Review Article

Antimicrobial Resistance: New Mechanisms, Surveillance Strategies and Novel Approaches

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Abstract

Antimicrobial resistance (AMR) represents a critical and escalating global public health threat, driven primarily by the overuse and misuse of antibiotics in human medicine, agriculture, and animal production. The emergence and dissemination of multidrug-resistant (MDR) organisms are further accelerated by horizontal gene transfer, environmental reservoirs, and inadequate infection prevention and control practices. Recent global estimates indicate that bacterial AMR was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths, with projections suggesting substantial increases in mortality and economic burden if effective interventions are not implemented.

This review summarizes the major molecular mechanisms underlying antimicrobial resistance, including enzymatic drug inactivation, target modification, porin modifications, efflux pump overexpression, and biofilm formation. Innovative approaches, including phage therapy, CRISPR-based antimicrobials, monoclonal antibodies, nanomaterials, vaccination and artificial intelligence (AI) are highlighted as promising next-generation alternatives.

Despite scientific advances, the antibiotic development pipeline remains constrained by economic and regulatory challenges. Sustained research and development, strengthened antimicrobial stewardship, global surveillance, and collaborative industry-academic partnerships are essential to preserve existing therapies and ensure future treatment options against MDR pathogens.

Keywords: Antimicrobial resistance, Antibiotic stewardship, Novel approaches, Phage therapy, Antimicrobial peptides

Introduction

The discovery and widespread clinical implementation of antibiotics represent one of the most transformative achievements in modern medicine. Antibacterial agents have dramatically reduced morbidity and mortality associated with

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infectious diseases and enabled complex medical interventions such as organ transplantation, cancer chemotherapy, neonatal intensive care, and major surgical procedures. However, these advances are increasingly threatened by the rapid emergence and global dissemination of antimicrobial resistance (AMR).[1,2]

Antimicrobial resistance arises when bacteria, viruses, fungi, and parasites develop the ability to survive despite the use of antimicrobial medicines designed to kill or inhibit them. When this happens, antibiotics and other treatments become less effective or even ineffective. As a result, infections become harder or sometimes impossible to treat, which increases the risk of disease spreading, severe illness, disability, and death.[1,2]

Drug-resistant bacterial infections are currently estimated to cause over 1.2 million deaths annually worldwide, with substantially higher mortality when associated deaths are included. The extensive and often inappropriate use of antibiotics in human medicine, veterinary care, and agriculture has accelerated the selection of resistant strains. Environmental contamination with residual antibacterial compounds further contributes to the persistence and spread of resistance determinants. Recent global analyses estimate that in 2019 alone, drug-resistant infections were associated with nearly 4.95 million deaths, of which approximately 1.27 million were directly attributable to bacterial AMR. These findings underscore the scale and urgency of the crisis.[2,3]

The frequent use of broad-spectrum antibiotics, invasive medical procedures, and the presence of immuno-compromised patients create conditions that favor resistant organisms. Medical devices such as catheters, ventilators, and prosthetic implants provide surfaces for bacterial colonization and biofilm formation, leading to persistent hospital-associated infections. Biofilms confer additional protection against antimicrobial agents and host immune responses, complicating eradication and promoting recurrent infections.[1,2,4,5,6]

In parallel with traditional antibiotic discovery, attention has shifted toward alternative and next-generation therapeutic strategies. Drug repurpose strategies have gained traction by leveraging existing non-antibacterial agents with newly identified antimicrobial properties.[1,2,4,5]

Combination therapies represent another promising approach, pairing conventional antibiotics with adjuvant compounds such as efflux pump inhibitors or quorum-sensing antagonists to enhance efficacy and suppress resistance development. Emerging strategies including antimicrobial peptides, bacteriophage therapy, CRISPR-based antimicrobials, monoclonal antibodies, nanotechnology-driven drug delivery systems, and microbiome-modulating strategies are being actively investigated as alternative or adjunctive therapies. These approaches aim to improve specificity, reduce collateral damage to beneficial microbiota, and minimize selective pressure that drives resistance. The integration of artificial intelligence (AI) and machine learning into drug discovery pipelines further accelerates the identification and optimization of promising antibacterial candidates.[1,2,4,5]

Despite these advances, critical gaps remain. There is limited integration of emerging therapies such as phage therapy, CRISPR-based antimicrobials, and microbiome modulation with conventional antibiotics in clinical practice. Comparative data on efficacy, safety, and scalability of these next-generation interventions are scarce, and knowledge is fragmented regarding AI-driven drug discovery and drug repurposing in antimicrobial development. These gaps hinder the translation of promising research into practical solutions for AMR.

Therapeutic innovation alone cannot resolve the AMR crisis. Effective stewardship programs, rational prescribing practices, enhanced infection prevention and control measures, and robust global surveillance systems are essential to preserve the efficacy of both existing and emerging therapies. International initiatives such as the Global Antimicrobial Resistance and Use Surveillance System (GLASS) underscore the importance of coordinated data collection and monitoring of resistance trends worldwide. Addressing AMR requires sustained interdisciplinary collaboration among researchers, clinicians, policymakers, industry stakeholders, and global health organizations.[1,2,4,5]

Even with significant progress in understanding how antimicrobial resistance works and the emergence of various new treatments, substantial gaps in knowledge and practical application still exist. Current research often examines resistance mechanisms, surveillance frameworks, and emerging therapies separately; it rarely compares their potential, scalability, or readiness for clinical use. What's more, few reviews systematically assess why some treatment strategies have failed, which approaches truly show promise for real-world application, or how new tools like artificial intelligence might fit into existing stewardship and surveillance systems. This review aims to fill these gaps by synthesizing and critically evaluating resistance mechanisms, surveillance strategies, and novel therapies. It then compares their advantages, limitations, and barriers to implementation.

Mechanisms of Antimicrobial Resistance: Clinical Relevance and Therapeutic Implications

Antimicrobial resistance (AMR) mechanisms are more than just molecular adaptations. They're critical in determining clinical failure, how long treatments last, and patient outcomes. While we categorize resistance mechanisms as intrinsic or acquired, their true impact in the real world depends on how they co-exist, whether they can be induced, and how they interact with host and environmental factors. Multidrug resistance often arises from several mechanisms accumulating and acting in concert, rather than just one pathway taking over.[4,5]

These mechanisms collectively reduce antibiotic efficacy, enabling bacterial survival under therapeutic pressure and facilitating the spread of resistance across and within species.

The major mechanisms of antimicrobial resistance are summarized in Figure 1. The schematic highlights how bacteria employ multiple complementary strategies to evade antimicrobial activity, including enzymatic inactivation of drugs, modification of antibiotic target sites, activation of efflux pumps that expel antibiotics from the cell, and reduced membrane permeability due to porin alterations. In addition, structural changes in penicillin-binding proteins (PBPs) further decrease antibiotic binding. Importantly, these mechanisms often coexist within a single bacterial cell, resulting in multidrug resistance and significantly limiting therapeutic options.

Enzymatic Inactivation of Antibiotics

Enzymatic inactivation is one of the most prevalent resistance mechanisms, whereby bacteria produce enzymes that degrade or chemically modify antimicrobial agents. The most well-known example is the hydrolysis of β-lactam antibiotics by β-lactamases, which disrupt the β-lactam ring and render penicillins, cephalosporins and related drugs ineffective. In addition, enzymes may inactivate antibiotics through acetylation, phosphorylation, or nucleotidylation, affecting aminoglycosides, chloramphenicol, rifamycins, lincosamides, tetracyclines, and streptogramins. [2,5] Among these, β-lactamases including penicillinases, AmpC enzymes, extended-spectrum β-lactamases (ESBLs), and carbapenemases (e.g., KPC, VIM, IMP, and OXA-type)are of clinical concern due to their broad substrate spectrum and rapid dissemination, especially in Gram-negative bacteria.[2,5,7,8,9]

Biofilm-Associated Resistance

Biofilm formation represents an important adaptive mechanism in which bacteria grow as structured communities embedded in a self-produced extracellular matrix composed of polysaccharides, proteins, and extracellular DNA. Biofilm-associated bacteria can exhibit up to 10,000-fold increase resistance compared with planktonic cells. This enhanced resistance results from limited antibiotic penetration, altered metabolic states, and increased expression of resistance determinants.[5,10,11] Clinically significant pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* frequently combine biofilm formation with additional resistance mechanisms, contributing to persistent and difficult-to-treat infections.[2]

Efflux Pump-Mediated Resistance

Efflux pumps (EPs) enable bacteria to eliminate a wide range of toxic substances, including antibiotics, heavy metals, disinfectants, and antiseptics. These systems actively expel antibiotics and other toxic compounds from bacterial cells, maintaining intracellular drug concentrations below bactericidal levels. Efflux pumps may be constitutively expressed or induced in response to environmental stimuli, including antibiotic exposure.[2,8,12]

There are five major families of efflux pumps: (i) the major facilitator superfamily (MFs), (ii) the small multidrug resistance family (SMR), (iii) the resistance-nodulation cell-division family (RND), (iv) the ATP-binding cassette family, and (v) the multidrug and toxic compound extrusion family. These efflux pump families vary in their structural organization, energy sources, substrate specificity, and distribution across different bacterial species.[5,7,12]

Target Site Modification

Modification of antibiotic target sites reduces drug binding and represents a major resistance strategy. This may occur through mutations or enzymatic alterations affecting ribosomes, DNA replication enzymes, or cell wall synthesis proteins.

For example, mutations in DNA gyrase and topoisomerase confer resistance to quinolones, while methylation of ribosomal RNA mediated by *erm* genes leads to resistance to macrolides and related agents. Similarly, alterations in penicillin-binding proteins (PBPs), which are essential for peptidoglycan synthesis, reduce β-lactam binding. The acquisition of PBP2a, encoded by the *mecA* gene and its homologs, is a well-known mechanism conferring resistance to β-lactam antibiotics. Enzymatic drug inactivation and efflux pump overexpression are major clinical challenges in resistance, stemming from their broad substrate profile and rapid horizontal dissemination.[5,7,8,12]

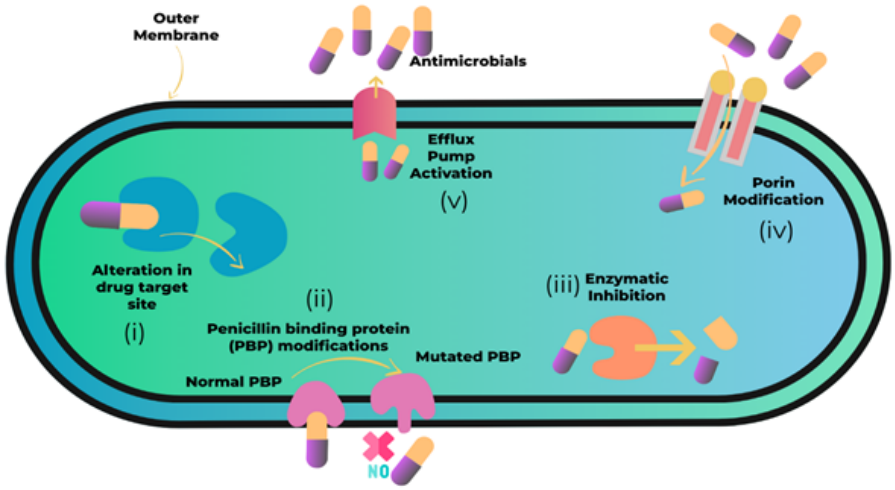

Figure 1: **Overview of major mechanisms of antimicrobial resistance in bacteria**

This schematic representation illustrates the principal mechanisms by which bacteria resist antimicrobial agents. These include: (i) alteration of drug target sites that reduces antibiotic binding, (ii) modification of penicillin-binding proteins (PBPs), (iii) enzymatic inactivation of antibiotics (e.g., β-lactamase-mediated degradation), (iv) porin modifications that limit antibiotic entry and (v) activation of efflux pumps that actively remove antibiotics from the bacterial cell. The figure also emphasizes the combined effect of these mechanisms in reducing intracellular drug concentrations and promoting the development of multidrug-resistant bacterial strains.

Reduced Membrane Permeability (Porin Modification)

Porins act as channels that facilitate the passive diffusion of hydrophilic molecules, including certain antibiotics, into bacterial cells. Reduced permeability of the bacterial cell envelope limits antibiotic entry, particularly in Gram-negative bacteria. Porins may undergo structural alterations or decreased expression, restricting drug uptake.

Examples include OmpF, OmpC, and PhoE in *Escherichia coli*, and OprD in *Pseudomonas aeruginosa*. Loss or modification of OprD is associated with resistance to carbapenems such as imipenem and meropenem. These permeability changes often act

synergistically with other mechanisms, including efflux pump overexpression.[5,7,12]

Summary of antimicrobial resistance mechanisms are given in Table 1.

Table 1: Summary of antimicrobial resistance mechanisms

Resistance Mechanism	Primary Advantage to Bacteria	Why It Matters Clinically	Key Limitation
Enzymatic inactivation	Rapid antibiotic neutralization	Leads to broad ß-lactam failure	Can be targeted by inhibitors
Efflux pumps	Multidrug resistance	Limits intracellular drug levels	Energetically costly
Target modification	High specificity	Causes class-specific failure	Often requires mutations
Reduced permeability	Prevents drug entry	Critical in Gram-negative MDR	Synergistic, not standalone
Biofilm formation	Community protection	Causes chronic, recurrent infections	Vulnerable to physical disruption

Global Strategies for Tracking Antimicrobial Resistance

Antimicrobial Stewardship

Antimicrobial stewardship (AMS) is central to global efforts to mitigate AMR by promoting the rational use of antibiotics. Antimicrobial Stewardship Programs (ASPs) involve systematic monitoring and coordinated interventions among clinicians, infection control personnel, pharmacists, and information technology teams. These programs aim to ensure the optimal use of antibiotics, including appropriate selection, dosing, route of administration, and treatment duration.[13]

To support the appropriate use of antibiotics, the WHO developed the AWaRe (Access, Watch, Reserve) classification. The AWaRe antibiotic book provides clear, evidence-based guidance on antibiotic selection, dosing, route of administration, and treatment duration for over 30 common infections in children and adults in both primary care and hospital settings. In parallel, WHO Priority Pathogen Lists (PPLs) identify high-risk drug–pathogen combinations requiring urgent research and policy attention. Together, these frameworks connect surveillance data with clinical practice, ensuring that prescribing behavior aligns with evolving resistance patterns.[14,15]

However, stewardship alone cannot address the AMR crisis without parallel advances in drug development. Global initiatives such as the Global Antibiotic Research & Development Partnership (GARDP), CARB-X, and the AMR Action Fund aim to address persistent gaps in antimicrobial innovation. These efforts highlight the need for coordinated strategies that align stewardship with research investment and equitable access to new therapeutics.[14,16]

WHO BPPL: Guiding Antimicrobial Research and Investment

Since 2017, the WHO Bacterial Priority Pathogens List (BPPL) has guided R&D investment and AMR surveillance. Despite these efforts, antibiotic innovation and access remain limited. The 2024 BPPL updates the list, categorizing 15 antibiotic-resistant pathogen families into critical, high, and medium priorities. Critical pathogens include *Acinetobacter baumannii*, Enterobacterales, and rifampicin-resistant *Mycobacterium tuberculosis* due to their severity, transmissibility, and global burden, particularly in LMICs. High-priority pathogens include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, multidrug-resistant *Neisseria gonorrhoeae*, and *Enterococcus faecium*. Medium-priority pathogens, such as Group A and B Streptococci, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, pose significant risks to vulnerable populations.[17,18,19]

While the BPPL provides a valuable global benchmark, its impact depends on regional adaptation. Differences in pathogen distribution, healthcare infrastructure, and antibiotic use patterns require context-specific prioritization to ensure relevance and effectiveness, particularly in high-burden settings.[17]

Strengthening AMR Surveillance: WHO's GLASS Initiative

Surveillance systems play a vital role in controlling antimicrobial resistance. Yet, their real strength lies not just in gathering data, but in how effectively that information shapes clinical choices, enhances stewardship efforts, and guides research priorities.

WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) represented a significant advance. It harmonized AMR and AMU data across countries under a "One Health" approach. This standardized method allows for international comparisons, helps spot resistance trends early, and aligns prescribing practices with epidemiological data.

For instance, limited lab capacity, underrepresentation from low- and middle-income countries, and slow reporting all hinder real-time responses. Furthermore, surveillance data rarely incorporate genomic sequencing, environmental monitoring, or analyses of prescribing behavior. This makes the data less useful for prediction.

Future surveillance needs to go beyond passive reporting and truly embrace predictive modeling. This means incorporating AI-driven analytics, real-time genomic surveillance, and clinical outcome data. Otherwise, surveillance risks staying merely descriptive, rather than becoming genuinely transformative.

Effective AMR control relies on robust and standardized surveillance systems. Historically, global surveillance has been limited by fragmented data and inconsistent methodologies. The WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS), established in 2015, addresses these challenges by harmonizing AMR and antimicrobial use (AMU) data across countries within a One Health framework. [15,20]

Since its inception, GLASS has accumulated data from over 23 million laboratory confirmed infections reported by 104 countries. By focusing on priority pathogens and key infection syndromes, it ensures that surveillance remains targeted and policy-relevant. Importantly, GLASS employs statistical modeling to adjust for variations in laboratory capacity and reporting completeness, enabling more reliable cross-country comparisons and trend analysis.

Despite these advances, important limitations persist. Participation and data quality remain uneven, with low-and middle-income countries often facing constraints in laboratory infrastructure and data systems. This can lead to underrepresentation of high-burden regions and limit the precision of global estimates.

Nevertheless, GLASS represents a critical shift from passive data collection to actionable surveillance. By enabling benchmarking, informing stewardship interventions, and guiding research priorities, it serves as a cornerstone of global AMR governance. Strengthening national surveillance capacity, improving data completeness, and integrating real-time and genomic tools will be essential to maximize its impact.[14,15,20]

EMERGING AND INNOVATIVE SOLUTIONS

Recent advancements in the discovery and development of novel therapeutics such as phage therapy, antimicrobial peptides (AMPs), CRISPR-Cas9, monoclonal antibodies, drug repurposing strategies and use of artificial intelligence (AI) and computational strategies have shown significant promise in addressing antimicrobial resistance.

Collectively, these emerging therapeutic strategies differ in their mechanisms, specificity, stage of clinical development, and translational challenges. While approaches such as phage therapy and CRISPR-based antimicrobials offer high specificity and precision, others including antimicrobial peptides and nanoparticles provide broad-spectrum activity. In contrast, vaccines and probiotics function as preventive strategies, reducing infection burden and antibiotic use. Despite their promise, limitations such as cost, delivery challenges, regulatory hurdles, and scalability issues continue to influence their clinical applicability, highlighting the need for integrated and combination approaches to effectively combat antimicrobial resistance. Comparison of these novel therapeutic approaches for antimicrobial resistance is presented in Table 2.

Table 2: Comparison of novel therapeutic approaches for antimicrobial resistance

Approach	Mechanism of Action	Advantages	Limitations
Phage therapy	Lytic bacteriophages infect and lyse bacterial hosts through lytic cycle.	High specificity, preserves beneficial microbiota, low toxicity and good tolerance, cost-effective, effectively kill gram positive and gram-negative bacteria, effective against biofilms.	Narrow host range, Maintenance, regulatory and logistic challenges, phage selection & production complexity.
Antimicrobial peptides (AMPs)	Membrane disruption (pore formation, leakage) and non-membrane mechanisms (inhibition of DNA, RNA, protein synthesis)	Broad-spectrum activity, low risk of resistance development, effective against MDR pathogens.	Short half-life, hostcytotoxicity, high production cost.
Monoclonal antibodies	Neutralization of bacterial toxins, targeting virulence factors and immune system enhancement, direct bactericidal production for killing the bacteria.	High specificity, favorable safety profile, low toxicity, preserves microbiota, reduced resistance development	High production cost, intravenous administration.
CRISPR-based antimicrobials	Sequence-specific targeting and cleavage of resistance genes or plasmids using CRISPR-Cas systems	Highly specific and programmable, targets AMR genes directly, effective in MDR pathogens.	Narrow host range and delivery challenges.
Drug repurposing	New use of existing drugs	reduces costs and time, accelerates the development of new treatments, faster approval.	Limited efficacy, unknown mechanisms, Patent related issues.
Nanoparticles, Nanomaterials	Bactericidal activity, ROS generation, membrane damage or act as nanocarriers for antibiotics and AMPs.	Broad spectrum of activity, Multifunctional, synergistic effects, reduces resistance development.	Toxicity concerns, scalability
Probiotics	Production of antimicrobial bacteriocins, microbiome modulation, enhancement of mucosal barrier to prevent bacterial attachment.	Safe, preventive approach, active against biofilms and virulence factors.	Strain-specific effects, variability in host response, stability and storage issues.
Algae-based treatment	Removal of antibiotic-resistant bacteria (ARB) and genes (ARGs)	Eco-friendly, sustainable, reduces antibiotic residues	Limited clinical relevance, variability in efficiency, scalability challenges
Vaccines	Prevent infections	Reduces antibiotic use and resistance, long-term impact	Variable efficacy, pathogen-specific, development gaps
AI & computational tools	Drug discovery, prediction, surveillance	Rapid, data-driven, enables drug repurposing	Data dependency, validation needed, algorithm bias

Phage Therapy

Bacteriophages (phages) are viruses that infect and multiply within bacteria. The global rise of AMR has renewed attention to phages as promising alternatives to antibiotics, particularly in Eastern European countries where phage therapy has long been integrated into clinical practice.[2,21]

Phage therapy involves the administration of lytic phages to selectively eliminate pathogenic bacteria, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. Clinical and preclinical studies have demonstrated efficacy against pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiellapneumoniae*. Phages also show potential in preventing and disrupting biofilms, which are major contributors to chronic and resistant infections. Additionally, innovative approaches such as phage–nanoparticle conjugates (e.g., T7 phages with silver nanoparticles) have demonstrated synergistic antibiofilm activity without significant toxicity.[2,11,21,22,23,24]

Overall, phage therapy represents a highly specific, adaptable, and promising strategy for combating AMR, particularly in the context of personalized medicine.

Antimicrobial Peptides (AMPs)

AMPs primarily exert antimicrobial effect through membrane disruption by interacting with negatively charged components of bacterial cell membranes, leading to pore formation, leakage of intracellular contents, and cell death. Some AMPs also act via non–membrane-disruptive mechanisms, including inhibition of DNA, RNA, or protein synthesis and interference with enzymatic and metabolic pathways. Their multi-targeted mechanisms reduce the likelihood of resistance development compared to traditional antibiotics.

Several AMPs, including polymyxins, gramicidin, daptomycin, and lipoglycopeptides such as dalbavancin and telavancin, have received regulatory approval. Combination strategies, such as peptide–antibiotic conjugates, have demonstrated enhanced efficacy against MDR pathogens.[4,11,21,22,24]

Monoclonal Antibody-Based Therapies (mAbs)

Monoclonal antibodies (mAbs) are laboratory-engineered proteins that selectively target specific antigens, offering high specificity and a favorable safety profile.mAbs exert antimicrobial effects by neutralizing bacterial toxins, targeting virulence factors, promoting complement-mediated killing, and enhancing immune clearance.

Currently, only a limited number of mAbs have received regulatory approval for bacterial infections, including bezlotoxumab (for recurrent *Clostridioides difficile* infection) and raxibacumab and obiltoxaximab (for inhalational anthrax).

Despite their therapeutic potential, widespread clinical use is limited by high production costs and intravenous administration requirements. Nevertheless, mAbs represent a targeted and adjunctive strategy for combating multidrug-resistant bacterial infections.[11,21,22,25]

CRISPR-Based Antimicrobials

CRISPR–Cas technologies particularly CRISPR–Cas9 have been repurposed as novel antimicrobial tools to combat AMR. CRISPR-based antimicrobials function by selectively targeting and cleaving antibiotic resistance genes or virulence determinants within bacterial genomes or plasmids. Delivery systems such as bacteriophages, phagemids, and conjugative plasmids have been used to introduce CRISPR constructs into MDR pathogens, including *Escherichia coli* and *Staphylococcus aureus*.Despite its promise, several challenges limit clinical translation.

Overall, CRISPR-based antimicrobials represent a highly specific and programmable strategy with significant potential to complement existing therapies and restore antibiotic susceptibility in resistant bacterial populations.[4,23,24,26]

Drug Repurposing Strategies

Drug repurposing involves identifying new antimicrobial applications for existing drugs that have already undergone safety and clinical evaluation.

In response to the growing AMR crisis, drug repurposing has gained increasing attention. Collaborative initiatives and compound libraries from organizations such as Medicines for Malaria

Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi) facilitate large-scale screening of approved and investigational molecules. Several non-antibiotic drugs, including certain anticancer agents and statins, have demonstrated antibacterial or antibiotic-sensitizing effects against multidrug-resistant pathogens.[4,17,24,27]

Nanoparticles and Nanotechnology-Based Approaches

Nanoparticles offer a promising strategy to combat AMR due to their high surface-to-volume ratio, tunable surface chemistry, and ability to interact efficiently with microbial cells. They exhibit dual functionality: intrinsic antimicrobial activity and use as nanocarriers for antibiotics or antimicrobial peptides (AMPs).

Metal nanoparticles particularly silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs), exert antimicrobial effect by disrupting bacterial membranes, generating reactive oxygen species (ROS), interfering with biofilms, and damaging cellular proteins and DNA. These multimodal mechanisms reduce the likelihood of resistance development and demonstrate activity against MDR Gram-positive and Gram-negative bacteria. Conjugation of antibiotics such as vancomycin, ampicillin, and gentamicin with nanoparticles have shown synergistic antibacterial effects.[21,22,25]

Probiotics

Probiotics are live microorganisms, commonly from *Bifidobacterium, Lactobacillus, Saccharomyces,* and *Bacillus* species, that confer health benefits when administered in adequate amounts. They combat pathogenic bacteria by producing antimicrobial compounds (bacteriocins), enhancing gut barrier function, restoring microbiome balance, and modulating immunity. This reduces infections and the need for antibiotics, lowering selective pressure for AMR.Advantages include targeted activity, no risk of AMR, and improved host health, while limitations involve strain-specific efficacy, host variability, and production or storage challenges. Despite these, probiotics offer a natural and effective strategy to reduce infections, antibiotic use, and AMR.[11,21]

Algae mediated treatments

Domestic and agricultural wastewaters are significant sources of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) due to widespread antibiotic use. Algae-mediated treatments, particularly using green algae, have emerged as an eco-friendly alternative. Microalgae efficiently remove nutrients, heavy metals, pathogens, and antibiotic residues while reducing ARB and ARGs.[22]

A study comparing conventional wastewater treatment with an algae-based system found that the algal system achieved significantly greater reductions in sulfamethoxazole- and erythromycin-resistant bacteria than the conventional treatment.[28]

Vaccines for Reducing Antibiotic Use

Vaccination plays critical role in combating AMR by preventing infections and reducing the need for antibiotics, thereby lowering selective pressure for emergence of resistant strains. Long-term vaccination against diseases like pertussis, diphtheria, *Haemophilus influenzae* type b (Hib), and *Streptococcus pneumoniae* has led to substantial reductions in infections and multidrug-resistant cases.[24] For example, the PCV7 pneumococcal vaccine reduced multidrug-resistant invasive pneumococcal disease by 84%.[22]

While vaccines exist for some WHO priority pathogens (e.g., *S. pneumoniae*, *H. influenzae*, *Salmonella Typhi*), effective vaccines are still under development for other major AMR contributors, including *S. aureus*, *E. coli*, *K. pneumoniae*, and *A. baumannii*.[15]

Overall, vaccines provide direct and indirect protection against AMR, representing a sustainable and preventative strategy that complements other antimicrobial interventions.

Artificial Intelligence and Computational Strategies

Artificial intelligence (AI) and machine learning (ML) are increasingly recognized as transformative tools in combating AMR, particularly in resistance prediction, surveillance, and antimicrobial discovery. AI-driven models can integrate genomic data, phenotypic susceptibility profiles, and clinical metadata to accurately predict resistance phenotypes and identify novel resistance determinants.

In addition, AI enhances AMR surveillance by detecting emerging resistance patterns, forecasting outbreak risks, and informing antimicrobial stewardship strategies. Beyond diagnostics and surveillance, computational platforms leveraging deep learning and advanced bioinformatics are accelerating antimicrobial discovery by enabling virtual screening of large compound libraries and facilitating the rational design of novel agents capable of overcoming existing resistance mechanisms.[29,30]

No single emerging therapy is sufficient to replace antibiotics. Phage therapy and antimicrobial peptides appear most promising for multidrug-resistant and biofilm-associated infections, yet face significant challenges in delivery, regulation, and scalability. Notably, many approaches have stalled not due to lack of efficacy, but economic, regulatory, and logistical barriers.

Conclusion

Antimicrobial resistance represents a multifaceted global crisis driven by microbial evolution, antibiotic misuse, and systemic gaps in surveillance and innovation. This review demonstrates that while remarkable progress has been made in understanding resistance mechanisms and developing alternative therapies, fragmentation between science, clinical practice, and policy continues to limit impact.

We won't find one "replacement" for antibiotics. Instead, the most promising path forward combines next-generation therapies, strong surveillance, antimicrobial stewardship, and preventive measures like vaccination. Precision tools, such as CRISPR-based antimicrobials and AI-enabled drug discovery, hold great promise. But they'll only truly transform things if we back them with scalable delivery systems and fair global access.

To truly combat AMR, we'll need to shift away from just reacting with drugs. Instead, we must adopt proactive, system-based strategies guided by One Health principles. Ongoing collaboration across disciplines, practical research, and aligned policies are essential. These are what we'll need to preserve how well antimicrobials work and to protect global health.

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