly in individuals suffering from respiratory tract infections or influenza. In the absence of reliable diagnostic tools, healthcare providers frequently prescribe antibiotics without justification, exacerbating the issue of resistance. This challenge is particularly pronounced in low-resource settings, where diagnostic capabilities are often insufficient or entirely lacking. Research indicates that in several low- and middle-income countries (LMICs), as many as 70% of antibiotic prescriptions are made on the basis of empirical evidence, disregarding laboratory test results in the decision-making process[50]. In low-income nations, the accessibility and affordability of rapid diagnostic antimicrobial susceptibility testing for antibiotic-resistant bacteria represent a vital resource for healthcare providers aiming to prescribe effective antibiotics. Notable advancements in this area can be observed through the implementation of rapid diagnostic tests (RDTs) for various diseases, including malaria and tuberculosis. Nevertheless, these technologies have yet to achieve significant market penetration and remain prohibitively expensive. Conversely, in high-income countries, where diagnostic tools are more widely accessible, the primary challenge is the integration of these tools into clinical workflows to ensure their consistent and effective utilization[51].

Economic impact

The increasing challenge of antibiotic resistance represents a significant public health concern that has deteriorated over time. This phenomenon not only poses serious health risks but also has substantial economic implications, contributing to a broader expansion of its impact on healthcare systems and society at large.[52]. Antimicrobial resistance is projected to have significant economic implications, potentially resulting in a loss of $100 trillion in global income by the year 2050. This phenomenon is also expected to contribute to an annual mortality rate of 10 million individuals. Consequently, the global economy may experience substantial detriment, leading to

considerable forfeiture of potential growth[53]. The financial implications of antibiotic resistance, characterized by the ability of microorganisms to withstand the effects of antibiotics, are substantial. These implications include increased healthcare expenditures, extended durations of hospitalization, and the need for more expensive and intricate treatment protocols. In the United States, the direct costs associated with managing resistant infections exceed $20 billion each year, alongside an estimated $35 billion in lost productivity attributable to employee illness[54,55].

In low- and middle-income countries (LMICs), the economic ramifications of healthcare challenges are particularly pronounced, exacerbated by elevated rates of antibiotic resistance and the limitations of healthcare infrastructure[56]. The prevention of common infections poses significant challenges in countries where such issues are pervasive. However, the primary concern lies in the overwhelming prevalence of diseases, which leads to unnecessary mortality. This situation underscores the urgent need for effective public health strategies to address the multitude of health threats faced by the population[57]. The inability to effectively manage simple infections leads to increased mortality rates, which in turn diminishes work productivity and hinders overall development. The World Bank projects that low-income countries will experience the most severe consequences, with an estimated 28 million individuals potentially falling into extreme poverty by 2030 due to the decline in migrant labour caused by the proliferation of resistant microbes. This issue predominantly impacts low-income nations. To address antibiotic resistance and mitigate the associated economic repercussions, the development of new pharmaceuticals and the establishment of effective diagnostic methodologies as critical components of disease prevention and public health initiatives are essential[44].

Current strategies to combat antibiotic resistance

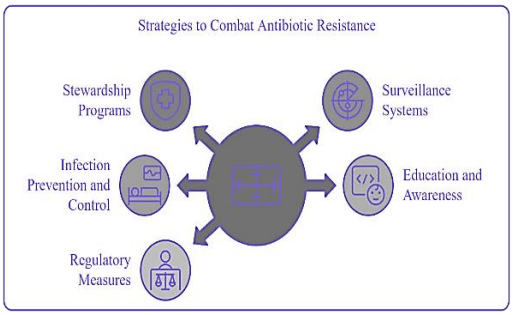

Figure 3 Current Strategies to Combat Antibiotic Resistance

Stewardship Programs

Antimicrobial stewardship programs (ASPs) represent organized initiatives aimed at optimizing antibiotic use to enhance patient outcomes while minimizing the development of resistance. These programs ensure that antibiotic prescriptions are issued only when clinically warranted and that the most appropriate antibiotic, dosage, and treatment duration are selected. Typically, ASPs are supported by a specialized advisory committee comprising infectious disease specialists, pharmacists, and microbiologists. A key component of these stewardship efforts is the implementation of prospective audits of antibiotic prescriptions, which provide valuable feedback to prescribers. Research indicates that such audits can lead to a reduction in unnecessary antibiotic use of 20–36%[58]. In the United States, hospitals that have implemented antimicrobial stewardship programs (ASPs) have reported significant reductions in antibiotic usage and a decrease in healthcare-associated infections (HAIs) attributed

to multidrug-resistant organisms (MDROs), including methicillin-resistant *Staphylococcus aureus* (MRSA)[59]. The promising potential of the aforementioned programs has been envisioned in high-income countries; however, their implementation in low- and middle-income countries (LMICs) remains constrained by a lack of adequate resources [60].

Surveillance Systems

Surveillance systems have emerged as essential instruments for monitoring antibiotic utilization and resistance trends on a global scale. These systems are crucial for informing public health policies and interventions, as well as for tracking shifts in microbial populations. The Global Antimicrobial Resistance Surveillance System (GLASS), initiated by the World Health Organization (WHO), aggregates data related to antimicrobial resistance (AMR) across human, animal, and environmental domains from over 100 countries worldwide. In nations such as the United Kingdom, where surveillance frameworks are robustly established, early detection of resistance trends has facilitated targeted interventions. A notable example is the implementation of the Five-Year Antimicrobial Resistance Strategy in 2015, which stemmed from the national surveillance program and aimed to reduce antibiotic prescriptions by 7% within a three-year timeframe[61,62]. The infrastructure necessary for comprehensive surveillance is often lacking in numerous low- and middle-income countries (LMICs). As a result, these nations face significant challenges in both monitoring resistance and implementing the necessary measures to effectively control outbreaks[47].

Infection prevention and control (IPC)

Infection prevention and control (IPC) strategies are essential for mitigating the transmission of drug-resistant infections, particularly within healthcare settings. Effective IPC measures, such as hand hygiene, environmental sanitation, and isolation of infected individuals, have demonstrated significant efficacy in curtailing the dissemination of multidrug-resistant organisms (MDROs). A comprehensive analysis of a six-year survey conducted on *Pseudomonas aeruginosa* in China indicated that the implementation of IPC strategies, with a specific focus on hand hygiene and environmental cleaning, yielded remarkable success, resulting in a greater than 60% reduction in the incidence of multidrug-resistant *P. aeruginosa* infections[63]. In affluent nations, healthcare-associated infections (HAIs) have prompted the adaptation of infection prevention and control (IPC) programs, with a focus on mitigating the transmission of antibiotic-resistant bacteria. The integration of both IPC measures and antimicrobial stewardship programs (ASPs) has proven to be particularly efficacious, as it reduces the overuse of antibiotics, thereby alleviating the selective pressure that contributes to the emergence of resistance[64].

Education and awareness programs

Education and awareness initiatives play crucial roles in combating antibiotic resistance by fostering an environment in which both healthcare professionals and the general public utilize antibiotics judiciously. The primary focus of these programs is to influence healthcare providers to modify their prescribing behaviours and to educate patients on reducing the necessity for antibiotic prescriptions[65]. In Europe, the "European Antibiotic Awareness Day" campaign has effectively enhanced public understanding of antibiotic usage, contributing to a reduction in inappropriate consumption of these medications. Furthermore, providing comprehensive training for healthcare professionals, including nurses and doctors, is essential to ensure the appropriate application of antibiotics in clinical practice[66]. A study conducted among medical students across various European countries revealed that while a significant number of students acknowledged the

importance of reducing drug usage, a considerable proportion lacked the confidence to prescribe appropriately. This indicates a critical area for improvement within the educational framework [67].

Regulatory Measures

Governments and international organizations have established essential regulations aimed at restricting the use of antibiotics and promoting their appropriate application to mitigate misuse. In 2017, the World Health Organization (WHO) issued guidelines to reduce the administration of antibiotics in healthy animals. Additionally, the European Union implemented a stringent directive prohibiting the use of antibiotics as growth promoters in livestock[68,69]. In countries such as Sweden, the procurement of veterinary prescriptions for antibiotics is strictly regulated, permitted only when their use is substantiated as essential for animal welfare and serves as a definitive measure. This approach reflects a broader trend towards the humanization of agricultural policies. Consequently, these regions have experienced significantly reduced levels of antibiotic usage in livestock, which correlates with a lower incidence of antibiotic resistance in human populations during the same timeframe, particularly compared with other areas.[70]. The healthcare sector has witnessed significant advancements through the implementation of prescription auditing and the regulation of over-the-counter drug sales. These measures have contributed to the judicious use of antibiotics and the mitigation of antibiotic resistance in nations such as Australia and South Korea[71,72].

Future Directions in Research and Development

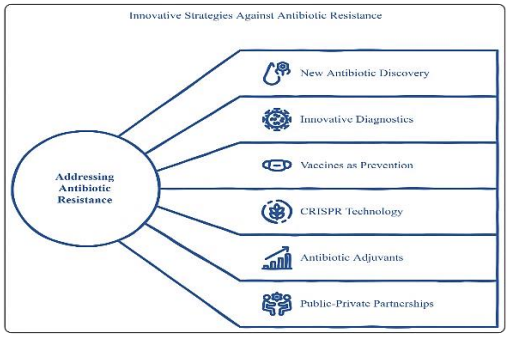

Figure 4 Future Directions in Research and Development

New Antibiotic Discovery

The development of novel antibiotics represents a critical strategy to address the significant challenge posed by antimicrobial resistance (AMR). Despite the pressing need for new antibiotics, the decline in their development can be attributed to several factors, including substantial research expenditures, limited financial incentives, and the rapid emergence of bacterial resistance to newly developed medications. Nevertheless, innovative research avenues have emerged, facilitating the creation of new classes of antibiotics that target bacterial pathogens through diverse mechanisms. Notably, recent studies have concentrated on antibiotics that disrupt bacterial communication, particularly through the quorum-sensing pathway, which plays a pivotal role in biofilm formation and subsequent pathogenicity [54]. Advancements in genomics and synthetic biology have facilitated the identification of novel bacterial targets through the utilization of innovative screening technologies that were previously inaccessible[74]. Recent advancements in antibiotic research offer promising prospects for addressing bacterial infections. Notably, the antibiotic teixobactin, identified through a novel soil screening technique, specifically targets lipids within bacterial cell walls. This mechanism of action contributes to its efficacy against gram-positive bacteria, including *Staphylococcus aureus*

and *Escherichia coli*, while demonstrating a reduced likelihood of immediate resistance development[[40]. Recent research has identified a novel class of antibiotics, referred to as odilorhabdins (ODLs), which demonstrate efficacy in combating drug-resistant bacterial strains. These compounds exert their antimicrobial effects by inhibiting the ribosomal translation process, thereby disrupting protein synthesis in targeted pathogens[75]. Despite advancements in the field, there remains a pressing need for increased investment in antibiotic research and development. This underscores the necessity for innovative incentives and robust regulatory support, alongside efforts to encourage pharmaceutical companies to engage in this critical yet challenging area of study.

Innovative Diagnostics

The advancement of technology in the realm of diagnostics plays a crucial role in enhancing the accuracy of antibiotic stewardship and mitigating the risks associated with antibiotic misuse. Rapid and precise diagnostic techniques enable healthcare professionals to swiftly determine the nature of an infection, distinguish between bacterial and viral origins, accurately identify the specific pathogen, and assess its susceptibility to antibiotics. Traditional diagnostic approaches, which depend on the culture of bacterial pathogens, present several limitations, including protracted timelines and the potential for unnecessary antibiotic prescriptions. In contrast, innovative molecular diagnostic methods, such as polymerase chain reaction (PCR) and next-generation sequencing (NGS), offer the advantage of delivering results within hours, significantly reducing the time required for diagnosis[76] The advancement of point-of-care diagnostics is increasingly evident, offering portable and user-friendly devices suitable for deployment in constrained laboratory environments, particularly in low-resource settings. A significant focus within this domain is the CRISPR-based diagnostic tool, which leverages CRISPR–Cas systems to accurately identify specific bacterial DNA sequences with high precision[77]. The utilization of these tools is particularly crucial in regions with inadequate antimicrobial resistance surveillance, as they have the potential to revolutionize therapeutic approaches and reduce reliance on empirical treatments in favour of pathogen-targeted therapies. However, the widespread implementation of these tools necessitates a prolonged process of enhancement concerning both affordability and accessibility.

Vaccines as Prevention Agents

Vaccines play a crucial role in combating antibiotic overuse by preventing bacterial infections prior to their onset. They not only serve as a means of pathogen prevention, providing lasting immunity to vaccinated individuals but also contribute to a reduction in the overall prevalence of pathogens within the community. This collective immunity helps mitigate the emergence of antibiotic-resistant strains. A pertinent example is the pneumococcal conjugate vaccine (PCV), which has been widely implemented and has significantly reduced the incidence of infections caused by *Streptococcus pneumoniae*, including drug-resistant variants such as penicillin-resistant strains[78]. The ongoing challenge in vaccine development for highly resistant pathogens, including *Staphylococcus aureus* and *Mycobacterium tuberculosis*, is significant. The primary hurdle lies in creating vaccines capable of combating bacteria that are continuously evolving. Recent advancements in reverse vaccinology and immunogenomics are paving the way for the design of innovative vaccine types that offer protection against various bacterial species. This progress not only reduces the reliance on antibiotics but also addresses the issue of antibiotic resistance proliferation[79].

CRISPR Technology

CRISPR technology represents a significant advancement in genetic editing, offering potential solutions to the pressing issue of antibiotic resistance. CRISPR–Cas systems can be strategically engineered to target and eliminate antibiotic resistance genes within bacterial populations. These CRISPR-based therapeutic approaches function by cleaving DNA at specific resistance gene loci, facilitating the proliferation of bacterial strains that are either eradicated or rendered susceptible to antibiotic treatment.[80]. Precision CRISPR systems present a viable alternative to traditional antibiotics by specifically targeting pathogenic bacteria while preserving the beneficial microbiota. The application of CRISPR technology in bacteriophage therapy involves the engineering of bacteriophages that are programmed via CRISPR–Cas systems to selectively attack antibiotic-resistant strains. Laboratory experiments have demonstrated that these engineered bacteriophages effectively eliminate only antibiotic-resistant strains of *Escherichia coli* and *Staphylococcus aureus*, highlighting their potential in combating antibiotic resistance[81]. The application of this technology remains limited; however, it holds significant promise in addressing resistance issues, offering an alternative to traditional antibiotics.

Antibiotic Adjuvants

Antibiotic adjuvants are specialized compounds that increase the efficacy of existing antibiotics by either increasing their therapeutic effects or mitigating the impact of bacterial resistance mechanisms. These adjuvants operate through various mechanisms, such as inactivation of bacterial resistance enzymes, including beta-lactamases, or modification of bacterial efflux pumps that expel antibiotics from the cell. A notable example is clavulanic acid, a beta-lactamase inhibitor that is utilized in combination with beta-lactam antibiotics to prevent the enzymatic degradation of these drugs, thereby improving their effectiveness against resistant bacterial strains [82]. Recent research on novel adjuvants has identified compounds capable of inhibiting efflux pumps, which represent a primary mechanism employed by bacteria to evade the effects of antibiotics. The incorporation of these adjuvants has the potential to extend the effective lifespan of current antibiotics by circumventing resistance mechanisms, thereby allowing for the reutilization of antibiotics against resistant bacterial strains.[83]. Adjuvants represent a cost-effective strategy for utilizing previously established antibiotics that have been supplanted by more potent alternatives because of their demonstrated efficacy in combating specific infections.

Public–private partnerships

There is a pressing need for enhanced international collaboration among governmental bodies, academic institutions, and private sector entities to effectively address the global challenge posed by antibiotic resistance. The synergy between the public and private sectors has emerged as a critical determinant for the successful development of antibiotics[84]. Global initiatives, including the Global Antibiotic Research and Development Partnership (GARDP) and the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), represent prominent organizations dedicated to fostering collaboration among various stakeholders in the fight against antibiotic resistance[85]. Joint ventures play a pivotal role in advancing the manufacturing of novel antibiotics, diagnostics, and alternatives by providing essential financial resources, facilities, and expertise. For example, the Global Antibiotic Research and Development Partnership (GARDP) aims to develop five new drug alternatives by 2025, specifically those that target the treatment of drug-resistant bacterial infections, particularly in low- and middle-income countries (LMICs), where this issue is most pronounced. Public-

private partnerships (PPPs) are crucial for fostering sustained research initiatives, as they facilitate the distribution of financial risk and promote market engagement through innovative solutions. Strengthening these collaborative efforts is fundamental to addressing the global antibiotic crisis effectively[86,87].

Policy recommendations

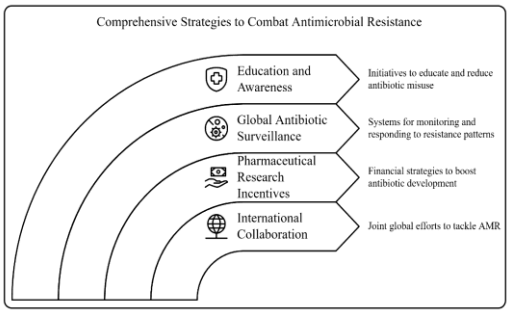

Figure 5 Strategies to Combat Antimicrobial Resistance

International Collaboration

Antimicrobial resistance represents a global challenge that transcends national boundaries, necessitating collaborative international efforts to address and overcome this pressing issue effectively.[88]. Countries must collaborate through established frameworks, such as the World Health Organization's (WHO) Global Action Plan on Antimicrobial Resistance (AMR). This initiative facilitates the responsible utilization of antibiotics across human, animal, and environmental contexts while also promoting the sharing of research, data, and strategic approaches among nations[89]. The Global Antimicrobial Resistance Surveillance System (GLASS) exemplifies a significant achievement in international collaboration, as it facilitates the collection of antimicrobial resistance (AMR) data from more than 100 countries. This extensive data aggregation enables the global monitoring of resistance patterns and offers essential insights for the development of targeted interventions.[90] The Fleming Fund, along with various other initiatives, exemplifies a significant global partnership based in the United Kingdom that aims to enhance antimicrobial surveillance and laboratory capabilities in low- and middle-income countries. Such collaborations illustrate the effectiveness of pooling resources, expertise, and information to address the pressing issue of antimicrobial resistance (AMR) efficiently. Furthermore, the establishment of regional networks, such as the European Antimicrobial Resistance Surveillance Network (EARS-Net), serves as a prime illustration of multinational cooperation, which can fortify surveillance, research, and response strategies in combating antibiotic resistance.

Incentives for Pharmaceutical Research

Governments play a critical role in establishing a sustainable financial framework for the development of antibiotics by allocating essential funding to pharmaceutical companies. The current trajectory of antibiotic drug development is significantly impacted by substantial research and development expenses coupled with limited financial returns, primarily due to the swift emergence of resistance and the relatively brief treatment duration of antibiotics in contrast to that of medications for chronic diseases[45]. Governments can address the challenges associated with antibiotic development by implementing a dual strategy of "push" and "pull" incentives. Push incentives, which encompass financial support mechanisms such as grants and tax credits for early-stage companies, alleviate the economic pressures these entities face. Conversely, pull incentives, including market

entry bonuses and advance purchase agreements, ensure a guaranteed return on investment, thereby increasing the profitability of newly developed antibiotics. This comprehensive approach fosters innovation and encourages the sustainable development of essential medical treatments[91].

The Generating Antibiotic Incentives Now (GAIN) Act represents a notable instance of effective incentive programs within the United States aimed at addressing the critical issue of antibiotic resistance[92]. The legislation incentivizes pharmaceutical companies by extending market exclusivity for those that successfully develop and obtain approval for new antibiotics. Additionally, it has facilitated the development of various novel antibiotics, including ceftolozane/tazobactam, which have demonstrated efficacy against multidrug-resistant gram-negative bacteria[93]. The Global Antibiotic Research and Development Partnership (GARDP) exemplifies an effective model for research and development through public-private partnerships, focusing on the creation of cost-effective and accessible treatments, particularly for low-income nations. Enhancing these global incentives is crucial for sustaining the development pipeline of novel antibiotics[87].

Global Antibiotic Surveillance

The monitoring of resistance trends and corresponding policy responses is essential for the efficacy of global antibiotic surveillance. Surveillance systems serve as critical mechanisms for the real-time observation of resistance patterns across nations, enabling early detection and the implementation of targeted interventions. However, numerous low- and middle-income countries face significant challenges due to inadequate infrastructure for comprehensive surveillance. Consequently, the expansion of global initiatives, such as the Global Antimicrobial Resistance and Use Surveillance System (GLASS), represents a pivotal strategy for addressing these deficiencies and ensuring that all nations possess the capacity to engage in antimicrobial resistance (AMR) surveillance effectively[46]. The five-year antimicrobial resistance strategy implemented in the United Kingdom exemplifies a comprehensive approach to addressing antimicrobial resistance through the establishment of a robust surveillance system. This initiative has proven to be an effective model for the management of antibiotic use across the human, animal, and environmental health sectors[94,95]. The implementation of this system resulted in a 7% reduction in unnecessary antibiotic prescriptions, subsequently facilitating the development of public health policies grounded in empirical data. It is imperative for international organizations to sustain their support for the advancement of such systems, particularly in resource-limited regions where surveillance capabilities are notably deficient.

Education issues

Educational initiatives aimed at raising awareness about the nature of antibiotic resistance and discouraging imprudent usage are crucial components of efforts to mitigate the abuse and misuse of antibiotics[96]. Research indicates that public education, particularly when integrated with medical education, can significantly mitigate antibiotic misuse, potentially reducing rates by as much as 50%. A pertinent example is the European Union's annual European Antibiotic Awareness Day (EAAD), which has effectively raised awareness regarding the dangers of antibiotic misuse. Consequently, a notable 15% decrease in antibiotic consumption has been observed in countries such as France and the Netherlands over the past decade[97]. In addition to extensive publicity initiatives, healthcare providers necessitate comprehensive and sustained educational and training programs, particularly in the selection of appropriate medications[98]. Existing initiatives, such as the

National Prescribing Service (NPS) in Australia, exemplify effective educational strategies aimed at enhancing the understanding of antibiotic utilization and misuse among medical professionals. These initiatives have contributed to a significant reduction in the irrational prescription of antibiotics for respiratory infections. The global dissemination of similar programs, particularly in low-resource settings, would ensure that both the general public and healthcare practitioners are better equipped with the essential skills and knowledge required to combat the escalating issue of antibiotic resistance[99–101].

CONCLUSION

Antibiotic resistance poses a significant threat to public health globally, primarily driven by the inappropriate use of antibiotics in both healthcare and agricultural settings, insufficient new drug development, and the rapid emergence of multidrug-resistant organisms. The prevalence of resistant pathogens, such as MRSA, VRE, and MDR-TB, complicates the treatment of common infections, leading to prolonged hospital stays, increased healthcare costs, and increased mortality rates. To effectively combat this issue, implementing a comprehensive strategy that encompasses stewardship programs, surveillance systems, infection prevention and control measures, public education, and regulatory frameworks that promote responsible antibiotic use is crucial. Additionally, it is essential to allocate funding towards the research and development of new antibiotics, vaccines, and alternative therapies to keep pace with the evolving landscape of bacterial resistance. Collaborative efforts among governments, healthcare providers, researchers, and the public are necessary to formulate policies aimed at mitigating antibiotic resistance. Key initiatives include enhancing antimicrobial stewardship and expanding surveillance systems globally to minimize unnecessary antibiotic usage and detect emerging resistance patterns. Furthermore, prioritizing funding for pharmaceutical companies is vital to rejuvenating antibiotic research and development. Public awareness regarding the risks associated with antibiotic misuse should be fostered through educational campaigns, and healthcare professionals must be trained to prescribe antibiotics judiciously. A unified and sustained effort is imperative to address the increasing challenge of increasing antibiotic resistance effectively. The future of antibiotic resistance management hinges on the development of innovative treatments and collaborative international efforts. By consistently investing in research and enacting policy reforms, it is feasible to diminish the adverse effects of resistance and preserve the efficacy of antibiotics in combating bacterial infections. However, immediate action is needed to prevent the onset of a post-antibiotic era.

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Abbreviations

Methicillin-resistant *Staphylococcus aureus* (MRSA) Vancomycin-resistant *Enterococci* (VRE) Multidrug-Resistant Tuberculosis (MDR-TB) Antibiotic resistance (ABR) Carbapenem-resistant *Enterobacteriaceae* (CRE) extended spectrum beta-lactamases (ESBLs) penicillin-binding proteins (PBPs) tuberculosis (TB), *Klebsiella pneumoniae* carbapenemase (KPC) Global Antibiotic Research and Development Partnership (GARDP) low- and middle-income countries (LMICs) rapid diagnostic tests (RDTs)

Antimicrobial stewardship programs (ASPs) multidrug-resistant organisms (MDROs) healthcare-associated infections (HAIs) Global Antimicrobial Resistance Surveillance System (GLASS) Infection prevention and control (IPC) polymerase chain reaction (PCR) next-generation sequencing (NGS) pneumococcal conjugate vaccine (PCV) Combating an Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) European Antimicrobial Resistance Surveillance Network (EARS-Net) Generating Antibiotic Incentives Now (GAIN) National Prescribing Service (NPS).

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