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# ANTIMICROBIAL RESISTANCE IN THE ANTIBIOTIC ERA: EVOLUTION, MECHANISMS, MEASUREMENT, AND STRATEGIES FOR SUSTAINABLE CONTROL

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## ABSTRACT

Antimicrobials, particularly antibiotics, have revolutionized modern medicine by significantly reducing mortality from infectious diseases and enabling complex medical procedures. However, their extensive and often inappropriate use in human health, veterinary practice, agriculture, and the environment has accelerated the global emergence of antimicrobial resistance (AMR). This review provides a comprehensive overview of antibiotic resistance, including its types, causes, mechanisms, and measurement methods. It also highlights the historical timeline of antibiotic discovery alongside the rapid development of resistance, underscoring the persistent evolutionary arms race between pathogens and antimicrobial agents. Furthermore, this review discusses preventive strategies, such as antimicrobial stewardship, infection control, one health surveillance, and global and national action plans. Recent advances in improving existing antibiotics, the development of novel antimicrobials, and the identification of new bacterial targets are also discussed. Collectively, this review emphasizes the urgent need for coordinated, multidisciplinary, and sustainable approaches to preserve antimicrobial efficacy and mitigate the growing threat of AMR.

**KEYWORDS:** Antimicrobial resistance, Antibiotic Resistance, Global actions, One health

surveillance, Precision antimicrobial stewardship.

## INTRODUCTION

Antimicrobials, particularly antibiotics, represent one of the most groundbreaking discoveries of the twentieth century and have profoundly transformed medical practices. Their introduction revolutionized the treatment of infectious diseases, dramatically reducing mortality and morbidity and enabling the advancement of complex medical procedures, such as surgery, organ transplantation, cancer chemotherapy, and neonatal care. Since Alexander Fleming discovered penicillin in 1928, antibiotics have saved millions of lives and reshaped global health outcomes.[1,3] However, the extraordinary success of antimicrobials has been undermined by their extensive and often inappropriate use in human medicine, veterinary practice, agriculture, and animal husbandry sectors. This misuse has accelerated the emergence of antimicrobial resistance (AMR), which is now recognized by the World Health Organization (WHO) as one of the top global public health threats. AMR jeopardizes decades of medical progress and raises the alarming possibility of a post-antibiotic era in which common infections may become lethal.[2,4,5]

## LITERATURE SEARCH STRATERGY

A structured literature search was performed using PubMed, Scopus, Web of Science, Google Scholar, and Embase to identify relevant studies on antimicrobial resistance (AMR) published between 20 and 2026. Search terms included combinations of keywords such as “antimicrobial resistance,” “artificial intelligence,” “CRISPR,” “whole-genome sequencing,” “antimicrobial peptides,” “phage therapy,” and “One Health surveillance” using Boolean operators (AND, OR). Peer-reviewed research articles, systematic reviews, clinical studies, genomic surveillance reports, and publications from international organizations including WHO, FAO, and WOAH were included. Articles unrelated to AMR, duplicate records, conference abstracts, and non-English publications were excluded. Eligible studies were screened based on title, abstract, and full-text review. The selected literature was then categorized according to major themes and synthesized narratively to summarize recent advances in AMR prevention, surveillance, and treatment strategies.

## ANTIBIOTIC RESISTANCE

Antibiotic resistance refers to the ability of bacteria to survive or grow in the presence of antimicrobial agents that were previously effective. This phenomenon arises when bacteria undergo genetic or phenotypic changes that reduce or eliminate their efficacy. Antibiotic

resistance is now recognized as a major global health crisis that undermines the success of modern medicine and threatens the management of infectious diseases worldwide. The rapid emergence of resistant pathogens has been largely attributed to antibiotic overuse, misuse, and stagnation of new antibiotic development, resulting in infections that are increasingly difficult or impossible to treat.[2,4]

## EMERGENCE OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance emerges when microorganisms evolve mechanisms that allow them to survive drug exposure intended to kill or inhibit them. Resistance may be intrinsic or acquired through genetic mutations and horizontal gene transfer mediated by plasmids, transposons, and integrons.[9,15] Excessive and irrational use of antibiotics, inappropriate prescribing, self-medication, poor infection control practices, and widespread antimicrobial use in livestock feeds are the primary drivers of resistance development.[4,8] At the molecular level, bacteria deploy multiple resistance strategies, including enzymatic drug inactivation (e.g., β-lactamases), modification of antimicrobial targets, decreased membrane permeability, and active drug efflux. Biofilm formation further enhances resistance by providing a physical and metabolic barrier that limits antibiotic penetration and facilitates persistent infection.[1,9,16] These mechanisms collectively contribute to the rapid global dissemination of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) pathogens, significantly complicating clinical management.[5,15]

## TYPES OF ANTIBIOTIC RESISTANCE

Antibiotic resistance can be classified as intrinsic (natural), acquired, or adaptive. Intrinsic resistance is an inherent property of certain bacterial species due to their structural or functional characteristics, such as the impermeable outer membrane of gram-negative bacteria or the absence of antibiotic targets, as seen in *Mycoplasma* species.[6,7]

Acquired resistance develops when previously susceptible bacteria gain resistance through chromosomal mutations or horizontal gene transfer**,** involving plasmids, transposons, and integrons. This form of resistance is particularly concerning because it can spread rapidly among bacterial populations and across species.[7,9]

Adaptive resistance is a transient and reversible state in which bacteria temporarily alter their gene expression in response to environmental stressors, such as sub-inhibitory antibiotic concentrations, pH changes, or nutrient limitation. Although reversible, adaptive resistance

contributes to persistent infection and facilitates the development of stable resistance mechanisms.[6,10]

## CAUSES AND THREATS OF ANTIBIOTIC RESISTANCE

The primary drivers of antibiotic resistance include the overuse and misuse of antibiotics in human medicine, inappropriate prescribing, self-medication, incomplete treatment courses, and extensive antibiotic use in agriculture and animal husbandry. Ventola reported that up to 50% of antibiotic prescriptions are inappropriate, providing selective pressure that favors resistant strains.[2]

The agricultural use of antibiotics, particularly as growth promoters in livestock, accounts for a significant proportion of global antibiotic consumption. Bacteria resistant to antibiotics in animals can be transmitted to humans through food, water, and the environment, amplifying the dissemination of resistance.[2,4]

The threats posed by antibiotic resistance are profound, including increased morbidity and mortality, prolonged hospital stays, higher healthcare costs, and reduced effectiveness of life-saving medical procedures, such as surgery, chemotherapy, and organ transplantation. Globally, resistant infections are responsible for millions of deaths annually and represent a silent pandemic.[4,11]

## MECHANISM OF ANTIBIOTIC RESISTANCE

Bacteria employ several molecular mechanisms to evade the action of antibiotics.

**Enzymatic inactivation:** is a common mechanism, exemplified by β-lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferases, which chemically inactivate antibiotics.[7,3]

**Target modification or replacement:** It occurs when mutations or enzymatic alterations reduce antibiotic binding to the essential bacterial targets. Examples include altered penicillin-binding proteins (PBPs) in methicillin-resistant *Staphylococcus aureus* (MRSA) and ribosomal RNA methylation, leading to macrolide resistance.[7,3]

**Reduced intracellular drug accumulation:** It is achieved through decreased membrane permeability (e.g., porin loss in gram-negative bacteria) or increased activity of efflux pumps, which expel antibiotics from the cell before they reach inhibitory concentrations.[7,12]

Additionally, **Biofilm formation:** It provides a physical and metabolic barrier that protects bacterial communities from antibiotics and host immune responses, facilitating chronic and recurrent infections.[7,9]

**Table 1: Major Mechanisms of Antibiotic Resistance.**

| Mechanism | Description | Example |
|---|---|---|
| Enzymatic degradation | Drug inactivation | β-lactamase |
| Target modification | Altered drug target | MRSA |
| Efflux pumps | Drug removal | TetA pump |
| Reduced permeability | Porin loss | Pseudomonas |
| Biofilm formation | Protective matrix | Chronic infections |

## METHODS OF MEASUREMENT OF ANTIBIOTIC RESISTANCE

Antibiotic resistance is routinely measured using both phenotypic and genotypic methods. Phenotypic techniques include disk diffusion (Kirby–Bauer method), minimum inhibitory concentration (MIC) determination using broth dilution or E-test, and automated susceptibility testing. These methods assess bacterial growth inhibition in the presence of antibiotics and guide clinical therapy.[8,3]

Genotypic methods detect specific resistance genes using polymerase chain reaction (PCR), whole-genome sequencing, and molecular hybridization. Wilkie et al. demonstrated the use of PCR to identify resistance genes, such as *mecA*, *blaSHV*, and *tetA*, providing insights into resistance mechanisms and epidemiology.[8] Genotypic approaches offer high sensitivity and allow for the early detection of emerging resistance.

## PREVENTION OF ANTIBIOTIC RESISTANCE

Preventing antibiotic resistance requires a multifaceted approach involving antimicrobial stewardship, infection prevention, surveillance, and education. Rational antibiotic prescribing, adherence to treatment guidelines, and restriction of over-the-counter antibiotic sales are critical strategies to combat AMR.[2,4]

Infection control measures, such as hand hygiene, vaccination, sanitation, and improved diagnostics, reduce infection rates and antibiotic demand. Limiting antibiotic use in agriculture and promoting alternatives for animal growth and disease prevention are essential.[2,6]

Global initiatives, including the WHO Global Action Plan on Antimicrobial Resistance,

emphasize coordinated international efforts to preserve antibiotic effectiveness and slow the development of resistance.[4,11]

## ANTIMICROBIALS AS MIRACLES IN MODERN MEDICINE

Antimicrobials are often referred to as "magic bullets" because of their unparalleled impact on modern medicine. The antibiotic era has enabled the effective treatment of once-fatal bacterial infections, such as pneumonia, sepsis, tuberculosis, and wound infections. It has also facilitated safe surgical interventions, reduced maternal and neonatal mortality, and supported immunosuppressive therapies.[2,3,13] The "golden age" of antibiotic discovery between the 1940s and the 1960s yielded multiple drug classes, including β-lactams, aminoglycosides, macrolides, and tetracyclines, providing broad-spectrum therapeutic coverage.[3,14] Despite the current resistance crisis, antimicrobials remain indispensable in healthcare systems worldwide. Their continued effectiveness relies heavily on antimicrobial stewardship, rational prescribing, surveillance, and drug development innovation.[4,11]

**Improvement of Antimicrobials:** To extend the lifespan of existing antibiotics, several strategies have been adopted. These include the chemical modification of existing drug scaffolds, development of β-lactamase inhibitors, and combination therapies that enhance efficacy and reduce resistance emergence.[7,3]

The optimization of pharmacokinetics, targeted drug delivery systems, and synergy-based regimens has further improved antimicrobial performance against resistant pathogens.[7,13]

## NOVEL ANTIMICROBIALS

Novel antimicrobial strategies aim to overcome conventional resistance. These include antimicrobial peptides, bacteriophage therapy, CRISPR-Cas–based antimicrobials, and immuno-antibiotics that enhance host immune responses.[7,18,13]

Natural products, synthetic biology, and metagenomic approaches are increasingly being explored to identify new antimicrobial compounds from previously untapped sources.[6,18]

## NEW TARGETS FOR ANTIMICROBIALS

Emerging antimicrobial targets focus on pathways beyond classical cell wall or protein synthesis pathways. These include virulence factors, quorum-sensing systems, biofilm formation pathways, efflux pump inhibition, and metabolic bypass pathways.[9,21]

Targeting bacterial communication and pathogenicity rather than viability may reduce selective pressure and slow resistance development, representing a promising paradigm shift in antimicrobial therapy.[7,18,13]

## TIMELINE OF ANTIBIOTIC DISCOVERY AND RESISTANCE

The concept of antimicrobial therapy existed long before modern medicine, as ancient civilizations used plant extracts, molds, and other natural compounds to treat infections. Modern studies have confirmed that antibiotic resistance genes predate clinical antibiotic use, indicating that resistance is a natural evolutionary phenomenon rather than a purely modern problem.[2,6]

The modern antibiotic era began in 1909 with the introduction of Salvarsan, developed by Paul Ehrlich for syphilis treatment, which introduced the concept of selective antimicrobial chemotherapy. This was followed in the 1930s by sulfonamides (Prontosil), the first widely used systemic antibacterial agents.[6,4]

A major breakthrough occurred in 1928 with the discovery of penicillin by Alexander Fleming, which entered widespread clinical use in the early 1940s and dramatically reduced infection-related mortality, particularly during the World War II. Notably, penicillin-resistant *Staphylococcus* strains were reported shortly after its introduction, marking early recognition of antibiotic resistance.[2,4]

The period from the 1940s to the 1960s, known as the Golden Age of Antibiotics, saw the discovery of most major antibiotic classes, including aminoglycosides, tetracyclines, macrolides, chloramphenicol, and cephalosporins. Resistance to these agents has emerged rapidly; for example, tetracycline-resistant *Shigella* was reported within a decade of its introduction.[2,4,3]

In response to increasing resistance, semisynthetic antibiotics such as methicillin were introduced in the late 1950s; however, methicillin-resistant *Staphylococcus aureus* (MRSA) appeared within a year. Vancomycin, introduced as a last-resort drug, faced resistance in enterococci and staphylococci by the late 1970s–1990s.[2,4]

The the 1980s and the 1990s saw the introduction of carbapenems and fluoroquinolones, which became critical for treating multidrug-resistant infections. However, resistance to these agents, including fluoroquinolone-resistant pneumococci and carbapenem-resistant

Enterobacterales, has emerged rapidly.[2,4,3]

Since the 2000s, antibiotic discovery has significantly declined owing to economic and regulatory challenges, while resistance has accelerated. The rise of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) pathogens has led to warnings of a potential post-antibiotic era in medicine. Current efforts focus on stewardship, surveillance, One Health approaches, and alternative therapies rather than relying solely on new antibiotics.[2,3,11]

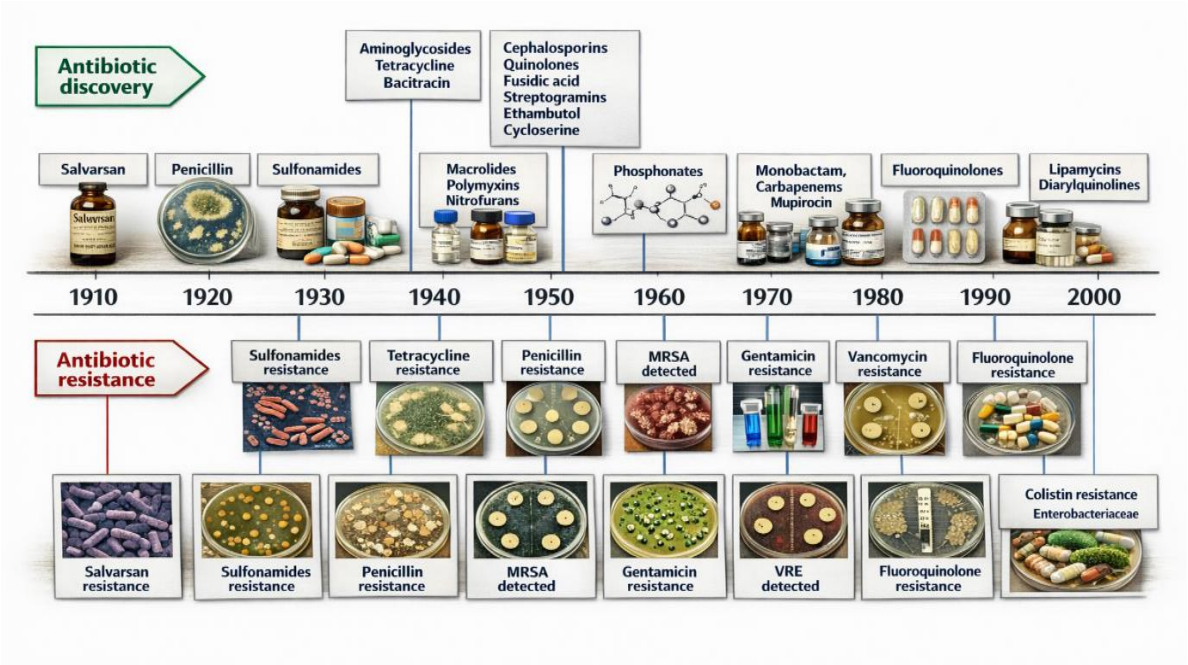


**Fig No.1: Timeline of Antibiotic Discovery and Resistance.**

## GLOBAL AND NATIONAL ACTIONS TO RESIST ANTIMICROBIAL RESISTANCE

### Global Actions to Combat Antimicrobial Resistance

Antimicrobial resistance (AMR) has been recognized as a global health emergency that requires coordinated international action. The World Health Organization (WHO), in collaboration with the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (WOAH) has promoted a One Health approach that integrates human, animal, and environmental health to address AMR comprehensively. A landmark initiative is the WHO Global Action Plan on Antimicrobial Resistance (GAP-AMR), launched in 2015, which outlines five strategic objectives: improving awareness and understanding of AMR, strengthening surveillance and research, reducing infection incidence, optimizing

antimicrobial use, and ensuring sustainable investment in counter measures.[3,11]

Global surveillance systems, such as the Global Antimicrobial Resistance and Use Surveillance System (GLASS), have been established to standardize data collection and monitor resistance trends worldwide. The GLASS data have revealed widespread resistance among common pathogens, such as *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*, reinforcing the urgency for global collaboration.[13,4] Additionally, the WHO has published a priority pathogen list to guide the research and development of new antibiotics, focusing on critical multidrug-resistant gram-negative bacteria.[4]

International funding and innovation platforms, such as CARB-X, GARDP, and New Drugs for Bad Bugs (ND4BB), support antibiotic research, diagnostics, and alternative therapies. These initiatives aim to revitalize the stagnant antibiotic pipeline and encourage public–private partnerships to overcome the economic barriers associated with antimicrobial development.[3,2]

## ROLE OF INTERNATIONAL ORGANIZATION AND POLICY FRAMEWORKS

The United Nations General Assembly has recognized AMR as a global development issue and endorsed multisectoral action plans aligned with the Sustainable Development Goals (SDGs). The WHO, FAO, and WOAH jointly emphasize the need to regulate antimicrobial use in agriculture, improve veterinary practices, and phase out antibiotics as growth promoters in livestock.[3,20]

Public awareness campaigns, such as the World Antimicrobial Awareness Week (WAAW), promote responsible antimicrobial use among healthcare professionals, policymakers, farmers, and the general public. These global advocacy efforts are crucial for reducing inappropriate antibiotic consumption and fostering behavioral changes.[11,20]

### National Actions to Resist Antimicrobial Resistance

At the national level, countries are encouraged to develop and implement National Action Plans on AMR (NAP-AMR) aligned with the WHO Global Action Plan. These plans focus on antimicrobial stewardship, infection prevention and control, surveillance, and regulatory enforcement. Many countries have established hospital-based antimicrobial stewardship programs (ASPs) to optimize antibiotic prescription, reduce misuse, and improve patient

outcomes.[3,4]

National surveillance networks play a critical role in tracking resistance patterns and guiding treatment. For example, the European Antimicrobial Resistance Surveillance Network (EARS-Net) monitors resistance trends across European Union member states, while the CDC Antibiotic Resistance Threats Report provides regular assessments in the United States.[4,21] These surveillance efforts support evidence-based policymaking and resource allocation.

## NATIONAL ACTIONS IN LOW- AND MIDDLE-INCOME COUNTRIES

Low- and middle-income countries (LMICs) face unique challenges, including weak regulatory frameworks, over-the-counter antibiotic sales, limited diagnostic capacity, and poor sanitation. Countries such as India have implemented national strategies emphasizing prescription regulation, hospital infection control, and public education. Despite these efforts, high rates of antibiotic consumption and resistance persist, highlighting the need for stronger enforcement and healthcare infrastructure development.[4,22]

National policies increasingly target the agricultural and veterinary sectors, promoting vaccination, biosecurity measures, and alternatives to antibiotics in animal husbandry. Restricting non-therapeutic antibiotic use in livestock has been identified as a critical step in reducing environmental and food-chain transmission of resistant bacteria.[20,22]

## ROLE OF HEALTHCARE PROFESSIONALS, POLICYMAKERS AND INDIVIDUALS

Healthcare professionals play a pivotal role in combating AMR through rational prescribing, adherence to treatment guidelines, and patient education. Policymakers are responsible for implementing regulatory controls, supporting surveillance systems, and funding research and innovation. At the individual level, public compliance with prescribed treatments, avoidance of self-medication, and improved hygiene practices are essential to reducing selective pressure for resistance.[3,4,20]

## FUTURE PERSPECTIVES

Advances in artificial intelligence, whole-genome sequencing, and novel therapeutics such as bacteriophages and CRISPR-based antimicrobials are expected to transform the prevention, diagnosis, and treatment of antimicrobial-resistant infections.[23,24,25] Strengthening One

Health surveillance, antimicrobial stewardship, and global collaborative research will be crucial for ensuring sustainable control of antimicrobial resistance and preserving antimicrobial efficacy for future generations.[26,27]

- **AI-Assisted Antimicrobial Discovery**

Artificial intelligence (AI) is transforming antimicrobial drug discovery by addressing several limitations of conventional antibiotic development, including high costs, prolonged timelines, and low success rates. Traditional screening methods require the evaluation of thousands of compounds in laboratory settings, whereas AI-based approaches can rapidly analyze extensive chemical and biological datasets to identify promising antimicrobial candidates with greater efficiency. Recent advances in machine learning, deep learning, and generative AI have enabled researchers to predict antimicrobial activity, optimize molecular structures, identify novel drug targets, and design entirely new compounds with potential therapeutic value.[28,23]

One of the most notable achievements of AI-assisted antimicrobial discovery is the identification of novel antibiotics such as halicin and abaucin. Halicin was discovered through a deep-learning model trained to recognize compounds with antibacterial properties and demonstrated potent activity against several multidrug-resistant pathogens.[29] Similarly, abaucin was identified using AI-guided screening and showed selective activity against *Acinetobacter baumannii*, a priority pathogen recognized by the World Health Organization due to its extensive drug resistance.[30] These discoveries highlighted the ability of AI to explore chemical spaces that are often overlooked by conventional drug discovery approaches.

Recent studies have further expanded the application of AI in antimicrobial research. Generative AI models are now capable of designing novel molecules and antimicrobial peptides with desired pharmacological properties, reducing the time required for lead optimization.[28,31] Machine-learning algorithms have also been employed to mine genomic and microbiome datasets, leading to the identification of hundreds of thousands of previously unknown antimicrobial candidates.[32] Furthermore, advanced computational methods such as graph neural networks and structure-based prediction models are improving the accuracy of virtual screening and target identification, thereby increasing the probability of successful drug development.[28,23]

Despite these advances, challenges remain. The reliability of AI models depends heavily on the quality and diversity of training datasets, and experimental validation remains essential before clinical application. Issues related to model interpretability, regulatory acceptance, and integration with laboratory workflows also require further attention.[23,33] Nevertheless, AI-assisted antimicrobial discovery represents a promising strategy for overcoming the global antimicrobial resistance crisis by accelerating the development of novel and effective therapeutic agents.

- **CRISPR-Based Antimicrobials**

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based antimicrobials have emerged as a promising next-generation strategy to combat antimicrobial resistance (AMR). Unlike conventional antibiotics, which often affect both pathogenic and beneficial microorganisms, CRISPR-Cas systems offer sequence-specific targeting of bacterial genomes and resistance determinants. This precision enables the selective elimination of resistant pathogens while preserving the normal microbiota, thereby reducing the selective pressure that drives the emergence of further resistance.[34,35]

The antimicrobial activity of CRISPR systems is primarily mediated through CRISPR-associated (Cas) nucleases such as Cas9, Cas3, and Cas12a. Guided by engineered RNA molecules, these nucleases recognize and cleave specific DNA sequences within bacterial chromosomes or plasmids carrying antimicrobial resistance genes. Targeting essential bacterial genes can directly induce bacterial cell death, whereas targeting resistance-conferring plasmids can eliminate resistance genes and restore susceptibility to existing antibiotics.[36,37] Recent studies have demonstrated successful removal of genes encoding carbapenem, β-lactam, and colistin resistance, highlighting the therapeutic potential of this technology.[35,38]

A major area of current research focuses on improving delivery systems for CRISPR antimicrobials. Since CRISPR components must reach target bacteria efficiently, investigators have explored bacteriophages, conjugative plasmids, and nanoparticle-based carriers as delivery vehicles. Bacteriophage-mediated delivery has shown particular promise because of its ability to specifically infect bacterial cells and introduce CRISPR constructs directly into resistant pathogens.[36,39] Recent advances integrating CRISPR-Cas systems with nanotechnology have further enhanced delivery efficiency and demonstrated effectiveness

against biofilm-associated infections, which are often highly resistant to conventional therapies.[39]

Beyond direct therapeutic applications, CRISPR technology also contributes to rapid detection and surveillance of resistant pathogens. CRISPR-based diagnostic platforms provide highly sensitive identification of antimicrobial resistance genes, facilitating timely clinical decision-making and targeted therapy.[38] Despite these encouraging developments, challenges remain, including potential off-target effects, bacterial resistance to CRISPR delivery systems, large-scale manufacturing, and regulatory approval processes.[34,37] Nevertheless, recent evidence suggests that CRISPR-based antimicrobials have the potential to revolutionize infectious disease management by providing highly specific, programmable, and effective alternatives to traditional antibiotics, thereby contributing significantly to global efforts against antimicrobial resistance.[34,35,38]

- **Whole-Genome Sequencing for AMR Prediction**

Whole-genome sequencing (WGS) has emerged as a transformative tool for predicting antimicrobial resistance (AMR) and strengthening surveillance systems. Unlike conventional antimicrobial susceptibility testing (AST), which relies on phenotypic assessment and may require several days to generate results, WGS provides comprehensive information about the genetic determinants of resistance within a single assay. By identifying resistance genes, mutations, mobile genetic elements, and plasmids, WGS enables the prediction of resistance phenotypes while simultaneously offering insights into pathogen evolution and transmission dynamics.[40,41]

Recent advances in sequencing technologies and bioinformatics have significantly improved the accuracy of AMR prediction. WGS-based approaches can detect both known resistance genes and novel genetic mechanisms associated with reduced antimicrobial susceptibility. Studies have demonstrated strong concordance between genomic predictions and conventional susceptibility testing for major bacterial pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Acinetobacter baumannii*.[24,42] Furthermore, long-read sequencing platforms such as Oxford Nanopore and PacBio have enhanced the ability to characterize plasmids and other mobile genetic elements that play critical roles in the dissemination of resistance genes across bacterial populations.[40,43]

The integration of machine learning with WGS has further expanded the potential of genomic

AMR prediction. Machine-learning algorithms can analyze large genomic datasets to identify complex associations between genetic variations and resistance phenotypes, even when resistance mechanisms are not fully understood. Recent systematic reviews indicate that combining WGS data with artificial intelligence models can achieve high predictive performance for multiple antibiotic classes, supporting rapid and accurate clinical decision-making.[24,44]

Beyond clinical diagnostics, WGS has become a cornerstone of AMR surveillance programs. Genomic surveillance allows real-time monitoring of resistant pathogens, detection of emerging resistance mechanisms, and tracking of transmission pathways across human, animal, and environmental sectors within a One Health framework.[41,45] Recent studies have shown that WGS-based surveillance can identify hidden transmission events and resistance determinants that may be missed by conventional epidemiological methods, thereby improving outbreak investigations and informing public health interventions.[45,46]

Despite its advantages, challenges remain regarding standardization, data interpretation, bioinformatics infrastructure, and implementation in resource-limited settings. Nevertheless, continued reductions in sequencing costs and advances in computational tools are expected to facilitate broader adoption of WGS. As genomic technologies become increasingly accessible, WGS is poised to play a central role in precision antimicrobial therapy and global AMR surveillance efforts.[40,41,43]

- **Novel Antimicrobial Peptides and Phage Therapy**

The growing burden of antimicrobial resistance (AMR) has accelerated the search for alternative therapeutic approaches beyond conventional antibiotics. Among the most promising strategies are antimicrobial peptides (AMPs) and bacteriophage (phage) therapy, both of which have demonstrated significant potential in recent preclinical and clinical investigations. These biologically derived agents possess unique mechanisms of action that can overcome many limitations associated with traditional antimicrobial drugs.[47,48]

Antimicrobial peptides are naturally occurring molecules produced by various organisms as part of their innate immune defense. Unlike conventional antibiotics that often target specific metabolic pathways, AMPs primarily disrupt microbial cell membranes, leading to rapid bacterial killing and a reduced likelihood of resistance development.[49] Recent studies have focused on engineering synthetic and modified AMPs with improved stability, reduced

toxicity, and enhanced antimicrobial activity. Several next-generation peptides have demonstrated efficacy against multidrug-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Acinetobacter baumannii*, and resistant *Pseudomonas aeruginosa* in animal models.[47,50] Advances in computational biology and artificial intelligence have further accelerated AMP discovery by enabling the design of peptides with optimized antimicrobial and pharmacokinetic properties.[50]

Bacteriophage therapy represents another innovative approach for combating resistant bacterial infections. Phages are viruses that selectively infect and lyse bacterial cells without affecting human cells or beneficial microbiota. Renewed interest in phage therapy has emerged because of its ability to target multidrug-resistant pathogens with high specificity.[48,51] Recent clinical studies have reported encouraging outcomes in patients with chronic wound infections, respiratory infections, osteomyelitis, and other difficult-to-treat bacterial diseases where conventional antibiotics had limited effectiveness.[51,52] Systematic analyses of clinical trials have demonstrated favorable safety profiles and evidence of therapeutic benefit, although larger randomized studies are still needed to establish standardized treatment protocols.[52]

Current research increasingly explores the combined use of AMPs, phages, and conventional antibiotics. Such combination therapies may enhance bacterial killing, disrupt biofilms, and reduce the emergence of resistance.[48,53] Furthermore, advances in phage engineering have enabled the development of modified phages with broader host ranges and improved antibacterial activity, while nanotechnology-based delivery systems are being investigated to improve the stability and efficacy of both AMPs and phages.[47,53] Although challenges related to manufacturing, regulation, and large-scale clinical validation remain, recent evidence suggests that antimicrobial peptides and phage therapy could become important components of future strategies to address the global AMR crisis.[48,51,53]

## PRECISION ANTIMICROBIAL STEWARDSHIP

The growing burden of antimicrobial resistance has highlighted the limitations of traditional antimicrobial stewardship programs and has led to the emergence of precision antimicrobial stewardship (PAS) as a more individualized approach to antimicrobial management. PAS combines advances in rapid diagnostics, microbial genomics, clinical informatics, and artificial intelligence (AI) to support targeted therapeutic decisions tailored to individual patients and specific pathogens.[59,61]

Unlike conventional stewardship strategies that often rely on empirical treatment and broad institutional guidelines, PAS emphasizes the selection of the most appropriate antimicrobial agent based on pathogen identification, resistance mechanisms, host characteristics, and local epidemiological data.[59] Recent developments in molecular diagnostic techniques and whole-genome sequencing have significantly improved the speed and accuracy of pathogen detection, enabling clinicians to initiate targeted therapy earlier and reduce unnecessary exposure to broad-spectrum antibiotics.[61]

Artificial intelligence and machine-learning tools are increasingly being explored to assist clinicians in interpreting complex clinical and microbiological data. These technologies can help predict antimicrobial susceptibility patterns, identify patients at risk of resistant infections, and support evidence-based prescribing decisions.[62] Such innovations have the potential to improve treatment outcomes while simultaneously reducing selective pressure that drives the emergence of resistant microorganisms.

Despite its promising applications, the implementation of PAS remains challenging in many healthcare settings because of financial constraints, limited access to advanced diagnostic platforms, and the need for specialized expertise.[60] Nevertheless, as diagnostic technologies become more accessible and digital healthcare systems continue to evolve, precision antimicrobial stewardship is expected to play an increasingly important role in preserving antimicrobial effectiveness and strengthening global efforts to combat antimicrobial resistance.

## ONE HEALTH SURVEILLANCE EXPANSION

The expansion of One Health surveillance has become a central component of global strategies to combat antimicrobial resistance (AMR). Recognizing that resistant microorganisms and antimicrobial residues circulate across humans, animals, food systems, and the environment, international organizations have increasingly advocated for integrated surveillance systems that transcend traditional sector-specific approaches.[54,55] The One Health concept promotes coordinated monitoring and data sharing across these interconnected domains, enabling a more comprehensive understanding of the emergence and spread of AMR.

Recent initiatives led by the Quadripartite organizations—World Health Organization (WHO), Food and Agriculture Organization (FAO), World Organisation for Animal Health

(WOAH), and the United Nations Environment Programme (UNEP)—have accelerated efforts to establish integrated surveillance frameworks. The One Health Joint Plan of Action (2022–2026) emphasizes the development of harmonized surveillance systems capable of generating actionable evidence from human, animal, plant, food, and environmental sectors (20). In support of this objective, the Quadripartite recently released guidance on One Health integrated surveillance of antimicrobial resistance and antimicrobial use, providing countries with practical roadmaps for designing and strengthening context-appropriate surveillance programs.[54,56]

A key advancement in surveillance expansion is the inclusion of environmental monitoring. Earlier AMR surveillance systems primarily focused on clinical and veterinary settings; however, recent evidence has highlighted the role of wastewater, surface water, soil, and agricultural environments as important reservoirs and transmission pathways for resistant microorganisms and resistance genes.[55,57] Consequently, modern One Health surveillance frameworks increasingly incorporate environmental sampling alongside human and animal health data, improving the ability to identify emerging resistance threats and transmission networks.

Genomic technologies and digital surveillance tools are also enhancing One Health surveillance capacity. Whole-genome sequencing, metagenomics, and integrated data platforms facilitate real-time tracking of resistance determinants across sectors and geographical regions.[27] These approaches support outbreak detection, source attribution, and the identification of novel resistance mechanisms. Furthermore, international initiatives such as the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) are progressively incorporating multisectoral data streams to strengthen global AMR monitoring.[58]

Despite substantial progress, challenges remain regarding laboratory capacity, data standardization, interoperability, and sustainable financing, particularly in low- and middle-income countries. Nevertheless, recent One Health publications emphasize that integrated surveillance is essential for evidence-based policymaking, early warning systems, and coordinated interventions against AMR.[54,55,56] Continued expansion of One Health surveillance will therefore play a crucial role in mitigating the global burden of antimicrobial resistance while strengthening preparedness for future health threats.

## CONCLUSION

Antimicrobial resistance represents one of the most critical challenges to global public health, threatening to undermine decades of progress in infectious disease management. The historical timeline of antibiotic discovery clearly demonstrates that resistance has consistently followed the introduction of new antimicrobial agents, a pattern exacerbated by misuse, overuse, and limited innovation in drug development. While antibiotics remain indispensable to modern medicine, their continued effectiveness depends on rational use, robust surveillance, effective infection prevention, and strong antimicrobial stewardship programs. Advances in novel antimicrobials and alternative therapeutic strategies offer promising avenues, but they must be supported by global and national policy actions, public awareness, and sustained investment in research and development. Without coordinated and proactive intervention, the world risks entering a post-antibiotic era in which common infections and routine medical procedures may once again become life-threatening.

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