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ANTIMICROBIAL RESISTANCE A GLOBAL BURDEN - MECHANISMS, CURRENT INSIGHTS, AND FUTURE DIRECTIONS

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Antimicrobial resistance (AMR) poses a significant global health threat, characterized by the increasing prevalence of drug-resistant infections and the diminishing pipeline of novel antibiotics. The development of resistance mechanisms, including target site alteration, efflux pumps, and enzymatic inactivation, has contributed to the spread of AMR among human pathogens, both within healthcare settings and the broader community. These resistance mechanisms often arise in response to the misuse and overuse of antibiotics. Antimicrobial agents exert their effects through various mechanisms, such as inhibiting cell wall synthesis (e.g., β-lactams), protein synthesis (macrolides, tetracyclines), nucleic acid synthesis (fluoroquinolones, rifampin), or metabolic pathways (trimethoprim-sulfamethoxazole). However, the emergence of AMR has challenged the efficacy of these agents. Addressing AMR requires a multifaceted approach, including optimizing antibiotic use, strengthening infection prevention and control measures, and accelerating the development of new antimicrobial agents and diagnostics. While some studies have shown the potential for reversing antimicrobial resistance under specific conditions, the overall challenge remains complex and multifaceted. This review provides an overview of AMR, its underlying mechanisms, and the critical need for global action to mitigate its impact.

Keywords: *Antimicrobial resistance, Cell wall synthesis, Macrolides, Tetracyclines, Fluoroquinolones*

INTRODUCTION

Antibiotic resistance is a term used for significant worldwide public health concerns that will grow more serious in the upcoming years.[1,2] Worldwide, public health continues to be seriously threatened by antimicrobial resistance (AMR), which requires an in-depth understanding of its scope and effects. The increasing prevalence of AMR undermines the effectiveness of antimicrobial agents, jeopardizing the treatment of various infections. To address this challenge, a comprehensive understanding of the extent and impact of AMR is crucial.[3]

In 2022, a thorough investigation was undertaken to determine the global burden of bacterial AMR. Fungal resistance to antibiotics, which develops with modifications to microbes and decreases the effectiveness of antibiotics applied for therapy diseases, was identified as among the most severe health problems in our 21st era.[4] According to a worldwide cost of disease and risk factors

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inquiry, it may be concluded that in 2019, antibiotic resistance was the third most common reason for deaths (as compared to each of the levels in the system), with severe heart states and a stroke.[1,5] The World Health Organization Worldwide Plan for Antibiotic Resistance was published in 2001, and it provides methods to prevent the creation and spread of anti-resistant organisms.[6] The United States Agency for Control and Prevention of Disease Board says that antibiotic-resistant diseases affect more than 2 million people annually, causing at least 23,000 deaths.[7]

Antibiotic resistance grows worldwide with increased use and the distribution of medicines in underdeveloped nations.[8] AMR is a necessary evolutionary result, as every species produces mutations that prevent harmful selection. While medicines treat personal infections, the microbe could keep growing with applied immunity causes.[9] AMR is an international threat as novel resistance mechanisms are appearing and spreading worldwide, harming the capacity to cure prevalent illnesses that cause extra sickness, disorder, or death.[10] To ensure people's security, the Global Council of Health Promotion Unions established the World Association for Public Health and many international experts to assist with the delivery of difficult health policies.[12-13] It provides instructions for both services (core activities (safety, detection, and growth) and functions (catalyst roles like administration, representation, limit, and knowledge).

The escalating global health crisis of AMR is driven by the overuse and misuse of antimicrobials, particularly in low- and middle-income countries. This phenomenon has led to a significant increase in morbidity and mortality rates associated with infectious diseases. [14-16] Both primary facilities with helping roles have been required to support the administration about vital global fitness issues like AMR. To address this pressing issue, a multi-faceted approach involving global, national, and individual efforts is imperative. While scientific research has highlighted the risks of AMR, translating this knowledge into effective policy and public health interventions remains a challenge. [11] The urgent need for international collaboration and coordinated action is underscored by the alarming statistic that AMR is responsible for an estimated 50,000 deaths annually in the US and EU alone. [17,18] The World Medical Association has called for a global strategy to combat antimicrobial resistance, emphasizing the importance of a coordinated response from the global health community. [19]

AMR poses a significant global health threat, particularly in regions with high burdens of infectious diseases. *Staphylococcus aureus*, a common cause of serious infections, has developed resistance to multiple antibiotics, leading to increased morbidity and mortality.[20] AMR exacerbates the severity of infections, prolongs hospital stays, and elevates healthcare costs, including the need for more expensive treatment options.[21]

India and Africa are particularly vulnerable to the impact of AMR. India's high burden of infectious diseases, compounded by poor sanitation and malnutrition, creates a conducive environment for the emergence and spread of AMR.[22] Similarly, in Africa, infectious diseases are a leading cause of death, especially among children under six years, further exacerbating the challenges posed by AMR.[23] The prevalence of hunger in these regions, coupled with the high burden of infectious diseases, makes them particularly susceptible to the devastating consequences of AMR.[5]

This growing crisis is fueled by factors such as the overuse and misuse of antibiotics, the dissemination of resistant strains, and the limited development of novel antibiotics. In recent years, there has been a surge in reports of AMR among various pathogens, including *Escherichia coli* and respiratory tract pathogens. For instance, resistance rates to fifth-generation cephalosporins and fluoroquinolones in *E. coli* have been documented to range from 0.88% to 0.98%, while resistance to ketolides among different bacterial strains varies from 8% to 77%.[24] Similarly, respiratory pathogens exhibit resistance rates ranging from 0% to 99%, and *E. coli* resistance to fluoroquinolones is estimated to be between 1% and 40%.[25] This alarming rise in AMR has positioned it as a major global health challenge in the 21st century, underscoring the urgent need for innovative solutions to combat this crisis.[26]

By 2051, infections could become the leading cause of death worldwide if effective measures are not implemented.[27] The global economic burden of AMR-related deaths is projected to reach a staggering one trillion dollars annually by 2030.[28] Regulatory bodies, often hindered by limited funding, struggle to effectively address this crisis.[29] To combat AMR, it is imperative to explore innovative strategies beyond conventional approaches. Emerging technologies, such as advanced therapeutic combinations, smart delivery systems, and AI-powered drug discovery, hold promise in addressing this challenge.[30] This review delves into these novel approaches, highlighting the need for adaptive, multidisciplinary strategies to mitigate the devastating impact of AMR on global health systems.[31]

Understanding the Drivers of Antimicrobial Resistance

The emergence and spread of AMR is a complex global health challenge driven by a combination of human, animal, and environmental factors.[32] Inappropriate antibiotic use in healthcare settings, including overprescription, misuse, and non-adherence, contributes significantly to the development of resistant strains.[25,33] Over-the-counter antibiotic availability and self-medication practices further exacerbate this issue. Poor infection control measures and inadequate sanitation in healthcare facilities and communities facilitate the transmission of resistant organisms.[44]

In agriculture and veterinary medicine, the widespread use of antibiotics as growth promoters and disease preventatives in animals contributes to the development of resistant bacteria. These resistant organisms can then enter the human food chain through contaminated food products or direct contact with animals.[35,36] Environmental contamination, resulting from pharmaceutical waste and agricultural runoff, introduces antibiotics into the environment, creating selective pressures that promote the emergence of resistant bacterial populations.[37,38]

Globalization and increased travel facilitate the rapid dissemination of resistant bacteria across borders, further challenging global health efforts.[39] Economic and policy-related barriers, particularly in low- and middle-income countries, hinder effective AMR management.[40,41] Limited investment in AMR surveillance and stewardship programs, coupled with a shortage of novel antibiotics due to high research costs and low financial incentives, exacerbate the problem.[41,42] Finally, public behavior and social factors, such as misconceptions about antibiotic use, lack of awareness, and limited access to healthcare, contribute to inappropriate antibiotic consumption and the spread of AMR.[43,44] Cultural and socioeconomic factors often influence self-medication practices and unregulated access to antibiotics, accelerating the global AMR crisis.

Perspectives on Antibiotic Resistance

AMR is the ability of microorganisms to resist the effects of antimicrobial medications, such as antibiotics, antivirals, antifungals, and antiparasitics. This phenomenon poses a significant threat to global health, as it can lead to treatment failures, prolonged illness, increased healthcare costs, and higher mortality rates.[25,45] AMR arises from the natural ability of microorganisms to adapt and evolve over time. However, human activities, including the overuse and misuse of antimicrobials in medicine, agriculture, and animal husbandry, have accelerated the development and spread of drug-resistant pathogens.[46]

Sources of Bacterial Resistance

Bacterial susceptibility to antimicrobial agents varies widely among different species and strains.[47] Minimum Inhibitory Concentration (MIC) is a critical factor determining resistance levels, with high MICs indicating resistance and low MICs suggesting susceptibility.[48] Intrinsic resistance, a natural characteristic of certain species, results in consistently high MICs for specific drugs.[49]

Bacteria can acquire resistance through the acquisition of resistance genes, which can be transferred horizontally between different species.[50] The effectiveness of these acquired resistance genes varies, with some conferring minimal protection and others providing significant resistance. Understanding the complex interplay between intrinsic resistance, acquired resistance mechanisms, and horizontal gene transfer is essential for developing

effective antimicrobial strategies and mitigating the emergence of drug resistance.[51]

Natural/intrinsic resistance

Bacterial resistance can be broadly categorized into intrinsic and acquired/induced resistance.[52] Intrinsic resistance, a fundamental characteristic of a bacterial species, is not influenced by prior antibiotic exposure and is independent of horizontal gene transfer.[53] This inherent resistance is often associated with reduced outer membrane permeability, particularly in Gram-negative bacteria, and the intrinsic activity of efflux pumps.[54]

In contrast, acquired resistance results from the acquisition of resistance genes through various mechanisms, including mutation and horizontal gene transfer.[55] The activation of multidrug efflux pumps is a common mechanism underlying acquired resistance, enabling bacteria to expel antibiotics from the cell. **Table 1** provides examples of bacterial species exhibiting intrinsic resistance to specific antimicrobials.

Acquired resistance

Bacteria can acquire resistance genes through various mechanisms. Horizontal gene transfer (HGT), which encompasses transformation, transposition, and conjugation, is a primary route for acquiring external genetic material.[56] Plasmid-mediated transmission is the most common method for transferring resistance genes between bacteria, while phage-mediated transfer is less frequent.[58] Some bacteria, such as Acinetobacter species, can naturally take up DNA from their environment.[59] Within the bacterial cell, genetic material can move through processes involving insertion sequences and integrons.[60]

Stressful conditions, including starvation, UV radiation, and chemical exposure, can induce genetic mutations such as substitutions and deletions.[61] Bacteria typically experience one mutation for every 10^6 to 10^9 cell divisions, and most of these mutations harm the cell.[62] While the majority of mutations are detrimental to the bacterium, those that confer resistance to antimicrobial agents can confer a significant survival advantage. Such mutations often occur in genes encoding antibiotic-modifying enzymes, drug transporters, drug targets, or regulators of drug transporter activity.[50]

Table 1: Instances of Bacteria Exhibiting Intrinsic Resistance to Antimicrobials.

Intrinsic against	**Organism**
Aminoglycosides, many β-lactams, quinolones	*Bacteroides* (anaerobes)
Aztreonam	All Gram positives
Aminoglycosides, cephalosporins, lincosamides	*Enterococci*
Cephalosporins	*Listeria monocytogenes*
Glycopeptides, lipopeptides	All Gram negatives
Macrolides	*Escherichia coli*
Ampicillin	*Klebsiella* spp.
Macrolides	*Serratia marcescens*
Sulfonamides, ampicillin, cephalosporins, chloramphenicol, tetracycline	*Pseudomonas aeruginosa*
Aminoglycosides, β-lactams, carbapenems, quinolones	*Stenotrophomonas maltophilia*
Acinetobacter spp.	ampicillin, glycopeptides

Adaptive resistance

Adaptive resistance is a transient, reversible mechanism employed by bacteria to survive adverse conditions, including sub-inhibitory antibiotic concentrations, pH fluctuations, nutrient limitations, and oxidative stress.[63] Unlike acquired resistance, which involves permanent genetic alterations or horizontal gene transfer, adaptive resistance relies on temporary physiological and metabolic adjustments.[64] These adaptations often involve changes in gene expression or protein activity, enhancing bacterial resilience to antimicrobial agents under challenging circumstances.[65] Once the stressful conditions subside, bacteria typically revert to their original, non-resistant state.[66]

This adaptive strategy is crucial for bacterial survival in hostile environments, such as during antibiotic therapy. By temporarily altering their physiology, bacteria can evade the effects of antimicrobial agents.[67] However, these adaptive responses often come at a cost. For instance, methicillin-resistant *Staphylococcus aureus* (MRSA) exhibits slower growth rates.[68] Using these medications increases resistance, a major problem related to antimicrobial resistance.[69] Moreover, repeated exposure to sub-inhibitory antibiotic concentrations can select for resistant strains, leading to the emergence of hypermutable bacteria with increased rates of mutation and enhanced resistance to multiple antimicrobial agents.[70-71]

Mechanism of Resistance

Microorganisms have evolved a diverse array of mechanisms to resist antimicrobial agents. These strategies can be broadly categorized into four primary types, as detailed in **Table 2**.

Gram-negative bacteria, with their outer membrane, can employ a combination of these mechanisms, including efflux pumps, drug inactivation, and reduced permeability. In contrast, gram-positive bacteria, lacking an outer membrane, rely more heavily on mechanisms such as target site modification and metabolic adaptation. These intricate strategies contribute to the emergence and spread of antibiotic resistance, posing significant challenges to global health.[79,80] The general mechanisms of AMR are mentioned in **Fig. 1**.

Table 2: Mechanisms of Antimicrobial Resistance.

Types	**Detailed mechanism**
Reduced Drug Uptake	Bacteria can modify their cell membranes to limit the entry of antimicrobial agents, thus reducing their intracellular concentration and efficacy.[72]
Target Site Modification	Microorganisms can alter the structure or function of their cellular targets, such as ribosomes or enzymes, to diminish the binding affinity of antimicrobial drugs.[73]
Efflux Pump Overexpression	Bacteria can actively expel antimicrobial agents from their cytoplasm using efflux pumps, thereby reducing their intracellular concentration. This mechanism, often mediated by proteins like AcrAB-TolC in *E. coli*, can be upregulated in response to sublethal antibiotic exposure.[74,75]
Metabolic Adaptation	Some bacteria can enter a dormant or slow-growing state, known as the "persister" phenotype. This metabolic adaptation allows bacteria to tolerate antibiotic stress by reducing their metabolic activity and susceptibility to drug-targeted processes.[76,77] Certain bacteria can produce enzymes that inactivate or degrade antibiotics, neutralizing their antimicrobial activity.[78]

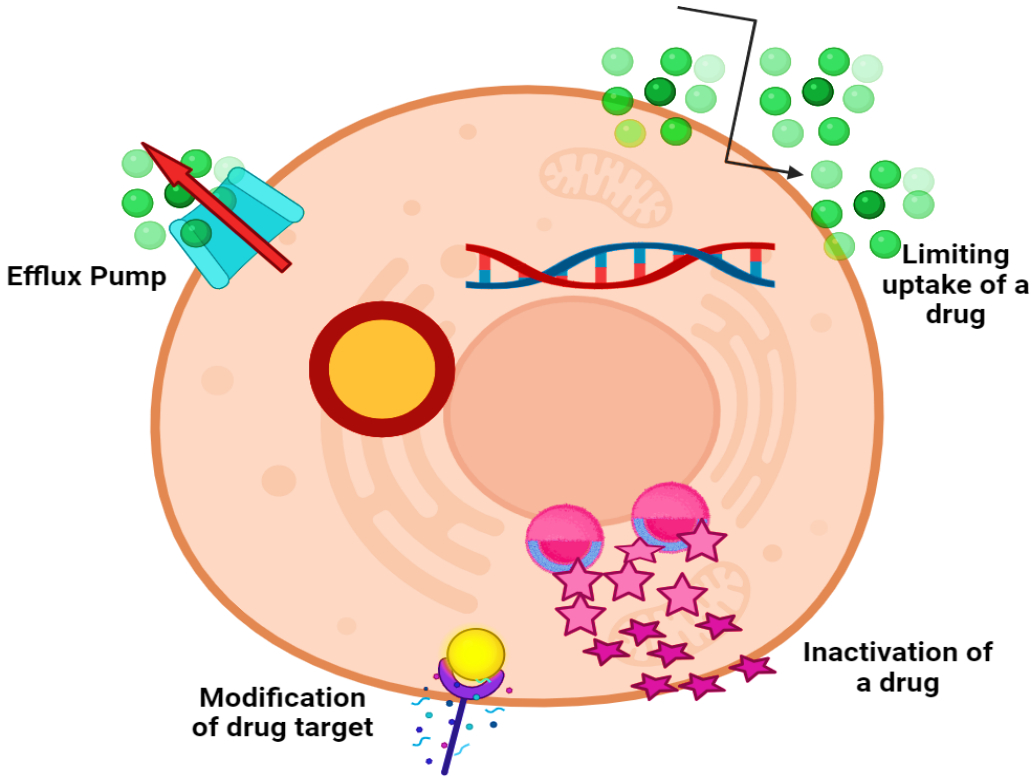

Fig. 1: The general mechanisms of AMR.

Bacteria have evolved various mechanisms to evade the antimicrobial effects of antibiotics. One common strategy involves limiting drug uptake. Gram-negative bacteria, with their outer lipopolysaccharide (LPS) layer, form a barrier against certain antibiotics. This structural feature contributes to the intrinsic resistance of some bacteria, such as the reduced susceptibility of mycobacteria to hydrophilic drugs due to their high lipid content.[72]

In contrast, Gram-positive bacteria, lacking an outer membrane, are generally more susceptible to antibiotic entry. However, some species, like enterococci, exhibit inherent resistance to aminoglycosides due to their cell wall structure.[81] Furthermore, bacteria can modify porin channels, which are protein pores in the outer membrane of Gram-negative bacteria. Alterations in porin number or structure can hinder the entry of drugs like carbapenems in Enterobacteriaceae[82] and tetracyclines and beta-lactams in *Neisseria gonorrhoeae*.[83] Biofilms, complex structures formed by bacterial communities, play a significant role in antimicrobial resistance. These biofilms, often composed of species like Pseudomonas aeruginosa, can limit drug penetration and shield bacteria from immune responses, necessitating higher drug dosages for effective treatment.[84] Furthermore, biofilms facilitate horizontal gene transfer, thereby promoting the spread of resistance genes among bacterial populations.[85]

Bacteria can also develop resistance by modifying drug targets. For instance, alterations in penicillin-binding proteins (PBPs), particularly in Gram-positive bacteria, hinder the binding of beta-lactam antibiotics. The mecA gene in *S. aureus* encodes a modified PBP (PBP2a), which confers resistance to beta-lactam antibiotics.[86] In Gram-negative bacteria, LPS can impede the entry of drugs like vancomycin, while mutations in cell wall components can compromise the effectiveness of antibiotics such as daptomycin and vancomycin.[87] Additionally, mutations in ribosomal subunits or DNA synthesis proteins can confer resistance. Moreover, alterations in folate biosynthesis enzymes can render bacteria resistant to sulfonamides and trimethoprim.[88]

Bacteria can directly inactivate antibiotics through enzymatic degradation or chemical modification. For example, beta-lactamase enzymes hydrolyze the beta-lactam ring of antibiotics, rendering them ineffective.

Similarly, transferases can add chemical groups to antibiotics, altering their structure and function.[89]

Efflux pumps, encoded by bacterial genes, play a pivotal role in antibiotic resistance by actively expelling antimicrobial agents from the bacterial cell.[90] These pumps are categorized into five major families: ABC, RND, SMR, MATE, and MFS. While each family possesses distinct structural and functional characteristics, they collectively contribute to multidrug resistance (MDR) phenotypes. Notably, gram-negative bacteria often utilize multi-component efflux systems to efficiently expel drugs across their complex cell envelope. In contrast, gram-positive bacteria primarily rely on MFS-type pumps to efflux drugs like fluoroquinolones, whereas RND pumps are particularly significant in Gram-negative bacteria.[91] These intricate defense mechanisms pose significant challenges in the treatment of bacterial infections.[80] **Fig. 2** illustrates the fundamental structures of different efflux pump families.

Recent Advances, and Trends in AMR Research

AMR is an increasingly urgent global health crisis, undermining the effectiveness of traditional treatments for bacterial and fungal infections. The alarming prevalence of drug-resistant microorganisms, such as third-generation cephalosporin-resistant *E. coli* and MRSA), highlights the urgent need for innovative solutions.[92] The World Health Organization (WHO) has emphasized the growing threat of antimicrobial resistance, particularly its impact on human health.[93] Fungal infections, especially in immunocompromised individuals, are notoriously difficult to treat and often exhibit resistance to conventional antifungal agents.[94]

AMR is a pressing global health crisis, causing millions of infections and deaths annually. A recent study published in The Lancet estimated that AMR resulted in approximately 5 million deaths worldwide in 2020.[95] In the United States alone, the CDC's 2018-2019 antimicrobial-resistant risks survey reported nearly 2.8 million AMR-related infections and approximately 35,000 associated deaths.[96] These alarming figures underscore the urgent need for continued research and innovative strategies to combat this growing threat.

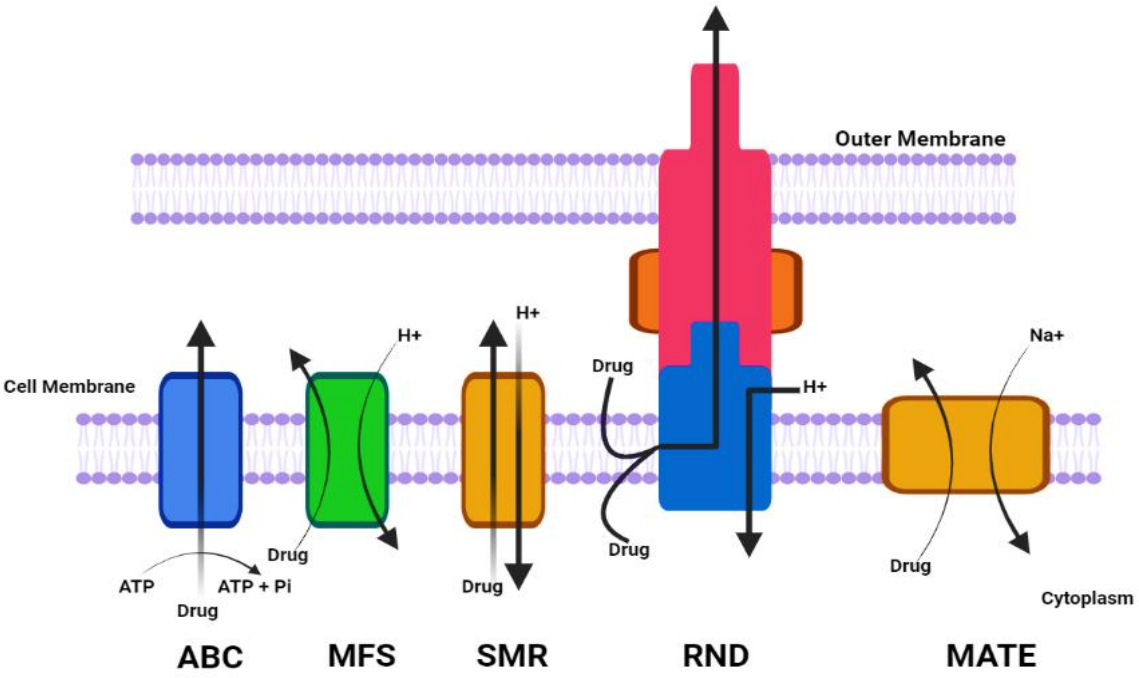

Fig. 2: Fundamental structure of different efflux pump families.

AMR poses a significant global health threat by compromising the efficacy of treatments for various infections, including bacterial, fungal, parasitic, and viral.[21] This growing challenge is driven by the overuse and misuse of antimicrobial agents in human medicine, agriculture, and animal husbandry.[65] Consequently, the prevalence of AMR continues to rise, impacting both common and severe infections.[97] The increasing resistance to antibiotics, antivirals, antifungals, and antiparasitics further complicates the management of infectious diseases.

Addressing the global challenge of AMR necessitates a One Health approach, recognizing the interconnectedness of human, animal, and environmental health. Collaborative efforts across these sectors are crucial to promote prudent antimicrobial use, strengthen surveillance systems, and implement effective infection prevention and control measures.[98] Research and innovation are pivotal in combating AMR. Ongoing efforts focus on developing novel antimicrobial agents, exploring alternative therapeutic strategies, and refining diagnostic tools. These advancements aim to address the growing threat of AMR and improve patient outcomes.[99]

Global efforts to combat AMR have gained significant momentum in recent years. Organizations such as WHO and the Food and Agriculture Organization (FAO) have spearheaded initiatives to strengthen surveillance systems, promote responsible antimicrobial use, and foster innovation in antimicrobial research and development.[100] Governments worldwide are implementing policies and regulations to curb the misuse of antimicrobials in various sectors, including human health, animal health, and agriculture.[101] Public awareness campaigns and educational initiatives are also being employed to raise awareness about AMR and the importance of infection prevention practices.[102] However, AMR remains a formidable challenge that requires ongoing attention and collaboration. Despite substantial progress, significant hurdles persist in effectively addressing this global health crisis.[103]

Clinical Implications of AMR

AMR has profound clinical implications, impacting patient outcomes, healthcare costs, and treatment strategies.[25] The emergence of resistant pathogens prolongs hospital stays, increases medical expenses, and elevates the risk of complications and mortality.[104] Infections caused by resistant microorganisms often necessitate more aggressive treatment regimens, including the use of last-resort antibiotics, which may exhibit reduced efficacy and increased side effects.[105]

Patients with AMR infections often experience prolonged illness, increased morbidity, and mortality.[106] Patients with resistant infections may experience prolonged illness and require additional medical interventions, which not only affects their quality of life but also strains healthcare resources. The extended duration of these infections can lead to secondary complications and chronic health problems, further straining healthcare resources.[107,108]

From an economic perspective, AMR contributes to soaring healthcare costs. The emergence of drug-resistant infections necessitates the use of more expensive and less effective treatments, prolonging hospital stays and increasing healthcare expenditures.[21] Beyond direct medical costs, AMR indirectly impacts economies through lost productivity and the broader societal consequences of increased illness and death.[109]

Moreover, AMR complicates treatment regimens, forcing healthcare providers to adapt their strategies in response to evolving resistance patterns.[110] This often necessitates empirical therapy, which may not always be optimal and can lead to treatment delays and suboptimal clinical outcomes.[111] As a result, frequent consultations with infectious disease specialists may be required, further hindering the timely initiation of appropriate treatment.[112]

The clinical implications of AMR are far-reaching, influencing not only individual patient outcomes but also the efficiency and effectiveness of healthcare systems worldwide.[113] Combating AMR necessitates a multi-faceted approach, including optimizing antibiotic stewardship, investing in research and development of novel antimicrobial agents, and implementing robust surveillance systems to monitor resistance trends.[114] By

comprehending and addressing the clinical consequences of AMR, we can significantly improve patient care and mitigate the global health burden associated with antimicrobial resistance.[100]

Smart Delivery and Combination Strategies for AMR

A promising approach to combat AMR involves the combination of novel drugs with advanced drug delivery systems.[115] These strategies offer several advantages, including enhanced drug efficacy, reduced side effects, and a decreased likelihood of resistance development.[116] By targeting drugs directly to the infection site, these approaches can maximize therapeutic benefits while minimizing damage to healthy tissues.[117]

Innovative delivery systems, including nanoparticles, liposomes, and infection-responsive polymers, offer promising solutions to address AMR.[118] These technologies enable targeted drug delivery, ensuring optimal antibiotic concentrations at the infection site.[119] For instance, nanoparticles can be designed to release antibiotics in response to infection-specific cues, leading to more precise and controlled drug release.[120] Additionally, liposomal carriers can enhance drug stability and bioavailability, while infection-responsive polymers can adapt to changes in the infection microenvironment.[121] Combining these smart delivery systems with synergistic drug combinations offers a powerful approach to combat AMR.[122] This integrated strategy has the potential to improve treatment efficacy and minimize the development of resistance, ultimately preserving the effectiveness of antibiotics for future generations.[123] Key innovative methods include:

Nanoparticle-Directed Delivery Systems

Nanoparticles (NPs) have emerged as promising tools for targeted drug delivery due to their tunable size, surface properties, and ease of functionalization.[122] Metallic NPs, including silver, gold, and zinc oxide, exhibit intrinsic antimicrobial properties.[124] These NPs can be engineered to target bacterial membranes or even penetrate resistant bacteria, enabling direct delivery of antibiotics to the infection site.[125] Polymeric NPs offer the advantage of encapsulating antibiotics, protecting them from degradation and minimizing off-target effects, thereby reducing toxicity to host cells. Furthermore, these NPs can be designed to release their payload in response to specific bacterial cues, such as enzymes or pH changes, enhancing efficacy and mitigating the development of resistance.

Liposome-Based Delivery Systems

Liposomes, spherical vesicles composed of phospholipid bilayers, have emerged as promising drug delivery systems for targeting bacterial infections. By encapsulating drugs within their lipid bilayer, liposomes protect them from degradation and enhance their delivery to the target site. Cationic liposomes, in particular, can interact with the negatively charged bacterial cell membrane, facilitating drug uptake and release.[126] Further, liposomes can be modified with targeting ligands to selectively bind to bacterial cells, thereby minimizing off-target effects and reducing the risk of antibiotic resistance. This approach has been successfully applied to deliver antibiotics to intracellular pathogens like *Mycobacterium tuberculosis*, enhancing drug accumulation within infected cells.[127]

Infection-Responsive Polymer-Controlled Delivery Systems

One promising approach to combat antibiotic resistance involves the development of infection-responsive polymer-based delivery systems. These systems utilize polymers that are designed to respond to specific infection-associated cues, such as bacterial enzymes or acidic environments, to release antibiotics precisely at the site of infection. For example, pH-responsive hydrogels can release their drug payload in the acidic microenvironment typically found in infected tissues. Additionally, enzyme-sensitive polymers, which degrade in the presence of bacterial enzymes like beta-lactamase, can trigger targeted drug release when pathogenic bacteria are present.[128] By limiting systemic exposure to antibiotics, these systems can help reduce the development of antibiotic resistance.

Combination Therapies with Localized Delivery

A promising strategy to combat antimicrobial resistance involves combining

antibiotics with non-antibiotic adjuvants and delivering them using advanced carrier systems.[129,130] Nanocarriers, such as liposomes and Layer-by-layer (LbL) nanoparticles, offer the potential to co-deliver multiple agents directly to the infection site. By co-delivering antibiotics with adjuvants, these nanocarriers can enhance antibiotic efficacy by overcoming resistance mechanisms like efflux pump activity or biofilm formation. Moreover, LbL nanoparticles enable the controlled release of multiple drugs over time, optimizing therapeutic outcomes for complex infections. Multi-drug-loaded liposomes can synchronize the release of two or more drugs, further potentiating their antimicrobial effects against multi-drug-resistant pathogens.[131]

CRISPR-Cas9 Guided Antimicrobial Therapy

CRISPR-Cas9 technology offers a novel approach to combat antibiotic resistance. By precisely targeting and inactivating resistance genes within bacterial populations, CRISPR-Cas9 systems can enhance the efficacy of conventional antibiotics. This innovative strategy involves the delivery of CRISPR-Cas9 systems directly to resistant bacteria, often utilizing phage-based vectors or nanoparticles. By reducing the prevalence of resistant strains, this approach aims to minimize the development of further resistance.[132]

Bacteriophage-Polymer Hybrid Systems

Bacteriophages, viruses that infect bacteria, have emerged as promising tools to combat antibiotic-resistant infections. Combining bacteriophage therapy with antimicrobial agents can provide a synergistic approach to combat multidrug-resistant bacteria. Encapsulation of phages within responsive polymers or nanoparticles offers several advantages, including enhanced stability, targeted delivery, and controlled release. These hybrid systems can protect phages from environmental degradation, extend their lifespan, and improve their ability to reach the infection site. Furthermore, by combining phage therapy with antibiotics, these systems can effectively reduce bacterial load and potentially prevent the development of antibiotic resistance.[133]

Localized Antimicrobial Photodynamic Therapy

Antimicrobial photodynamic therapy (aPDT) offers a promising alternative to traditional antibiotics by leveraging the power of light and photosensitizers. This approach involves the use of photosensitizing agents, often encapsulated in nanoparticles, that generate reactive oxygen species (ROS) upon exposure to light. These highly reactive species can effectively kill bacteria without relying on antibiotic mechanisms, thereby reducing the risk of developing antibiotic resistance. Gold nanoparticles and other metal-based nanoparticles are commonly used due to their efficient light absorption properties and ease of functionalization.

By targeting the delivery of photosensitizers to specific sites, aPDT aims to overcome key mechanisms of antibiotic resistance, including reduced permeability, efflux pumps, and biofilm formation. This localized and controlled approach offers a potential solution to the growing challenge of antibiotic resistance. Additionally, combining aPDT with traditional antibiotics or other antimicrobial agents may provide synergistic effects, further enhancing their therapeutic efficacy.[134]

Global and National Strategies to Combat AMR

The WHO's Global Action Plan on AMR, launched in 2015, provides a comprehensive framework to address this challenge. Key strategies outlined in the plan include raising awareness, strengthening surveillance systems, optimizing antimicrobial use, and investing in research and development for new antimicrobial agents and diagnostics.[135,32] To support member countries, the WHO has established the Global Antimicrobial Resistance Surveillance System (GLASS) to track AMR trends and inform evidence-based policy decisions.[136]

The global community has recognized the urgent need to address AMR and has implemented various strategies. A key approach is the One Health framework, advocated by the WHO, the FAO, and the World Organisation for Animal Health (WOAH). This framework emphasizes the interconnectedness of human, animal, and

environmental health and promotes a coordinated response to AMR.[21,137]

The United Nations Interagency Coordination Group (IACG) on AMR, established in 2016, further facilitates international cooperation, sustainable funding, and improved agricultural practices to combat AMR.[138] Organizations such as the Welcome Trust and the Bill & Melinda Gates Foundation have made significant contributions through funding AMR research. Additionally, the Global Antibiotic Research and Development Partnership (GARDP) is actively working to develop novel antibiotics and alternative treatments.[139,140]

In this global fight, India faces the dual challenge of a high infectious disease burden and rising AMR levels.[141] Recognizing this, India has implemented a comprehensive National Action Plan on AMR (2017-2021) to address AMR across both human and animal health sectors.[142] A key component of India's strategy is the establishment of a robust AMR surveillance network by the National Centre for Disease Control (NCDC). This network monitors resistance patterns in various pathogens, informing clinical guidelines and facilitating timely public health interventions.[143] To promote rational antibiotic use, India has implemented Antibiotic Stewardship Programs (ASPs) in healthcare facilities, emphasizing evidence-based prescribing practices and educating healthcare professionals.[144] Additionally, public awareness campaigns, in collaboration with the WHO, aim to educate the public about the risks of self-medication and the importance of appropriate antibiotic use.[145] Infection Prevention and Control (IPC) measures, including hand hygiene, sterilization, and isolation protocols, play a crucial role in preventing the spread of resistant bacteria and are a central part of India's AMR strategy.[146]

The global challenge of AMR necessitates a multi-faceted approach. India has made strides in addressing this issue through regulatory measures restricting the use of antibiotics as growth promoters in livestock.[147] Additionally, surveillance of antibiotic residues in food products underscores the importance of the One Health approach, which recognizes the interconnectedness of human, animal, and environmental health.[148]

Globally, countries have established surveillance networks like the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) and India's National Antimicrobial Resistance Surveillance Network (NARS-Net) to monitor AMR trends and inform evidence-based policymaking.[149] National Action Plans (NAPs), aligned with WHO guidelines, are tailored to specific national contexts.[150] For example, India's NAP prioritizes antibiotic stewardship and public awareness, while the UK's AMR Strategy (2019-2024) emphasizes reducing antimicrobial demand through improved hygiene and infection control.[151]

To mitigate the growing threat of AMR, countries worldwide have implemented various strategies. These include legislative measures to restrict over-the-counter antibiotic sales and regulate their use in agriculture.[152] For example, Europe has tightened regulations on livestock antibiotic use, while India's "red-line" campaign has limited antibiotic access without prescriptions.[22] National investments in AMR research have also increased, with organizations like India's Biotechnology Industry Research Assistance Council (BIRAC) and the United States Biomedical Advanced Research and Development Authority (BARDA) supporting innovations in diagnostics, antibiotics, and alternative therapies.[153]

However, challenges persist, including limited funding, inconsistent regulatory standards, and data-sharing gaps.[154] To effectively combat AMR, enhanced international collaboration, stricter regulatory enforcement, and investment in novel detection and therapeutic technologies are imperative.[155] A unified, multi-sectoral approach is crucial for achieving sustainable outcomes and safeguarding global health systems.[156]

The Role of Artificial Intelligence and Computational Tools in AMR Mitigation

Artificial intelligence (AI) and computational biology are rapidly transforming the landscape of AMR research. These technologies offer powerful tools to expedite drug discovery, predict resistance patterns, and improve diagnostic accuracy. AI-driven algorithms are revolutionizing drug discovery and repurposing by analyzing vast datasets to

identify novel antimicrobial compounds or repurpose existing drugs for combating resistant bacteria.[157] These algorithms can screen chemical databases and predict the efficacy of compounds, significantly accelerating the identification of potential therapeutic candidates. Furthermore, AI-assisted drug repurposing offers a cost-effective alternative to traditional discovery approaches, enabling researchers to leverage approved drugs in innovative ways.[158] Machine learning (ML) models are being employed to analyze genomic and epidemiological data, enabling the prediction of resistance patterns and the identification of high-risk areas for the emergence of resistant infections.[159] These predictive capabilities empower healthcare providers to make informed decisions, tailor treatment plans, and implement targeted interventions to prevent the spread of resistant infections.

Advanced computational biology plays a pivotal role in combating AMR. Bioinformatics tools enable the decoding of bacterial genomes, facilitating the identification of genes associated with resistance.[160] These tools facilitate the analysis of genomic mutations and the detection of resistance markers, guiding the development of precision therapies and enhancing real-time surveillance.[161] Whole-genome sequencing (WGS) and metagenomics provide a comprehensive understanding of resistance mechanisms, enabling targeted interventions.[162]

AI-powered rapid diagnostics streamline the identification of resistant pathogens, significantly reducing diagnosis time from days to hours.[163] AI-driven techniques such as deep learning and pattern recognition can analyze microbiological images, automate susceptibility testing, and identify resistance genes directly from clinical samples. This leads to faster and more accurate diagnoses, enabling the timely administration of targeted therapies, thereby reducing the need for broad-spectrum antibiotics and mitigating the further spread of AMR.[164]

Moreover, AI platforms can aggregate vast amounts of data from diverse sources, including hospitals, public health records, and environmental samples, to monitor global AMR trends.[165] By analyzing real-time data, these systems enable the early detection of resistance outbreaks, track the spread of resistant organisms, and provide critical insights to inform timely public health interventions.[166] These innovative applications of AI and computational biology have the potential to revolutionize our approach to AMR, leading to more effective strategies and improved patient outcomes.

Perspectives on Future Directions of AMR

The future of combating AMR presents a complex interplay of promise and challenge. Recent advancements, such as the development of novel antimicrobial agents, diagnostic tools, and therapeutic strategies, offer hope for addressing this pressing global health issue[167]. However, significant hurdles remain. Substantial investments in research and development are essential to fuel the pipeline of innovative antimicrobial therapies. Moreover, enhanced global surveillance and data sharing are crucial for monitoring resistance trends and informing effective interventions. Implementing robust antimicrobial stewardship programs across human health, animal health, and agriculture is imperative to mitigate the spread of AMR[33].

The multifaceted nature of AMR necessitates a comprehensive One Health approach that considers the interconnectedness of human, animal, and environmental health[21]. Continuous education and global collaboration are crucial to raising awareness and fostering international cooperation. This requires exploring novel therapeutic targets, harnessing advanced technologies like genetics and artificial intelligence, and researching unconventional antibacterial agents.[168] To ensure the long-term efficacy of antimicrobial therapies, a concerted effort is needed to promote prudent antibiotic use, invest in research and development, and implement coordinated global strategies[169].

To combat the rising threat of AMR, a comprehensive approach that integrates healthcare interventions is essential. Expanding current intermediate-care antimicrobial stewardship (AMS) programs can address many of the challenges associated with AMR.[170] The identification of potential genetic risk factors, such as human leukocyte antigen (HLA) or non-HLA markers, may aid in early detection and targeted management of

individuals at risk for AMR. Studies have indicated a correlation between the presence of donor-specific antibodies (DSA) and the development of AMR in transplant recipients, highlighting the importance of careful patient selection and immunosuppression management[171].

Effective antibiotic stewardship is crucial in mitigating AMR. This involves optimizing antibiotic prescribing practices, promoting adherence to treatment guidelines, and reducing unnecessary antibiotic use[172]. Establishing and strengthening hospital-based antibiotic stewardship programs, educating healthcare providers and the public about appropriate antibiotic use, and fostering interdisciplinary collaboration are key strategies for achieving these goals[173].

To combat the escalating threat of AMR, robust preventive and inhibitory measures are imperative[174]. This necessitates the implementation of stringent sanitation protocols, vigilant oversight of healthcare-associated infections, and strict adherence to preventive measures within healthcare settings[175]. Furthermore, disseminating information on early detection strategies can significantly mitigate the adverse consequences of drug-resistant infections[176].

Discussion

Antimicrobial resistance (AMR) poses an escalating threat to global health, fueled by the overuse of antibiotics, insufficient regulatory measures, and inadequate monitoring in resource-limited regions. This review emphasizes the complexity of resistance mechanisms and the urgent call for innovative solutions. While emerging strategies like nanoparticle-based delivery systems, liposome-targeted therapies, and CRISPR-Cas9 technology show promise, they also face significant obstacles in terms of cost, scalability, and clinical validation.[132]

Artificial intelligence and computational biology have advanced the fight against AMR by improving our ability to track resistance patterns and accelerate drug discovery. However, these technologies bring ethical concerns and highlight skill gaps that must be addressed. India's efforts to curb AMR through regulatory actions and public awareness initiatives are a step forward, though there remains a need for stronger infrastructure and more rigorous enforcement. Global cooperation is vital to establish robust AMR surveillance and coordinated strategies that can prevent the spread of resistance internationally.

On a clinical level, AMR has driven up treatment costs and mortality rates, underscoring the importance of rigorous antibiotic stewardship and enhanced public education. Although there are challenges, a comprehensive approach including advanced drug delivery systems, AI integration, policy reinforcement, and international collaboration is essential to curb AMR's impact and support sustainable treatment pathways.

Conclusion

This review highlights the escalating threat of AMR to global public health. The emergence and spread of antibiotic-resistant pathogens are driven by a complex interplay of genetic factors, horizontal gene transfer, and selective pressures. To combat this challenge, a multi-faceted approach is essential, encompassing judicious antibiotic use, enhanced surveillance, the development of novel antimicrobial agents, and the exploration of alternative therapies like phage therapy and immune modulation. Strengthening collaboration among healthcare providers, policymakers, researchers, and the pharmaceutical industry is crucial to mitigating the rising burden of antibiotic resistance. Vulnerable populations, such as children, the elderly, and immunocompromised individuals, are particularly susceptible to the consequences of antibiotic resistance. Urgent action is necessary to reduce health disparities and ensure equitable access to effective antimicrobial treatments worldwide.

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REFERENCE

1. M.A. Salam, M.Y. Al-Amin, M.T. Salam, J.S. Pawar, N. Akhter, A.A. Rabaan, and M.A.A. Alqumber, "Antimicrobial Resistance: A Growing Serious Threat for Global Public Health", ***Healthcare***, 11(3), 1946 (2023).
2. C.J. Murray, K.S. Ikuta, F. Sharara, L. Swetschinski, G.R. Aguilar, A. Gray, C. Han, C. Bisignano, P. Rao, E. Wool, and S.C. Johnson, "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis", ***Lancet***, 399(10325), 629-655 (2022).
3. J. Williams-Nguyen, J.B. Sallach, S. Bartelt-Hunt, A.B. Boxall, L.M. Durso, J.E. McLain, R.S. Singer, D.D. Snow, and J.L. Zilles, "Antibiotics and antibiotic resistance in agroecosystems: state of the science", ***J Environ Qual***, 45, 394–406 (2016).
4. K.W. Tang, B.C. Millar, and J.E. Moore, "Antimicrobial resistance (AMR)", ***Br J Biomed Sci***, 80, 11387 (2023).
5. GBD 2019 Diseases and Injuries Collaborators, "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019", ***Lancet***, 396(10258), 1204–1222 (2020).
6. E. Leung, D.E. Weil, M. Raiglione, H. Nakatani, and World Health Organization World Health Day Antimicrobial Resistance Technical Working Group, "The WHO policy package to combat antimicrobial resistance", ***Bull World Health Organ***, 89(5), 390-392 (2011).
7. Antimicrobial Resistance Collaborators, "The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis", ***Lancet Reg Health Am***, 25, 100561 (2023).
8. G. Muteeb, M.T. Rehman, M. Shahwan, and M. Aatif, "Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review", ***Pharmaceuticals***, 16(11), 1615 (2023).
9. T.M. Uddin, A.J. Chakraborty, A. Khusro, B.R.M. Zidan, S. Mitra, T.B. Emran, K. Dhama, M.K.H. Ripon, M. Gajdács, M.U.K. Sahibzada, M.J. Hossain, and N. Koirala, "Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects", ***J Infect Public Health***, 14(12), 1750-1766 (2021).
10. GBD 2021 Antimicrobial Resistance Collaborators, "Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050", ***Lancet***, 404(10459) 1199-1226 (2024).
11. M. Lomazzi, "A global charter for the Public's health-the public health system: role, functions, competencies and education requirements", ***Eur J Public Health***, 26(2) 210–212 (2016).
12. M. Lomazzi, C. Jenkins, and B. Borisch, "Global public health today: connecting the dots," ***Glob. Health Action***, 9, 28772 (2016).
13. F.C. Tenover, "Mechanisms of antimicrobial resistance in bacteria," ***Am J Med***, 119(6), S3–S10 (2006).
14. G. Zhou, Q.S. Shi, X.M. Huang, and X.B. Xie, "The Three Bacterial Lines of Defense against Antimicrobial Agents", ***Int J Mol Sci***, 16(9), 21711–21733 (2015).
15. B. Khameneh, R. Diab, K. Ghazvini, and B.S.F. Bazzaz, "Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them," ***Microb Pathog***, 95, 32–42 (2016).
16. B. Borisch, M. Lomazzi, M. Moore, and R. Krech, "Update on the global charter for the Public's health", ***Bull World Health Organ***, 96(6), 439–440 (2018).
17. I.M. Gould and A.M. Bal, "New antibiotic agents in the pipeline and how they can help overcome microbial resistance", ***Virulence***, 4(2), 185–191 (2013).
18. S.J. Hoffman, G.M. Caleo, N. Daulaire, S. Elbe, P. Matsoso, E. Mossialos, Z. Rizvi, and J.A. Røttingen, "Strategies for achieving global collective action on antimicrobial resistance", ***Bull World Health Organ***, 93(12), 867–876 (2015).
19. D.J. Payne, L.F. Miller, D. Findlay, J. Anderson, and L. Marks, "Time for a

change: addressing R&D and commercialization challenges for antibacterials", ***Philos Trans R Soc Lond B Biol Sci***, 370(1670), 20140086 (2015).
20. T.J. Foster, "Antibiotic resistance in Staphylococcus aureus. Current status and future prospects", ***FEMS Microbiol Rev***, 41(3), 430-449 (2017).
21. P. Kumar, S. Singh, and M.R.F. Pratama, "Synthesis of some novel 1H-indole derivatives with antibacterial activity and antifungal activity", ***Lett Appl NanoBioScience***, 9(2), 961-967 (2020).
22. R. Laxminarayan and R.R. Chaudhury, "Antibiotic resistance in India: Drivers and opportunities for action", ***PLoS Med***, 13(3), e1001974 (2016).
23. S. Kariuki, K. Kering, C. Wairimu, R. Onsare, and C. Mbae, "Antimicrobial Resistance Rates and Surveillance in Sub-Saharan Africa: Where Are We Now?", ***Infect Drug Resist***, 15, 3589-3609 (2022).
24. M.R. Bidell, M. Palchak, J. Mohr, and T.P. Lodise, "Fluoroquinolone and Third-Generation-Cephalosporin Resistance among Hospitalized Patients with Urinary Tract Infections Due to Escherichia coli: Do Rates Vary by Hospital Characteristics and Geographic Region?", ***Antimicrob Agents Chemother***, 60(5), 3170-3173 (2016).
25. C.L. Ventola, "The antibiotic resistance crisis: part 1: causes and threats", ***P T***, 40(4), 277-283 (2015).
26. Y.P. Shelke, N.J. Bankar, G.R. Bandre, D.V. Hawale, and P. Dawande, "An Overview of Preventive Strategies and the Role of Various Organizations in Combating Antimicrobial Resistance", ***Cureus***, 15(9), e44666 (2023).
27. D.R. Ha, N.M. Haste, and D.P. Gluckstein, "The Role of Antibiotic Stewardship in Promoting Appropriate Antibiotic Use", ***Am J Lifestyle Med***, 13(4), 376-383 (2017).
28. M.E.A. de Kraker, A.J. Stewardson, and S. Harbarth, "Will 10 million people die a year due to antimicrobial resistance by 2050?", ***PLoS Med***, 13(11), e1002184 (2016).
29. B. Aslam, R. Asghar, S. Muzammil, M. Shafique, A.B. Siddique, M. Khurshid, M. Ijaz, M.H. Rasool, T.H. Chaudhry, A. Aamir, and Z. Baloch, "AMR and Sustainable Development Goals: at a crossroads", ***Global Health***, 20, 73 (2024).
30. G.D. Wright, "Something old, something new: revisiting natural products in antibiotic drug discovery", ***Can J Microbiol***, 60(3), 147-154 (2014).
31. S.K. Ahmed, S. Hussein, K. Qurbani, R.H. Ibrahim, A. Fareeq, K.A. Mahmood, and M.G. Mohamed, "Antimicrobial resistance: Impacts, challenges, and future prospects", ***J Med Surg Public Health***, 2, 100081 (2024).
32. A.H. Holmes, L.S. Moore, A. Sundsfjord, M. Steinbakk, S. Regmi, A. Karkey, P.J. Guerin, and L.J.V. Piddock, "Understanding the mechanisms and drivers of antimicrobial resistance", ***Lancet***, 387(10014), 176-187 (2016).
33. R. Laxminarayan, P. Matsoso, S. Pant, C. Brower, J.A. Røttingen, K. Klugman, and S. Davies, "Access to effective antimicrobials: a worldwide challenge", ***Lancet***, 387(10014), 168-175 (2016).
34. M.P. Ferraz, "Antimicrobial Resistance: The Impact from and on Society According to One Health Approach", ***Society***, 14(9), 187 (2024).
35. B.M. Marshall and S.B. Levy, "Food animals and antimicrobials: impacts on human health", ***Clin Microbiol Rev***, 24(4), 718-733 (2011).
36. S.E. Mshana, C. Sindato, M.I. Matee, and L.E.G. Mboera, "Antimicrobial Use and Resistance in Agriculture and Food Production Systems in Africa: A Systematic Review", ***Antibiotics***, 10(8), 976 (2021).
37. K. Kümmerer, "Antibiotics in the aquatic environment – A review – Part I", ***Chemosphere***, 75(4), 417-434 (2009).
38. D.G.J. Larsson, A. Andremont A, J. Bengtsson-Palme, K.K. Brandt, A.M.d.R. Husman, P. Fagerstedt, J. Fick, C.F. Flach, W.H. Gaze, M. Kuroda, K. Kvint, R. Laxminarayan, C.M. Manaia, K.M. Nielsen, L. Plant, M.C. Ploy, C. Segovia, P. Simonet, K. Smalla, J. Snape, E. Topp, A.J. van Hengel, D.W. Verner-Jeffreys, M.P.J. Virta, E.M. Wellington, and A.S. Wernersson, "Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic

resistance", ***Environ Int***, 117, 132-138 (2018).
39. C.A. Michael, D. Dominey-Howes, and M. Labbate, "The antimicrobial resistance crisis: causes, consequences, and management", ***Front Public Health***, 2, 145 (2014).
40. M. Mendelson, J.A. Røttingen, U. Gopinathan, D.H. Hamer, H. Wertheim, B. Basnyat, C. Butler, G. Tomson, and M. Balasegaram, "Maximizing access to achieve appropriate human antimicrobial use in low-income and middle-income countries", ***Lancet***, 387(10014), 188-198 (2016).
41. M. Kanan, M. Ramadan, H. Haif, B. Abdullah, J. Mubarak, W. Ahmad, S. Mari, S. Hassan, R. Eid, M. Hasan, M. Qahl, A. Assiri, M. Sultan, F. Alrumaih, and A. Alenzi, "Empowering Low- and Middle-Income Countries to Combat AMR by Minimal Use of Antibiotics: A Way Forward", ***Antibiotics***, 12(10), 1504 (2023).
42. G.D. Wright, "Antibiotic adjuvants: rescuing antibiotics from resistance", ***Trends Microbiol***, 24(9), 862-871 (2016).
43. E.Y. Klein, T.P. Van Boeckel, E.M. Martinez, S. Pant, S. Gandra, S.A. Levin, H. Goossens, and R. Laxminarayan, "Global increase and geographic convergence in antibiotic consumption between 2000 and 2015", ***Proc Natl Acad Sci U S A***, 115(15), E3463-E3470 (2018).
44. M.R. Gualano, R. Gili, G. Scaioli, F. Bert F, and R. Siliquini, "General population's knowledge and attitudes about antibiotics: a systematic review and meta-analysis", ***Pharmacoepidemiol Drug Saf***, 24(1), 2-10 (2015).
45. M. Oliveira, W. Antunes, S. Mota, A. Madueira-Carvalho, R.J. Dinis-Oliveira, and D.D. da Silva, "An Overview of the Recent Advances in Antimicrobial Resistance", ***Microorganisms***, 12(9), 1920 (2024).
46. R. Laxminarayan, D. Sridhar, M. Blaser, M. Wang, and M. Woolhouse, "Achieving global targets for antimicrobial resistance", ***Science***, 353(6302), 874-875 (2016).
47. B. Li and T.J. Webster, "Bacteria antibiotic resistance: New challenges and opportunities for implant-associated orthopedic infections", ***J Orthop Res***, 36(1) 22-32 (2018).
48. N.Q. Balaban, S. Helaine, K. Lewis, M. Ackermann, B. Aldridge, D.I. Andersson, M.P. Brynildsen, D. Bumann, A. Camilli, J.J. Collins, C. Dehio, S. Fortune, J.M. Ghigo, W.D. Hardt, A. Harms, M. Heinemann, D.T. Hung, U. Jenal, B.R. Levin, J. Michiels, G. Storz, M.W. Tan, T. Tenson, L.V. Melderen, and A. Zinkernagel, "Definitions and guidelines for research on antibiotic persistence". ***Nat Rev Microbiol***, 17(7), 441-448 (2019).
49. J.M. Munita and C.A. Arias, "Mechanisms of antibiotic resistance", ***Microbiol Spectr***, 4(2), VMBF-0016-2015 (2016).
50. J.M. Blair, M.A. Webber, A.J. Baylay, D.O. Ogbolu, and L.J. Piddock, "Molecular mechanisms of antibiotic resistance", ***Nat Rev Microbiol***, 13(1), 42-51 (2015).
51. H.K. Allen, J. Donato, H.H. Wang, K.A. Cloud-Hansen, J. Davies, and J. Handelsman, "Call of the wild: antibiotic resistance genes in natural environments", ***Nat Rev Microbiol***, 8(4) 251-259 (2010).
52. K. Poole, "Bacterial stress responses as determinants of antimicrobial resistance", ***J Antimicrob Chemother***, 67(9), 2069-2089 (2012).
53. J.L. Martínez and F. Baquero, "Emergence and spread of antibiotic resistance: setting a parameter space", ***Ups J Med Sci***, 119(2), 68-77 (2014).
54. H. Nikaido, "Multidrug resistance in bacteria", ***Annu Rev Biochem***, 78, 119-146 (2009).
55. L.J. Piddock, "Multidrug-resistance efflux pumps - not just for resistance", ***Nat Rev Microbiol***, 4(8), 629-636 (2006).
56. H. Ochman, J.G. Lawrence, and E.A. Groisman, "Lateral gene transfer and the nature of bacterial innovation", ***Nature***, 405(6784), 299-304 (2000).
57. J. Davies and D. Davies, "Origins and evolution of antibiotic resistance", ***Microbiol Mol Biol Rev***, 74(3), 417-433 (2010).
58. P.M. Bennett, "Plasmid encoded antibiotic resistance: acquisition and transfer of antibiotic resistance genes in bacteria", ***Br***

J Pharmacol, 153(Suppl 1), S347-S357 (2008).
59. C.M. Harding, S.W. Hennon, and M.F Feldman, "Uncovering the mechanisms of Acinetobacter baumannii virulence", ***Nat Rev Microbiol***, 16(2), 91-102 (2018).
60. M.R. Gillings, "Integrons: past, present, and future", ***Microbiol Mol Biol Rev***, 78(2), 257-277 (2014).
61. D.M. Fitzgerald and S.M. Rosenberg, "What is mutation? A chapter in the grammar of biology", ***Genetics***, 212(2), 397-399 (2019).
62. M. Lynch, M.S. Ackerman, J.F. Gout, H. Long, *et al.,* "Genetic drift, selection and the evolution of the mutation rate", ***Nat Rev Genet,*** 17(11),704-714 (2016).
63. J. Hör, S.A. Gorski, J. Vogel "Bacterial RNA biology on a genome scale", ***Molecular cell***, 70(5), 785-99 (2018).
64. A.D. Berti, E. B.Hirsch, "Tolerance to antibiotics affects response", ***Science***, 367(6474), 141-142 (2020).
65. T. P. Van Boeckel, C. Brower, M. Gilbert, B.T. Grenfell, S. A. Levin, T.P. Robinson, A. Teillant, R. Laxminarayan, "Global trends in antimicrobial use in food animals", ***PNAS***, 112(18), 5649-5654 (2015).
66. M. E. Elyass, A. A. Mahdi, A. E. Semeih, F. I. Eltaib, I.H. Attitalla, "Exploratory investigation on the antibacterial effect of antimicrobial peptides of four mammalian plasmas", ***Microb Pathog,*** 156, 104839 (2021).
67. B. M. Marshall, S. B. Levy, "Food animals and antimicrobials: impacts on human health", CMR, 24(4), 718-733 (2011).
68. M. E. De Kraker, P.G. Davey, H. Grundmann, BURDEN Study Group. "Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe", ***PLoS Med,*** 8(10), e1001104 (2011).
69. A. Pantosti, A. Sanchini and M. Monaco, "Mechanisms of antibiotic resistance in Staphylococcus aureus", ***Future Microbiol,*** 2(3), 323-334 (2007).
70. K. Fisher and C. Phillips, "The ecology, epidemiology and virulence of Enterococcus", ***Microbiol.*** 155(6), 1749-1757 (2009).
71. D. A. Baltrus, "Exploring the costs of horizontal gene transfer", ***TREE or Trends Ecol Evol,*** 28(8), 489-495 (2013).
72. E. M. Darby, E. Trampari, P. Siasat, M.S. Gaya, I. Alav, M. A. Webber, J. M. Blair "Molecular mechanisms of antibiotic resistance revisited", ***Nat Rev Microbiol.*** 21(5), 280-295 (2023).
73. E. D. Brown and G. D. Wright, "Antibacterial drug discovery in the resistance era", ***Nat*** 529(7586), 336-343 (2016).
74. M. A. Webber and L. J. Piddock, "The importance of efflux pumps in bacterial antibiotic resistance", ***JAC,*** 51(1), 9-11 (2003).
75. N. Weston, P. Sharma, V. Ricci, L. J. Piddock, "Regulation of the AcrAB-TolC efflux pump in Enterobacteriaceae", ***Microbiol Res,*** 169(7-8),425-31 (2018).
76. J. L. Martínez and F. Rojo, "Metabolic regulation of antibiotic resistance", ***FEMS Microbiol Rev,*** 35(5), 768-789 (2011).
77. J. Iredell, J. Brown and K. Tagg, "Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications", ***Bmj,*** 8, 352 (2016).
78. T. Gil-Gil, F. Corona, J. L. Martínez and A. Bernardini, "The inactivation of enzymes belonging to the central carbon metabolism is a novel mechanism of developing antibiotic resistance", ***mSystems,*** 5(3), 10-128 (2020).
79. B. Berger-Bächi, "Resistance mechanisms of gram-positive bacteria", ***IJMM,*** 292(1), 27-35 (2002).
80. World Health Organization. Antimicrobial resistance: global report on surveillance. ***WHO***, (2014).
81. E.D. Brown and G.D. Wright, "Antibacterial drug discovery in the resistance era", ***Nat,*** Jan 529(7586), 336-43 (2016).
82. J. M. Munita and C. A. Arias, "Mechanisms of antibiotic resistance", ***VFs,*** 22, 481-511 (2016).
83. B. Shaskolskiy, E. Dementieva, A. Leinsoo, N. Petrova, A. Chestkov, A. Kubanov, D. Deryabin and D. Gryadunov, "Tetracycline resistance of Neisseria

gonorrhoeae in Russia, 2015–2017", ***Infect Genet Evol,*** 63, 236-242 (2018).
84. L. Hall-Stoodley and P. Stoodley, "Evolving concepts in biofilm infections", ***Cell Microbiol,*** 11(7), 1034-1043 (2009).
85. R. M. Donlan, "Role of biofilms in antimicrobial resistance", ***ASAIO Jour,*** 46(6),S47-S52 (2000).
86. J. Heesemann, "Mechanisms of resistance to beta-lactam antibiotics", ***Inf,*** 21, S4-S9 (1993).
87. S. Gruenheid and H. Le Moual, "Resistance to antimicrobial peptides in Gram-negative bacteria", ***FEMS Microbiol Lett,*** 330(2), 81-89 (2012).
88. C. R.Bourne, "Utility of the biosynthetic folate pathway for targets in antimicrobial discovery", ***AB,*** 3(1), 1-28 (2014).
89. W.C. Reygaert, "An overview of the antimicrobial resistance mechanisms of bacteria", ***AIMS microbiol***,4(3), 482 (2018).
90. K. Poole, "Efflux-mediated antimicrobial resistance. ***JAC***. 2005 Jul 1,56(1):20-51.
91. H. Nikaido, "Multidrug resistance in bacteria", ***Annu Rev Biochem,*** 78(1), 119-146 (2009).
92. A. S. Chaudhary "A review of global initiatives to fight antibiotic resistance and recent antibiotics′ discovery", ***Acta Pharm Sin B,*** 6(6), 552-556 (2016).
93. F. Prestinaci, P. Pezzotti and A. Pantosti, "Antimicrobial resistance: a global multifaceted phenomenon", ***Pathog Glob Health,*** 109(7), 309-318 (2015).
94. A. H. Limper, A. Adenis, T. Le and T. S. Harrison, "Fungal infections in HIV/AIDS", ***Lancet Infect Dis,*** 17(11), e334-e343 (2017).
95. J. I. O'neill,"Antimicrobial resistance: tackling a crisis for the health and wealth of nations", ***Rev Antimicrob Resist,*** (2014).
96. S. S. Kadri, "Key takeaways from the US CDC's 2019 antibiotic resistance threats report for frontline providers", ***Crit Care Med,*** 48(7), 939-945 (2020).
97. K. L. Tang, N. P. Caffrey, D. B. Nóbrega, S. C. Cork, P. E. Ronksley, H. W. Barkema, *et al.*, "Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis", ***Lancet Planet Health,*** 1(8), e316-e327 (2017).
98. E. P.Gibbs, "The evolution of One Health: a decade of progress and challenges for the future", ***Vet Rec,*** 174(4), 85-91 (2014).
99. N. E. Eleraky, A. Allam, Hassan, Omar MM. Nanomedicine fight against antibacterial resistance: an overview of the recent pharmaceutical innovations. ***Pharm.*** 2020 Feb 8,12(2):142.
100. S.Y. Essack, A.T. Desta, R.E. Abotsi and E. Agoba, "Antimicrobial resistance in the WHO African region: current status and roadmap for action", ***JPH***, 39(1), 8-13 (2017).
101. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe, ***EARS-net,***2017 May 29 (2015).
102. J. Redfern, L. Bowater, L. Coulthwaite and J. Verran, "Raising awareness of antimicrobial resistance among the general public in the UK: the role of public engagement activities", ***JAC-AMR,*** 2(1), dlaa012 (2020).
103. E. Baekkeskov, O. Rubin, L. Munkholm and W. Zaman, "Antimicrobial resistance as a global health crisis", ***ORE,*** 28,1-24 (2020).
104. M.E. De Kraker, P.G. Davey, H. Grundmann and BURDEN Study Group, "Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe", ***PLoS Med,***8(10), e1001104 (2011).
105. R. Laxminarayan, A. Duse, C. Wattal, A.K. Zaidi, H.F. Wertheim, N. Sumpradit, *et al.*, Antibiotic resistance—the need for global solutions. ***Lancet Infect Dis.*** 13(12),1057-1098 (2013).
106. F. Tanwir and F. Khiyani, "Antibiotic resistance: a global concern", ***JCPSP***, 21(3), 127-9 (2011).
107. J.A. Jernigan, K.M. Hatfield, H. Wolford, R.E. Nelson, B. Olubajo, S.C. Reddy, *et al.*, "Multidrug-resistant bacterial infections in US hospitalized patients, 2012–2017", ***NEJM***, 382(14),1309-1319 (2020).

108. A. Chokshi, Z. Sifri, D. Cennimo and H. Horng, "Global contributors to antibiotic resistance", ***JGID,*** 11(1),36-42 (2019).
109. R.D. Smith and J. Coast, "Antimicrobial resistance: a global response", ***Bull W H O***, 80,126-33 (2002).
110. D. van Duin and Y. Doi, "The global epidemiology of carbapenemase-producing Enterobacteriaceae", ***Virulence***, 8(4), 460-469 (2017).
111. E.H. Ibrahim, G. Sherman, S. Ward, V.J. Fraser, M.H. Kollef, "The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting", ***Chest***, 118(1),146-155 (2000).
112. S. Mudenda, "Global Burden of Fungal Infections and Antifungal Resistance from 1961 to 2024: Findings and Future Implications", ***JPP***, 15(4), 81-112 (2024).
113. World Health Organization, Antimicrobial resistance: global report on surveillance. ***WHO***, (2014).
114. C. E. Luyt, "Antimicrobial stewardship: A systematic review of the impact of antimicrobial stewardship on clinical outcomes in adult intensive care unit patients", ***Crit Care Med***, 44(2), 310-319 (2016).
115. A. Parmanik, S. Das, B. Kar, A. Bose, G. R. Dwivedi and M. M. Pandey, "Current treatment strategies against multidrug-resistant bacteria: a review", ***Curr Microbiol,*** 79(12), 388 (2022).
116. C. Ye, C. Wang, Z. Li, X. Li, J. Pan, L. Liu and Z. Wang, "The effect of combination therapy on mortality and adverse events in patients with Staphylococcus aureus bacteraemia: a systematic review and meta-analysis of randomized controlled trials", ***AIDT,*** 10, 2643-2660 (2021).
117. T.X. Zong, A. P. Silveira, J.A. Morais, M. C. Sampaio, L.A. Muehlmann, J. Zhang, C.S. Jiang and S. K. Liu, "Recent advances in antimicrobial nano-drug delivery systems", ***Nanomater,*** 12(11),1855 (2022).
118. R. J. Worthington and C. Melander, "Combination approaches to combat multidrug-resistant bacteria", ***Trends Biotechnol,*** 31(3),177-184 (2013).
119. H. Chen, Y. Jin, J. Wang, Y. Wang, W. Jiang, H. Dai, S. Pang, L. Lei, J. Ji and B. Wang, "Design of smart targeted and responsive drug delivery systems with enhanced antibacterial properties", Nanoscale**,** 10(45), 20946-20962 (2018).
120. Y. Liu, H. Miyoshi and M. Nakamura, "Nanomedicine for drug delivery and imaging: a promising avenue for cancer therapy and diagnosis using targeted functional nanoparticles", ***IJC,*** 120(12), 2527-2537 (2007).
121. N. Weiner, F. Martin and M. Riaz, "Liposomes as a drug delivery system", ***Drug Dev Ind Pharm,*** 15(10), 1523-1554 (1989).
122. E.C. Farmer and R. A. Seaton, "Recent innovations and new applications of outpatient parenteral antimicrobial therapy", ***Anti-Infect Ther,*** 19(1), 55-64 (2021).
123. L. Rahbarnia, S. Farajnia, B. Naghili, V. Ahmadzadeh, K. Veisi, R. Baghban and S. Toraby, "Current trends in targeted therapy for drug-resistant infections", ***Appl Microbiol Biotechnol,*** 103, 8301-8314 (2019).
124. J. Y. Maillard and P. Hartemann, "Silver as an antimicrobial: facts and gaps in knowledge", ***Crit Rev Microbiol,*** 39(4), 373-383 (2013).
125. A. M. Basudan, "Nanoparticle based periodontal drug delivery–A review on current trends and future perspectives", ***Saudi Dent J,*** 34(8),669-680 (2022).
126. T.M. Allen and P. R.Cullis, "Liposomal drug delivery systems: from concept to clinical applications", ***Adv Drug Deliv Rev,*** 65(1), 36-48 (2013).
127. A. Gonzalez Gomez and Z. Hosseinidoust, "Liposomes for antibiotic encapsulation and delivery", ***ACS Infect Dis,*** 6(5), 896-908 (2020).
128. D. Pranantyo, K. Zhang, Z. Si, Z. Hou, M. B. Chan-Park, "Smart multifunctional polymer systems as alternatives or supplements of antibiotics to overcome bacterial resistance", ***Biomacromolecules***, 23(5),1873-1891 (2022).
129. J. Liang, X. Peng, X. Zhou, J. Zou and L. Cheng, "Emerging applications of drug delivery systems in oral infectious diseases prevention and treatment", ***Mol,*** 25(3), 516 (2020).

130. O. Lomovskaya, M.S. Warren, A. Lee, J. Galazzo, *et al.*, "Identification and characterization of inhibitors of multidrug resistance efflux pumps in Pseudomonas aeruginosa: novel agents for combination therapy", ***AAC,*** 45(1),105-116 (2001).
131. V.K. Panthi, K. E. Fairfull-Smith and N. Islam, "Liposomal drug delivery strategies to eradicate bacterial biofilms: Challenges, recent advances, and future perspectives", ***IJP,*** 29, 124046 (2024).
132. T. Zohra, M. Numan, A. Ikram, M. Salman, T. Khan, M. Din, *et al.*, "Cracking the challenge of antimicrobial drug resistance with CRISPR/Cas9, nanotechnology and other strategies in ESKAPE pathogens", ***Microorg,*** 9(5), 954 (2021).
133. T.M. Viertel, K. Ritter and H. P. Horz, "Viruses versus bacteria—novel approaches to phage therapy as a tool against multidrug-resistant pathogens", ***JAC,*** 69(9), 2326-2336 (2014).
134. M. A. Sherwani, S. Tufail, A.A. Khan and M. Owais, "Gold nanoparticle-photosensitizer conjugate based photodynamic inactivation of biofilm producing cells: potential for treatment of C. albicans infection in BALB/c mice", ***PLoS One,*** 10(7), e0131684 (2015).
135. P. Dadgostar, "Antimicrobial Resistance: Implications and Costs", ***Infect Drug Resist***, 12, 3903-3910 (2019).
136. World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report 2022, ***WHO***, 2022 Dec 8.
137. T.P. Robinson, D.P. Bu, J. Carrique-Mas, E.M. Fèvre, M. Gilbert, D. Grace, S.I. Hay, *et al.*, "Antibiotic resistance is the quintessential One Health issue", ***TRSTMH,*** 110(7), 377-380 (2016).
138. D. Reynolds, J.P. Burnham, C.V. Guillamet, M. McCabe, V. Yuenger, K. Betthauser, S.T. Micek and M.H. Kollef, "The threat of multidrug-resistant/extensively drug-resistant Gram-negative respiratory infections: another pandemic", ***ERR,*** 31(166), 220068 (2022).
139. G.K. Innes, A. Markos, K.R. Dalton, C.A. Gould, K.E. Nachman, J. Fanzo, A. Barnhill, S. Frattaroli and M. F. Davis, "How animal agriculture stakeholders define, perceive, and are impacted by antimicrobial resistance: challenging the Wellcome Trust's Reframing Resistance principles", ***Agric Human Values,*** 1, 1-7 (2021).
140. L. J. Piddock, "The global antibiotic research and development partnership (GARDP): researching and developing new antibiotics to meet global public health needs", ***MedChemComm,*** 10(8), 1227-1230 (2019).
141. S.G. Kumar, C. Adithan, B.N. Harish, S. Sujatha, G. Roy and A. Malini, "Antimicrobial resistance in India: A review", ***J Nat Sci Biol Med,*** 4(2), 286 (2013).
142. D. A. Goff, "Antimicrobial stewardship: bridging the gap between quality care and cost", ***Curr Opin Infect Dis,*** 24, S11-20 (2011).
143. A. M. Bal and I. M. Gould, "Antibiotic stewardship: overcoming implementation barriers. ***Curr Opin Infect Dis,*** 24(4), 357-362 (2011).
144. D. T. Sathyapalan, J. James, S. Sudhir, V. Nampoothiri, *et al.*, "Antimicrobial stewardship and its impact on the changing epidemiology of polymyxin use in a South Indian healthcare setting", ***Antibiotics,*** 10(5), 470 (2021).
145. M. A. Majumder, S. Rahman, D. Cohall, A. Bharatha, K. Singh, M. Haque and M. Gittens-St Hilaire, "Antimicrobial stewardship: fighting antimicrobial resistance and protecting global public health", ***Infect Drug Resist,*** 13, 4713-4738 (2020).
146. B. Allegranzi and D. Pittet, "Role of hand hygiene in healthcare-associated infection prevention", ***J Hosp Infect***, 73(4), 305-315 (2009).
147. V.P. Singh, D. Jha, B. U. Rehman, V. S. Dhayal, M. S. Dhar and N. Sharma, "A mini-review on the burden of antimicrobial resistance and its regulation across one health sectors in India", ***J Agric Food Res,*** 15, 100973 (2024).
148. T. F. Landers, B. Cohen, T. E. Wittum and E. L. Larson, "A review of antibiotic use in food animals: perspective, policy, and potential", ***Public Health Rep,*** 127(1), 4-22 (2012).

149. E. Ricchizzi, K. Latour, T. Kärki, R. Buttazzi, *et al.*, "Antimicrobial use in European long-term care facilities: results from the third point prevalence survey of healthcare-associated infections and antimicrobial use, 2016 to 2017", ***Eurosurveillance,*** 23(46), 1800394 (2018).
150. World Health Organization. Antimicrobial resistance: a manual for developing national action plans. (2016).
151. D. Murphy, "Antimicrobial resistance: UK's five-year plan aims to reduce antibiotic use by 5% by 2029.
152. P. Dadgostar, "Antimicrobial resistance: implications and costs", ***Infect Drug Resist,*** 12, 3903-3910 (2019).
153. K. Iskandar, L. Molinier, S. Hallit, M. Sartelli, T.C. Hardcastle, *et al.*, "Surveillance of antimicrobial resistance in low-and middle-income countries: a scattered picture", ***Antimicrob Resist Infect Control,*** 10,1-9 (2021).
154. M. Mendelson, O.A. Dar, S. J. Hoffman, R. Laxminarayan, M. M. Mpundu and J. A. Røttingen, "A global antimicrobial conservation fund for low-and middle-income countries", ***Int J Infect Dis,*** 51,70-72 (2016).
155. A. Sharma, A. Singh, M. A. Dar, R. J. Kaur, J. Charan, K. Iskandar, *et al.*, "Menace of antimicrobial resistance in LMICs: Current surveillance practices and control measures to tackle hostility", ***J Infect Public Health,*** 15(2), 172-181 (2022).
156. F. Prestinaci, P. Pezzotti and A. Pantosti, "Antimicrobial resistance: a global multifaceted phenomenon", ***Pathog Glob Health,*** 109(7), 309-318 (2015).
157. F. Branda and F. Scarpa, "Implications of Artificial Intelligence in Addressing Antimicrobial Resistance: Innovations, Global Challenges, and Healthcare's Future", ***Antibiotics,*** 13(6), 502 (2024).
158. A. Aliper, S. Plis, A. Artemov, A. Ulloa, P. Mamoshina, A. Zhavoronkov, "Deep learning applications for predicting pharmacological properties of drugs and drug repurposing using transcriptomic data", ***Mol Pharm***, 13(7), 2524-2530 (2016).
159. J.I. Kim, F. Maguire, K.K. Tsang, T. Gouliouris, S.J. Peacock, T.A. McAllister, A.G. McArthur and R. G. Beiko, "Machine learning for antimicrobial resistance prediction: current practice, limitations, and clinical perspective", ***Clin Microbiol Rev,*** 35(3),e0017921 (2022).
160. A. G. McArthur and G. D. Wright, "Bioinformatics of antimicrobial resistance in the age of molecular epidemiology", ***Curr Opin Microbiol***, 27,45-50 (2015).
161. A. Seoane and G. Bou, "Bioinformatics approaches to the study of antimicrobial resistance", ***Revista Espanola de Quimioterapia,*** 34(Suppl1),15 (2021).
162. M.A. Ozma, S.R. Moaddab, H. Hosseini, E. Khodadadi, R. Ghotaslou, M. Asgharzadeh, A. Abbasi, F. S. Kamounah, L. Aghebati Maleki, K. Ganbarov and H. Samadi Kafil, "A critical review of novel antibiotic resistance prevention approaches with a focus on postbiotics", ***Crit Rev Food Sci Nutr,*** 64(26), 9637-9655 (2024).
163. A. A. Rabaan, S. Alhumaid, A. A. Mutair, M. Garout, Y. Abulhamayel, M. A. Halwani, J.H. Alestad, A.A. Bshabshe, T. Sulaiman, M.K. AlFonaisan, T. Almusawi, "Application of artificial intelligence in combating high antimicrobial resistance rates", ***Antibiotics***, 11(6), 784 (2022).
164. G. Arango-Argoty, E. Garner, A. Pruden, L. S. Heath, P. Vikesland, L. Zhang, "DeepARG: a deep learning approach for predicting antibiotic resistance genes from metagenomic data", ***Microbiome,*** 6, 1-5 (2018).
165. D. Yamin, V. Uskoković, A.M. Wakil, M. D. Goni, S.H. Shamsuddin, F.H. Mustafa, W.A. Alfouzan, *et al.*, "Current and future technologies for the detection of antibiotic-resistant bacteria", ***Diagnostics***, 13(20), 3246 (2023).
166. U. Fanelli, M. Pappalardo, V. Chinè, P. Gismondi, C. Neglia, A. Argentiero, A. Calderaro, A. Prati and S. Esposito, "Role of artificial intelligence in fighting antimicrobial resistance in paediatrics", ***Antibiotics,*** 9(11),767 (2020).
167. J. Murugaiyan, P. A. Kumar, G. S. Rao, K. Iskandar, S. Hawser, *et al.*, "Progress in alternative strategies to combat

antimicrobial resistance: Focus on antibiotics", ***Antibiotics,*** 11(2), 200 (2022).
168. M. E. Velazquez-Meza, M. Galarde-López, B. Carrillo-Quiróz and C. M. Alpuche-Aranda, "Antimicrobial resistance: one health approach", ***Vet World,*** 15(3), 743 (2022).
169. S. K. Ahmed, S. Hussein, K. Qurbani, R. H. Ibrahim, A. Fareeq, K. A. Mahmood and M. G. Mohamed, "Antimicrobial resistance: impacts, challenges, and future prospects. ***J Med Surg Public Health,*** 2, 100081 (2024).
170. B. Aslam, R. Asghar, S. Muzammil, M. Shafique, A. B. Siddique, M. Khurshid, *et al.,* "AMR and Sustainable Development Goals: at a crossroads", ***Glob Health,*** , 20(1), 73 (2024).
171. A. P. Kunnath, M. Suodha Suoodh, D. K. Chellappan, J. Chellian and K. Palaniveloo, "Bacterial persister cells and development of antibiotic resistance in chronic infections: an update", ***Br J Biomed Sci,*** 81, 12958 (2024).
172. N. J. Tinker, R. A. Foster, B. J. Webb, S. Haydoura, W. R. Buckel and E. A. Stenehjem "Interventions to optimize antimicrobial stewardship", ***Antimicrob Steward Healthc Epidemiol,*** 1(1), e46 (2021).
173. M.A. Salam, M.Y. Al-Amin, M.T. Salam, J.S. Pawar, N. Akhter, A.A. Rabaan, M. A. Alqumber, "Antimicrobial resistance: a growing serious threat for global public health. ***Healthcare (Basel),*** 11(13), 1946(2023)
174. M. Haque, McKimm J, Sartelli M, Dhingra S, Labricciosa FM, Islam S, Jahan D, Nusrat T, Chowdhury TS, Coccolini F, Iskandar K. Strategies to prevent healthcare-associated infections: a narrative overview", ***Risk Manag Healthc Policy,*** 28,1765-1780 (2020).
175. K. Gidey, M.T. Gidey, B.Y. Hailu, Z. B. Gebreamlak and Y.L.Niriayo "Clinical and economic burden of healthcare-associated infections: A prospective cohort study", ***Plos One***, 18(2), e0282141 (2023).
176. S. Bhattacharya, "Early diagnosis of resistant pathogens: how can it improve antimicrobial treatment", ***Virulence,*** 4(2),172-184 (2013).

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مقاومة مضادات الميكروبات عبء عالمي – الآليات والرؤى الحالية والاتجاهات المستقبلية

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تشكل مقاومة مضادات الميكروبات تهديدًا صحيًا عالميًا كبيرًا، وتتميز بالانتشار المتزايد للعدوى المقاومة للأدوية وتناقص خط إنتاج المضادات الحيوية الجديدة. لقد ساهم تطوير آليات المقاومة، بما في ذلك تغيير موقع الهدف، ومضخات التدفق، وتعطيل الأنزيم، في انتشار مقاومة مضادات الميكروبات بين مسببات الأمراض البشرية، سواء داخل إعدادات الرعاية الصحية (المستشفيات) أو المجتمع الخارجي. من المعروف أنه تنشأ آليات المقاومة هذه في كثير من الأحيان استجابة لسوء استخدام المضادات الحيوية أو الإفراط في استخدامها.

تعمل العوامل المضادة للميكروبات تأثيراتها من خلال آليات مختلفة، مثل تثبيط تخليق جدار الخلية (على سبيل المثال، β-lactams)، أو تخليق البروتين (الماكروليدات، التتراسيكلينات)، أو تخليق الأحماض النووية (الفلوروكينولونات، ريفامبين)، أو المسارات الأيضية (تريميثوبريم–سلفاميثوكسازول).

ولكن ظهور مقاومة مضادات الميكروبات قد أثار تحدياً لفعالية هذه العوامل. ويتطلب التصدي لمقاومة مضادات الميكروبات اتباع نهج متعدد الأوجه، بما في ذلك تحسين استخدام المضادات الحيوية، وتعزيز تدابير الوقاية من العدوى ومكافحتها، وتسريع تطوير عوامل مضادة للميكروبات ووسائل تشخيصية جديدة.

وفي حين أظهرت بعض الدراسات إمكانية عكس مقاومة مضادات الميكروبات في ظل ظروف محددة، فإن التحدي الإجمالي يظل معقدًا ومتعدد الأوجه.

وتقدم هذه الدراسة نظرة عامة على مقاومة مضادات الميكروبات، والآليات الأساسية التي تقوم عليها، والحاجة الملحة إلى اتخاذ إجراءات عالمية للتخفيف من تأثيرها.