Review Article

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THE SILENT PANDEMIC OF ANTIMICROBIAL RESISTANCE: A ONE HEALTH SYSTEMS APPROACH

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ABSTRACT

Antimicrobial resistance (AMR) has emerged as a critical global health challenge, threatening the effective treatment of infectious diseases across human, animal, and environmental systems and reflecting the interconnected nature of the One Health framework. Current estimates indicate that AMR caused approximately 1.27 million deaths in 2019, with projections suggesting it could lead to up to 10 million deaths annually by 2050 if left unaddressed. This review synthesizes evidence on the major molecular mechanisms driving resistance, including enzymatic inactivation of antibiotics, target site modification, efflux pump activity, and horizontal gene transfer mediated by mobile genetic elements. It further examines the growing resistance to critically important and last-resort antibiotics such as cephalosporins, fluoroquinolones, and colistin, highlighting the role of antimicrobial use in livestock, aquaculture, and clinical settings in accelerating resistance. Environmental reservoirs, including pharmaceutical effluents, wastewater systems, and agricultural runoff, are identified as key contributors to the persistence and dissemination of antimicrobial resistance genes. The review also evaluates global surveillance systems and antimicrobial stewardship programs, while emphasizing persistent gaps in low- and middle-income countries due to limited infrastructure, regulation, and awareness. Socioeconomic factors, inadequate sanitation, and unregulated antibiotic use further compound the burden of AMR, while the declining pipeline of new antimicrobials underscores the urgency for innovation. Addressing AMR requires coordinated global action through strengthened stewardship, integrated surveillance, regulatory reforms, environmental management, and investment in research, guided by a comprehensive One Health approach. Without immediate and sustained intervention, AMR is poised to undermine decades of medical progress and become a leading cause of mortality worldwide.

Keywords: Antimicrobial resistance; One Health; Horizontal gene transfer; Antimicrobial stewardship; Environmental AMR; Surveillance systems; Multidrug resistance; Public health

1. INTRODUCTION

Antimicrobial resistance (AMR) is defined as the ability of microorganisms, including bacteria, viruses, fungi, and parasites, to survive exposure to antimicrobial agents that were previously effective against them (Laxminarayan *et al.*, 2013). Since the introduction of penicillin in the 1940s, antimicrobial resistance has progressively evolved from a localized clinical observation into a widespread global health crisis (McEwen & Collignon, 2018). Recent global estimates indicate that approximately 1.27 million deaths were directly attributable to bacterial antimicrobial resistance in 2019, reflecting its substantial contribution to global mortality (Naghavi *et al.*, 2024). Furthermore, projections suggest that, in the absence of effective interventions, AMR could result in up to 10 million deaths annually by the year 2050, potentially surpassing cancer as a leading cause of death (O'Neill, 2016). The problem of AMR extends beyond human healthcare, as antimicrobials are extensively used in veterinary medicine, livestock production, and aquaculture, contributing to environmental contamination (Van Boeckel *et al*., 2015). Antibiotic residues and resistant microorganisms are frequently introduced into soil and water systems through agricultural runoff, wastewater discharge, and improper disposal practices (Bürgmann *et al*., 2018). These resistant bacteria and antimicrobial resistance genes (ARGs) can circulate among humans, animals, and environmental compartments, creating a complex transmission network (Collignon *et al*., 2018).This interconnected nature of AMR has led to its recognition as a quintessential One Health issue, requiring integrated, multisectoral approaches (Velazquez-Meza *et al*., 2022). The One Health concept emphasizes collaboration among human health, veterinary, and environmental disciplines to achieve optimal health outcomes across all sector. Historically, the foundations of One Health can be traced to the work of Rudolf Virchow, who introduced the concept of zoonotic diseases, highlighting the link between human and animal health. This idea was later expanded by Calvin Schwabe through the concept of "One Medicine," which recognized the shared nature of diseases across species (McEwen & Collignon, 2018). Modern global initiatives, including the Global Action Plan on AMR developed by the World Health Organization, have institutionalized the One Health approach as a central strategy for combating AMR (World Health Organization, 2015). International collaborations involving organizations such as the Food and Agriculture Organization, World Organisation for Animal Health, and United Nations Environment Programme further reinforce the importance of coordinated global action (Velazquez-Meza *et al*., 2022).

2. Mechanisms of Antimicrobial Resistance

2.1 Classical Resistance Mechanisms

Bacteria develop resistance to antimicrobial agents through several well-established mechanisms, including enzymatic inactivation, modification of target sites, reduced membrane permeability, and active efflux of drugs (Nazir *et al*., 2025). Enzymatic inactivation remains a primary threat, particularly in Gram-negative bacteria where beta-lactamases hydrolyze the beta-lactam ring (Madec *et al*., 2017). Extended-spectrum beta-lactamases (ESBLs) and carbapenemases confer resistance to a broad range of antibiotics, including penicillins and cephalosporins. Genes such as *bla*$_{CTX\text{-}M}$, *bla*$_{TEM}$, and *bla*$_{NDM}$ are frequently located on mobile plasmids, though recent trends show increasing chromosomal integration, stabilizing their presence in populations (Madec *et al*., 2017; Nazir *et al*., 2025). Target site modification also plays a critical role. For instance, methicillin-resistant *Staphylococcus aureus* (MRSA) utilizes the *mecA* gene to produce a modified penicillin-binding protein (PBP2a) with low affinity for beta-lactams (Hassoun *et al*., 2017). Similarly, fluoroquinolone resistance often results from specific mutations in *gyrA* (DNA gyrase) and *parC* (topoisomerase IV) (Hooper & Jacoby, 2015). To maintain low intracellular drug concentrations, bacteria employ diverse efflux pump families, most notably the Resistance-Nodulation-Division (RND), Major Facilitator Superfamily (MFS), and ATP-binding cassette (ABC) transporters, alongside smaller families like SMR (Small Multidrug Resistance) and MATE (Multidrug And Toxic Compound Extrusion) (Nazir *et al*., 2025). Finally, reduced permeability—often via the loss of porin proteins-limits drug entry in pathogens such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Madec *et al*., 2017).

2.2 Horizontal Gene Transfer (HGT)

HGT is the cornerstone of rapid resistance dissemination across human, animal, and environmental niches (Sundin & Wang, 2018). This occurs via: Conjugation: Plasmid transfer through direct cell-to-cell contact; the most prevalent mechanism in clinical settings. Transformation: The uptake of "naked" environmental DNA. Transduction: Bacteriophage-mediated genetic exchange. Mobile genetic elements like transposons and integrons further drive this process. Integrons are especially significant due to the integrase enzyme (*intI*), which allows for the capture and expression of multiple gene cassettes, leading to multidrug-resistant (MDR) phenotypes (Berendonk *et al*., 2015). The presence of these genes in environmental microbiomes facilitates a continuous exchange between clinical and natural bacterial communities (Larsson & Flach, 2022).

2.2 Adaptive and Phenotypic Resistance

Beyond genetic inheritance, bacteria exhibit adaptive survival strategies (Nazir *et al*., 2025). Persister cells-a dormant subpopulation can survive lethal antibiotic concentrations without genetic mutations, often leading to recurrent infections once treatment ceases. Environmental stressors, including sub-inhibitory concentrations of antibiotics, can trigger the SOS response, increasing mutation rates and accelerating resistance evolution (Hooper & Jacoby, 2015; Larsson & Flach, 2022). Furthermore, biofilm formation provides a physical and metabolic shield, restricting antibiotic penetration and altering bacterial metabolism. This protective matrix can result in resistance levels significantly higher-historically cited up to 1000-fold than those of planktonic (free-floating) cells (Berendonk *et al*., 2015).

3. AMR Through the One Health Framework: Key Antibiotic Classes

3.1 Third-Generation Cephalosporins

Third-generation cephalosporins, such as ceftriaxone, cefotaxime, and ceftiofur, are classified as critically important antimicrobials for human medicine due to their broad-spectrum activity and clinical importance (World Health Organization, 2017). These antibiotics are widely used in both human and veterinary medicine for treating infections including respiratory tract infections, urinary tract infections, and septicemia (Mehdi *et al*., 2018). Resistance to third-generation cephalosporins is primarily mediated by extended-spectrum beta-lactamases (ESBLs) and Amp-C beta-lactamases, which hydrolyze the amide bond of the ring and render these drugs ineffective (Madec *et al*., 2017).

The genes encoding these enzymes are often located on mobile genetic elements such as plasmids and transposons, enabling rapid dissemination across bacterial populations (Madec *et al*., 2017). Global surveillance data have reported a high prevalence of resistance in *Escherichia coli* and *Klebsiella pneumoniae*, posing significant challenges for treatment (World Health Organization, 2015). The use of ceftiofur in poultry production has been associated with the emergence of cephalosporin-resistant *Salmonella enterica* serovar Heidelberg, which can be transmitted to humans through the food chain (Dutil *et al*., 2010). Studies have demonstrated a temporal relationship between the use of ceftiofur in hatcheries and increased resistance in both poultry and human isolates (Dutil *et al*., 2010). Importantly, the withdrawal of ceftiofur use in certain regions resulted in a measurable decline in resistance levels, demonstrating the effectiveness of targeted interventions (Dutil *et al*., 2010). These findings highlight the critical role of veterinary antibiotic use in shaping resistance patterns that directly impact human health (Collignon *et al*., 2018).

3.2 Fluoroquinolones

Fluoroquinolones are broad-spectrum antimicrobial agents widely used to treat infections caused by both Gram-positive and Gram-negative bacteria (Hooper & Jacoby, 2015).They are commonly prescribed for respiratory infections, urinary tract infections, and gastrointestinal infections in human medicine (Hooper & Jacoby, 2015). In veterinary settings, fluoroquinolones have been extensively used in poultry production, contributing to the emergence of resistant bacterial strains (Mehdi *et al*., 2018). The use of fluoroquinolones in poultry has been strongly associated with the development of resistance in *Campylobacter jejuni*, a major cause of foodborne illness in humans (Nelson *et al.*, 2007). Countries that have restricted or avoided the use of fluoroquinolones in food animals, such as Australia, report significantly lower levels of resistance in *Campylobacter* species (Nelson *et al.*, 2007). Resistance to fluoroquinolones arises primarily through mutations in target enzymes such as DNA gyrase and topoisomerase IV, as well as through plasmid-mediated resistance genes such as qnr (Hooper & Jacoby, 2015). The presence of these resistance determinants on mobile genetic elements facilitates their rapid spread across bacterial populations (Sundin & Wang, 2018). These observations underscore the importance of regulating antibiotic use in agriculture to prevent the spread of resistance to clinically important drugs (World Health Organization, 2017).

3.3 Colistin and the mcr-1 Gene

Colistin (polymyxin E) has long been considered a last-resort antibiotic for treating infections caused by multidrug-resistant Gram-negative bacteria. Its clinical use in humans has been limited due to nephrotoxicity, but it has been widely used in veterinary medicine, particularly in livestock production (Falagas & Kasiakou, 2006). Extensive use of colistin in animals has created significant selective pressure for the development of resistance (Van Boeckel *et al.*, 2015). In 2015, the discovery of the plasmid-mediated *mcr-1* gene marked a major turning point in the understanding of colistin resistance. The *mcr-1* gene encodes a phosphoethanolamine transferase that mediates the addition of a phosphoethanolamine (pEtN) moiety to the terminal phosphate groups of lipid A. This structural modification reduces the net negative charge of the lipopolysaccharide (LPS), thereby significantly decreasing the binding affinity of cationic polymyxins like colistin (Liu *et al.*, 2016). The *mcr-1* gene has since been detected globally in bacteria isolated from humans, animals, food products, and environmental samples. The rapid dissemination of this gene highlights the role of mobile genetic elements in spreading resistance across different ecological niches (Wang *et al.*, 2018). This case illustrates how the use of antibiotics in agriculture can compromise the effectiveness of last-resort drugs in human medicine (Collignon *et al.*, 2018).

4. Environmental Dimensions of AMR

4.1 Pharmaceutical Effluents

Pharmaceutical manufacturing facilities are recognized as significant sources of antibiotic contamination in the environment. Effluents from these facilities may contain antibiotic concentrations high enough to exert strong selective pressure on environmental microbial communities. Studies conducted in industrial regions have detected extremely high concentrations of antibiotics such as ciprofloxacin in wastewater effluents (Larsson & Flach, 2022). These conditions create “hotspots” for the selection and proliferation of antimicrobial resistance genes (Berendonk *et al.*, 2015). Such resistance genes can persist in environmental reservoirs and potentially re-enter human populations through contaminated water and food systems (Bürgmann *et al.*, 2018).

4.2 Agricultural Runoff and Soil Reservoirs

A large proportion of antibiotics administered to livestock is excreted in active form, contributing to environmental contamination (Van Boeckel *et al.*, 2015). Animal manure contains antibiotic residues, resistant bacteria, and resistance genes, which can be introduced into soil ecosystems when used as fertilizer (Mehdi *et al.*, 2018). Rainfall and irrigation facilitate the movement of these contaminants into surface water and groundwater systems. Repeated exposure of soil microbiota to antibiotics promotes the establishment of stable resistance gene reservoirs. Co-selection mechanisms involving heavy metals and biocides further enhance the persistence and spread of resistance in agricultural environments (Berendonk *et al.*, 2015).

4.3 Wastewater Treatment Systems

Wastewater treatment plants (WWTPs) serve as critical convergence points for antimicrobial residues and resistant bacteria from multiple sources (Larsson & Flach, 2022). Conventional treatment processes are often insufficient to completely remove antibiotics and resistance genes (Berendonk *et al*., 2015). High microbial densities and the presence of mobile genetic elements in WWTPs facilitate horizontal gene transfer (Sundin & Wang, 2018). As a result, treated effluents may still contain antimicrobial resistance determinants that are released into natural water bodies (Larsson & Flach, 2022). Advanced treatment technologies such as ozonation, membrane filtration, and ultraviolet irradiation have shown improved effectiveness in reducing AMR contamination (Berendonk *et al*., 2015).

4.4 Wildlife and Environmental Spread

Wildlife species play an important role in the environmental dissemination of antimicrobial resistance. Animals such as birds, rodents, and bats can acquire resistant bacteria from contaminated environments and act as vectors for long-distance transmission (Arnold *et al*., 2024). The detection of resistant bacteria in remote ecosystems highlights the widespread nature of AMR dissemination (Collignon *et al*., 2018). These findings emphasize the need to include environmental and wildlife surveillance in AMR monitoring strategies (Velazquez-Meza *et al*., 2022).

5. AMR in Livestock, Aquaculture, and the Food Chain

The global consumption of antimicrobials in food-producing animals exceeds that in humans, reflecting the scale of intensive livestock production systems (Van Boeckel *et al*., 2015). Many of the antimicrobial classes used in animals, including cephalosporins, fluoroquinolones, and macrolides, are also critically important in human medicine (World Health Organization, 2017). The use of antibiotics for growth promotion, disease prevention, and metaphylaxis in animals is a major driver of antimicrobial resistance (Mehdi *et al*., 2018). In dairy farming, frequent use of antibiotics for mastitis treatment has been associated with the emergence of resistant strains of *Escherichia coli* and *Staphylococcus aureus*. Contamination of milk and dairy products with resistant bacteria represents a direct route of transmission to humans (Sharma *et al*., 2018). In poultry production, antimicrobial use has been strongly linked to resistance in pathogens such as *Salmonella* and *Campylobacter* species (Mehdi *et al*., 2018). Similarly, in aquaculture systems, antibiotics applied directly to water bodies contribute to the development of resistant bacteria such as *Vibrio* and *Aeromonas* species (Watts *et al*., 2017). Transmission of antimicrobial resistance from animals to humans can occur through direct contact, consumption of contaminated food products, and environmental exposure (Collignon *et al*., 2018). The application of animal manure to agricultural fields further contributes to the dissemination of resistance genes into soil and water systems (Bürgmann *et al*., 2018). These interconnected pathways highlight the importance of implementing a One Health approach to control antimicrobial use across all sectors (Velazquez-Meza *et al*., 2022).

6. Global AMR Surveillance: Frameworks, Strengths, and Gaps

Effective surveillance systems are essential for monitoring antimicrobial resistance trends and informing policy decisions. The World Health Organization established the Global Antimicrobial Resistance and Use Surveillance System (GLASS) to standardize data collection and reporting across countries. GLASS provides valuable insights into global resistance patterns and antimicrobial consumption trends (World Health Organization, 2015). In Europe, surveillance is coordinated by the ECDC (European Centre for Disease Prevention and Control) through EARS-Net (European Medicines Agency, 2019). In the United States, the National Antimicrobial Resistance Monitoring System (NARMS) tracks resistance in foodborne bacteria from humans, animals, and retail meat (Food and

Drug Administration, 2018). Despite these advancements, significant gaps remain, particularly in low- and middle-income countries (LMICs), where laboratory infrastructure and data reporting systems are limited (Patel *et al.*, 2023). The lack of integration between human, animal, and environmental surveillance systems further hinders comprehensive analysis (Velazquez-Meza *et al.*, 2022). Technological innovations such as whole-genome sequencing and metagenomics are improving the resolution and accuracy of AMR surveillance (Larsson & Flach, 2022). Artificial intelligence and machine learning tools are also being explored to predict resistance trends and support clinical decision-making (James *et al.*, 2026). Strengthening global surveillance requires investment in infrastructure, capacity building, and data-sharing frameworks, particularly in resource-limited settings (Patel *et al.*, 2023).

7. Antimicrobial Stewardship

Antimicrobial stewardship programs (ASPs) are designed to optimize antimicrobial use and reduce the emergence of resistance. Core elements of stewardship include appropriate drug selection, dosing, duration, and route of administration (Davey *et al.*, 2017). Studies have shown that stewardship programs can significantly reduce inappropriate antibiotic use in healthcare settings (Zay Ya *et al.*, 2023). In hospital environments, strategies such as prospective audit and feedback, formulary restriction, and rapid diagnostic testing have proven effective (Davey *et al.*, 2017). The concept of the “Four Ds” — right drug, right dose, de-escalation, and right duration-provides a practical framework for clinicians (Zay Ya *et al.*, 2023). In veterinary medicine, stewardship efforts are complicated by economic and regulatory challenges, particularly in LMICs (Mehdi *et al.*, 2018). The World Health Organization recommends restricting the use of medically important antibiotics in food-producing animals (World Health Organization, 2017). Several countries have successfully reduced antibiotic use through regulatory measures, including bans on growth promoters (Mehdi *et al.*, 2018). Digital health tools, including clinical decision support systems and artificial intelligence, are increasingly being used to guide antimicrobial prescribing. However, challenges such as data quality, infrastructure limitations, and lack of validation in diverse settings remain significant barriers (James *et al.*, 2026).

8. Socioeconomic and Global Health Dimensions

Antimicrobial resistance disproportionately affects low- and middle-income countries, where healthcare resources and infrastructure are limited (Collignon *et al.*, 2018). Factors such as poor sanitation, inadequate infection control, and limited access to diagnostics contribute to the spread of resistant infections (Bürgmann *et al.*, 2018). Self-medication and over-the-counter access to antibiotics further exacerbate the problem in many regions (Laxminarayan *et al.*, 2013). Economic analyses suggest that AMR could result in substantial global financial losses and increased poverty levels if not addressed (O’Neill, 2016). The development pipeline for new antibiotics remains insufficient, with only a limited number of truly novel agents under development. Public-private partnerships such as the Global Antibiotic Research and Development Partnership are working to address this gap (World Health Organization, 2015). Social determinants, including education, income, and access to healthcare, play a critical role in shaping antimicrobial use and resistance patterns (Collignon *et al.*, 2018). Addressing AMR therefore requires not only scientific and medical interventions but also broader socioeconomic and policy reforms (Velazquez-Meza *et al.*, 2022).

9. Future Directions

Addressing antimicrobial resistance requires a systems-based approach that integrates data from human, animal, and environmental health sectors. Advanced modeling techniques, including agent-based models and network analysis, can help predict resistance trends and evaluate intervention strategies (Arnold *et al*., 2024). Climate change is emerging as an important driver of antimicrobial resistance by influencing disease patterns and antibiotic use. Environmental changes such as rising temperatures and extreme weather events can facilitate the spread of resistant pathogens (Burnham, 2021). Future research priorities include expanding surveillance systems, improving diagnostic tools, and developing alternative therapies such as bacteriophages and antimicrobial peptides (Larsson & Flach, 2022). Integrating AMR strategies into broader global health and pandemic preparedness frameworks is also essential (World Health Organization, 2015). A coordinated global response based on the One Health framework is critical to effectively mitigate the long-term impact of antimicrobial resistance (Velazquez-Meza *et al*., 2022).

10. Conclusion

Antimicrobial resistance represents a complex and multifaceted global health challenge that spans human, animal, and environmental domains. The evidence clearly demonstrates that resistance emerges and spreads through interconnected pathways that cannot be addressed in isolation. The One Health framework provides a comprehensive approach for understanding and managing antimicrobial resistance across sectors. Effective control strategies must include rational antimicrobial use, strengthened surveillance systems, and robust stewardship programs. Environmental regulation, improved sanitation, and responsible agricultural practices are also essential components of AMR mitigation. Investment in research and development of new antimicrobial agents and alternative therapies remains a critical priority. Ultimately, coordinated global action, supported by strong political commitment and sustainable funding, is required to preserve the effectiveness of antimicrobials for future generations.

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