



ANTIMICROBIAL RESISTANCE AT THE ONE HEALTH INTERFACE: GENOMIC DRIVERS, HORIZONTAL GENE TRANSFER, ENVIRONMENTAL RESERVOIRS, AND EMERGING CONTROL STRATEGIES

Dr. Stephen Kayode Ojo^{1*}, Prof. Jo-Anne Dillon²

^{1*}*Department of Microbiology, Federal University Oye-Ekiti, Ekiti State, Nigeria*

Email: stephen.ojo@fuoye.edu.ng

Department of Biochemistry, Microbiology and Immunology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

***Corresponding Author:** Dr. Stephen Kayode Ojo, stephen.ojo@fuoye.edu.ng

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ABSTRACT

Antimicrobial resistance (AMR) has emerged as a significant One Health challenge as resistant bacteria and resistance genes spread continually within and between human, animal, food and environmental systems. It is a combination of genomic adaptation, selective pressure, mobile genetic elements and horizontal gene transfer that propel the emergence, persistence and dissemination of resistant populations. The review focused on the most important molecular and ecological factors that are driving AMR, including resistance mechanisms, the resistome and mobilome, plasmids, integrons, transposons, bacteriophages and conjugation, transformation and transduction. It also took into account the contribution of livestock, companion animals, food production, wastewater, agricultural soils, manure, surface waters and other environmental reservoirs to maintaining and promoting resistance determinants. Advances in whole-genome sequencing, metagenomics, genomic epidemiology, and bioinformatic resistance-gene detection have improved the capacity to trace resistant lineages and characterize antimicrobial resistomes across sectors. New control tactics include antimicrobial stewardship, infection prevention, antimicrobial peptides, bacteriophage, probiotics, anti-virulence strategies, plasmid-targeting strategies, clustered regularly interspaced short palindromic repeats (CRISPR)-based antimicrobials and improved wastewater treatment. Therefore, coordinated One Health surveillance, judicious use of antimicrobials, environmental stewardship, and precision genomic interventions are crucial for minimizing the spread and long-term prevalence of AMR worldwide.

Keyword: antimicrobial resistance; One Health; horizontal gene transfer; resistome; genomic surveillance; environmental reservoirs

Introduction

Antimicrobial resistance (AMR) is one of the biggest threats to contemporary medicine as it diminishes the efficacy of antibiotics in tackling common and lifethreatening bacterial infections. Resistant infections are linked to prolonged illness, increased complexity of treatment, increased cost of health care and an increased risk of death. The problem is huge, if we consider it in the global context. Bacterial AMR directly caused 1.27 million deaths in 2019, and is responsible for nearly 4.95 million deaths globally, meaning resistance already makes a significant contribution to the global burden of disease (Antimicrobial Resistance Collaborators, 2022). However, more recent analyses suggest that AMR continues to be a significant public health threat in the near future, especially if prevention, surveillance and access to effective treatment is unequal between regions (GBD 2021 Antimicrobial Resistance Collaborators, 2024).

Resistance is a clinical issue and it's not sufficient to consider AMR as such because resistant microorganisms and resistance genes flow freely, constantly, between humans, animals, food systems and the environment. The use of antimicrobial agents in health care, animal husbandry, livestock and aquaculture systems can result in selective pressure that can be advantageous to the resistant populations. These organisms and their genetic characteristics can then be transferred from compartment to compartment via direct contact, food production chains, wastewater, soil, surface water, wildlife and other environmental routes. This interdependence highlights the need to consider antibiotic resistance as a One Health issue, as one that needs to be addressed in the context of human, animal and environmental health as interdependent rather than distinct systems (Robinson et al., 2016).

Therefore the One Health perspective is relevant in understanding origin, spread and potential interventions to limit the spread of resistance. Responsible use of antibiotics in clinical practice is essential for effective control, along with coordinated measures involving veterinary medicine, agricultural production, food production, sanitation and environmental management and public policy (Collignon & McEwen, 2019). This is especially significant, as resistance genes can be present in the microbial community and not in pathogenic bacteria.

One of the most important findings in the molecular mechanisms of AMR has been the simultaneous occurrence of both chromosomal changes and acquisition of resistance determinants. The resistome, which is the collection of resistance genes in microbial communities, is found in diverse environments such as clinical, agricultural, and natural habitats, and serves as a reservoir for emerging or spreading resistance genes (Kim & Cha, 2021). This process is further enhanced by horizontal gene transfer, which involves the transfer of bacterial resistance genes via plasmids, transposons, integrons, bacteriophages and other mobile genetic elements between bacterial cells. Furthermore, contamination of the environment with antimicrobials, biocides, metals, and resistant organisms can create selectable conditions that can help to preserve and spread these genes.

Therefore, a more comprehensive strategy that integrates molecular biology, genomic surveillance, microbial ecology, stewardship, infection prevention, environment control and coordinated policy is needed for AMR control. While individual behaviour is a key factor in addressing a problem defined by health systems, food production, sanitation, access to antimicrobials, regulation and social practices in various sectors (Hernando-Amado et al., 2020). This review explored AMR at the One Health interface through the lens of genomic drivers, HGT, environmental reservoirs and transmission pathways. It also assessed progress in genomic surveillance and novel strategies aimed at reducing the emergence, maintenance and dissemination of antimicrobial resistance in the interlinked human, animal and environmental systems.

2. Methodology

2.1 Review Design

The review aimed to be a structured narrative synthesis to explore the issue of antimicrobial resistance in related human, animal, food, and environmental settings. The framework was organized around the major themes defined by the article scope, including genomic drivers, horizontal gene transfer, environmental reservoirs, surveillance tools, and emerging control strategies. The literature examined contained a wide variety of study designs, study populations, ecosystems, and analytical methods, and evidence was analyzed comparatively rather than in a quantitative fashion. Mechanistic understanding, cross-sector connections, recent advances, and research needs were highlighted.

2.2 Literature Search Strategy

Literature search was conducted on PubMed/MEDLINE, Scopus, Web of Science and Google Scholar databases. The publications searched were mainly published from 2015 to 2015. The terms ‘antimicrobial resistance’, ‘One Health’, ‘resistome’, ‘genomics’, ‘horizontal gene transfer’, ‘mobile genetic elements’, ‘environmental reservoirs’, ‘zoonotic transmission’, ‘whole genome sequencing’, ‘metagenomics’ and ‘AMR control’ were used. Search terms were optimized for search across databases. Reference lists of articles of high relevance were also retrieved to find more relevant articles that matched the predetermined thematic scope.

2.3 Eligibility and Study Selection

Studies that were original research articles, systematic reviews, meta-analyses, or authoritative reports that covered the antimicrobial resistance mechanisms, genomic epidemiology, transmission, environmental reservoirs, surveillance, or One Health interventions were included. Studies were included if the aims and conclusions of the study clearly related to one or more parts of the review. Publications were excluded that did not have clear methods, were not relevant to the review questions, contained

duplicate reporting, did not have full text access, or did not have a clear connection to the review questions. Preference was given to recent, methodologically sound, open-access evidence from recognized journals and international organizations with clear scientific or policy relevance.

2.4 Data Organization and Narrative Synthesis

Information from the selected sources was extracted and arranged according to recurring themes rather than analyzed statistically. The results were categorized into genomic and molecular resistance, horizontal gene transfer, human–animal–environment interfaces, human genomic surveillance, control measures, and future research priorities. These findings were compared across studies to see if there were commonalities, differences, and unknowns. Particular attention was given to links between resistance genes, mobile elements, ecological reservoirs, and cross-sector transmission. The synthesis was employed to illuminate gaps in knowledge, practical issues and emerging avenues in integrated One Health AMR control.

3. Genomic and Molecular Drivers of Antimicrobial Resistance

The emergence of antimicrobial resistance is a result of a combination of intrinsic cellular properties and acquired genetic changes that enable bacteria to resist antimicrobial exposure. Enzymatic drug inactivation, changes in the antimicrobial target, decreased membrane permeability, active efflux and metabolic pathway alteration that circumvent inhibited cellular functions are major mechanisms (Reygaert, 2018). There is a possibility that resistance determinants are broadly distributed beyond healthcare-related environments, as these mechanisms are present in clinical pathogens, environmental microorganisms, and antibiotic-producing bacteria all of which are not part of the healthcare system (Peterson & Kaur, 2018). The expression and accumulation of these can lead to resistance against multiple classes of antimicrobial agents, and to the development of multidrug-resistant bacterial populations (Sultan et al., 2018).

Additionally, genomic evolution drives resistance as a result of spontaneous mutations that are selected for in the presence of an antimicrobial agent. Mutations that give the bacteria a survival edge have the potential to persist in the bacterial population, but at first, resistance can come at a cost, such as growth or reproduction or fitness (Melnik et al., 2015). Individual resistance mutations may also have interactions with other genes, which can affect the development and stability of resistance phenotypes (epistasis) (Wong, 2017). Such lineages could therefore be adapted if they gain an advantage for their increased exposure to antimicrobials, and certain genetic backgrounds may maintain resistance as a result.

At the community level, resistance is also understood as resistome - the totality of the resistance genes found within a microbial ecosystem. The human gut microbiome is an important reservoir where various resistance determinants can be present and may be made available to pathogenic organisms (Singh et al., 2019). Antibiotic treatment may impact this reservoir in various ways, such as by changing microbial composition and diversifying the resistome (Li et al., 2019). Further, there is evidence coming from

relatively undisturbed ecosystems that the genes for resistance are not only produced in the present age by the use of modern antibiotics, but have also existed for long periods in evolution (Agudo & Reche, 2024). Today, their dissemination is greatly shaped by the mobilome, such as by mobile genetic elements associated with resistance genes that can be transferred between bacterial hosts (Slizovskiy et al., 2020).

4. Horizontal Gene Transfer as a Major Driver of AMR Dissemination

Horizontal gene transfer is a key mechanism enabling dissemination of antimicrobial resistance genes across species and ecosystems. Three mechanisms are used to acquire genetic material, namely conjugation, transformation and transduction, which allow bacteria to acquire genes without the vertical transmission method from parent bacteria (von Wintersdorff et al., 2016). Of these processes, the most significant is conjugation where plasmids may include multiple resistance genes and can be directly transferred between compatible bacterial hosts. They might be a fitness cost in the beginning, but compensatory mutations can decrease this fitness cost and reduce the loss of resistance plasmids from populations (Hall et al., 2021).

Mobile genetic elements add to the flexibility of resistance gene exchange. Integrins are able to capture and express gene cassettes, which are genes belonging to different classes of antimicrobial, and can also be integrated with plasmids and transposons which allow for greater dissemination (Akrami et al., 2019). In addition to gene movement via HGT, a possibility is provided by 'transduction' (Colavecchio et al., 2017), which may facilitate the spread of resistance determinants among bacteria, including food-borne strains of the Enterobacteriaceae family.

The occurrence of horizontal transfer can vary greatly depending on environmental and biological factors. However, biofilms form dense, structured microbial communities where cells are in close contact, enhancing chances for plasmid exchange and other resistance elements to be passed on (Michaelis & Grohmann, 2023). Selection is not driven by antibiotics alone. When genes for resistance to different stresses are physically or functionally linked, the resistance traits can be sustained in the event of exposure to biocides and heavy metals (Wales & Davies, 2015). The high prevalence of co-selection of genes for antibiotic resistance, metal resistance and biocide resistance also supports the hypothesis that co-selection plays a key role in the maintenance of MDR in environments other than the clinic (Pal et al., 2015). Thus, exposed environmental bacteria may continue to be antibiotic resistant even when there are low or no concentrations of antibiotics (Gillieatt & Coleman, 2024). The interactions demonstrate that AMR can spread and be sustained by both gene transfer and mobile elements, as well as environmental selection. Table 1 summarizes the major molecular mechanisms, genetic elements and selective processes involved in the emergence and dissemination of AMR.

Table 1. Core molecular and genetic drivers of antimicrobial resistance

Driver/mechanism		Biological basis	Role in AMR	Major relevance
Enzymatic inactivation	drug	Bacterial enzymes modify or degrade antimicrobial compounds	Prevents the drug from reaching or retaining activity against its target	Common mechanism of acquired resistance
Target modification		Mutation or acquired genes alter antimicrobial-binding sites	Reduces drug–target interaction	Supports resistance to multiple antimicrobial classes
Reduced permeability		Changes in membrane proteins or porins restrict antimicrobial entry	Lowers intracellular drug concentration	Particularly important in Gram-negative bacteria
Active efflux		Membrane transport systems remove antimicrobial compounds	Reduces effective intracellular exposure	Can contribute to multidrug resistance
Metabolic bypass		Alternative biochemical pathways replace inhibited functions	Allows growth despite antimicrobial action	Supports survival under selective pressure
Chromosomal mutation		Spontaneous genetic changes followed by antimicrobial selection	Produces stable resistant variants and adapted lineages	Central to evolutionary development of resistance
Plasmids		Extrachromosomal DNA capable of transfer between bacterial cells	Carry and disseminate multiple resistance genes	Major vehicles of conjugative gene transfer
Integrans and transposons		Mobile systems capture, rearrange, or relocate resistance determinants	Assemble and mobilize resistance gene combinations	Facilitate multidrug resistance and genomic flexibility
Bacteriophages		Viral transfer of bacterial DNA through transduction	May transfer resistance determinants between bacteria	Provides an additional route of horizontal gene transfer
Environmental selection	co-	Antibiotics, metals, and biocides favor linked resistance traits	Maintains resistance even when antibiotic pressure is limited	Important in polluted environmental reservoirs

Biofilm-associated transfer	Dense communities contact and genetic exchange	microbial increase cell of	Enhances transfer and persistence of resistant populations	plasmid	Relevant to clinical, industrial, and environmental settings
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Note: AMR, antimicrobial resistance. The table synthesizes the mechanisms and processes discussed in Sections 3 and 4.

5. AMR Across the One Health Interface

The spread of antimicrobial resistance is multi-sectoral, between humans, animals, food and the environment, and is not easy to control with one single sectoral strategy. Resistant bacteria are present in humans in both health and community settings and the intestinal microbiota may be a reservoir of resistant genes which can be transferred to opportunistic or pathogenic bacteria (van Schaik, 2015). Additional factors related to human antimicrobial use, sanitation and waste disposal can have an impact on the release and movement of resistant organisms to the environment.

Another vital part of this network are food-producing animals as antibiotic usage in livestock can lead to the selection of resistant bacteria that could be transmitted by direct contact, manure or food products (Rhouma et al., 2022). The use of antimicrobials in food-animal production continues to be significant globally, indicating the need for judicious use in the sector (Mulchandani et al., 2023). Limiting use of antibiotics in food production animals has been shown to limit the development of antibiotic resistance in food animals, and may also lower prevalence of antibiotic-resistant bacteria in the human populations studied that are in direct contact with food producing animals. (Tang et al., 2017) Another mechanism for transmission of resistant organisms between people and companion animals is through close and frequent contact between the two species (Marco-Fuertes et al., 2022). In addition, resistant bacteria can be transferred to humans via meats and produce and other food products in the food chain (Founou et al., 2016).

The environment links these reservoirs with the ability to maintain and spread antimicrobial resistance genes. Resistant bacteria and resistance determinants can be transferred to soil through livestock manure and may interact with the natural microbial communities in agricultural soils (Checcucci et al., 2020). Wastewater treatment systems are the source of resistant organisms, antimicrobial residues, and a wide variety of genetic material, all from domestic, clinical and industrial origins (Uluseker et al., 2021). Thus, resistance may also persist or be established in receiving environments such as rivers, sediments, soils, etc., if receiving environments are suitable for reinforcing resistance (Singer et al., 2016). Other factors, like antimicrobial residues, metals, nutrients and microbial density, have the potential to modify resistance development and spread in such environments (Bengtsson-Palme et al., 2018). Together, these pathways show that human use, animal production, environmental contamination, and cross-sector transmission are closely linked drivers of AMR, requiring coordinated One Health surveillance and control (Boonton et al.,

2021). The interconnected reservoirs and major transmission pathways involved in the One Health circulation of AMR are illustrated in Figure 1.

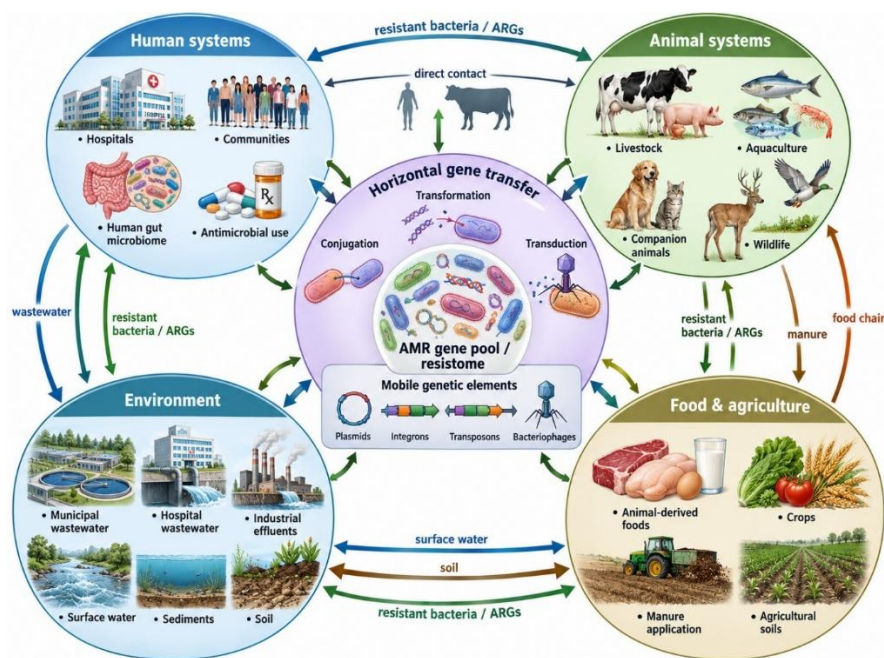


Figure 1. One Health Circulation of Antimicrobial Resistance

Note: AMR, antimicrobial resistance; ARGs, antimicrobial resistance genes.

6. Genomic Surveillance and Emerging Tools for Tracking AMR

Genomic surveillance has improved the capacity to identify, describe and monitor antimicrobial resistance, both in the clinic and the environment. WGS will be able to detect resistance determinants, differentiate between related bacterial strains and aid in tracing transmission events and outbreaks. Therefore, its inclusion in national and international surveillance has been recommended as a crucial step towards more accurate AMR trends and tracking of AMR lineages (NIHR Global Health Research Unit on Genomic Surveillance of AMR, 2020). The emergence of a public health genomics sequenceable data ecosystem has also created opportunities for routine public health genomic epidemiology and comparative data from across the border on infectious diseases (Revez et al., 2017).

Whole-metagenome sequencing is especially useful when individual bacterial isolates can be cultured and whole genome sequencing is useful for detecting resistance genes from complex microbial communities without prior culture of organisms (Oniciuc et al., 2018). Metagenomic surveillance can therefore be beneficial in other (non-clinical) systems where the diversity of microorganisms is not fully represented by conventional culture, such as wastewater, soil and animal production systems (Pillay et al., 2022). These methods can help to gain a more general understanding of environmental resistomes and possible reservoirs of resistance genes.

Reliable bioinformatic tools and reference resources are key to the value of sequencing data. MEGARes was created to facilitate the high throughput identification and classification of antimicrobial resistance genes based on sequence data (Lakin et al., 2017). AMRFinderPlus also allows for standardized identification of resistance determinants and provides the ability to connect genomic data with stress-response and virulence traits (Feldgarden et al., 2021). Recently, computational approaches have also been used for the identification of resistance genes from metagenomic sequences, including DeepARG, which can predict resistance genes for sequences with low similarity to the known genes (Arango-Argoty et al., 2018). Although significant progress has been made, existing surveillance efforts for effective One Health monitoring are hampered by the lack of harmonised sampling approaches, common standards for metadata, interoperability of databases and improved integration of human, veterinary, food and environmental genomic surveillance datasets. An integrated pathway linking One Health sampling, genomic analysis, resistance detection, and public health response is presented in Figure 2.

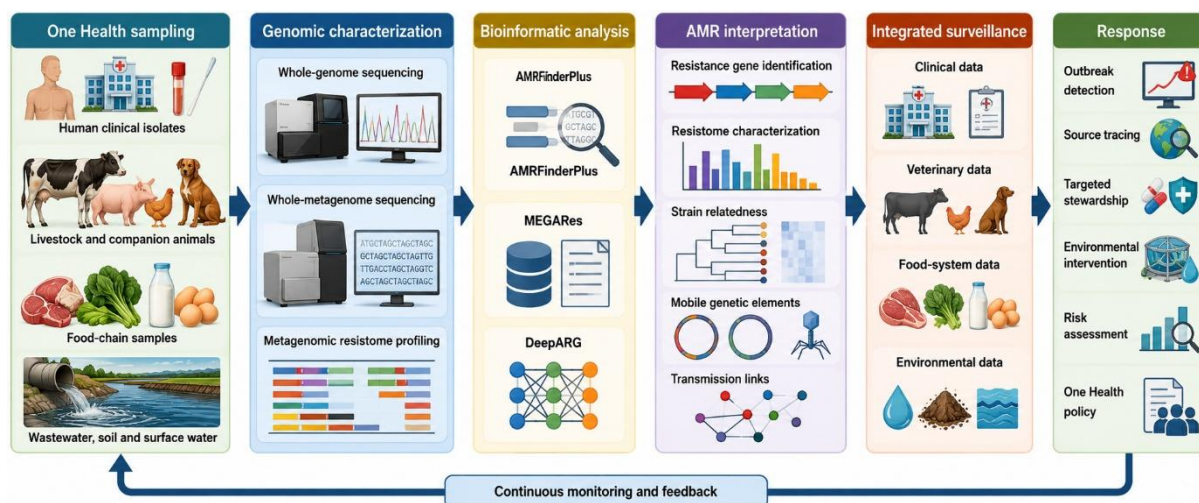


Figure 2. Integrated Genomic Surveillance Framework for AMR

Note: AMR, antimicrobial resistance.

7. Emerging Strategies for AMR Control

To address antimicrobial resistance, steps should be taken to minimize unnecessary antimicrobial use and the spread of antimicrobial resistance organism in healthcare, agriculture and the environment. Rational prescribing, timely diagnosis, surveillance-guided treatment and infection-prevention practices are key to this effort, as they can help minimize unnecessary antibiotic use, and rate of acquisition of resistant strains (Majumder et al., 2020). These same concepts are also applicable to animal production, in which the use of antimicrobials must be associated to an apparent clinical necessity, veterinary supervision, and enhanced biosecurity.

There are a number of options under investigation other than conventional antibiotics to minimize reliance on broad-spectrum antibiotics. They can selectively infect bacteria, and may be used in

conjunction with existing treatments, especially in the case of multidrug-resistant bacteria (MDRs) (Barber et al., 2021). Another alternative is the antimicrobial peptides which work quickly on bacterial membranes and some even remain active on resistant bacteria (Mwangi et al., 2019). Probiotics and microbiome targeting strategies can help with colonization resistance, bolster host defenses, and decrease the chances for pathogenic bacteria to infect the host (Raheem et al., 2021). Anti-virulence approaches are another avenue, as they target pathogenic functions instead of bacterial survival, and could potentially decrease selection for resistance (Calvert et al., 2018).

Genomic and molecular interventions have also expanded the range of possible control strategies. CRISPR systems can be engineered to specifically target resistance genes or a resistant bacterial population with high precision (Palacios Araya et al., 2021). Measures to block the maintenance and transfer of resistance plasmids in the environment or to remove resistance plasmids might also further restrict the ability for horizontal gene transfer and limit the long-term survival of transferred resistance determinants (Buckner et al., 2018).

Environmental control is also crucial in a One Health approach. Environmental dissemination pathways can be interrupted by wastewater treatment technologies that can minimize the presence of resistant bacteria, resistance genes and antimicrobial residues. (Starling et al., 2021) Sectors need to work together, as the following factors are essential to effective AMR control: stewardship, infection prevention, targeted therapeutics, genomic tools, environmental treatment, agricultural management and coordinated surveillance. The principal emerging approaches for controlling AMR and their potential roles within a One Health framework are compared in Table 2.

Table 2. Emerging strategies for antimicrobial resistance control across the One Health interface

Strategy	Primary target/action	Main value	potential	Key limitation	One Health relevance
Antimicrobial stewardship	Optimizes antimicrobial selection, dose, duration, and indication	Reduces unnecessary antimicrobial exposure and selective pressure		Requires sustained surveillance, diagnostics, and compliance	Human and veterinary healthcare
Infection prevention and biosecurity	Interrupts pathogen transmission	Reduces infections and subsequent antimicrobial demand		Effectiveness depends on consistent implementation	Hospitals, farms, food systems
Bacteriophage	Selectively infects	High	target	Narrow host range	Human,

therapy	bacterial pathogens	specificity and activity against some resistant bacteria	and emergence of phage resistance	possible veterinary, and food applications
Antimicrobial peptides	Disrupt bacterial membranes or other cellular processes	Potential activity against multidrug-resistant organisms	Stability, toxicity, and delivery remain challenges	Therapeutic and biotechnology applications
Probiotics and microbiome approaches	Promote beneficial microbial communities and colonization resistance	May reduce pathogen establishment and support host defenses	Effects may vary by strain, host, and setting	Human and animal health
Anti-virulence therapy	Blocks pathogenic functions rather than bacterial survival	May impose less direct selection for conventional resistance	Limited clinical translation for many targets	Precision infection management
CRISPR-based antimicrobials	Selectively targets resistance genes or specific bacterial populations	High genetic specificity	Delivery to target bacteria remains a major barrier	Precision AMR control
Anti-plasmid/plasmid-curing approaches	Prevent plasmid maintenance, replication, or transfer	Could reduce horizontally transferable resistance	Translation beyond experimental systems remains limited	Control of mobile resistance determinants
Advanced wastewater treatment	Removes or damages resistant bacteria, ARGs, and antimicrobial residues	Limits environmental dissemination	Performance and cost vary among treatment systems	Environmental and municipal AMR control
Integrated genomic surveillance	Detects resistance determinants and tracks	Enables early detection and targeted	Requires harmonized data, infrastructure, and	Links human, animal, food, and environmental

transmission

intervention

expertise

sectors

Note: AMR, antimicrobial resistance; ARGs, antimicrobial resistance genes; CRISPR, clustered regularly interspaced short palindromic repeats.

8. Knowledge Gaps and Future Research Priorities

There is still a lack of knowledge about the transmission of antimicrobial resistance between humans, animals and environment. Poor integration of clinical, veterinary, food and environmental surveillance data is one of the main limitations. An integrated One Health approach is thus required to enhance the sharing, cooperation and coordination in monitoring and decision-making across sectors (Food and Agriculture Organization of the United Nations et al., 2022). Resistomes in the environment and wildlife are also under studied when compared to those from clinical and livestock sources, and they may help to maintain and disseminate resistance genes. More efforts are required to determine resistance gene reservoirs and their persistence in the environment, as well as under which conditions they can be transmitted between microbial communities (United Nations Environment Programme, 2023).

Continued research is also needed on the standardized genomic surveillance tools, similar metadata, and harmonized analytical pipelines, enabling interpretation across countries and sectors. Priority research should involve elucidating the relationships between antimicrobial use, mobile genetic elements, ecological reservoirs and transmission risk (Food and Agriculture Organization of the United Nations et al., 2023). Genomic discoveries will require translation to tools for surveillance, prevention, diagnosis and targeted intervention as well. To fill these gaps and assist in evidence-based AMR control strategies, greater international coordination, continued infrastructure and research capacity will be crucial (World Health Organization, 2025).

9. Conclusion

AMR is a complex phenomenon involving genomic, ecological and evolutionary processes that go beyond the clinical environment. Chromosomal mutations, resistance genes, mobile genetic elements, selective pressures, and microbial adaptation together influence the emergence and persistence of resistant populations. The rapid spread of resistance determinants between different bacterial hosts via horizontal gene transfer and the ability of environmental reservoirs (including wastewater, soil, manure, surface water and food production systems) to carry and spread these genes between humans and animals is of particular concern. The resulting network of transmission raises the awareness of a need to consider AMR as a collective One Health issue not limited to any one sector. The whole genome sequencing, metagenomics, resistome profiling and genomic epidemiology are important developments that offer strong tools to detect resistant organisms, trace the transmission pathways and identify emerging threats. But, their importance relies on the coordinated monitoring, standardized data collection, and effective integration of clinical, veterinary, agricultural, food, and environmental data. Prevention, responsible use

of antimicrobials, sanitary and hygienic practices, early detection and targeted biological or molecular interventions should be emphasized in future control measures. Genomic surveillance and stewardship, environmental control, and cross-sector collaboration provide the best practical approach for slowing the emergence, maintenance and transmission of antimicrobial resistance.

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