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Antibiotic Pollution and Environmental Antimicrobial Resistance: Resistomes, Gene Transfer and One Health Implications

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ABSTRACT

Antimicrobial resistance (AMR) is conventionally framed as a clinical problem, yet its evolutionary origins and many of its transmission routes lie in the environment. Antibiotics are released into soils, rivers, sediments, and coastal waters through human and veterinary excretion, inadequately treated municipal and hospital wastewater, manure application, aquaculture, and discharges from drug manufacturing. These emissions, together with co-pollutants such as metals and biocides, exert selective pressure on microbial communities and enrich antibiotic resistance genes (ARGs) in environmental reservoirs collectively termed the environmental resistome. Horizontal gene transfer (HGT), mediated by plasmids, integrons, transposons, integrative and conjugative elements, and bacteriophages, connects these reservoirs with human and animal pathogens. This review synthesizes current evidence on the sources and fate of antibiotic pollution, the composition and origins of environmental resistomes, the mechanisms and environmental modulators of gene transfer, and the implications for human, animal, and ecosystem health within a One Health framework. It also evaluates risk assessment concepts and mitigation options, including manufacturing effluent controls, advanced wastewater treatment, stewardship in agriculture, sanitation, and integrated surveillance. Pharmacologists are well placed to contribute to this agenda by linking pharmacokinetics, excretion, environmental concentration thresholds, and stewardship. Key knowledge gaps remain in quantifying transmission risk, defining enforceable environmental concentration limits, and standardizing surveillance.

Keywords: antimicrobial resistance; antibiotic pollution; resistome; horizontal gene transfer; mobile genetic elements; wastewater; One Health

1. Introduction

The discovery and mass production of antibiotics transformed medicine and agriculture during the twentieth century. Surgery, cancer chemotherapy, organ transplantation, neonatal care, and intensive livestock production all depend on effective antibacterial agents. This dependence now faces a sustained threat. A systematic analysis estimated that bacterial AMR was directly responsible for roughly 1.27 million deaths and was associated with nearly 4.95 million deaths worldwide in 2019, with the highest burden in sub-Saharan Africa and South Asia (Murray et al., 2022). Because these regions also bear gaps in sanitation, wastewater treatment, and regulatory capacity, the clinical and environmental dimensions of resistance cannot be cleanly separated.

Resistance itself is not a modern invention. Phylogenetic and functional analyses of ancient permafrost DNA have shown that genes encoding resistance to β-lactams, tetracyclines, and glycopeptides were present in bacterial communities tens of thousands of years before the antibiotic era (D'Costa et al., 2011). Many ARGs originate in environmental bacteria, including antibiotic producers and their neighbors, where they serve roles in self-protection, signaling, metabolism, and competition (Allen et al., 2010). Wright (2007) introduced the term "resistome" for the collection of all resistance determinants in a given habitat, including those in pathogens, commensals, and non-pathogenic environmental organisms, as well as cryptic genes that may become functional resistance determinants after mobilization or mutation. Functional metagenomic work later demonstrated that soil bacteria and clinical pathogens can share identical resistance genes, indicating that gene flow between these compartments has occurred in the recent past (Forsberg et al., 2012).

What has changed in recent decades is the scale of anthropogenic input. Human activity introduces antibiotic residues, resistant bacteria, and mobile genetic elements (MGEs) into environments that previously received them at low or negligible rates. The result is a reshaping of environmental resistomes

toward higher ARG abundance and a greater proportion of mobile determinants. Berendonk et al. (2015) argued that the environment should be treated as an integral part of the AMR problem rather than a passive backdrop, because it supplies the raw genetic diversity from which new resistance mechanisms emerge, provides conditions favoring their selection and exchange, and serves as a route of exposure for people and animals. Larsson and Flach (2022) similarly concluded that the environment contributes to the evolution of resistance, to transmission, and to the dissemination of resistant organisms across ecosystems.

This framing aligns with the One Health perspective, which recognizes the interdependence of human, animal, and ecosystem health. Antimicrobial resistance has been called a quintessential One Health problem because resistant bacteria and genes move among people, livestock, companion animals, wildlife, food, water, and soil (Robinson et al., 2016; Hernando-Amado et al., 2019). Intergovernmental institutions have adopted this view in policy, and the One Health Joint Plan of Action (Food and Agriculture Organization et al., 2022) and the United Nations Environment Programme assessment on environmental action against AMR (United Nations Environment Programme [UNEP], 2023) both call for environmental dimensions to be integrated into national action plans.

From a pharmacological standpoint, the topic is particularly relevant. Pharmacologists characterize absorption, metabolism, and excretion; many antibiotics are excreted largely unchanged or as active metabolites, and these excreted fractions are precisely what enter wastewater and manure. Concepts such as minimum inhibitory concentration (MIC), the mutant selection window, and sub-MIC selection, which are central to clinical dosing, have direct counterparts in environmental risk assessment. The present review therefore proceeds in four steps. First, it examines sources, fate, and selective effects of antibiotic pollution. Second, it describes environmental resistomes and the mechanisms of gene transfer that mobilize them. Third, it considers One Health implications and risk assessment. Finally, it discusses mitigation strategies, knowledge gaps, and conclusions.

2. Antibiotic Pollution: Sources, Environmental Fate and Selective Pressure

Sources and pathways of release. Antibiotic residues reach the environment along the entire life cycle of a drug: manufacture, consumption, excretion, and disposal. Human consumption is the dominant diffuse source in most urban catchments. After oral or parenteral administration, a substantial proportion of many agents, including β-lactams, fluoroquinolones, sulfonamides, macrolides, and tetracyclines, is eliminated in urine and feces as the parent compound or active metabolites. These enter sewage, where they mix with resistant gut bacteria, MGEs, disinfectants, and metals. Hospital effluents are concentrated sources of clinically important agents and multidrug-resistant organisms, although in many settings they represent a minority of the total antibiotic load compared with community sewage.

Livestock and aquaculture constitute a second major pathway. Global estimates indicate that a large fraction of medically important antimicrobials is used in food animals, and projections suggest continued increases in consumption, especially in rapidly industrializing economies (Van Boeckel et al., 2015). Because animals often excrete a large share of administered doses, manure and slurry are enriched in residues and resistant bacteria. When manure is applied to agricultural land as fertilizer, it delivers antibiotics, ARGs, and MGEs directly to soil. Zhu et al. (2013) documented diverse and exceptionally abundant ARGs in swine farms in China, with manure and associated soils carrying far higher loads than control soils, and found strong associations with MGEs. Reviews of agricultural practice have likewise emphasized that irrigation with reclaimed water, biosolid application, and manure fertilization are routes by which resistance determinants enter food-production systems (Thanner et al., 2016).

A third pathway, long underappreciated, is pollution from pharmaceutical manufacturing. Effluents from bulk drug production can contain antibiotics at concentrations that approach or exceed therapeutic plasma levels. Larsson et al. (2007) measured extremely high concentrations of multiple pharmaceuticals, including fluoroquinolones, in effluent from a treatment plant receiving wastewater from drug manufacturers near Hyderabad, India. Subsequent investigations of surface water, groundwater, and drinking water near production sites reported contamination by pharmaceutical ingredients at levels orders of magnitude above typical municipal exposures (Fick et al., 2009). Reviews of the topic concluded that manufacturing discharges are a neglected but regulatable source, since the responsible facilities are point sources that can in principle be controlled (Larsson, 2014). River sediments heavily contaminated by such effluent harbored extraordinarily high levels of resistance genes and gene-transfer elements such as integrases and transposases (Kristiansson et al., 2011). Epidemiological and environmental work in the same industrial region of South India linked pollution from bulk drug manufacturing with the dissemination of extended-spectrum β-lactamase- and carbapenemase-producing bacteria (Lübbert et al., 2017). These observations are especially instructive for countries that host large generic-drug industries, because they illustrate how production geography can create resistance hotspots that affect local communities.

Other pathways include leakage from landfills and septic systems, runoff from fields and feedlots, direct application of antibiotics to crops and ornamental plants, medicated feed in aquaculture, and the improper disposal of unused medicines. Large-scale monitoring has confirmed the ubiquity of the phenomenon. An early national reconnaissance of U.S. streams detected pharmaceuticals, including antibiotics, hormones, and other organic wastewater contaminants, in a large proportion of sampled sites (Kolpin et al., 2002). In China, basin-scale emission modeling and monitoring estimated large annual antibiotic releases and identified heavily affected river systems (Zhang et al., 2015).

Environmental fate and persistence. Once released, antibiotics are subject to sorption, photolysis, hydrolysis, and biodegradation. Their persistence depends on physicochemical properties and environmental conditions. Tetracyclines and fluoroquinolones bind strongly to particles and organic matter, accumulating in sludge, sediments, and soils; this sorption reduces aqueous concentrations but creates long-term reservoirs and complicates estimates of bioavailable exposure. Sulfonamides and some macrolides are more mobile and may leach into groundwater. β-Lactams are chemically labile and often

degrade quickly, though degradation products and the presence of β-lactamases may modulate their ecological effects. Because of this heterogeneity, simple correlations between measured total antibiotic concentration and resistance outcomes are often weak, and the bioavailable fraction is what matters for selection.

Conventional municipal wastewater treatment plants (WWTPs) were not designed to remove antibiotics, ARGs, or resistant bacteria. Treatment reduces total bacterial load and removes a proportion of antibiotic residues, but removal of individual compounds is variable, and ARGs and MGEs persist in effluent and sludge. WWTPs have been described as hotspots where high bacterial densities, nutrients, sub-inhibitory residues, and mixing of diverse communities favor gene exchange, and they release resistant organisms into receiving waters (Rizzo et al., 2013; Karkman et al., 2018). At the same time, some analyses indicate that treatment markedly reduces the relative abundance of many ARGs, so the net effect depends on plant configuration, retention times, and the metric considered. European-scale work showed that ARG patterns in treatment plant influents and effluents mirror regional clinical resistance prevalence, supporting wastewater's usefulness as an epidemiological sentinel (Pärnänen et al., 2019).

Selection at low concentrations. A central pharmacological question is what concentrations of antibiotics are sufficient to select for resistance. Traditional thinking emphasized concentrations above the MIC of susceptible strains, but experimental work has overturned this assumption. Gullberg et al. (2011) showed that resistant strains of *Escherichia coli* and *Salmonella* could be selected at concentrations hundreds of times below the MIC of susceptible strains, extending down to a small fraction of the MIC for some drugs. Andersson and Hughes (2014) reviewed the mechanisms by which sub-MIC antibiotics enrich pre-existing resistant mutants, increase mutation and recombination rates, and promote gene transfer and biofilm formation. These findings mean that even the low, chronic concentrations typical of polluted rivers, sewage, and manured soils can shift community composition.

Building on such data, Bengtsson-Palme and Larsson (2016) derived predicted no-effect concentrations for resistance selection for 111 antibiotics, combining MIC distribution data and extrapolation. They proposed that these thresholds could inform environmental quality criteria and discharge limits. In many cases the predicted thresholds are lower than concentrations required to harm aquatic organisms in traditional ecotoxicological tests, which implies that resistance selection may be the more sensitive endpoint. Nevertheless, laboratory selection in monocultures can overstate effects in complex communities. Klümper et al. (2019) found that selection for resistance was reduced when resistant strains were embedded in natural microbial communities, due to competition and altered fitness costs. Environmental selection thus depends on community context, and threshold values should be applied as precautionary guidance rather than precise predictions.

Co-selection by non-antibiotic agents. Antibiotics are rarely the only stressor. Metals such as copper and zinc, widely used as feed supplements, and biocides such as quaternary ammonium compounds and triclosan can co-select for resistance when resistance genes are physically linked on the same MGE (co-resistance) or when a single mechanism, for example an efflux pump, confers tolerance to multiple agents (cross-resistance). A genome-scale analysis of bacterial genomes and plasmids revealed significant co-occurrence of genes conferring resistance to antibiotics, biocides, and metals, supporting a realistic potential for co-selection (Pal et al., 2015). Consequently, non-antibiotic pollution from mining, industry, and agriculture may sustain resistance even where antibiotic residues are low. Even non-antibiotic pharmaceuticals, as discussed below, can alter transfer processes. This multi-stressor reality complicates both monitoring and regulation and argues for mixture-oriented risk assessments.

3. Environmental Resistomes and the Mechanisms of Gene Transfer

Composition and drivers of environmental resistomes. The environmental resistome comprises genes encoding antibiotic inactivation enzymes, target modification or protection proteins, efflux pumps, and permeability changes (Blair et al., 2015). Metagenomic surveys show that resistomes vary considerably across habitats. Pristine soils and sediments harbor diverse ARGs, many of which are chromosomal, low in abundance, and divergent from clinically known variants. In contrast, wastewater, livestock manure, and contaminated sediments contain high densities of ARGs that closely match those in pathogens and frequently reside on MGEs. A network analysis of metagenomes from diverse habitats found that ARGs frequently co-occur with MGEs and that human-impacted environments share ARG profiles distinct from natural ones (Li et al., 2015). Studies of low-income human habitats have documented interconnected microbiomes and resistomes among soil, feces, and household environments, with resistance genes shared across them (Pehrsson et al., 2016).

Global sewage metagenomics has emerged as a powerful tool for characterizing resistomes at a population scale. Analysis of sewage from 74 cities worldwide showed that resistance gene composition clustered by geography and correlated with socioeconomic, health, and environmental factors, with higher ARG abundance in regions with poorer sanitation and lower health expenditure (Hendriksen et al., 2019). A later study of sewage from 101 countries described a global landscape in which clinically important resistance determinants were widespread, and in which regional and income-related patterns could be discerned (Munk et al., 2022). Such work supports the use of wastewater surveillance for tracking resistance without relying solely on clinical isolates, which are unevenly collected globally.

Environmental factors beyond antibiotic exposure also shape resistomes. Bengtsson-Palme et al. (2018) reviewed how temperature, nutrient availability, pH, metal content, microbial community structure, and anthropogenic inputs influence resistance development and spread. Hiltunen et al. (2017) emphasized an eco-evolutionary perspective in which resistance in wild populations is shaped by interspecies interactions, community diversity, and spatial structure. Informal urban settlements with inadequate sanitation, where human and animal waste mingle with drinking and washing water, have been highlighted as particularly intense settings for environmental transmission of resistant bacteria (Nadimpalli et al., 2020).

Origins of clinically relevant genes. Several important resistance determinants in pathogens have traceable environmental ancestors. The plasmid-mediated quinolone resistance gene *qnrA* was shown to derive from chromosomal genes in the aquatic bacterium *Shewanella algae* (Poirel et al., 2005). Chromosomal β-lactamases in environmental genera are the likely progenitors of widespread enzymes such as CTX-M extended-spectrum β-lactamases. Tracing such origins is difficult, but computational frameworks that compare genomic context and sequence similarity across large databases can estimate recent origins of mobile ARGs and identify environmental taxa that act as likely sources (Ebmeyer et al., 2021). The general lesson is that the movement of a gene from an environmental host into a mobile element, and then into a pathogen, is a rare but consequential event; the probability of such events scales with exposure of the environmental gene pool to selective and mobilizing conditions, and with the density and diversity of bacteria in contact. Gaze et al. (2013) argued that human activity both increases the opportunity for mobilization and selects for the resulting variants, accelerating what would otherwise be slow evolutionary processes.

Mobile genetic elements. Horizontal gene transfer is the mechanism that converts a local environmental gene into a global clinical problem. The principal categories of MGEs involved in AMR have been catalogued comprehensively (Partridge et al., 2018). Plasmids are self-replicating extrachromosomal elements that may carry multiple resistance determinants and, if conjugative, encode the machinery for their own transfer. Insertion sequences and transposons move resistance genes between replicons and chromosomes, and their activity helps assemble multiresistance regions. Integrative and conjugative elements integrate into chromosomes and can excise and transfer by conjugation.

Integrons deserve special mention. Class 1 integrons capture gene cassettes through site-specific recombination, express them from a common promoter, and are frequently embedded in transposons and plasmids. Gillings (2014) described how clinical class 1 integrons arose through the integration of an ancestral element into transposons, followed by selection under antibiotic, disinfectant, and metal exposure. Because the class 1 integron-integrase gene (*intI1*) is abundant in human- and animal-associated bacteria, varies in line with pollution, and can be quantified readily, it has been proposed as a proxy marker of anthropogenic pollution in environmental monitoring (Gillings et al., 2015). Its limitations include that it indicates mobilization potential and general pollution rather than direct health risk.

Mechanisms of horizontal transfer. Three classical mechanisms operate in the environment, and each has distinct ecological determinants (von Wintersdorff et al., 2016).

Conjugation is the direct transfer of DNA, usually plasmids, through cell-to-cell contact. It is typically considered the most important route for ARG dissemination because plasmids can carry large cargoes and cross taxonomic boundaries. Conjugation has been documented in wastewater, biofilms, soils, manure, and the gut. Lopatkin et al. (2016) demonstrated that antibiotics can influence conjugation dynamics, with effects that depend on the drug, the plasmid, and the host, rather than uniformly increasing transfer. Selection for plasmid-bearing cells under antibiotic pressure can also increase apparent transfer by amplifying donors. Ochman et al. (2000) established early that lateral transfer is a pervasive force in bacterial genome innovation, reinforcing the view that plasmid-mediated exchange is a normal and ancient process which human activities now channel toward resistance.

Transformation involves uptake of free extracellular DNA by naturally competent bacteria. Extracellular DNA is abundant in biofilms, sediments, and soils, where it can persist adsorbed to particles. Transformation is limited to species with competence systems, but these include environmentally and clinically relevant genera, and competence is regulated by stress and cell-density signals in ways that may link it to antibiotic exposure (Johnston et al., 2014). Relevant experiments have shown that some non-antibiotic pharmaceuticals can enhance transformation of exogenous ARGs, possibly by altering membrane permeability and stress responses, which suggests that wider chemical pollution may influence gene exchange (Wang et al., 2020).

Transduction is phage-mediated transfer of bacterial DNA. Bacteriophages are the most abundant biological entities in many habitats, and phage particles carrying ARGs have been detected in wastewater, rivers, soil, and food. Balcázar (2014) reviewed evidence that phages can serve as environmental vehicles and reservoirs for ARGs, although the frequency of functional transduction remains uncertain and some detections may reflect DNA contamination or technical artifacts. Experimental work in mice showed that antibiotic treatment can expand the resistance gene content of the gut phage metagenome (Modi et al., 2013), indicating that phage compartments respond to drug exposure.

Environmental modulators of transfer. Gene transfer rates depend on cell density, proximity, metabolic state, and stress. Sub-inhibitory antibiotics may induce the SOS response, which promotes mobilization of some elements; a classic example is the SOS-dependent induction of transfer of an integrative and conjugative element in *Vibrio cholerae* (Beaber et al., 2004). Metals, disinfectants, and engineered nanomaterials have been reported to increase conjugative transfer under experimental conditions, for example through oxidative stress and altered membrane permeability. Qiu et al. (2012) showed that nanoalumina promoted conjugative transfer of multiresistance plasmids across genera. Biofilms, which concentrate cells and DNA in structured matrices, are particularly permissive. Together, these observations reinforce the concept of the environment as a bioreactor in which pollution, microbial density, and genetic diversity interact.

Importantly, not every transfer event leads to establishment. A gene entering a new host must be expressed, tolerated, and maintained in competition with resident organisms. Smillie et al. (2011) showed in the human microbiome that gene exchange is shaped by ecology, with shared habitats and body sites predicting transfer far better than phylogenetic relatedness. A similar principle likely applies in the wider environment: transfer is concentrated where bacteria from different compartments coexist at high density under selective pressure, such as sewage systems, manured fields, and polluted sediments.

4. One Health Implications and Risk Assessment

Connectivity among human, animal, and environmental compartments. The One Health concept rests on evidence that resistance determinants circulate across compartments. Resistant bacteria from humans enter sewage and, if inadequately treated, surface waters used for irrigation, recreation, and drinking-water abstraction. Livestock-derived resistant bacteria and genes enter soils and waterways through manure and runoff and may re-enter humans via food, direct contact, or contaminated water. Wildlife, including birds, can acquire resistant bacteria from polluted habitats and move them across long distances. The emergence of plasmid-mediated colistin resistance (*mcr-1*) illustrates the cross-sectoral pattern: the gene was first described in *E. coli* from pigs, retail meat, and patients in China, where colistin had been widely used in animal production, and it was carried on a transferable plasmid capable of spreading to other Enterobacterales (Liu et al., 2016). Subsequent global detection of *mcr* variants in animals, humans, food, and the environment demonstrated how a single mobile determinant can traverse sectors.

Global analyses of animal resistance have likewise shown that resistance in food-producing animals in low- and middle-income countries has risen sharply, with hotspots in regions of intensifying production (Van Boeckel et al., 2019). In human health, direct exposure studies provide evidence that environmental contact matters. For example, surveys of coastal water users in the United Kingdom reported higher likelihood of colonization by antibiotic-resistant *E. coli* among those with greater recreational water exposure, which suggests that environmental routes can contribute to human acquisition (Leonard et al., 2018). In settings with limited access to safe water and sanitation, environmental pathways such as contaminated drinking water, floodwater, and fecal contamination of food likely contribute more substantially, which is why sanitation and water infrastructure have been described as an essential battlefront in addressing AMR (Bürgmann et al., 2018).

Ecological consequences. Beyond human health, antibiotic pollution and associated resistance affect ecosystem functions. Antibiotics can alter the composition and activity of microbial communities that drive nutrient cycling, organic matter decomposition, and biogeochemical processes in soils and sediments. A critical evaluation of ecotoxicological assessment highlighted that standard test organisms such as algae, daphnids, and fish may not capture effects on microbial communities and that more sensitive microbial endpoints are needed (Brandt et al., 2015). Soil biota also play a role in the planetary health dimension of AMR, since soils are both a reservoir of resistance and a basis for food production (Zhu et al., 2019). Furthermore, the concept of resistance as a form of biological pollution, in which genes can replicate and spread beyond the point of emission, differentiates it from chemical contaminants that dilute and degrade. Kraemer et al. (2019) noted that this self-propagating quality, combined with the persistence of selection pressure, complicates conventional regulatory approaches that rely on dose–response and dilution.

Risk assessment frameworks. Quantifying the risk that environmental resistance poses to human health is difficult. Ashbolt et al. (2013) proposed a human health risk assessment framework that considers sources, environmental development, transfer routes, exposure, and consequences. They emphasized that the key steps include the emergence of novel resistant strains or genes in the environment, the exposure of people, and the likelihood that exposure leads to colonization, infection, or transfer of resistance to human-associated flora. Manaia (2017) cautioned against assuming a direct proportionality between abundance of ARGs and risk: genes in environmental bacteria that are unlikely to interact with human microbiota, are not mobilizable, or are not expressed in relevant hosts may pose little immediate risk, whereas low-abundance, highly mobile genes associated with pathogens may be of greater concern.

Singer et al. (2016) reviewed the relevance of environmental AMR to regulators and noted that several approaches could prioritize risk, including ranking ARGs by clinical relevance, mobility, and host range, and identifying high-exposure scenarios such as irrigation with wastewater of crops eaten raw. Larsson and Flach (2022) distinguished several categories of environmental risk: the risk that resistant pathogens in the environment infect humans; the risk that environmental conditions allow resistant bacteria to emerge or evolve; and the risk that resistance genes transfer to pathogens. They argued that the highest priority is minimizing contact between environmental and human-associated bacteria and preventing conditions that favor the emergence of new resistant strains, for example high-level contamination near manufacturing sites. Within this approach, the thresholds proposed by Bengtsson-Palme and Larsson (2016) provide a practical benchmark for pharmaceutical effluent standards and for the interpretation of environmental monitoring data.

Despite these frameworks, empirical quantification remains thin. Direct evidence for specific environment-to-clinic transmission events is limited because tracking a gene's path from environmental reservoir to patient requires deep sampling across compartments and high-resolution genomic data. Most evidence is therefore indirect, drawing on co-occurrence patterns, historical reconstructions of gene origins, and exposure studies. This does not imply that the risk is negligible, but it does mean that policy should combine precaution with research aimed at reducing uncertainty.

Socioeconomic and equity dimensions. The burden of environmental AMR is unequally distributed. Communities near drug manufacturing facilities, informal settlements without sewerage, and farming communities with intensive livestock production are often those with the least capacity to adapt. Because some of the highest-volume antibiotic production occurs in low- and middle-income countries, which also bear the greatest AMR mortality, pollution control intersects with questions of global governance, procurement, and supply-chain responsibility. Pharmacology and public health scholars have therefore called for including environmental criteria in procurement standards and good-manufacturing-practice certification, thereby aligning incentives for manufacturers and purchasers.

5. Mitigation Strategies, Knowledge Gaps and Conclusions

Controlling emissions at source. The most direct strategy is to reduce the release of antibiotics and resistant organisms at their points of origin. For

manufacturing, this involves setting enforceable limits on antibiotic concentrations in effluent, informed by resistance-selection thresholds, along with monitoring, transparency across supply chains, and incorporation of environmental criteria into manufacturing standards and public procurement (Larsson, 2014; Bengtsson-Palme & Larsson, 2016). Because production facilities are identifiable point sources, regulation is more tractable than for diffuse sources, and the cost of effluent treatment is small relative to the value of the drug supply chain.

For human medicine, reducing inappropriate prescribing through stewardship programs, diagnostics, vaccination, and infection prevention reduces both selection in patients and excretion into wastewater. In agriculture, restricting non-therapeutic use, such as growth promotion and routine prophylaxis, and improving husbandry, biosecurity, and vaccination can lower antibiotic consumption. Several jurisdictions have restricted or banned growth promoters, and the experience suggests that production can be maintained when alternative management is adopted, though results vary with context. Manure management, including composting, anaerobic digestion, and storage, can reduce residues and bacterial loads, although effectiveness against ARGs and MGEs varies and requires evaluation. The pharmacologist's role includes designing dosing regimens that minimize exposure and excretion, developing narrow-spectrum agents and non-antibiotic alternatives, and evaluating the environmental fate of new compounds as part of drug development, an approach that environmental risk assessment for human medicines currently addresses only partially.

Wastewater and sanitation infrastructure. Expanding access to safe water, sanitation, and hygiene (WASH) is among the most effective means of interrupting environmental transmission, particularly where open defecation and untreated sewage discharge are common (Bürgmann et al., 2018; Nadimpalli et al., 2020). Upgrading WWTPs with advanced processes such as membrane bioreactors, ozonation, advanced oxidation, activated carbon, and ultraviolet disinfection can improve removal of antibiotics, resistant bacteria, and in some cases ARGs. These technologies involve trade-offs: ozonation and chlorination may generate transformation products, disinfection can select for tolerant organisms or fail to degrade extracellular DNA, and costs and energy demands are high. Targeted treatment of hospital and manufacturing effluents at source, where concentrations and loads are high, may be more cost-effective than upgrading entire municipal systems. For regions that cannot immediately afford advanced treatment, decentralized solutions, constructed wetlands, and improved sludge management offer partial benefits.

Surveillance and monitoring. An integrated surveillance system should combine clinical, veterinary, food, and environmental data. Wastewater-based metagenomics offers a population-level, cost-efficient, and noninvasive complement to clinical surveillance and can detect emerging resistance determinants early (Hendriksen et al., 2019; Pärnänen et al., 2019). Environmental monitoring would benefit from harmonized methods, including shared protocols for sampling, DNA extraction, quantitative PCR, and metagenomic analysis, and from the selection of indicator targets such as *intI1* and priority ARGs (Gillings et al., 2015; Berendonk et al., 2015). Berendonk et al. (2015) specifically suggested establishing a short list of genes and bacterial indicators to be tracked across environments, along with the development of standardized risk-prioritization criteria. Combining culture-independent data with whole-genome sequencing of isolates and long-read approaches that resolve plasmid structure can improve inference of transmission pathways. Sharing data through open repositories, coupled with metadata on sources and context, would enable global comparisons.

Policy and governance. The One Health Joint Plan of Action (Food and Agriculture Organization et al., 2022) and UNEP (2023) provide a policy architecture in which environmental measures are explicitly part of national action plans. Translating this into practice requires environmental regulators to adopt AMR-relevant standards, including effluent limits for antibiotics, guidance on use of manure and biosolids, and surveillance mandates. It also requires coordination among ministries of health, agriculture, and environment, a historically difficult task. Economic instruments, such as extended producer responsibility, tax incentives for cleaner production, and conditions in procurement contracts, could align commercial and public health goals. International coordination is crucial because resistant organisms and genes move across borders through trade, travel, and ecosystems.

Knowledge gaps and research priorities. Several uncertainties limit evidence-based policy. First, the quantitative contribution of environmental routes to human colonization and infection, relative to person-to-person, healthcare, and food-borne transmission, is poorly defined. Second, the frequency and conditions of HGT events in situ, especially for transformation and transduction, remain difficult to measure, and laboratory rates may not reflect natural conditions. Third, while predicted no-effect concentrations provide a useful starting point, they require validation in complex communities and across mixtures that include metals, biocides, and non-antibiotic pharmaceuticals (Klümper et al., 2019; Pal et al., 2015; Wang et al., 2020). Fourth, the ecological effects of resistance and antibiotic pollution on ecosystem functions are insufficiently characterized (Brandt et al., 2015). Fifth, data from low- and middle-income countries, where exposure may be highest, are sparse. Finally, there is a need for evaluations of mitigation technologies in terms of ARG removal, selection of tolerance, formation of by-products, cost-effectiveness, and feasibility in resource-limited settings. Methodologically, integrating long-read metagenomics, single-cell approaches, and experimental evolution with epidemiological modeling is a promising route to link environmental gene flow with clinical outcomes.

Conclusions. Evidence from metagenomics, experimental evolution, and epidemiology converges on the conclusion that the environment is both a reservoir and a driver of antimicrobial resistance. Antibiotic pollution from households, hospitals, farms, aquaculture, and manufacturing exerts selective pressure, even at low concentrations, and co-pollutants may amplify this effect. Environmental resistomes are ancient and diverse, but human activity enriches mobile, clinically relevant genes and creates conditions, including dense microbial communities, stress, and mixing of human and animal flora, that favor horizontal gene transfer. The resulting connectivity among human, animal, and ecosystem compartments makes AMR a paradigmatic One Health problem. While direct quantification of environmental transmission risk remains a research challenge, available evidence is sufficient to justify precautionary action, particularly the control of manufacturing effluent, improved sanitation and wastewater treatment, prudent use in humans and animals, and integrated surveillance. Pharmacologists can contribute by incorporating excretion profiles and environmental fate into drug development and stewardship, refining concentration thresholds for resistance selection, and engaging with environmental scientists, microbiologists, veterinarians, and policymakers. Addressing environmental dimensions alongside clinical measures is essential to preserve the effectiveness of antibiotics for future

generations.

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