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Environmental Drivers of Antimicrobial Resistance and Strategies for Mitigation

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ABSTRACT

Spread of antibiotic resistance among pathogenic bacteria has reached a critical point, with the emergence of resistant strains for last line antibiotics, alongside a dwindling discovery pipeline for novel antimicrobials. This review aims to highlight the dual role of the environment in the development of antimicrobial resistance as well as the source for the discovery of novel antimicrobials. Microorganisms live in heterogeneous communities and competition for survival applies evolutionary pressure to both antimicrobial metabolite production and tolerance development. Exposure to environmental chemicals, either naturally occurring or due to anthropogenic activities, also leads to the development of tolerance mechanisms. Further, antimicrobial resistance genes, which attain mobility during evolution, may be transferred to other species through horizontal gene transfer. While overuse and misuse of antibiotics is identified as a key agent for antimicrobial resistance, we should take into consideration that resistance mechanisms existed in the environment long before their discovery. The biosynthetic capacity of microorganisms for secondary metabolites far exceeds what has been characterized so far. Similarly, mechanisms for tolerance and resistance for these natural antibiotics may still be awaiting discovery. Future challenges lie in the discovery of novel antibiotic classes for which tolerance mechanisms have not yet been transferred to clinical strains. Novel strategies, guided by genomics and computational methods, will accelerate antibiotic discovery.

Keywords: Antimicrobial Resistance, Drug Resistance, Environmental Microbiology, Horizontal Gene Transfer, Secondary Metabolite, Tolerance Mechanism

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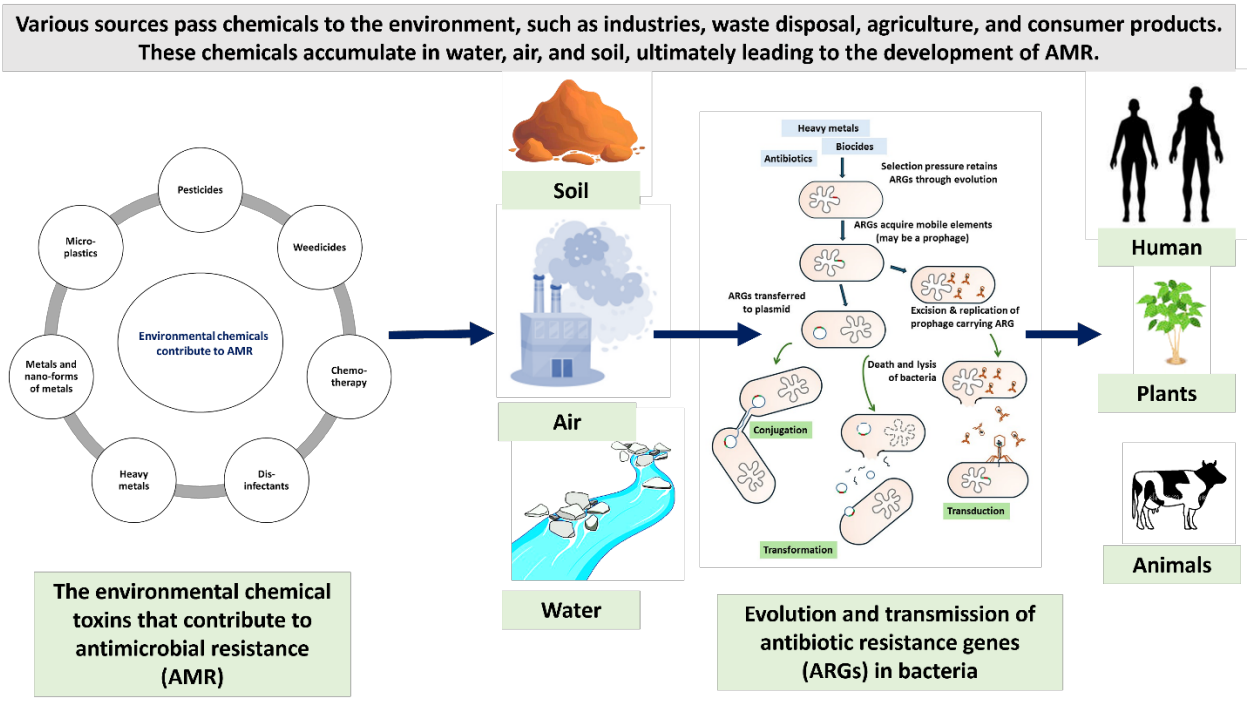
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Graphical Abstract



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1. Introduction

The appearance of pathogenic microorganisms, particularly bacteria, displaying antimicrobial resistance (AMR) has reached an alarming rise in recent years. It has been predicted that by 2050, AMR would be responsible for 10 million deaths per year (1). Consequently, the World Health Organization (WHO) has categorized AMR as a global threat (2).

AMR issue is multifaceted, encompassing the spread of resistant pathogenic strains demonstrated by their emergence in new environments inhabited by humans, particularly hospitals, the appearance of new pathogenic species that have acquired resistance to existing antibiotics through the acquisition of resistance genes, and the emergence of new strains resistant to 'last line' antibiotics.

The ESKAPE pathogens (*Enterococcus (E.) faecium, Staphylococcus (S.) aureus, Klebsiella (K.) pneumoniae, Acinetobacter (A.) baumannii, Pseudomonas (P.) aeruginosa and Enterobacter (E.)* spp) continue to challenge healthcare therapeutic intervention despite introduction of new antibiotics (3). Extensive-Drug-Resistant tuberculosis (XDR-TB) is now considered a global pandemic with low detection rates contributing to mortality (4). Furthermore, new resistant isolates continue to be reported across the globe. For example, tigecycline-resistant *Escherichia (E.) coli* isolates that exert resistance through a mobile resistance mechanism (plasmid mediated) has been reported from China (5). In 2024, a novel strain of XDR *Shigella sonnei* was reported in California (6). An emerging highly resistant clone (ST164) of Carbapenam-resistant *Acinetobactoer baumannii* was identified through a longitudinal genomics study in an ICU in Hangzhou China in 2024 (7). These examples represent just a few of the reports that highlight the increasing threat of AMR.

In addition to bacteria, the spread of multi-drug resistant (MDR) *Plasmodium falciparum* challenges malaria control and elimination efforts in affected countries. The resistance mechanisms; chloroquine resistance transporter (Pfcrt) and multidrug-resistant gene 1 (Pfmdr-1) are well established (8).

Furthermore, clinically relevant antiviral resistance is also observed for some viral pathogens such as human immunodeficiency virus (HIV), herpes simplex virus (HSV), hepatitis B virus (HBV) and SARS-CoV-2. Due to high mutation rates of viruses, particularly RNA viruses, the development of antiviral therapies may often be outpaced by the appearance of viral variants, where often a single base substitution in their genome may be sufficient to confer resistance (9).

Although AMR cumulatively refers to resistance of bacteria, fungi, viruses, and parasites by definition, a significant portion of the global burden of AMR is borne by antibiotic resistant bacteria **(10)**. As such, this review predominantly focuses on the issue of antibiotic resistance.

All these aspects of AMR have negatively impacted the treatment options particularly for bacterial infections **(10)**, and they are predicted to result in a significant mortality burden in the next few decades **(1)**. Therefore, there is an urgent need to control the spread of AMR while simultaneously seeking novel antimicrobials to combat infections.

The implementation of programs to combat AMR in low-income countries may be adversely affected by prioritization of programs to combat other issues amidst ongoing economic struggles **(11)**. However, an alarming increasing trend of antibiotic resistance has been observed in several South-East Asian countries, despite WHO initiatives advocating for antimicrobial stewardship **(12)**. AMR itself further imposes significant economic losses, particularly in the eleven countries of the WHO South-East Asian region. A recent study conducted in Sri Lanka reported the highest resistance among human samples towards beta (β)-lactam antibiotics, while among poultry and aquaculture samples, the highest resistance was found to be towards erythromycin **(11)**. Furthermore, while much of the emphasis has been focused on the use of antibiotics in the medical sector, their use in crop management is likely another significant environmental driver in the spread of AMR, particularly in the low- and middle-income countries countries **(13)**.

The overuse and misuse of antibiotics is considered a primary cause for the spread of resistance and their regulated use is considered as the path to control this issue. This review aims to emphasize the critical role of the environment in the evolution and spread of antimicrobial resistance. More importantly, it highlights the need to consider the mechanisms of microbial responses to environmental chemicals, particularly in terms of how resistance is induced, with the aim of guiding future research in the discovery of new antimicrobials.

2. The Environment as a Reservoir for AMR

The groundbreaking discovery and experimental determination of the antibacterial activity of 'penicillin' secreted by the mold *Penicillium*, which contaminated a petri dish of *Staphylococcus* **(14)**, and the subsequent isolation and chemical characterization of penicillin led to a paradigm shift in the treatment of infections in the 1940s. The two decades which followed (1940s-1960s), were in essence, the 'age of discoveries' for antimicrobial natural products, with the isolation of numerous antibiotic-producing bacteria from the environment, particularly soil **(15)**.

The environment plays a crucial role in the evolution of AMR by acting as a reservoir for resistant bacteria and resistance genes, and enabling their dissemination through water, soil, and air, where they can persevere and possibly encounter humans, animals, and plants. In addition, the environment can also enable the selection and maintenance of resistant bacteria through several mechanisms. Survival pressures or external influences in the environment, temperature fluctuations, exposure to natural antibiotics, and competition with other microorganisms, can drive the evolution of resistant bacteria **(10)**.

Antimicrobials (eg: antibiotics, antivirals, antifungals, and antiparasitic drugs) as well as heavy metals and biocides (biosurfactants & disinfectants) are key environmental drivers of AMR. Antibiotics and the microorganisms secreting them were present in the environment long before being discovered and exploited by humans. This is evidenced by the isolation of bacteria from pristine environments with the capacity to produce antibiotics as well as carrying antibiotic resistance genes (ARGs) **(16)**.

Multiple ARGs associated with different antibiotic classes were discovered in ancient viable bacteria (*Staphylococcus hominis*) isolated from permafrost (soil that remain at -10 to -5°C for at least two years) in the River Lena region in Russia, estimated to be up to 3.5 million years old **(17)**. More recently, Nawas et al **(18)** reported the presence of multiple ARGs among 65 culturable Gram-positive and Gram-negative bacteria isolated from the Karakorum Mountain range in Pakistan. Reports of various bacterial genera with the capacity to secrete antimicrobials isolated from Antarctica have been reviewed by Núñez-Montero and Barriento **(19)**.

Antibiotics are essentially microbial weaponry, enabling them to both overcome their competitors and protect themselves from surrounding threats. The ability to secrete an antibiotic gives an organism an edge over the others, enabling them to colonize and potentially dominate a particular environmental niche **(20)**. In response, bacteria habituating these environments would evolve mechanisms to resist and tolerate these chemical attacks.

Another factor to bear in mind is that much of the research on AMR has been on organisms encountered in human infections and animal husbandry and the

antibiotics currently developed for societal use. This also includes the investigations carried out into ancient bacteria. A significantly larger fraction of microorganisms that produce antimicrobials and harbor resistance genes are present in the environment **(21)**. Most importantly, one can postulate that there will be novel antibiotic classes and resistance mechanisms among them yet undiscovered. Table 1 provides a comprehensive overview of various antibiotic classes developed for clinical use, including their origins, mechanisms of action, and resistance mechanisms. The chemical structures of key antibiotics of different classes, highlighting their structural diversity and variation in size are shown in Figure 1.

Table 1. Antibiotic classification, action and resistance mechanisms.

Classes of antibiotics	Example/s	Discovery period	Organism/ origin	Mechanism of action (Target)	Common resistance mechanism	References
	Antibiotics from Actinomycetes					
Aminoglycosides	Streptomycin	1944	*Streptomyces griseus*	Inhibits protein synthesis (30S ribosomal subunit)	Enzymatic inactivation (ribosome methyltransferases)	**(22, 23)**
Amphenicols	Chloramphenicol	1947	*Streptomyces venezuelae*	Inhibits protein synthesis (50S ribosomal subunit)	Enzymatic inactivation (chloramphenicol acetyltransferases)	**(24, 25)**
Tetracyclines	Tetracycline	1948	*Streptomyces aureofaciens*	Inhibits protein synthesis (30S ribosomal subunit)	Target modification and efflux pumps	**(26)**
Tuberactinomycins	Viomycin (a peptide antibiotic)	1951	*Streptomyces puniceus*	Inhibits protein synthesis: mRNA translocation (Inter-subunit bridge of 30S and 50S ribosomal subunits)	Target modification	**(27, 28)**
Macrolides	Erythromycin azithromycin	1952	*Saccharopolyspora erythraea*	Inhibits protein synthesis (50S ribosomal subunit)	Target modification and efflux pumps	**(29, 30)**
Streptogramins*	Pristinamycin	1953	*Streptomyces pristinaespiralis*	Inhibits protein synthesis-elongation (50S ribosomal subunit)	Target modification, antibiotic inactivation and efflux pumps	**(31)**
Glycopeptides	Vancomycin	1955	*Amycolatopsis orientalis*	Inhibits cell wall synthesis (PG precursor lipid II)	Target modification	**(32, 33)**
Cycloserines	Seromycin	1955	*Streptomyces orchdaceus*	Inhibits cell wall synthesis (inhibits alanine racemase (Alr) and D-lla:D-ala ligase (Ddl))	Target modification (low mutation rate)	**(34, 35)**
Lincosamides	Lincomycine (Clindamycin) *	1962	*Streptomyces lincolnensis*	Inhibits protein synthesis (50S ribosomal subunit)	Target modification: ribosome methylation	**(30, 36)**
Ansamycins	Rifampicin	1965	*Amycolatopsis rifamycinica*	Inhibits RNA synthesis	Target modification by mutation (rpoB gene)	**(37, 38)**

Classes of antibiotics	Example/s	Discovery period	Organism/ origin	Mechanism of action (Target)	Common resistance mechanism	References
Phosphonates	Fosfomycin	1969	*Streptomyces fradiae*	Inhibits cell wall synthesis MurA (UDP-GlcNAc- 3-enolpyruvyltransferase)	Mutational target modification (murA), enzymatic inactivation	(39)
Carbapenems (β- lactam antibiotics)	thienamycin	1976	*Streptomyces cattleya*	Inhibits cell wall synthesis	Enzymatic inhibition	(40)
Lipopeptides	Daptomycin	1987	*Streptomyces roseosporus*	Gram-positive cell membranes undergo depolarization and permeabilization.	Target modification, antibiotic inactivation and efflux.	(41)
Antibiotics from other bacteria						
Mupirocin	Mupirocin	1971	*P. fluorescens*	Inhibits protein synthesis (isoleucyl t-RNA synthetase)		(42)
Monobactams (β-lactam antibiotics)	Aztreonam (synthetic)	1981	*Chromobacterium violaceum*	Inhibits cell wall synthesis: penicillin-binding proteins	Enzymatic inhibition of antibiotic (β lactamase)	(43)
Polypeptides	Gramicidin A	1940s	*Bacillus brevis*	Increase cell membrane permeation (formation of ion channels); hydroxyl radical formation		(44)
	Bacitracin (topical use)	1945	*Bacillus subtilis* group	Inhibits cell wall synthesis	Efflux pumps	(45)
Polymixins* (lipopeptide)	Polymyxin E (colistin)		*Paenibacillus polymyxa*	Cell wall: outer membrane disruption	Target modification	(46)
Antibiotics of fungal origin						
Penicillins (β-lactams)	Penicillin, amoxicillin* and flucloxacillin*	1929	*Penicillium notatum, P. chrysogenum*	Inhibits cell wall (peptidoglycan) synthesis	Enzymatic inhibition (β lactamase)	(14, 47)
Cephalosporins (β-lactams)	Cephalexin	1948	*Cephalosporium acremonium*	Inhibits cell wall synthesis: penicillin-binding proteins	Enzymatic inhibition (β lactamase)	(47)
Pleuromutilins	Pleuromutilin Retapamulin*	1950s	*Pleurotus mutilus (Clitophilus scyphoides)*	Inhibits protein synthesis (50S ribosomal subunit - peptidyl transferase center)	Target modification (resistance is low)	(48)
Fusidic acid	Fusidic acid	1958	*Fusidium coccineum*	Inhibits protein synthesis (elongation factor G)	Target protection	(49)

***: show semisynthetic derivatives**

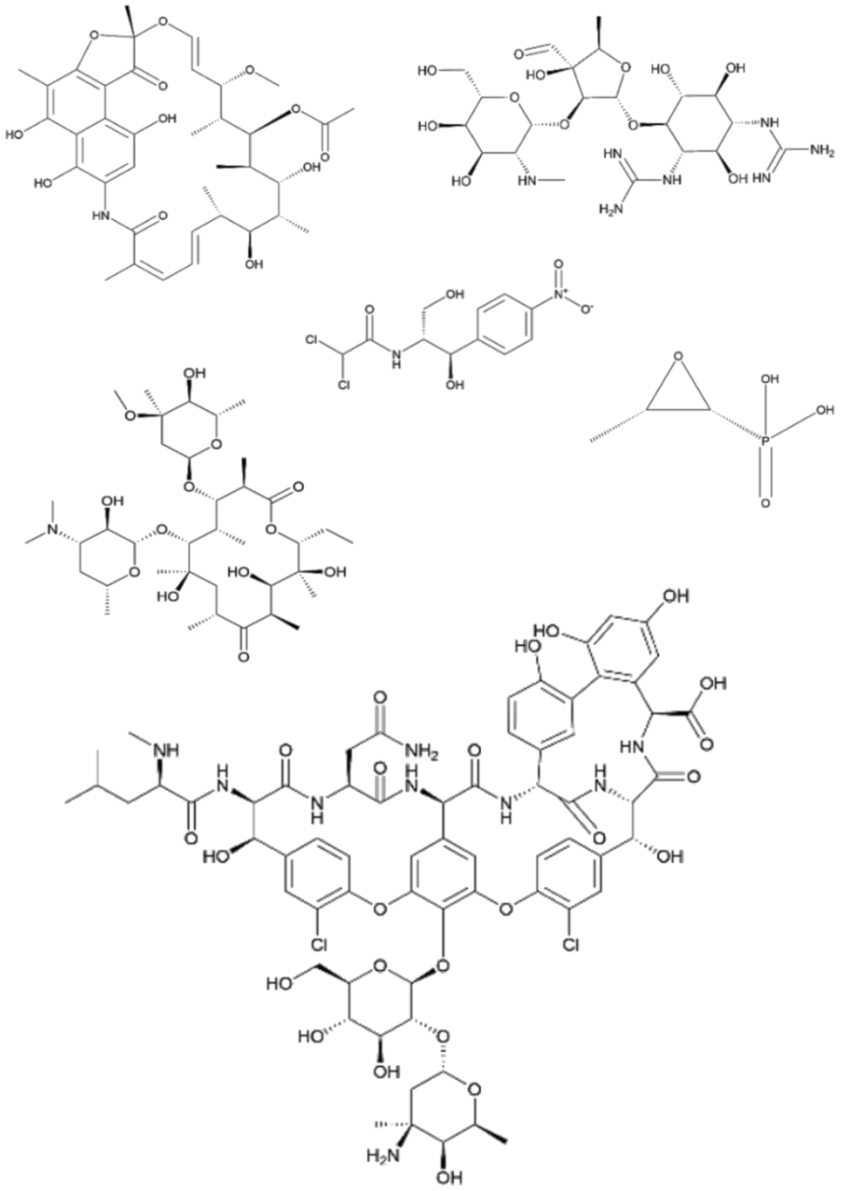


Figure 1. The chemical structures of key antibiotics of different classes. It highlights their structural diversity and variation in size **(Prepared by Authors, 2025)**

3. Microbial Strategies for Antibiotic Resistance

In the environment, microbial cell walls provide a physical barrier protecting them from a variety of chemical threats. The cell envelope of Gram-negative bacteria provides a more effective barrier for the entry of toxins, compared to that of Gram-positive bacteria **(21, 50)**. Fungal cell walls carry a layer of protective chitin over the cell membrane. Thus, a chemical that can modify the cell wall or interfere with the synthesis of its components will be an effective antimicrobial agent **(51)**. In fact, several antibiotics such as vancomycin and carbapenems in clinical use target microbial cell walls (Table 1).

Furthermore, most microbes when growing naturally, often live in heterologous communities, forming biofilms. The biofilm, which comprises a self-secreted and dynamic extracellular matrix in which the microbes are embedded, provides an additional layer of physical protection. The role of biofilms in promoting antibiotic resistance and tolerance has been recently reviewed **(52)**. Cells in a biofilm may be up to ~1000 fold more tolerant to antimicrobial agents than their planktonic counterparts, which may be in part associated with horizontal gene transfer (HGT) **(52)**.

The cell membranes also provide a permeability barrier for the passage of molecules in and out of the cell. The composition of the outer membrane lipids as well as the expression or function of porins determines the accessibility of hydrophilic antibiotics with intracellular targets **(53)**.

Additionally, microbes possess and utilize multiple complementary molecular mechanisms to resist the effects of environmental chemical onslaughts such as membrane efflux systems, enzymatic inactivation of antibiotics, and target modification. Resistance is often brought on by a combination of multiple modes of action.

All bacteria possess multiple efflux systems that serve to remove toxins from the cell, thereby preventing the accumulation of toxins to adequate levels and binding to their cellular targets. Some efflux systems may be specific for a particular antibiotic whereby they may be activated only in the presence of that antibiotic, while others may be non-selective, thus providing general protection. Bacterial efflux systems and the effect of inhibitors on resistance have been recently reviewed **(54)**. In a recent study, antibiotic–induced overexpression of 10 selected efflux pump genes was investigated in a mixture of drug resistant and sensitive *Mycobacterium (M.) tuberculosis* clinical isolates. The study suggests that rifampicin resistance was strongly linked to overexpression of efflux pumps **(55)**. Their investigations further supported the concept that microbes most likely use multiple mechanisms of resistance in response to antibiotics and other toxins.

Enzymatic inactivation of antibiotics is a key mechanism used by bacteria to counter the effects of antibiotics. Organisms such as *Pseudomonas* produce β lactamases, which break the amide bond of the β-lactam ring of antibiotics. Aminoglycoside-inactivating enzymes such as aminoglycoside phosphotransferases, acetyltransferases and aminonucleotidyltransferases have also been described in *Pseudomonas* cases **(56)**.

Structural alterations of antibiotic targets are major resistance mechanisms observed among bacteria. Modification of the target could be expected to arise as a self-resistance mechanism, by the antibiotic producer. It may also originate as a mutagenic alteration that is maintained through evolution based on fitness cost. The alteration in antibiotic targets has been mostly observed in *P. aeruginosa* among others **(56)**.

It can be rationalized that microorganisms that secrete antimicrobials have to ensure a mechanism to safeguard them, particularly if the antibiotic is produced in its active form. As such, self-resistance mechanisms would be expected to evolve along with the ability to produce an antimicrobial compound. In fact, these self-resistance mechanisms may account for the origin of at least some antimicrobial resistance **(56, 57)**.

The discovery of ARGs in bacteria isolated from the natural environments with little or no anthropogenic interference supports the concept that antibiotic resistance originated naturally from the environment, prior to the anthropogenic use of antibiotics **(56, 57)**. Genes providing resistance to rifampicin, amino coumarine, and glycopeptides were discovered in isolates from arctic permafrost while ARGs for macrolides and glycopeptides have been discovered in deep sea sediments in the gulf of Khanbhat and the Arabian Sea **(58, 59)**.

4. Role of Environmental Chemical Toxins in Driving AMR

The environment receives chemicals from various sources, including industrial activities, waste disposals, livestock farming, agriculture, some domestic activities, and consumer products. These chemicals can pass through water, air, and soil and accumulate in the environment, leading to the development of AMR. Common environmental chemical toxins such as heavy metals (cadmium, lead, and mercury), metals (zinc and silver), nanoparticle forms of metals, pesticides, disinfectants, as well as several pharmaceuticals including antibiotics, antifungal agents, and chemotherapeutics have been linked to AMR **(10, 16)**.

Silver has a long history in the treatment of bacterial infections before the invention of antibiotics. In comparison with other forms of silver, due to their smaller particle size, silver nanoparticles (AgNPs) exert promising broad-spectrum antibacterial effects by disrupting the architecture of bacterial cells and altering bacterial cell metabolism **(60)**. In addition to their antibacterial effects, AgNPs have shown wound healing properties and are used as anticancer drugs and drug delivery vehicles **(61)**. An estimated annual production of approximately 200 - 500 tons of AgNPs, suggests an extensive presence in various environments **(62, 63)**. Concentrations ranging from nanograms per liter (ng/L) to milligrams per liter (mg/L) are found in the environment, highlighting AgNPs as a growing environmental contaminant. AgNPs and Ag+ at environmentally relevant concentrations were found to promote the conjugative gene transfer of plasmid-borne ARGs through generation of reactive oxygen species (ROS) and increasing cell membrane permeability **(60)**.

Nano-titanium dioxide (nano-TiO2) is used to break down contaminants in air and water treatment processes. It is also used as a coloring agent in the cosmetic and food industry, paint and plastic production, as well as hydrogen production and the solar cell industry. This has raised concerns about the potential environmental accumulation of nano-TiO2 in large quantities. Due to its antimicrobial effects, nano-TiO2 is used to coat medical devices like implants and catheters to prevent infections **(64)**. Exposure to nano-TiO2 was also shown to prompt horizontal transfer of ARGs mediated by RP4 plasmid between *E. coli* strains, highlighting the potential role of nano-TiO2 in the development of AMR **(65)**.

Heavy metals, namely Cu(II), Ag(I), Cr(VI), and Zn(II), at environmentally relevant and sub-inhibitory concentrations, were found to trigger the conjugative transfer of ARGs between *E. coli* strains through the SOS response, ROS generation, and down-regulation of global regulatory genes associated with HGT (korA, korB, and trb) **(66)**. In addition to conjugative transfer of ARGs, heavy metals such as Hg(II), Cu(II), Zn(II) and Cd(II) have been reported to exert AMR through co-selection **(67)**. BacMet is an accurately curated database of bacterial genes that show resistance to metals and antibacterial biocides. It is interesting to note that, according to BacMet, metals and metalloids such as Cu and arsenic have a large number of genes associated with resistance **(68)**.

Vanadium is used as a steel additive and is also found in jet and ship fuels. High concentrations of vanadium have been reported in coastal sediments, raising concerns about its influence on the marine environment. An investigation by Suzuki et al **(69)** demonstrated that vanadium can promote the horizontal transfer of ARGs from Photobacterium to *E. coli*.

Liu et al **(70)** demonstrated that humic acid-like substances dissolved in biochar affect the transfer efficiency of ARGs between bacteria, with lower levels of humic acid-like substances in biochar significantly affecting conjugative transfer in bacteria.

Microplastics are a growing environmental concern due to their ubiquitous environmental occurrence, mainly in rivers and oceans. Human activities have been reported to be responsible for the accumulation of riverine microplastics. Microplastics serve as an ideal niche for microorganisms to live, colonize, and grow as biofilms **(71)**. A recent study investigated the role of microplastics (polyethylene, polypropylene, polystyrene, polyethylene-fiber, and poly-ethylene-fiber-polyethylene) as vectors for disseminating ARGs in riverine environments. The findings suggest a potential threat of ARG exposure for humans in urban areas that rely on river water **(72)**.

The improper use and disposal of clinical antibiotics has drawn significant attention in environmental research. Studies indicate that the presence of antibiotics in water and soil has a direct impact on the development of AMR in bacteria, which eventually affects the ecosystem **(73)**. A recent investigation indicates that cadmium stress enhanced the degradation of meropenem, a β-lactam antibiotic, by a meropenem resistant strain *P. putida* R51, indicating the potential use of this strain in bioremediation under cadmium stress **(74)**.

In agriculture, by controlling weed populations, herbicides ensure maximum crop productivity and plant growth. However, the overuse and widespread application of herbicides have raised environmental concerns about their impact on the development of AMR **(75)**. A recent study shows that commonly used herbicides, glyphosate, glufosinate, and dicamba trigger the dissemination of ARGs via conjugative transfer of MDR plasmids, facilitated by alterations to the cell membrane permeability and proton motive force **(76)**. The herbicide atrazine was found to reduce the susceptibility profile to aztreonam in isolates of *P. aeruginosa* **(77)**.

In addition to herbicides, pesticides are also associated with the development of AMR. A study by Pasha et al **(78)** showed that the pesticide imidacloprid can significantly influence resistance to antibiotics like carbapenems, aminoglycosides, and cephalosporins. In the environments where antibiotics and pesticides are present together, there is a higher chance of development of streptomycin resistance in pathogenic *E. coli* strains, posing a serious threat to public health **(79)**. Notably, commonly used disinfectants like hexadecylpyridinium chloride, sodium hypochlorite, and peracetic acid have also been identified as a risk factor for inducing AMR **(80)**. Figure 2 illustrates a summary of environmental chemical toxins driving AMR.

These toxins include heavy metals, such as zinc and silver, various forms of metal nanoparticles, pesticides, disinfectants, as well as several pharmaceuticals like antibiotics, antifungal agents, and chemotherapeutics.

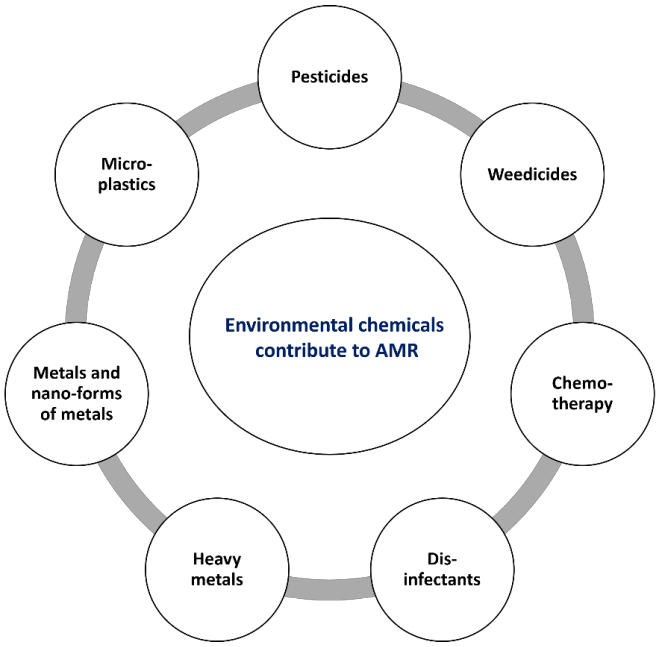


Figure 2. The environmental chemical toxins that contribute to antimicrobial resistance (AMR). These toxins include heavy metals, such as zinc and silver, various forms of metal nanoparticles, pesticides, disinfectants, as well as several pharmaceuticals like antibiotics, antifungal agents, and chemotherapeutics **(Prepared by Authors, 2025)**.

5. Role of Environment in Spread of AMR to and Among Pathogens

Antibiotic resistance may also occur as a response to environmental exposure. Novel types of antibiotic resistance would originate through mutagenic alterations to the key genes that may encode critical proteins such as the antibiotic targets or transport proteins. This will render the antibiotic ineffective against the resulting new strain. Such a *de novo* mutation, if compatible with survival, will provide an advantage for the strain, allowing it to survive and propagate in the presence of the antibiotic **(10, 57)**.

The mobilization of ARGs is thought to have evolved from immobile chromosomal genes that acquired mobile elements such as insertion sequences or integrons and subsequently transferred onto plasmids allowing the mobilization of the genes and passage to other bacteria within the same species or different species through HGT **(10)**. The presence of mobile elements on some of the ARGs found in the arctic permafrost isolates supports this concept **(57)**.

HGT has been identified as the major mechanism for the spread of ARGs among bacteria in the environment, contributing to the spread of drug-resistant pathogens across species boundaries. It may occur through mechanisms such as transformation, transduction, and conjugation (Figure 3).

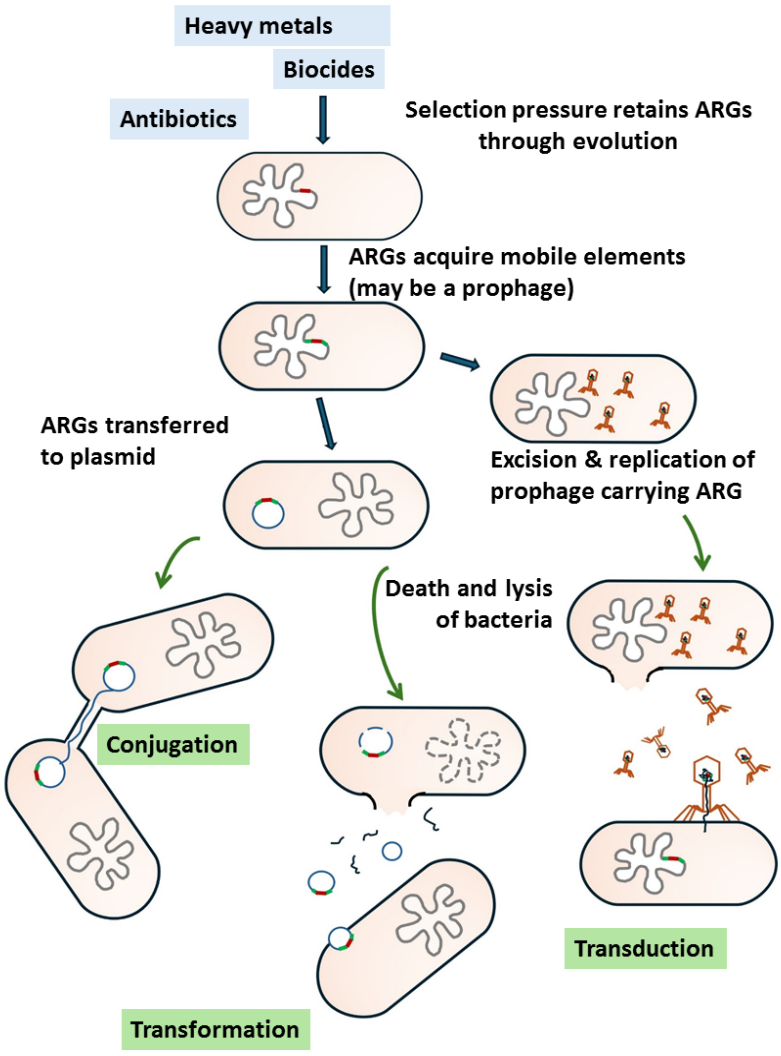


Figure 3. Evolution and Transmission of antibiotic resistance genes (ARGs) in bacteria. An antibiotic resistance gene (ARG) (red bar) arises as a mutation in response to exposures (highlighted in blue) (which may even be self-produced). Mobile elements (green bars) are acquired during evolution allowing the ARG to transfer to a plasmid or a phage. After mobilization, the ARG is more easily spread to other bacteria (green arrows) through several mechanisms (highlighted in green) **(Prepared by Authors, 2025)**.

5.1 Evolutionary Pressure and Fitness Cost

Although bacteria possess inherent mechanisms for HGT of ARGs, permanent establishment of these mobile elements, leading to development of resistant strains would require the establishment of a balance between fitness cost for their maintenance as well as a positive selection pressure. The fitness cost may be high in instances where their expression may interfere with critical cellular functions or until the gene has evolved sufficiently to optimal expression levels **(81)**. A positive selection pressure from the environment, therefore, would be required to maintain these genes until the fitness cost has been fine-tuned **(81)**. Positive selection pressure has been found to be induced when exposed not only to antibiotics in the environment but also to heavy metals **(82, 83)** and other biocides **(84)**, where co-selection of resistance has been often observed.

Exposure to inhibitory levels of chemicals may simultaneously select for antibiotic resistance along with resistance to the chemical in a process termed co-selection. Co-selection can occur through three mechanisms: namely (i) co-resistance (multiple resistance genes are genetically linked and transferred together), (ii) cross-resistance (where one mechanism provides resistance to more than one agent eg. multi drug efflux pumps), and (iii) co-regulation (linked regulation of gene expression leading to a coordinated response, for example, exposure to a single agent leads to expression of multiple efflux pumps) **(85)**.

In recent years, environmental contamination with clinically used antibiotics has become a significant concern. These antibiotics enter the environment through improper disposal of used /unused antibiotics and via human / animal excretions. Antibiotic contamination may exceed concentrations required

for the resistance in certain places **(10)**, imparting a huge positive selection pressure, which will promote HGT of ARGs across species boundaries.

6. Strategies for the Development of New Antimicrobials

The current global urgency necessitates the development of novel antibiotics that need to stay ahead of the rate of resistance appearance. Many of the antibiotic classes in clinical use are targeted against cell wall synthesis and protein synthesis and are of bacterial origin. Therefore, it is important to identify novel antibiotics with new cellular targets.

The environmental microbiome contains an immense and diverse gene pool of yet undiscovered bioactive secondary metabolite encoding genes. Modern approaches for antibiotic discovery, such as target-based discovery platforms and genome-mining approaches, rather than the traditional activity-based approaches, have the potential to efficiently yield fruitful results **(86)**.

Recently, antimicrobial peptides have emerged as promising alternatives to conventional antibiotics. A lasso peptide antibiotic, lariocidin from *Paenibacillus* sp M2 that inhibits bacterial protein synthesis by binding to the ribosome was reported **(87)**. A novel class of antibiotics that are promising inhibitors of Gram-negative bacteria was reported by Pahil et al **(88)**. The macrocyclic peptide antibiotic traps the lipopolysaccharide within the transport machine of *Acinetobacter* and thereby stalls the export of lipopolysaccharides required for the outer membrane synthesis.

Although penicillin, the first natural antibiotic discovered, originated from a fungus, a majority of the antibiotics in clinical use have since come from bacteria and mostly Streptomyces (Table 1). One must ask, however, if this is reflection of the potency of antimicrobial production or if it is skewed by the approaches taken by scientific investigations? The diversity of fungi and their resilience in harsh environments promises an immense reservoir of novel secondary metabolites having potent antimicrobial properties, and possibly novel targets.

Fungal genes encoding secondary metabolites have been found to be clustered together in the genome (Biosynthetic Gene Clusters; BGCs), a majority that remain silent, particularly under laboratory conditions. Activity-based approaches would require the identification of mechanisms to induce these pathways. Self-survival of antibiotic secretors necessitates that resistance genes co-evolve alongside antibiotic biosynthetic pathways. Interestingly, these resistance genes have been often found co-localized within the BGCs **(59)**. Several databases and screening tools are currently available (eg. DeepBGC fungal, FungiSMASH, TOUCAN) for mining fungal BGCs. The 'fungal bioactive compound resistant target seeker' (FunARTS) reported recently is an open-source mining tool that allows target-driven genome-mining **(89)**.

7. Conclusion

Spread of antimicrobial resistance to existing last line antibiotics in recent years looms as an impending crisis in upcoming years. In addition to microbial stewardship to control the spread of resistant microbes, the need to discover or develop novel antimicrobial classes for which resistance mechanisms have not spread to clinically relevant strains, has become urgent. The complex chemical structures of natural products, which are not necessarily reproducible through chemical synthesis in the current context, lend value to the search for natural antibiotics. It should not be considered that the natural antibiotic reservoir has been exhausted. The recent discovery of lasso peptides by Jangra et al (87) is an example. Natural products discovery should target extremophiles and rare microorganisms from non-conventional environments. Un-culturable bacteria may offer yet undiscovered material. Natural product discovery efforts need to be armed with modern tools such as genomics, transcriptomics, proteomics, and AI based design strategies for protein engineering and synthetic biology. Sustainable investments are needed to stimulate the establishment of novel drug discovery platforms, as recommended by the UK Government commissioned O'Neill report and WHO efforts.

8. Declarations

8.1 Acknowledgment

The authors thank the support given by the Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Colombo, Colombo 08, Sri Lanka.

8.2 Ethical Considerations

Not applicable.

8.3 Authors' Contributions

SJ: conceptualization, writing and reviewing; MKE: writing, reviewing and editing; CU: writing and editing; Reading the final version of manuscript: all authors.

8.4 Conflict of Interests

There are no conflicts of interest to declare.

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