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Poultry at the crossroads of antimicrobial resistance: Global challenges and sustainable solutions

V. Moskalov*, I. Ionov**, ***, H. Fotina****, *****, T. Fotina****,
O. Anisimova***, ******, I. Upatova*, R. Buriak****, O. Fotin****, *****

*Kharkiv Humanitarian-Pedagogical Academy, Kharkiv, Ukraine
**H. S. Skovoroda Kharkiv National Pedagogical University, Kharkiv, Ukraine
***National Academy of Agrarian Sciences of Ukraine, Kyiv, Ukraine
****Sumy National Agrarian University, Sumy, Ukraine
*****Biology Centre of the Czech Academy of Sciences, České Budějovice, Czech Republic
******Institute for Soil Science and Agrochemistry Research named after O. N. Sokolovsky, Kharkiv, Ukraine

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Department of Natural Sciences and Health Care, Municipal Establishment "Kharkiv Humanitarian-Pedagogical Academy" of Kharkiv Regional Council, Kharkiv, Ukraine. E-mail: vitmoskalov93@gmail.com

Department of Human Anatomy and Physiology, H. S. Skovoroda Kharkiv National Pedagogical University, Kharkiv, Ukraine. E-mail: ionov.igor2013@gmail.com

National Academy of Agrarian Sciences of Ukraine, Kyiv, Ukraine. E-mail: super.annafotina@ukr.net

Faculty of Veterinary Medicine, Sumy National Agrarian University, Sumy, Ukraine. E-mail: tif_ua@meta.ua

Institute of Parasitology, Biology Centre CAS, Branišovská 1160/31, 370 05 České Budějovice, Czech Republic. Tel: +420-385-310-351. E-mail: paru@paru.cas.cz

Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, České Budějovice, Czech Republic. E-mail: alexeyfotin79@gmail.com

National Scientific Center "Institute for Soil Science and Agrochemistry Research named after O. N. Sokolovsky", Kharkiv, Ukraine. E-mail: anisimova_o.v@ukr.net

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Antimicrobial resistance in poultry production represents a rapidly intensifying global challenge at the intersection of animal agriculture, human health and environmental sustainability. This review synthesizes molecular, epidemiological and ecological evidence to identify the mechanisms driving the emergence and spread of antimicrobial resistance within poultry systems. Analysis of international data shows that selective antimicrobial pressure, horizontal gene transfer and environmental co-selection contribute to the formation of a dynamic and interconnected resistome. Particular attention is given to plasmid-mediated ESBL and mcr determinants, which facilitate the exchange of resistance genes among *Escherichia coli, Salmonella enterica* and *Campylobacter* spp. across poultry, wildlife and human populations. These molecular processes are consistent with epidemiological findings demonstrating overlapping genomic profiles among isolates from farms, wild birds and clinical cases. The persistence of resistance reservoirs along the farm–environment interface is promoted by intensive production, inadequate biosecurity and manure mismanagement. Effective mitigation requires integrating antimicrobial stewardship, vaccination, improved biosecurity and precision livestock technologies, supported by promising biological alternatives such as probiotics, phytobiotics, bacteriophages and mesenchymal stem cell secretome. Strengthening molecular surveillance, environmental monitoring and One Health governance can shift AMR control from reactive interventions to preventive strategies, promoting a more sustainable and antibiotic-independent poultry sector.

Keywords: antimicrobial resistance; poultry production; One Health; environmental reservoirs; resistome; biological alternatives.

Introduction

Antimicrobial resistance (AMR) has emerged as one of the defining challenges of the 21st century, threatening the foundations of modern medicine, food security, and sustainable development (Laxminarayan et al., 2013; Larsson & Flach, 2022; Murray et al., 2022). The discovery of antibiotics and methods for their industrial synthesis in the first half of the 20th century was once a turning point in the struggle against infectious diseases.

However, humanity's greatest achievement in medicine soon began to crumble under the onslaught of its own success. The widespread, and often indiscriminate, use of antimicrobials in both humans and animals accelerated the evolution and spread of resistant pathogens across ecosystems, borders, and species.

While antimicrobial resistance is often portrayed as a clinical or hospital-based problem, its roots and ramifications extend far beyond the walls of healthcare facilities. The agricultural sector (particularly intensive poultry production) has become a critical interface where antibiotics, animals, humans, and the environment intersect (Marshall & Levy, 2011; Van Boeckel et al., 2019; Tang et al., 2022).

Poultry is among the most rapidly expanding livestock sectors globally, serving as a vital source of protein for billions of people. Yet this very expansion, driven by economic and demographic pressures, has come at an ecological and microbiological cost.

According to the landmark Review on Antimicrobial Resistance, AMR could cause up to ten million deaths annually by 2050 if no effective countermeasures are taken (O'Neill, 2016). Beyond the staggering human toll, the report warns of devastating economic impacts – potentially reducing global GDP by 2–3%. Recognizing the urgency of this threat, the World Health Organization adopted the Global Action Plan on Antimicrobial Resistance, calling for a "One Health" approach that bridges human, animal, and environmental health sectors (World Health Organization, 2015).

In this interconnected landscape, food animal production has been identified as both a contributor to and a potential control point for AMR dissemination (Van Boeckel et al., 2015). Antibiotics are commonly used in poultry farming not only for therapy and metaphylaxis but also for growth promotion and disease prevention – practices that vary widely across countries. Global data reveal that between 2000 and 2010, antimicrobial use in food animals increased by, more than 60%, with poultry representing one of the largest shares of consumption.

The intensive nature of modern poultry systems (high animal densities, short production cycles, and frequent antimicrobial exposure) creates ideal conditions for the selection and amplification of resistant bacteria. These organisms, often harboring mobile genetic elements such as plasmids and integrons, can easily transfer resistance genes among commensal and pathogenic species. Resistant strains of

Escherichia coli, *Salmonella*, and *Campylobacter* originating from poultry have been repeatedly implicated in zoonotic transmission and foodborne outbreaks (Nhung et al., 2017; Hedman et al., 2020).

The situation is particularly concerning in low- and middle-income countries (LMICs), where weak regulatory oversight, lack of veterinary supervision, and limited access to diagnostics lead to excessive or inappropriate antimicrobial use (Hedman et al., 2020). In such settings, poultry production often occurs in close proximity to human dwellings, facilitating microbial exchange between animals, humans, and the surrounding environment. Consequently, resistance genes selected within poultry production systems can rapidly disseminate via manure, dust aerosols, surface and groundwater, and contaminated food products, thereby entering wider ecological and human health networks. Recent studies demonstrate that these environmental pathways serve as major conduits for the spread of antimicrobial resistance genes (ARGs) beyond farm boundaries, linking agricultural practices with community- and hospital-associated resistomes (Berendonk et al., 2015; Woolhouse et al., 2015; Hedman et al., 2020). The genetic and ecological dynamics of resistance within poultry systems further underscore the complexity of the antimicrobial resistance (AMR) crisis. Resistance determinants are highly mobile, circulating across plasmids, transposons, and integrons that facilitate horizontal gene transfer among phylogenetically diverse bacterial taxa and across geographic regions (Partridge et al., 2018; Rozwandowicz et al., 2018). As a result, poultry farms function as dynamic hubs of resistance evolution rather than isolated reservoirs.The poultry farm resistome therefore represents a scaled-down but highly active model of the global AMR network – an interconnected microbial ecosystem shaped by antimicrobial selective pressure, animal management practices, and microbial adaptation. Genomic and metagenomic evidence increasingly supports the view that agricultural resistomes contribute directly to the global circulation of clinically relevant resistance genes within a One Health framework (Berendonk et al., 2015; Hendriksen et al., 2019; Larsson & Flach, 2022).

Addressing AMR in poultry cannot be achieved merely by restricting antibiotic use. Sustainable solutions must rest on three interconnected pillars: (i) antimicrobial stewardship, (ii) structural and management innovations in poultry production, and (iii) alternative antimicrobial and immunomodulatory strategies that maintain bird health and productivity without relying on antibiotics.

Recent meta-analyses have shown that interventions limiting non-therapeutic antimicrobial use in broiler production significantly reduce the prevalence of resistant *Escherichia coli*, *Campylobacter*, and *Enterococcus* isolates, confirming the effectiveness of stewardship policies (Costa et al., 2023).

However, stewardship alone is not sufficient. The poultry sector is increasingly exploring biological alternatives that support gut and immune health while reducing pathogen pressure. Probiotics, prebiotics, and synbiotics modulate intestinal microbiota, improving resilience to infections and mitigating colonisation by resistant bacteria (Yaqoob et al., 2022). Phytobiotics and essential oils (rich in polyphenols and terpenes) demonstrate antibacterial and anti-inflammatory properties and have gained traction as feed additives with dual productivity and health benefits (Hashemi & Davoodi, 2011).

Bacteriophages and phage-derived endolysins provide pathogen-specific antimicrobial action without disturbing commensal flora, an advantage over traditional broad-spectrum agents (Islam et al., 2023).

A particularly promising frontier involves immunomodulators and postbiotics, including the secretome of mesenchymal stem cells – a complex of cytokines, growth factors, and antimicrobial peptides capable of modulating host immunity and dampening inflammatory responses. Preliminary data indicate that MSC-derived secretome components enhance macrophage phagocytic activity and upregulate avian β-defensins, suggesting a role in prophylaxis and immune priming against bacterial challenges (Svoradova et al., 2021; Wang et al., 2022).

Yet, global adoption of these innovations remains uneven. Low- and middle-income countries (LMICs) face barriers including cost, inconsistent regulatory frameworks, and limited access to validated products (Hedman et al., 2020). Therefore, progress depends on integrating technological innovation with education, capacity building, and coherent One Health-based governance (World Health Organization, 2015).

This review synthesizes current knowledge on the role of poultry production in shaping the global ecology of antimicrobial resistance (AMR). Specifically, it aims to: (i) elucidate the mechanisms underpinning the emergence, persistence, and transmission of resistance within poultry systems; (ii) critically assess the epidemiological links between poultry-associated AMR and risks within a One Health framework; and (iii) evaluate sustainable mitigation strategies.

The molecular basis of AMR in poultry

The phenomenon of AMR. Poultry production represents a hotspot for the emergence and amplification of antimicrobial resistance (AMR) because it combines high host density, frequent antimicrobial exposure, and multiple pathways for environmental dissemination (Carattoli, 2013; Gillings, 2013). Understanding the molecular basis of AMR in poultry is essential for interpreting surveillance data, tracing transmission routes, and designing targeted interventions.

The emergence of antimicrobial resistance (AMR) represents one of the most striking examples of rapid microbial evolution driven by anthropogenic pressures. The antibiotic era, which began in the mid-20th century, has not only enabled the control of many infectious diseases but also facilitated the parallel selection of resistant bacterial populations. In poultry production, the frequent and sometimes indiscriminate use of antibiotics for therapeutic, prophylactic, and growth-promoting purposes has created a unique ecological niche that accelerates the selection and persistence of resistant strains.

The main factors that create regular and strong selective pressure on resistant variants in intensive poultry farming include high flock density, routine metaphylaxis or prophylaxis, and the frequent use of broad-spectrum drugs, all of which increase the likelihood of selecting and amplifying resistant mutants within flocks. These selection pressures act continuously at the farm level over many production cycles, creating persistent reservoirs of resistance (Carattoli, 2013; Ajayi et al., 2024).

Selective pressure in intensive poultry systems fosters both mutational and acquired resistance. The former arises through spontaneous genetic changes that modify antibiotic targets or efflux capacity, while the latter involves the horizontal uptake of resistance genes (ARGs) from other bacteria. The high microbial density within poultry gut ecosystems, coupled with environmental exposure through litter, water, and air, creates ideal conditions for horizontal gene transfer (HGT) via conjugation, transformation, or transduction. In poultry populations, resistance spreads both vertically (from parent to offspring through bacterial chromosomes or plasmids within a lineage) and horizontally (between co-colonizing bacteria of different lineages via HGT). HGT is particularly important for the rapid spread of clinically significant ARGs among different species in the gut of birds and under farm conditions (Partridge et al., 2018; Savelkoul & Wolffs, 2016).

Importantly, AMR in poultry is not a self-contained phenomenon – it is interconnected with human and environmental resistomes through the shared interfaces of food, water, and animal contact. This interdependence positions poultry farming as both a victim and vector within the One Health framework, reflecting a continuum of resistance evolution that transcends species and ecosystems. It is also worth noting that antibiotic resistance is an ancient, naturally occurring phenomenon that predates clinical antibiotic use; environmental bacteria have long carried resistance determinants as part of their ecological repertoire. Clinical and agricultural antibiotic use has, however, dramatically increased the selective pressure favouring those determinants and their mobilization into pathogens (Gillings, 2013; World Health Organization, 2015; Ajayi et al., 2024).

Genetic control and transmission mechanisms. Antimicrobial resistance arises via several biochemical strategies: enzymatic inactivation (e.g., β-lactamases hydrolysing β-lactam antibiotics), target modification (such as mutations altering antibiotic binding sites), decreased permeability, and active efflux pumps that reduce intracellular antibiotic concentrations. These mechanisms are widely recognised as the principal pathways by which bacteria withstand antimicrobial pressure and are frequently documented in contemporary studies of resistance biology (Elshobary et al., 2025; Xie et al., 2025). Antibiotic resistance genes (ARGs) found in poultry-associated bacteria (including members of the Enterobacteriaceae family and other taxa) encompass a wide spectrum of molecular targets and mechanisms. Among the most clinically significant are β-lactamases, including extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases such as *bla*$^{CTX\text{-}M}$, *bla*^{TEM}, and *bla*^{SHV}, which confer resistance to penicillins and cephalosporins and have been reported as prevalent in poultry-associated Enterobacterales in recent surveillance studies (Poirel et al., 2018; Senthamilselvan et al., 2024; Ali et al., 2025).

Moreover, mobilized colistin resistance genes (mcr variants) have become emblematic of last-resort antibiotic failure, highlighting the importance of monitoring resistance even in commensal poultry isolates. These genes have been repeatedly detected in both commensal and pathogenic isolates from poultry (Liu et al., 2016; Skov & Monnet, 2016; Ajayi et al., 2024).

In addition to ARGs directly conferring resistance, co-selection mechanisms play a crucial role in maintaining resistant populations. ARG expression can be influenced by adjacent regulatory sequences (promoters, insertion sequences) and by co-localized regulators such as integron integrase genes. Genes encoding tolerance to heavy metals (e.g., copper, zinc) and biocides often co-localize with ARGs on the same plasmids, transposons, or other mobile genetic elements, ensuring their persistence even when antibiotic exposure is reduced, as heavy metal and biocide exposure has been shown to co-select for antibiotic resistance determinants in bacteria from environmental and agricultural settings (Murray et al., 2024; Engobo et al., 2025). Regulatory systems, including two-component response regulators, global stress response networks, and stress-inducible promoters, further modulate ARG expression in response to environmental cues, integrating resistance gene expression with broader cellular adaptive responses under abiotic stressors such as metals and disinfectants (Islam et al., 2025; Li et al., 2025).

Transmission dynamics within the bird gut. The avian gut microbiota is a dense and dynamic microbial ecosystem where conjugation, transduction, and natural transformation can occur at appreciable rates. Conditions such as antibiotic exposure and inflammation may markedly increase the frequency of horizontal gene transfer (HGT). As a result, the gut functions both as an amplification chamber and as a crucible for novel ARG assemblies (Partridge et al., 2018; Savelkoul & Wolffs, 2016).

Mobile genetic elements driving AMR. The dissemination of antimicrobial resistance (AMR) within poultry systems is largely mediated by mobile genetic elements (MGEs) (including plasmids, integrons, transposons, and insertion sequences (IS elements)), which enable horizontal gene transfer (HGT) of antibiotic resistance genes (ARGs) across diverse bacterial taxa (Partridge et al., 2018; Rozwandowicz et al., 2018). Plasmids represent the primary vehicles of AMR dissemination. Conjugative plasmids belonging to incompatibility groups such as IncF, IncI, IncHI2 and IncX4 frequently carry ESBL and mcr genes in *Escherichia coli* and *Salmonella* isolates from poultry (Nadimpalli et al., 2020; Wang et al., 2022; Anyanwu et al., 2023). These plasmids often display complex modular architectures that combine ARGs, virulence determinants, and stability/maintenance systems, thereby enhancing both bacterial fitness and horizontal transmissibility (García-Fernández et al., 2020; Botelho & Schulenburg, 2021). Integrons function as gene-capturing platforms enabling the incorporation of resistance gene cassettes through site-specific recombination. Class 1 integrons are particularly prevalent in poultry-associated bacteria and are strongly associated with multidrug-resistant phenotypes (Partridge et al., 2018). IS elements such as IS26 and ISCR1 further promote mobilization and genomic rearrangements, driving rapid genetic diversification within the poultry resistome (Partridge et al., 2018; Harmer & Hall, 2020; Zheng et al., 2023). Recent genomic studies have identified "supermobilizable" plasmids that integrate features of multiple MGEs, facilitating broad host-range conjugation and accelerating global dissemination of ESBL-producing and colistin-resistant *E. coli* strains originating from poultry systems (Liu et al., 2016; Poirel et al., 2018; Rozwandowicz et al., 2018). Examples of ARG dissemination in poultry production include ESBLs (particularly CTX-M β-lactamases) widely reported in *E. coli* from poultry, where plasmid-borne CTX-M variants frequently cluster with other ARGs and virulence traits (Johnson & Nolan, 2009; Poirel et al., 2018). Another major example is colistin resistance mediated by mcr genes. The plasmid-encoded mcr-1 gene, initially identified in Enterobacteriaceae from animals and humans, is now reported worldwide in poultry isolates and is typically associated with composite transposons and IS elements enabling efficient mobilization (Liu et al., 2016; Skov & Monnet, 2016). A summary of the major molecular mechanisms facilitating the spread of AMR in poultry production is presented in Table 1.

Table 1
Major classes of antibiotic resistance genes (ARGs)
and their mobile genetic platforms in poultry-associated bacteria

Class of antibiotic	ARGs*	Typical carriers	Bacterial hosts	References
β-lactams	*bla*^{TEM}, *bla*$^{CTX\text{-}M}$, *bla*^{SHV}	IncF, IncI plasmids; *IS26*, *ISCR1*	*E. coli*, *Salmonella*	Poirel et al. (2018); Rozwandowicz et al. (2018)
Colistin	*mcr-1*, *mcr-3*	IncX4, IncI2 plasmids	*E. coli*, *Klebsiella*	Ajayi et al. (2024)
Tetracyclines	*tet(A)*, *tet(B)*	Tn1721, *IS26*	*E. coli*, *Enterococcus*	Partridge et al. (2018); Bennett (2008)
Sulfonamides	*sul1*, *sul2*	Class 1 integrons	*E. coli*, *Salmonella*	Dessie et al. (2013)
Quinolones	*qnrA*, *qnrB*, *qnrS*	IncQ plasmids; *ISCR1*	*E. coli*, *Campylobacter*	Carattoli (2013); Rozwandowicz et al. (2018)
Macrolides	*erm(B)*	*Tn917*, *IS1216*, class 1 integrons	*Enterococcus*, *Campylobacter*	Partridge et al. (2018)
Phenicols	*floR*, *catA1*	*IncA/C*, *IncFII*, *ISCR2*	*E. coli*, *Salmonella*	Rozwandowicz et al. (2018)

Note: the listed antibiotic resistance genes (ARGs) represent the most prevalent determinants reported in poultry production systems globally.

Epidemiological dimensions of poultry

Antimicrobial resistance (AMR) in poultry systems represents a complex ecological and epidemiological issue that spans veterinary, environmental, and public health domains. Poultry production is among the largest consumers of antimicrobials in animal agriculture, generating selective pressures that promote the persistence and spread of resistant bacteria and resistance genes across ecosystems (Singer & Hofacre, 2006; Nhung et al., 2016). Beyond farm settings, AMR dissemination involves interactions between domestic poultry and wild avifauna, where gene flow and bacterial exchange occur through shared habitats, contaminated water systems, and migratory pathways (Vittecoq et al., 2016; Wang et al., 2017). This section outlines the epidemiological context of poultry-associated AMR – its emergence in domestic production, spillover into wildlife, and broader food safety and public health implications.

AMR among domestic poultry pathogens and commensals. Domestic poultry function as both reservoirs and amplifiers of resistant microorganisms, including *Escherichia coli*, *Salmonella enterica*, *Campylobacter jejuni*, and *Enterococcus* spp. (Michael & Schwarz, 2016; Zong et al., 2022). Studies across Europe, Asia, and Latin America consistently report high prevalence of multidrug resistance (MDR) among isolates from broilers and laying hens, particularly resistance to β-lactams, tetracyclines, fluoroquinolones, and polymyxins (Nhung et al., 2016; Zong et al., 2022). The widespread detection of mcr-1–harboring plasmids in *E. coli* from poultry in China has heightened concerns about diminishing last-resort therapeutic options such as colistin (Zong et al., 2022).

Epidemiological surveillance in both the European Union and low- and middle-income countries (LMICs) highlights pronounced regional differences in resistance patterns. In high-income settings, restrictions on prophylactic antibiotic use have led to partial reductions in AMR prevalence (Berendonk et al., 2015). In contrast, in many LMICs, unregulated over-the-counter access to veterinary antimicrobials continues to drive intense selective pressure (Nhung et al., 2016). Phylogenetic and genomic analyses demonstrate substantial overlap between poultry-derived isolates and strains associated with human infections, suggesting zoonotic and foodborne transmission pathways (Michael & Schwarz, 2016). Comparative genotyping has revealed that some *E. coli* ST131 lineages and several *Salmonella* serovars share nearly identical antimicrobial resistance gene (ARG) profiles across human and avian hosts, reinforcing the "One Health" continuum (Singer & Hofacre, 2006; Zong et al., 2022).

The role of wild birds in AMR ecology. Wild birds represent an increasingly important vector and sentinel group for monitoring the environmental dissemination of antimicrobial resistance (AMR) (Carroll et al., 2015; Vittecoq et al., 2016). Due to their ecological mobility and frequent interactions with human-modified environments, migratory species can acquire resistant bacteria from agricultural, urban, and aquatic sources and redistribute them across extensive geographic ranges (Wang et al., 2017; Swift et al., 2019). Numerous studies have detected resistant Enterobacteriaceae, *Campylobacter*, and *Salmonella* in wild raptors, waterfowl, and urban scavenging birds (Molina-Lopez et al., 2011; Giacopello et al., 2016; Casalino et al., 2022).

Recent evidence indicates that wildlife is not merely a passive sink for resistant bacteria but an active participant in AMR ecology. For example, *E. coli* strains isolated from gulls and storks in Spain carried ESBLs and multidrug resistance (MDR) determinants similar to those circulating in nearby poultry farms and wastewater treatment systems (Martín-Maldonado et al., 2022). Likewise, *Campylobacter jejuni* isolates from wild birds often share resistance genotypes with those commonly detected in broiler populations, suggesting interspecies exchange of AMR traits (Casalino et al., 2022). Environmental interfaces such as shared water bodies, irrigation systems, and feeding sites act as hotspots for horizontal gene transfer (HGT), frequently mediated by plasmids, integrons, and other mobile genetic elements (Heuer et al., 2011; Stalder et al., 2012).

The ecological diversity of wild birds also shapes their AMR profiles. Scavenging and urban-adapted species (such as gulls, crows, and storks) tend to harbor higher levels of MDR bacteria due to their proximity to human waste streams, landfills, and livestock operations (Martín-Maldonado et al., 2022; Esposito et al., 2024). Conversely, migratory waterfowl can act as long-distance carriers capable of facilitating intercontinental movement of resistance genes via established flyway routes (Wang et al., 2017). According to a recent systematic review, up to 60% of *E. coli* isolates from wild birds globally exhibit resistance to at least one clinically relevant antimicrobial class (Carroll et al., 2015).

The distribution of antibiotic resistance across the domestic poultry – wild birds – humans triangle is illustrated in Figure 1. This schematic highlights the interconnected ecology of AMR at the interface of poultry farming, wildlife, and human populations. Bidirectional exchange of *Escherichia coli* and *Salmonella* strains carrying identical antimicrobial resistance genes (e.g., ESBLs, qnr, sul) occurs between humans and poultry (Singer & Hofacre, 2006; Michael & Schwarz, 2016). Shared *Campylobacter jejuni* genotypes containing resistance determinants such as tetO and gyrA have been documented in both domestic and wild bird populations, reinforcing the role of wildlife as a bridge for AMR dissemination (Wang et al., 2017; Casalino et al., 2022). Wild birds (including urban scavengers such as gulls, crows, and storks) serve as environmental reservoirs and long-range vectors of MDR bacteria, spreading AMR through fecal deposition, migration, and contact with contaminated habitats (Vittecoq et al., 2016; Swift et al., 2019; Martín-Maldonado et al., 2022). Environmental matrices such as soil, water, and manure also function as reservoirs and "genetic bridges" facilitating the circulation of ARGs between avian, human, and environmental microbiomes (Heuer et al., 2011; Berendonk et al., 2015).

Black arrows show interactions between subjects in the domestic poultry – wild birds – humans triangle; green arrows show interactions between subjects and the environment; black text above the arrows shows actual cases of interaction between subjects confirming the transfer of AMR genes; green text to the right of the arrows shows examples of AMR gene exchange between subjects and the environment. ARG(s) – antibiotic resistance gene(s); MDR – multidrug resistance; ESBLs – extended-spectrum β-lactamases.

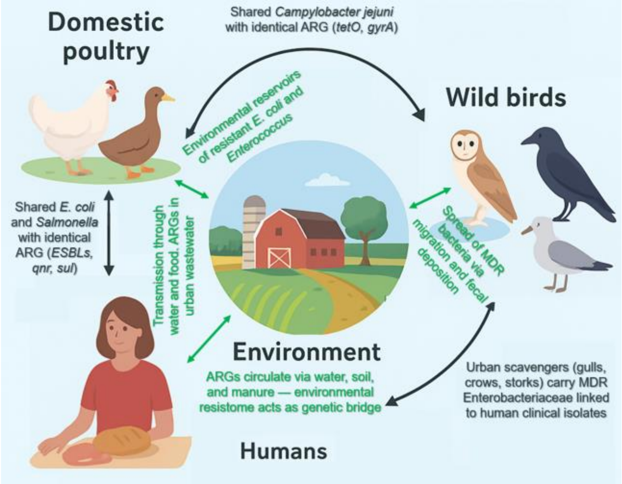

Fig. 1. Conceptual pathways of antimicrobial resistance (AMR) transmission among domestic poultry, wild birds, humans, and the environment

Poultry tick infestations as emerging interfaces linking ectoparasitism and antimicrobial resistence. Ectoparasites, particularly poultry-associated ticks, are increasingly recognized as relevant yet underexplored components of antimicrobial resistance (AMR) ecology within poultry production systems. In recent years, attention has shifted from viewing ticks solely as vectors of avian pathogens toward understanding their broader role in shaping antimicrobial usage patterns, microbial transmission, and resistance dynamics at the livestock–environment interface (Vittecoq et al., 2016; George et al., 2019).

Tick infestations in poultry flocks cause chronic stress, anemia, skin damage, and immunomodulation, leading to reduced productivity and increased susceptibility to secondary bacterial infections. These health impacts frequently prompt increased therapeutic, prophylactic, or metaphylactic antimicrobial use, particularly in systems with limited diagnostic capacity or weak veterinary oversight (George et al., 2019; Hedman et al., 2020). As a result, ectoparasite pressure indirectly amplifies selective forces favoring antimicrobial-resistant bacterial populations within poultry-associated microbiota.

Beyond indirect effects mediated through antimicrobial usage, accumulating evidence indicates that ticks can act as reservoirs and mechanical vectors of bacteria relevant to AMR. Studies conducted since 2016 have detected antimicrobial-resistant *Escherichia coli*, *Salmonella* spp., *Staphylococcus* spp., and *Enterococcus* spp. in ticks collected from livestock and poultry-associated environments, including strains carrying genes conferring resistance to β-lactams, tetracyclines, and fluoroquinolones (Rizzo et al., 2019; Tadesse et al., 2021). The prolonged feeding behavior and repeated host contact characteristic of argasid ticks facilitate bacterial persistence and inter-host transmission within poultry houses.

Ticks also provide microecological niches conducive to horizontal gene transfer (HGT). The tick gut and salivary glands support dense and diverse microbial communities, creating conditions favorable for plasmid exchange and recombination of antimicrobial resistance genes (ARGs). Arthropod vectors are therefore increasingly viewed as ecological "mixing vessels" linking environmental, animal, and human resistomes within a One Health framework (Rizzo et al., 2019; De la Fuente et al., 2020).

Environmental persistence further strengthens the role of poultry ticks in AMR dissemination. Poultry ticks can survive for extended periods in housing structures, litter, and surrounding environments, allowing resistant bacteria to persist across production cycles even in the absence of continuous antimicrobial exposure. This persistence enables the reintroduction of resistant microorganisms into successive flocks, contributing to farm-level AMR stability and recurrence (George et al., 2019).

At broader ecological scales, poultry ticks operate at the wildlife–livestock interface. Interactions between domestic poultry, synanthropic birds, and wild avifauna facilitate the exchange of ectoparasites and associated bacteria, reinforcing regional and transboundary dissemination of antimicrobial resistance (Vittecoq et al., 2016; Carroll et al., 2019). Such dynamics highlight the importance of integrating ectoparasite control into One Health-based AMR surveillance and mitigation strategies.

Collectively, poultry tick infestations function as indirect drivers and potential reservoirs of AMR by increasing antimicrobial usage, supporting bacterial persistence, and facilitating microbial exchange across hosts and environments. Despite this, ectoparasite management remains largely disconnected from antimicrobial stewardship frameworks. Integrating tick control into AMR mitigation strategies (through improved biosecurity, housing design, acaricide stewardship, and non-chemical control measures) represents a critical and currently underutilized opportunity to reduce antimicrobial reliance and interrupt resistance transmission pathways in poultry production systems. Moreover, the urgency of addressing ectoparasite-associated AMR extends beyond food-producing animals to companion animals, particularly dogs and cats, which frequently share environments with livestock or peridomestic settings.

Ticks infesting companion animals can harbor and disseminate antimicrobial-resistant bacteria, facilitating spillover between animal populations and increasing opportunities for human exposure.

Given the close physical contact between pets and humans, ectoparasite-mediated resistance transmission in dogs and cats represents an underrecognized but potentially significant public health concern. Integrating companion animals into ectoparasite surveillance and AMR mitigation strategies is therefore essential for a comprehensive One Health response (Rizzo et al., 2019; De la Fuente et al., 2020).

Implications for food safety and public health. The epidemiological overlap between poultry and wildlife antimicrobial resistance (AMR) reservoirs has direct implications for food safety and public health. Resistant bacteria and antimicrobial resistance genes (ARGs) have been detected not only in poultry meat and eggs but also in slaughterhouse wastewater and packaging environments (Singer & Hofacre, 2006; Berendonk et al., 2015).

Quantitative risk assessments indicate that, under inadequate hygiene and improper cooking practices, poultry products remain a major transmission vehicle for ESBL-producing *Escherichia coli*, fluoroquinolone-resistant *Campylobacter*, and multidrug-resistant *Salmonella* (Greig et al., 2015; Michael & Schwarz, 2016).

Integrated surveillance initiatives (including EARS-Net, EFSA AMR monitoring, and the WHO GLASS framework) identify poultry as a sentinel indicator of agricultural AMR trends (Berendonk et al., 2015). However, in many low- and middle-income countries (LMICs), data remain fragmented because of limited diagnostic capacity and the dominance of informal poultry markets (Nhung et al., 2016). Strengthening the integration of environmental and food-chain monitoring systems is therefore essential for tracing ARG dissemination across the "farm–fork–field" continuum. From a One Health standpoint, mitigating AMR in poultry requires a systemic, multisectoral approach. Evidence highlights the importance of reducing non-therapeutic antimicrobial use, improving farm biosecurity, expanding vaccination programs, promoting probiotics, and incorporating wildlife monitoring into national AMR surveillance networks (Carroll et al., 2015; Swift et al., 2019; Esposito et al., 2024).

The scientific consensus increasingly demonstrates that AMR in poultry cannot be viewed in isolation; rather, it exists within a multi-host and multi-environmental network that continually reshapes the global resistome. ARGs originating from poultry waste and urban wastewater can spread into agricultural soils and water systems, increasing human exposure through contaminated food and drinking water pathways (Nhung et al., 2016; Zong et al., 2022).

Drivers of resistance emergence

The emergence and spread of antimicrobial resistance (AMR) in poultry production is a multifactorial process shaped by antimicrobial use, farm management practices, and environmental interactions.

Poultry farming is among the fastest-growing livestock sectors worldwide and accounts for a substantial share of antimicrobial use in food-producing animals (Laxminarayan et al., 2015; Hedman et al., 2020). Intensive production systems characterized by high stocking densities and continuous antimicrobial exposure exert strong selective pressure on microbial communities, facilitating the evolution and dissemination of resistant strains (Roth et al., 2019). Understanding the main drivers (from antimicrobial use patterns to farm-level biosecurity failures) is essential for mitigating AMR transmission throughout the food chain and the environment (Agyare et al., 2018).

Antimicrobial use patterns in poultry. Antimicrobial usage (AMU) in poultry has increased substantially over the past three decades, driven by global growth in animal protein demand. Between 2017 and 2030, antimicrobial consumption in food-producing animals is projected to rise by 8–10%, particularly in Asia, South America, and Africa (Tiseo et al., 2020; Mulchandani et al., 2023). Although several high-income countries have introduced strict regulations and phased out antibiotic growth promoters (AGPs), many LMICs continue to rely on prophylactic and metaphylactic antibiotic use due to weak surveillance systems and limited veterinary oversight (Oluwasile et al., 2014; Agyare et al., 2018).

Patterns of antimicrobial application vary by region and production intensity. In Southeast Asia and Sub-Saharan Africa, poultry farmers frequently administer antibiotics without prescription, often incorporating them into feed or drinking water to prevent disease outbreaks (Mudenda et al., 2023; Mdemu et al., 2025).

By contrast, the United States and European Union report declining AMU following strengthened regulations and improved monitoring systems (Singer & Hofacre, 2006; Roth et al., 2019). Nevertheless, unreported, off-label, or undocumented use persists, complicating efforts to quantify AMU and correlate it with resistance trends (Agyare et al., 2018).

Antibiotics in poultry production serve roles beyond therapeutic treatment. Prophylactic use aims to suppress subclinical infections (particularly in young chicks) while AGPs are intended to enhance growth performance and feed efficiency (Roth et al., 2019).

Despite regulatory bans in many countries, evidence shows that informal AGP use persists, especially in LMICs where limited access to veterinary services and insufficient awareness of AMR risks contribute to unsupervised antimicrobial administration (Oluwasile et al., 2014; Agyare et al., 2018).

Sub-therapeutic antibiotic exposure fosters sustained selective pressure, promoting the co-selection of multidrug-resistant bacteria (Laxminarayan et al., 2015; Mulchandani et al., 2023).

Farm-level factors. At the farm level, the development and dissemination of antimicrobial resistance (AMR) are closely linked to management conditions and biosecurity practices. High stocking density, inadequate litter management, and insufficient ventilation increase physiological stress and facilitate pathogen circulation, thereby heightening reliance on antimicrobials (Kasabova et al., 2021). Cross-contamination between flocks through shared equipment, feed, water systems, or farm personnel further contributes to the spread of resistant bacteria within and between farms (Mdemu et al., 2025).

Studies conducted in regions across Africa and Asia demonstrate that poor biosecurity is strongly associated with higher prevalence of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and resistant *Enterococcus* spp. (Mudenda et al., 2023).

Behavioral and knowledge-related factors among poultry farmers further exacerbate AMR risks. Limited training, misunderstandings regarding antibiotic withdrawal periods, and economic pressure to reduce mortality frequently result in misuse or overuse of antimicrobials (Al Sattar et al., 2023; Mdemu et al., 2025).

Surveys from Tanzania and South Asia indicate that up to 70% of farmers purchase antibiotics over the counter without veterinary oversight, and only a minority adhere to recommended treatment durations (Agyare et al., 2018).

Such widespread misuse contributes not only to the emergence of resistant strains but also to contamination of manure, water, and farm dust with antimicrobial residues and resistance genes (Mudenda et al., 2023). Feed composition and the use of feed additives also influence resistance dynamics. The inclusion of trace metals such as copper and zinc (commonly used as growth promoters) may co-select for resistance plasmids carrying both metal- and antimicrobial-resistance determinants (Kasabova et al., 2021; Farkas et al., 2025). Similarly, the reuse of poultry litter as fertilizer or as a component of animal feed facilitates horizontal gene transfer between commensal and pathogenic bacteria, further accelerating resistance spread (Zhu et al., 2013; Yang et al., 2019).

Integrated farm management (addressing both antimicrobial stewardship and environmental hygiene) is therefore essential for mitigating AMR at the production level. The key farm-level drivers of antimicrobial resistance discussed above are summarized in Table 2.

Table 2
Key drivers of antimicrobial resistance emergence in poultry production systems

Category of driver	Specific factors	Potential consequences	Key references
Antimicrobial usage	Prophylactic and metaphylactic treatments; growth-promoting use; off-label application; lack of veterinary oversight	Selection and persistence of multidrug-resistant (MDR) strains; enrichment of resistance gene pools	Roth et al., 2019; Agyare et al., 2018; Tiseo et al., 2020; Mulchandani et al., 2023
Farm management and biosecurity	High stocking density; poor hygiene; reuse of litter; inadequate quarantine; cross-contamination between flocks	Horizontal transfer of ESBL-producing *E. coli* and other resistant Enterobacteriaceae	Mudenda et al., 2023; Kasabova et al., 2021
Environmental dissemination	Contaminated manure, litter, and wastewater; aerosolized particles; antibiotic residues in runoff	Diffusion of ARGs and resistant bacteria to soil, surface water, and wildlife	Yang et al., 2019; Zhu et al., 2013
Socio-economic and regulatory factors	Weak policy enforcement; over-the-counter antibiotic access; lack of farmer education and awareness	Uncontrolled antimicrobial usage and accumulation of resistance determinants	Laxminarayan et al., 2015; Al Sattar et al., 2023
Feed composition and co-selective agents	Heavy metals (Cu, Zn); coccidiostats; antibiotic growth promoters (AGPs)	Co-selection of antibiotic and metal resistance genes (ARG–MRG linkage)	Farkas et al., 2025; Radhouani et al., 2014

Sustainable solutions for AMR mitigation in poultry production

Antimicrobial stewardship and governance. The control of antimicrobial resistance (AMR) in poultry production requires a multidimensional strategy integrating responsible antimicrobial use, enhanced farm management, and innovative biological alternatives. Transitioning toward sustainable poultry systems represents not only a technical challenge but also a governance issue that demands cooperation among public health authorities, veterinarians, producers, policymakers, and international organizations. Global One Health frameworks emphasize coordinated AMR mitigation at the human–animal–environment interface (WHO, 2015; World Organisation for Animal Health, 2022).

The poultry sector (characterized by rapid intensification and historically high levels of antimicrobial consumption) acts both as a key driver of AMR and a critical leverage point for implementing mitigation strategies. This chapter examines sustainable pathways for reducing AMR emergence in poultry, including antimicrobial stewardship, farm-level interventions, and biotechnological innovations ranging from probiotics and phytobiotics to cell-derived immunomodulatory therapies.

Global antimicrobial stewardship (AMS) initiatives form the cornerstone of AMR mitigation in livestock. The WHO Global Action Plan on AMR (WHO, 2015) and the WOAH AMR Strategy (World Organisation for Animal Health, 2022) provide foundational policy frameworks adopted by more than 150 countries. These frameworks advocate for restricting non-therapeutic antimicrobial use, establishing coordinated surveillance networks, and strengthening education and awareness among farmers and veterinarians (Landers et al., 2012; Chantziaras et al., 2014). In the European Union, the 2006 ban on antibiotic growth promoters (AGPs) (sub-therapeutic antibiotics added to feed to improve growth and feed efficiency) marked a turning point. The ban contributed to measurable reductions in antimicrobial usage and strengthened integrated AMR monitoring systems such as EARS-Net and EFSA's zoonotic resistance surveillance programs (European Centre for Disease Prevention and Control, 2023; European Food Safety Authority & European Centre for Disease Prevention and Control, 2024). Although this regulatory success has inspired similar policies globally, enforcement remains inconsistent in many low- and middle-income countries (LMICs), where over-the-counter antibiotic sales and self-medication remain widespread (Grace, 2015; Caudell et al., 2020).

Effective governance depends on coupling regulatory restrictions with incentives and capacity-building measures. Evidence indicates that bans alone may drive antimicrobial use into informal or unregulated markets unless paired with farmer training, strengthened veterinary extension services, and transparent pharmaceutical supply chain oversight (Tang et al., 2017). In parts of Africa and Southeast Asia, voluntary AMS programs supported by NGOs and international development agencies have improved compliance by providing training and veterinary access alongside regulatory guidance (Caudell et al., 2020; Weier et al., 2021). High-income countries such as the United States, Denmark, and the Netherlands have implemented advanced AMS mechanisms that combine real-time antimicrobial use reporting, prescription audits, and benchmarking between farms. These systems have achieved substantial reductions in antimicrobial consumption (Aarestrup, 2015; de Greeff et al., 2023). Denmark's DANMAP program is widely regarded as a model of transparent cross-sectoral monitoring, integrating human, animal, and food-source AMR data to guide national decision-making (Duarte et al., 2024).

Veterinary oversight remains a crucial pillar of stewardship. Mandatory prescription systems and improved access to licensed veterinarians have been shown to reduce antimicrobial misuse, whereas limited veterinary capacity in LMICs fosters reliance on informal drug vendors and untrained intermediaries (Lekagul et al., 2020).

Educational programs (including those operated through the FAO AMR Learning Platform) are essential for disseminating knowledge about responsible antibiotic use, withdrawal periods, and AMR risks along the food chain (Food and Agriculture Organization of the United Nations, 2021). Economic incentives such as certification schemes, premium pricing for antibiotic-free poultry, and public procurement standards can further promote compliance (Van Boeckel et al., 2017). However, these strategies require adequate policy support and consumer awareness to ensure widespread adoption. Finally, international coordination remains central to effective stewardship. The One Health Joint Plan of Action, developed by WHO, WOAH, FAO, and UNEP, harmonizes cross-sectoral AMR surveillance, capacity building, and policy alignment (World Health Organization et al., 2022).

Despite such progress, major gaps persist in global data harmonization – particularly in LMICs, where laboratory capacity and surveillance systems remain underdeveloped (Schar et al., 2021; Singer et al., 2016). Strengthening these capacities is essential for evaluating AMS impacts and guiding adaptive policy responses.

Biosecurity and management interventions. Biosecurity represents the first physical and biological barrier to the spread of antimicrobial-resistant bacteria within and between poultry farms. Effective management interventions are central to reducing infection pressure, minimizing the need for antibiotic treatment, and ultimately curbing AMR selection (Postma et al., 2016; Singer et al., 2016). The principles of biosecurity encompass external measures – preventing pathogen introduction – and internal measures – limiting pathogen dissemination among flocks (Van Limbergen et al., 2018). Farm design and hygiene practices are foundational. Controlled entry systems, disinfection barriers, and separate clothing zones substantially reduce microbial loads in poultry facilities (Garcia-Graells et al., 2020). Regular cleaning and downtime between production cycles allow natural microbial recovery of the environment and help decrease pathogen persistence (Rothrock et al., 2016). Litter management is equally critical: maintaining proper moisture and pH reduces the survival of enteric pathogens such as *Salmonella* and *Campylobacter* (Bolder, 2007). Ventilation, temperature regulation, and stocking density influence both pathogen transmission and stress-mediated immunosuppression (Van Limbergen et al., 2018; Dunlop et al., 2022).

Vaccination strategies have proven highly effective in preventing bacterial infections that otherwise would require antibiotic therapy. For example, live and inactivated vaccines against *Salmonella enterica* and *Pasteurella multocida* significantly reduce infection rates and bacterial shedding, interrupting the farm-to-fork transmission cycle (Broom & Kogut, 2018). The development of multivalent and recombinant vaccines, including those targeting *Eimeria* spp. and *Clostridium perfringens*, further enhances flock immunity while supporting antibiotic reduction programs (Pietruska, 2023). Nevertheless, vaccination alone is insufficient without consistent biosecurity enforcement and post-vaccination monitoring (EFSA & ECDC, 2024).

Nutritional management also plays a decisive role in mitigating infection risks. Feed composition and hygiene influence gut integrity and immune competence, while contaminants such as mycotoxins may impair resistance to bacterial pathogens (Manafi et al., 2018). Balanced diets, adequate amino acid profiles, and supplementation with vitamins and minerals strengthen the mucosal barrier and immune response, indirectly reducing disease incidence (Kogut & Arsenault, 2016). Moreover, replacing antibiotic growth promoters (AGPs) with non-antibiotic feed additives (such as enzymes, organic acids, or phytobiotics) has demonstrated positive effects on growth performance and gut health, thereby minimizing the need for prophylactic antimicrobials (Yaqoob et al., 2022; Hashemi & Davoodi, 2011). Recent advances in precision poultry farming (PPF) have introduced digital technologies to enhance biosecurity compliance and early disease detection (Berckmans, 2017). Automated environmental monitoring systems track parameters such as temperature, humidity, ammonia levels, and bird behavior to identify deviations indicative of disease onset. Machine learning algorithms trained on large datasets can detect subtle changes in vocalization, feed intake, or movement patterns – providing real-time alerts before clinical symptoms emerge (Neethirajan, 2020a, 2020b; Marmelstein et al., 2024; Soster et al., 2025). These tools not only improve animal welfare and productivity but also reduce unnecessary antibiotic administration by promoting targeted interventions.

The microbiome management approach is an emerging frontier in poultry health. The intestinal microbiota acts as a natural defense against colonization by pathogenic bacteria and contributes to immune maturation (Oakley et al., 2014). Manipulating microbial communities through probiotics, prebiotics, and synbiotics can stabilize the gut ecosystem and enhance resilience to infection (Yaqoob et al., 2022). Integrating microbiome-based diagnostics into farm management allows dynamic monitoring of microbial shifts associated with dysbiosis, providing an early indicator of disease risk (Simon et al., 2025).

In developing regions, implementing biosecurity and management interventions faces logistical and economic challenges. Limited infrastructure, poor access to veterinary services, and lack of training often impede consistent adoption (Caudell et al., 2020; Weier et al., 2021). Simple and low-cost measures (such as controlled visitor access, basic sanitation, and separation of age groups) can nonetheless achieve substantial risk reduction (Grace, 2015; Tang et al., 2017). The introduction of biosecurity scoring systems and risk assessment tools provides practical methods to quantify compliance and prioritize critical control points (Postma et al., 2016; Van Limbergen et al., 2018). Overall, biosecurity and management interventions form the operational core of AMR prevention on farms. When integrated with antimicrobial stewardship policies and microbiome-based health strategies, these measures create a synergistic framework that reduces infection pressure, antibiotic reliance, and the emergence of resistant bacteria across poultry production systems. Strategies are complementary and most effective when integrated at the farm level within a One Health framework.

Table 3
Antimicrobial stewardship, governance, and management strategies in poultry production

Approach	Description	Expected Outcome	Supporting Frameworks / Examples
Antimicrobial stewardship programs (ASPs)	Implementation of WHO and OIE guidelines; restriction of critical antimicrobials; veterinary prescription control	Reduction of non-therapeutic antibiotic use, improved resistance monitoring	WHO GLASS (2015), OIE Standards (2021), EU AMR Action Plan
Education and training	Farmer and veterinarian education; awareness campaigns; certification of responsible AMU	Improved compliance, behavioral change	FAO Prudent Use Manual (2019)
Economic and policy incentives	Subsidies for antibiotic-free production; tax reliefs; market labeling	Encouragement of sustainable practices	EU Organic Regulation (2022)
Farm biosecurity	Zoning, hygiene protocols, pest and vector control	Prevention of pathogen introduction and spread	OIE Biosecurity Guidelines (2021)
Vaccination programs	Routine and targeted vaccination; use of autogenous vaccines	Reduced infection pressure, decreased antimicrobial demand	Yohannes & Tekle (2018)
Precision poultry farming (PPF)	Sensors, AI-based monitoring of health and feed efficiency	Early disease detection, optimized AMU	Neethirajan (2020a, 2020b); Soster et al. (2025); Marmelstein et al. (2024)
Microbiome management	Controlled feed additives and competitive exclusion cultures	Enhanced gut health and pathogen resistance	Oakley et al. (2014); Simon et al. (2025)

Note: AMR – antimicrobial resistance; AMU – antimicrobial use; ASPs – antimicrobial stewardship programs; PPF – precision poultry farming; AI – artificial intelligence.

Biological alternatives to antibiotics. The search for sustainable and effective alternatives to antibiotics has accelerated in response to the global challenge of antimicrobial resistance. Poultry production, as one of the most antibiotic-dependent sectors of animal agriculture, has become a primary testing ground for non-antibiotic interventions that maintain productivity and health without promoting resistance (Hashemi & Davoodi, 2011; Yaqoob et al., 2022;). Biological alternatives (including probiotics, prebiotics, synbiotics, phytobiotics, essential oils, bacteriophages, and immunomodulators) represent diverse approaches that converge on the common goal of supporting gut health, reducing pathogen load, and enhancing host immunity (Gadde et al., 2017; Islam et al., 2023).

Probiotics, prebiotics, and synbiotics. Probiotics, defined as live microorganisms conferring a health benefit to the host when administered in adequate amounts, have been extensively evaluated in poultry as alternatives to antibiotic growth promoters (Mountzouris et al., 2010; Yaqoob et al., 2022). Common probiotic strains include *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Bacillus* species, which modulate intestinal microflora by competitive exclusion, production of bacteriocins, and modulation of host immune responses (Abudabos et al., 2019). Supplementation of *Bacillus subtilis* or *Lactobacillus acidophilus* improves growth performance, feed conversion ratio, and gut morphology, while reducing colonization by *Salmonella* and *Clostridium perfringens* (Gadde et al., 2017). Prebiotics (non-digestible feed components such as inulin, fructooligosaccharides (FOS), and mannan-oligosaccharides (MOS)) serve as selective substrates for beneficial microbes, promoting the proliferation of commensals and enhancing the barrier function of the intestinal mucosa (Yang et al., 2009). The combination of probiotics and prebiotics, termed synbiotics, provides synergistic effects by optimizing both microbial composition and nutrient utilization. Studies demonstrate that synbiotic supplementation enhances villus height, shortens recovery time from enteric infections, and improves humoral immune response following vaccination (Abdelqader et al., 2020; Yaqoob et al., 2022). Beyond gut health, probiotic and synbiotic strategies also exhibit immunomodulatory properties by regulating cytokine expression and reducing systemic inflammation (Kogut & Arsenault, 2016). For instance, supplementation with *Lactobacillus plantarum* has been shown to elevate secretory IgA levels and modulate T-cell responses, contributing to improved resistance against *E. coli* and *Campylobacter* infections (Broom & Kogut, 2018).

Phytobiotics and essential oils. Plant-derived compounds (collectively referred to as phytobiotics) are another well-established category of antibiotic alternatives. These substances include herbs, spices, and plant extracts rich in bioactive compounds such as phenolics, terpenoids, and alkaloids (Hashemi & Davoodi, 2011). Phytobiotics exert antimicrobial, antioxidant, and anti-inflammatory effects, improving nutrient digestibility and reducing oxidative stress in poultry (Windisch et al., 2008). Essential oils from oregano (*Origanum vulgare*), thyme (*Thymus vulgaris*), and cinnamon (*Cinnamomum verum*) exhibit strong antibacterial activity against Gram-positive and Gram-negative bacteria through disruption of cell membranes and inhibition of quorum sensing (Brenes & Roura, 2010). For example, supplementation with thymol and carvacrol reduces intestinal *E. coli* and *Clostridium* loads while improving growth rate and feed efficiency (Hashemi & Davoodi, 2011; Yaqoob et al., 2022). Phytobiotic mixtures have also been reported to enhance immune competence by stimulating macrophage activity and promoting antioxidant enzyme expression, providing a multi-targeted approach to health management (Gadde et al., 2017). Although their variability in chemical composition and potential instability under feed processing conditions pose formulation challenges, standardized extracts and encapsulated forms have significantly improved their reliability in commercial applications (Windisch et al., 2008; Yang et al., 2009).

Bacteriophages and endolysins. The rise of multidrug-resistant bacteria has renewed interest in bacteriophages (viruses that specifically infect and lyse bacteria) as precision antimicrobials (Islam et al., 2023). Phage therapy in poultry targets major pathogens such as *Salmonella enterica*, *E. coli*, and *Campylobacter jejuni*, showing strong efficacy in both experimental and field conditions (Clavijo et al., 2019). Unlike broad-spectrum antibiotics, phages preserve beneficial gut microbiota and can evolve alongside bacterial hosts, reducing the risk of resistance emergence (Loc-Carrillo & Abedon, 2011). Systematic reviews indicate that phage administration in feed or water can reduce bacterial loads by up to 2–3 log units, lower mortality, and improve weight gain (Islam et al., 2023). However, environmental factors such as pH, temperature, and the presence of inhibitors can affect phage viability, necessitating optimized formulations and delivery systems. Phage-derived enzymes known as endolysins represent another innovative approach: these lytic enzymes degrade bacterial cell walls and are effective even against biofilm-forming and dormant bacteria (Fischetti, 2018). Recombinant endolysins and engineered phages with broadened host ranges are under investigation as next-generation antimicrobials for poultry and food processing environments (Cisek et al., 2017).

Immunomodulators and postbiotics. Recent years have witnessed increasing attention to immunomodulators and postbiotics — nonviable microbial products or metabolic by-products that confer health benefits (Tsilingiri & Rescigno, 2013). Postbiotics such as short-chain fatty acids (SCFAs), bacteriocins, and cell wall fragments have demonstrated the capacity to modulate immune signaling, enhance intestinal integrity, and suppress pathogen colonization (Saeed et al., 2023). Among immunomodulators, β-glucans, cytokine inducers, and derivatives of mesenchymal stem cells (MSCs) secretome have shown potential in promoting immune resilience and anti-inflammatory balance (Wang et al., 2022). For example, β-glucans derived from yeast cell walls stimulate macrophage and heterophil activity, improving protection against bacterial challenges (Vetvicka et al., 2019). MSC-derived products (particularly secretome rich in growth factors, defensins, and cytokines) will be explored in more depth in this section as a frontier of biological innovation for poultry AMR control (Svoradova et al., 2021). Collectively, these biological alternatives contribute to a multifactorial strategy for AMR mitigation, combining pathogen suppression, immune enhancement, and microbiome stabilization. Their integration into poultry management systems supports the global shift toward sustainable, antibiotic-free production models that preserve both productivity and public health.

The potential of mesenchymal stem cell–derived secretome. The secretome of mesenchymal stem cells (MSCs) (also referred to as stromal cells) comprises a complex mixture of soluble proteins, lipids, nucleic acids, and extracellular vesicles (EVs) released into the extracellular environment. In recent years, MSC-derived secretome has emerged as a potent cell-free therapeutic modality, capable of recapitulating many of the paracrine effects of whole-cell MSC therapies while avoiding several safety and logistical limitations associated with live-cell transplantation (Panda et al., 2021; Kou et al., 2022).

The MSC secretome contains a wide range of bioactive components, including cytokines, chemokines, growth factors (e.g., VEGF, TGF-β, HGF), antimicrobial peptides, and EV-associated microRNAs. Together, these components exert immunomodulatory, anti-inflammatory, pro-regenerative, and, in certain contexts, antimicrobial effects (Sandonà et al., 2021; Kou et al., 2022). These multimodal activities make MSC secretome particularly attractive for poultry health management, where modulation of mucosal immunity and reinforcement of gut barrier resilience are central to reducing infection pressure and antimicrobial use.

Composition and bioactivity. Proteomic and transcriptomic analyses of MSC-conditioned media consistently reveal a diverse repertoire of bioactive molecules involved in immune regulation, tissue protection, and regenerative processes (Panda et al., 2021; Chouaib et al., 2023). Among these components, extracellular vesicles (particularly exosomes) play a central role, transporting proteins, lipids, and regulatory RNAs that modulate recipient cell behavior, suppress excessive inflammatory signaling, and promote epithelial barrier integrity (Kou et al., 2022). Importantly, in infectious disease contexts, several studies indicate that MSC secretomes contain antimicrobial peptides and immune-enhancing factors capable of stimulating phagocyte activity or inducing antimicrobial pathways in epithelial cells. This suggests that MSC-derived secretome may reduce pathogen burden through both direct antimicrobial mechanisms and indirect immune modulation (Svoradova et al., 2021; Hussein et al., 2022). However, the quantitative and qualitative composition of the secretome is strongly influenced by multiple variables, including the MSC source (e.g., bone marrow, adipose tissue, Wharton's jelly, or avian peripheral blood), culture conditions, passage number, and preconditioning protocols. These factors substantially affect biological activity and remain a key challenge for standardization and translational application (Sandonà et al., 2021; Chouaib et al., 2023).

Mechanisms of action relevant to poultry. The mechanisms by which MSC-derived secretome may mitigate infectious challenges in poultry can be grouped into three interconnected domains: (i) immune priming and immunoregulation, (ii) enhancement of mucosal barrier function, and (iii) microbiome modulation.

First, secretome components modulate innate and adaptive immune responses by suppressing excessive or pathological inflammation while preserving or enhancing the pathogen-clearing functions of macrophages and heterophils (Panda et al., 2021; Kou et al., 2022). This immunological balancing effect may reduce tissue damage and pathogen shedding, thereby decreasing the need for antibiotic intervention.

Second, trophic factors and extracellular vesicle (EV) cargo promote epithelial restitution and reinforce tight-junction integrity, which reduces translocation of enteric pathogens and lowers the risk of systemic infection (Sandonà et al., 2021).

Third, by shaping local immune microenvironments and potentially exerting direct effects on microbial communities, secretome administration may support the development of a resilient gut microbiota that is less permissive to colonization by zoonotic pathogens (Svoradova et al., 2021). Collectively, these mechanisms target the underlying drivers of infection susceptibility in intensive poultry systems rather than merely suppressing pathogens.

Experimental evidence in avian and mammalian models. Preclinical evidence supporting the efficacy of MSC-derived secretome is currently more extensive in mammalian models, where secretome preparations and MSC-derived EVs have demonstrated therapeutic benefits in models of inflammatory lung injury, intestinal damage, sepsis, and wound healing – outcomes directly relevant to infection control and recovery (Panda et al., 2021; Kou et al., 2022). Studies using human MSC secretome or EVs consistently report anti-inflammatory effects, reduced bacterial translocation, and enhanced tissue repair in respiratory and gastrointestinal disease models (Panda et al., 2021; Kou et al., 2022). In avian systems, early reports describe the successful isolation and characterization of chicken MSCs and their conditioned media with demonstrable biological activity. Avian MSC-derived secretomes have been shown to contain factors with antimicrobial and regenerative properties and have been proposed as candidate biologics for diseases such as infectious bronchitis and intestinal inflammation (Svoradova et al., 2021; Harman et al., 2022). In addition, a study using human Wharton's jelly MSC secretome demonstrated potential efficacy against coronaviruses relevant to poultry disease models, suggesting a degree of cross-species translational potential for certain secretome preparations (Hussein et al., 2022). Taken together, these findings support biological plausibility but also highlight that robust, controlled trials in commercial poultry species remain limited, underscoring the need for targeted *in vivo* validation.

Delivery routes, dosing, and formulation. The practical application of MSC-derived secretome in poultry production requires delivery modalities compatible with large-scale farming systems. Potential routes include in-water administration, feed-based delivery, *in ovo* injection, and aerosolized formulations for respiratory protection.

Each delivery strategy presents specific technical challenges.

Oral administration must ensure stability of EVs and bioactive molecules under gastric conditions, *in ovo* delivery requires strict developmental safety, and aerosolized formulations must preserve bioactivity during nebulization and environmental exposure (Sandonà et al., 2021; Chouaib et al., 2023). At present, dose-finding studies and pharmacokinetic/pharmacodynamic data in avian species are scarce, limiting translational readiness. Therefore, successful implementation will require systematic optimization of dosage, frequency, formulation, and delivery method to balance efficacy, safety, and economic feasibility in commercial poultry operations.

Safety, standardization, and manufacturing challenges. A major advantage of secretome-based strategies is the avoidance of risks associated with live-cell therapies, including tumorigenicity, ectopic engraftment, and long-term immunogenicity. Nevertheless, cell-free products present distinct challenges related to safety, quality control, and regulatory approval. Batch-to-batch variability, donor heterogeneity, and sensitivity of secretome composition to culture conditions necessitate rigorous standardization procedures (Chouaib et al., 2023). Recent reviews emphasize the importance of well-defined production protocols, including cell source selection, conditioning duration, serum-free culture systems, and standardized EV purification methods. Equally critical is the development of robust potency assays that link biochemical or molecular signatures of the secretome to predictable biological effects (Sandonà et al., 2021; Chouaib et al., 2023). Downstream manufacturing considerations (such as sterility assurance, scalable concentration processes, and stabilization via lyophilization or encapsulation) remain active areas of research but pose substantial challenges for cost-effective commercialization (Harman et al., 2022). Regulatory pathways for MSC-derived secretome products are still evolving. Depending on jurisdiction, such products may be classified as biologics, advanced therapy medicinal products, or veterinary biologics, each category imposing distinct safety and efficacy requirements (Sandonà et al., 2021). In agricultural applications, additional regulatory scrutiny will focus on residue safety, food chain integrity, and environmental fate, all of which must be addressed prior to market authorization.

Future perspectives and research priorities. The MSC-derived secretome represents a promising and mechanistically diverse biological toolkit for reducing infection susceptibility and the consequent reliance on antibiotics in poultry production. To advance its translational application, several key research priorities must be addressed. These include: (i) rigorous characterization of avian-derived and cross-species MSC secretomes, with particular emphasis on identifying conserved bioactive components; (ii) controlled dose–response and safety studies in chickens, including broilers and layers, with evaluation of both *in ovo* and oral delivery routes; (iii) development of standardized manufacturing workflows and validated potency assays to ensure reproducibility and batch-to-batch consistency (Sandonà et al., 2021; Chouaib et al., 2023); and (iv) comprehensive assessment of ecological and food-safety implications, including potential effects on host microbiota and the theoretical transfer of extracellular RNAs or bioactive peptides into animal-derived food products.

Progress in these areas will require multidisciplinary collaboration among stem cell biologists, veterinary scientists, poultry nutritionists, microbiologists, and regulatory authorities in order to bridge the gap between experimental promise and field-scale applicability.

In conclusion, MSC-derived secretome constitutes a frontier biological alternative that aligns closely with One Health objectives. By modulating host immunity, reinforcing mucosal defenses, and promoting tissue homeostasis, secretome-based strategies have the potential to reduce disease incidence and antimicrobial demand in poultry systems. However, the realization of this potential depends on evidence-driven development, including standardized production, rigorous safety evaluation, and the design of pragmatic delivery solutions compatible with commercial poultry production.

Environmental and One Health surveillance

Monitoring antibiotic residues and ARGs in the environment. The persistence and spread of antimicrobial resistance (AMR) genes in the environment represent one of the most complex challenges within the One Health framework. Poultry production systems, through manure, litter, and effluent discharge, act as important reservoirs and dissemination routes for antibiotic residues and resistant microorganisms into soil, surface water, and air (Economou & Gousia, 2015). Because these environmental interfaces connect agricultural, wildlife, and human domains, their monitoring is essential for understanding resistance ecology and for implementing sustainable mitigation strategies (Founou et al., 2021).

Recent policy frameworks from the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the European Commission emphasize integrated surveillance as the cornerstone of global AMR control, aligning environmental monitoring with human and animal health programs (Aidara-Kane et al., 2013; European Commission, 2017; World Health Organization, 2017). Global surveillance data indicate alarming trends in AMR in food animals, particularly in low- and middle-income countries (Van Boeckel et al., 2019).

Environmental monitoring of AMR in poultry systems focuses on two complementary targets: detection of antibiotic residues and identification of antibiotic resistance genes (ARGs) in environmental matrices such as soil, litter, and wastewater. Advances in analytical methodologies (including quantitative polymerase chain reaction (qPCR), shotgun metagenomics, and resistome profiling) enable high-resolution mapping of resistance determinants and their bacterial hosts (Food and Agriculture Organization of the United Nations, 2024). These molecular tools are essential for quantifying both specific ARGs (e.g., bla^{CTX-M}, mcr, tet) and overall resistome diversity across production stages (Mughini-Gras et al., 2019). Globally, surveillance studies demonstrate that poultry farms function as significant point sources of ARG dissemination into surrounding ecosystems (Economou & Gousia, 2015; Van Boeckel et al., 2017). Runoff and leaching from poultry litter applied as fertilizer contribute to the persistence of β-lactam, sulfonamide, and tetracycline resistance genes in agricultural soils and groundwater (Andreoletti et al., 2011). Metagenomic analyses further reveal that microbial communities in poultry litter and adjacent water bodies may retain ARGs even after prolonged antibiotic withdrawal, indicating environmental stabilization of resistance traits (Founou et al., 2021).

The EFSA–EMA Joint Interagency Report highlighted a strong correlation between antimicrobial consumption in poultry and environmental resistance burdens, emphasizing the need for synchronized monitoring across farm and environmental compartments (European Food Safety Authority & European Medicines Agency, 2021). Regional case studies from China corroborate these findings, demonstrating that wastewater and effluent from intensive poultry operations harbor multidrug-resistant *Escherichia coli* strains reflecting resistance profiles observed in clinical isolates (Yassin et al., 2017). A rapid systematic review further confirmed that antimicrobial administration to food animals poses measurable risks to human health (Scott et al., 2018).

Table 4
Biological alternatives to antibiotics in poultry health

Category	Mechanism of Action	Target/Effect	Evidence/Examples
Probiotics and prebiotics	Competitive exclusion, SCFA production, immune modulation	Gut microbiota balance, pathogen suppression	Yaqoob et al. (2022)
Phytobiotics and essential oils	Antimicrobial, antioxidant, anti-inflammatory properties	Growth promotion, reduced oxidative stress	Hashemi & Davoodi (2011)
Bacteriophages and endolysins	Specific bacterial lysis; biofilm disruption	Control of *Salmonella*, *E. coli*, *Campylobacter*	Islam et al. (2023)
Immunomodulators and postbiotics	Cytokine induction, β-glucan signaling, gut barrier enhancement	Innate immune activation, mucosal protection	Tsilingiri & Rescigno (2013); Saeed et al. (2023); Vetvicka et al. (2019)
MSCs-derived secretome	Cytokines, growth factors, antimicrobial peptides	Immune priming, anti-inflammatory activity, microbiota stabilization	Svoradova et al. (2021); Wang et al. (2022)
Future applications	Nanodelivery, combined therapies with probiotics or vaccines	Integrated AMR mitigation strategy	Wang et al. (2022); Costa et al. (2023)

Note: SCFA – short-chain fatty acids; AMR – antimicrobial resistance; MSCs – mesenchymal stem cells; the examples listed represent the most commonly studied biological alternatives to antibiotics in poultry production systems and are not intended to be exhaustive.

The FAO's most recent technical guidance underscores the value of resistome-based indicators for environmental surveillance, recommending integration of metagenomic datasets with metadata on antimicrobial usage and farming intensity to support predictive modeling and regulatory decision-making (Food and Agriculture Organization of the United Nations, 2024). Recent advances in analytical and control strategies have been comprehensively summarized by Abreu et al. (2023), highlighting the growing role of molecular surveillance tools. Overall, environmental surveillance serves a critical early-warning function, revealing the extent to which poultry production contributes to the wider circulation of resistance determinants across agricultural landscapes.

Integrated One Health surveillance systems. The One Health approach recognizes that effective AMR control requires simultaneous and coordinated monitoring of human, animal, and environmental compartments within a unified surveillance framework (Aidara-Kane et al., 2013; World Health Organization, 2017). Integrated surveillance systems aim to harmonize data streams linking farm-level antimicrobial usage, clinical resistance patterns, and environmental contamination profiles. Such cross-sectoral integration improves the capacity to trace resistance emergence, identify epidemiological hotspots, and guide targeted interventions (European Commission, 2017).

In many low-resource settings, particularly within African poultry production systems, the absence of coordinated monitoring remains a major barrier to effective One Health surveillance (Selaledi et al., 2020). The WHO's Integrated Surveillance Guidelines provide a conceptual foundation for overcoming these challenges by promoting standardized sampling strategies, harmonized molecular detection methods, and interoperable data reporting platforms (World Health Organization, 2017). In parallel, the European One Health Action Plan emphasizes digital infrastructure to enable joint data management between veterinary and public health laboratories, facilitating real-time AMR trend analysis (European Commission, 2017).

The most recent EFSA–ECDC One Health report demonstrates the effectiveness of this integrated model within the European Union, where combined analysis of zoonotic and indicator bacteria has significantly strengthened risk assessment and policy translation (European Food Safety Authority & European Centre for Disease Prevention and Control, 2025).

Beyond Europe, initiatives led by FAO and the Pan American Health Organization stress the urgency of implementing integrated surveillance frameworks in low- and middle-income countries, where data gaps continue to hinder evidence-based AMR management (da Silva et al., 2020). Strengthening laboratory capacity, improving data interoperability, and fostering intersectoral collaboration remain central priorities. At the operational level, behavioral and governance dimensions play a critical role. Evidence indicates that improved communication between veterinarians and livestock producers enhances antimicrobial stewardship practices and data reliability, reinforcing the feedback loop necessary for surveillance-informed policymaking (Gozdzielewska et al., 2020). Modeling studies further identify the prevention of suboptimal antimicrobial use as a key leverage point for reducing selection pressure in food-animal systems (Lhermie et al., 2017). Importantly, even antibiotic-free production models require continuous environmental surveillance to ensure long-term sustainability (Cervantes, 2015).

In summary, One Health surveillance transforms AMR monitoring from a fragmented technical exercise into an integrated governance instrument. By linking molecular, ecological, behavioral, and socio-economic data, it enables proactive risk management and policy coherence across the entire food and health continuum.

Conclusions

Antimicrobial resistance (AMR) in poultry production represents a complex, multi-layered phenomenon driven by the convergence of molecular evolution, intensive farming practices, and environmental connectivity. The molecular landscape of AMR is shaped by the interplay of selective pressures, mobile genetic elements, and microbial community dynamics. Plasmids, integrons, and transposons enable the horizontal exchange of resistance genes among commensal and pathogenic bacteria, while co-selection with metal and biocide resistance determinants ensures their long-term persistence. These processes underscore that AMR is not an isolated microbiological issue but a systemic genetic network that transcends species and production boundaries.

From an epidemiological perspective, poultry production systems serve as key amplifiers and disseminators of resistance within the global One Health framework. Comparative genomic analyses reveal striking overlaps between poultry-derived and human clinical isolates of *Escherichia coli*, *Salmonella enterica*, and *Campylobacter jejuni*, confirming that the poultry sector is both a source and a conduit of resistance determinants. Wild and migratory birds further expand this ecological network, bridging agricultural and natural environments and facilitating transboundary spread of resistance genes along migratory routes. These findings highlight the necessity of coordinated surveillance that integrates animal, human, and environmental data streams. At the production level, intensive poultry farming remains one of the strongest selective environments for AMR emergence. The prophylactic and growth-promoting use of antimicrobials, coupled with suboptimal biosecurity and high animal densities, fosters both vertical and horizontal transmission of resistant strains. Co-exposure to heavy metals, disinfectants, and coccidiostats compounds this pressure by maintaining resistance even after antimicrobial use is reduced. Addressing these drivers requires the implementation of stewardship programs, improved farm management, and regulatory harmoniza-tion (particularly in regions with rapidly expanding poultry industries). Mitigation of AMR in poultry demands a paradigm shift from reactive control to preventive, system-level redesign. Sustainable solutions hinge on responsible antimicrobial use, robust biosecurity, vaccination programs, and precision livestock farming technologies that collectively reduce infection pressure.

Complementary biological strategies (such as probiotics, prebiotics, phytobiotics, bacteriophages, and enzyme-based therapies) provide promising non-antibiotic alternatives that enhance gut health and microbial resilience. Among emerging frontiers, the mesenchymal stem cell–derived secretome represents an innovative approach with potent immunomodulatory and antimicrobial properties, meriting further translational research in avian systems. Environmental surveillance closes the loop between farm management and ecosystem health. Poultry waste streams, including manure and wastewater, act as reservoirs of antibiotics and resistance genes that propagate into soil and water systems. The integration of metagenomics and quantitative PCR tools into monitoring frameworks enables early detection of resistance hotspots and supports risk assessment across the food–environment interface. Incorporating these tools into coordinated One Health surveillance transforms AMR monitoring from fragmented observation into proactive prevention.

Overall, combating AMR in poultry requires an integrated One Health approach that unites molecular insight, epidemiological vigilance, sustainable production practices, and environmental stewardship. The alignment of agricultural, veterinary, and public health governance (guided by international frameworks from WHO, WOAH, and FAO) will be decisive in mitigating the global spread of resistance. Such integration not only protects animal and human health but also reinforces the ecological and economic sustainability of food systems in the post-antibiotic era.

V.M. led the conceptualization of the study, performed the comprehensive literature review, coordinated the overall research framework, and took primary responsibility for manuscript preparation. I.I. and H.F. contributed to study conceptualization, supervised the research design, and supported coordination of manuscript development. I.I. contributed to the analysis of antimicrobial resistance mechanisms, while H.F. and O.F. focused on identifying and evaluating biological alternatives to antibiotics. T.F., O.A., and I.U. drafted the sections addressing poultry production systems, antimicrobial resistance challenges, and potential mitigation strategies. R.B. contributed to the analysis of sustainable development policies and organizational approaches related to antimicrobial resistance in poultry farming. O.F. provided critical review, editorial input, and methodological support to enhance the scientific quality of the manuscript. All authors contributed to the revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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