








A Perspective on the Role of the Environment in the Transmission of Antibiotic Resistance

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ABSTRACT

Antimicrobial-resistant infections have increased several fold over the past few decades. The irrational use and overuse of antibiotics in sectors such as medical healthcare, animal husbandry, bee-keeping, horticulture, antifouling paints and food preservation has led to the selection of microorganisms equipped with ways to combat antibiotics. Consequently, several antibiotic-resistant genes (ARGs) and their elements have spread across several bacterial species via horizontal transmission and to the next generations by vertical transmission. Horizontal gene transfer of ARGs is mediated by mobile genetic elements (MGEs) like integrative and conjugative elements, plasmids, transposons, integrons, and insertion sequences. Plasmids accommodate a vast array of multiple resistance genes and, through bacterial conjugation, contribute in transferring resistance to bacterial populations. Studies indicate the presence of multidrug-resistant airborne pathogens in hospital environments. The presence of ARGs and MGE genes in airborne particulate matter in urban areas and in environments using antibiotics extensively (e.g., hospitals, cattle feed yards, wastewater treatment plants, etc.) is alarming. This current article discusses the most serious global threat to the effective treatment of bacterial infections. The current paper highlights the need to regulate antibiotic usage to avert the emergence of antibiotic-resistant pathogens. Since antibiotics are unavoidable, therefore, it should be regulated and antibiotic resistance awareness programs should be promoted.

Keywords: Antibiotics, Antibiotic-resistant bacteria, Antibiotic resistance, Transmission.

Abbreviations: AMR: Antimicrobial resistance, ARB: Antibiotic-resistant bacteria, ARGs: Antibiotic-resistant genes, HAI: Hospital-associated infections, HAP: Hospital-associated pathogens, HGT: Horizontal gene transfer, ICEs: Integrative and conjugative elements, MCR: Mobilized colistin resistance, MDR: Multiple drug resistance, MIC: Minimum inhibitory concentration, MGE: Mobile genetic elements; ROS: Reacting oxygen species, NAAM: Non-antibiotic antimicrobials

1. INTRODUCTION

Antimicrobials are natural, synthetic or semisynthetic molecules that restrict microbial growth. Antimicrobials that inhibit the growth of bacteria are specifically classified as antibiotics. In addition to treating infectious diseases, antibiotics are also utilized extensively

in several other sectors, such as animal husbandry, apiculture, horticulture, antifouling paints and food preservation. Such overuse of antibiotics has accelerated the selection of microorganisms resistant to these compounds. Transmission of antibiotic-resistant genes (ARGs) among bacteria has led to further propagation of antibiotic-resistant strains. Though first-generation antibiotics have been modified to enhance their efficacy, bacteria seem to have acquired mechanisms to avoid antibiotic toxicity or antibiotic resistance (Gillings, 2013). Antibiotic-resistant strains of bacteria are rapidly spreading into microbial communities, which is a major concern. Research shows that both biotic and environmental factors contribute to the spread of such strains. The reckless use of antibiotics as pesticides on crops, poor waste management practices, and disposal of pharmaceutical waste into water bodies are among the factors that can contaminate the water and soil with antibiotics. Reports of water and soil-borne, and food-borne antibiotic-resistant bacteria (ARB) substantiate the role of these environmental factors in the spread of antibiotic-resistant strains (Kraemer et al., 2019; Van Boeckel et al., 2019).

Several environmental factors can contribute in making bacteria antibiotic-resistant and their proliferation, in addition to the type and amount of antibiotics used. Exposure to other chemicals and the duration of exposure can also impart resistance. Extremely low concentrations of antibiotics that fails to inhibit bacterial growth, can increase the mutation rate in bacteria, eventually giving rise to ARGs (Li et al., 2015). Most microorganisms develop antibiotic resistance through changes in antibiotic targets, drug uptake avoidance mechanisms, pumping out the harmful molecule, or modulation of regulatory networks and metabolic pathways (Munita et al., 2016).

There is limited knowledge of the environmental factors influencing antibiotic resistance in bacteria. Further, the variability of the response of different species and strains of bacteria to selection pressure with the same or different antibiotics, and the influence of interaction among cohabiting bacterial communities is not well understood (Koul et al., 2016). It is, therefore the need of hour to identify the high-risk factors and environmental conditions that promote resistance, particularly in vulnerable target groups. Elucidation of evolutionary processes using quantitative modelling would help to evaluate the occurrence of resistance in different environments. The resistance once acquired by a bacterial strain can be propagated not only to daughter cells (vertical transmission) but also to similar strains (horizontal transmission). Pathogenic bacteria developing antibiotic resistance can reduce the efficacy of antimicrobial pharmaceutical compounds. Further, understanding the mechanistic spread of Antibiotic resistance genes (ARGs) and the mode of environmental transfer of Antimicrobial-resistant bacteria (ARB) is pivotal for creating control measures (Manaiya et al., 2020).

2. MECHANISM OF ACQUISITION AND SPREADING OF ANTIBIOTIC RESISTANCE GENES (ARGS)

2.1. Bacterial strategies to develop antibiotic resistance

Human health is experiencing significant threats from numerous classes of resistant bacteria. Currently, there are 12 families of such bacteria which are categorized under the list of antibiotic-resistant priority pathogens by WHO, and classified as medium, critical and high priority, based on the level of urgency (Tacconelli et al., 2018; Shrivastava et al., 2018). The most critical ones are pan-drug resistant, multidrug and extensively drug-resistant. These cause inflated healthcare expenditures, prolonged illness, and a high risk of death (Asokan et al., 2019).

Bacterium's resistance mechanisms against antibiotics are solely dependent on its physiology and intrinsic characteristics. This crucial information must be acknowledged while developing

effective treatments for bacterial infections, to avoid the emergence of ARB, that could cause devastating consequences. By comprehending the mechanisms of resistance, we can develop better strategies to prevent and combat these infections. Important mechanisms of resistance against antibiotics are: inactivation of the antibiotic, alteration of the antibiotic, efflux pumping of antibiotics, and modifying the target molecules (Figure 1) (Kumar et al., 2019; Sodhi et al., 2021). Research was conducted on how *E. coli* adapts to antibiotics with a gradual increase in metabolic rates. Upon analyses and sequencing of the DNA of *E. coli* it was discovered that non-canonical genes are crucial for central carbon and energy metabolism. These non-canonical genes help *E. coli* develop resistance to antibiotics (Lopatkin et al., 2021). Antibiotic failure and multidrug resistance are significant global health issues affecting animals and humans (Ghosh et al., 2021; Pelfrene et al., 2021). Biofilms are essential in helping bacteria resist antimicrobial treatments. They are created by microorganisms that form associations and produce an extracellular matrix, which in turn provides tolerance to bacteria. Biofilms use various mechanisms to resist antimicrobials, depending on their composition, architecture, stage of development, and growth conditions (Uruén et al., 2021). The structure of biofilms obstructs antibiotics from lodging and penetrating, making it difficult for them to have their intended effect. As a result, biofilms are believed to prevent bactericides from functioning effectively.

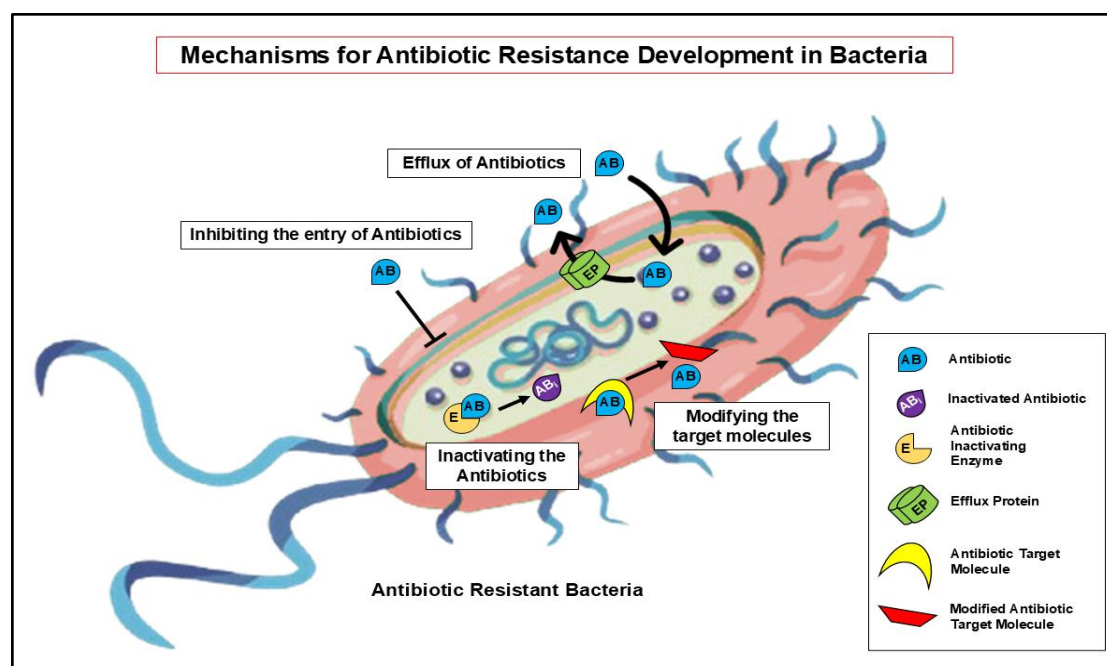


Figure 1: Key mechanisms of antibiotic resistance: Inactivation of the antibiotic, Chemical modification of the antibiotic, Active efflux pumping of antibiotics out of the cell, and modification of target molecules to reduce antibiotic binding. Illustration was prepared by using CorelDraw Graphics suite software (version 2022)

2.2. Spreading of Antibiotic Resistance Genes (ARGs)

Antibiotics are the most significant and direct selection pressure for the horizontal transfer of ARGs. Mobilisation of these ARGs is mediated by genetic exchanges among bacteria via conjugation by plasmids, transformation by extracellular DNA or bacteriophage-mediated transduction. Among microbial communities, horizontal gene transfer (HGT) results in the exchange of antibiotic resistance to several unrelated pathogenic organisms. Horizontal exchange is also facilitated by mobile genetic elements (MGE) that can move within or between DNA within an organism like transposons, integrons, or elements that can be

transferred between bacterial cells such as plasmids and integrative and conjugative elements (ICEs) (Botelho et al., 2021; Partridge, 2018) (see Table 1).

Table 1: Horizontal Gene Transfer (HGT) of antibiotic-resistant genes (ARGs) and associated mobile genetic elements (MGEs)

Gene Transfer Mechanism	Mobile Genetic Element (MGE)	Description
Conjugation	Plasmids	Extrachromosomal DNA molecules that are capable of replicating autonomously. Plasmids can transmit ARGs via conjugation between bacteria
Transduction	Bacteriophages	Bacteriophages are viruses that infect bacteria. They can transfer ARGs when they infect bacteria.
Transformation	Naked DNA	Transformation is the uptake of free DNA by bacteria, including ARGs, which can be incorporated into the recipient genome.
Transposon-Mediated Transfer	Transposons	DNA sequences that can move within the genome and carry ARGs along with them.
Integrations	Integrations	Integrations are genetic elements that capture and integrate gene cassettes, including antibiotic resistance genes, into their own structure.
Insertion Sequence (IS) Elements	Insertion Sequences	IS elements are short, mobile DNA sequences that can facilitate the movement of nearby antibiotic resistance genes.

2.2.1. Horizontal transfer of ARGs via natural transformation

ARGs may be present on extracellular DNA free-floating within the microbial systems (Figure 2). Natural transformation by such xenogenetic DNA fragments can render microbes resistant to various antibiotics. A study illustrated the presence of extracellular DNA in wastewater and reported that 65% of the MGEs were composed of exDNA. However, due to their low abundance in the resistome, the authors surmised that ARG uptake via natural transformation was not likely the major mode of transfer. MGEs on the other hand can indirectly drive the development of antibiotic resistance because of their spread in the exDNA (Calderón-Franco et al., 2021).

2.2.2. Horizontal transfer of ARGs via plasmids/ conjugation

The highly resistant bla_{NDM-1} gene which produces the New Delhi metallo- β -lactamase (NDM-1) enzyme, is also transmitted through plasmids (Rozwandowicz et al., 2018). This gene shows multidrug resistance and is highly resistant against the last resort of reserved carbapenem antibiotics. Besides India, bla_{NDM-1} gene carrying bacteria have been discovered in Pakistan and the UK (Sun et al., 2019; Khan et al., 2020). The development of ARGs on plasmids was observed in hosts lacking plasmids, suggesting that the presence of hosts and exposure to antibiotics can favor the emergence of highly contagious plasmids carrying significant antibiotic resistance (Figure 2) (Dimitriu et al., 2020).

Bacterial conjugation confers antibiotic resistance genes (ARGs) transfer in the environment (Figure 2). Plasmid carriage and the dependence on temperature play significant roles in both vertical and HGT (Mishra et al., 2021). The spread of ARGs and their prevalence is suggested to be a result of the progression of bacterial communities and their associated horizontal transfer genes (Zhang et al., 2020). Plasmids aid in spreading antibiotic resistance genes across environments (Li et al., 2015). Plasmids are also present in inhalable particulate matter (PM), which exhibit resistance to multiple drugs which can transfer via phenotypic and genotypic ways (Zhou et al., 2021). These findings prove the efficient relationship between PM concentrations and the spread of HGTs in the air, conferring multi-drug resistance via plasmid transfer among different potential environmental hosts.

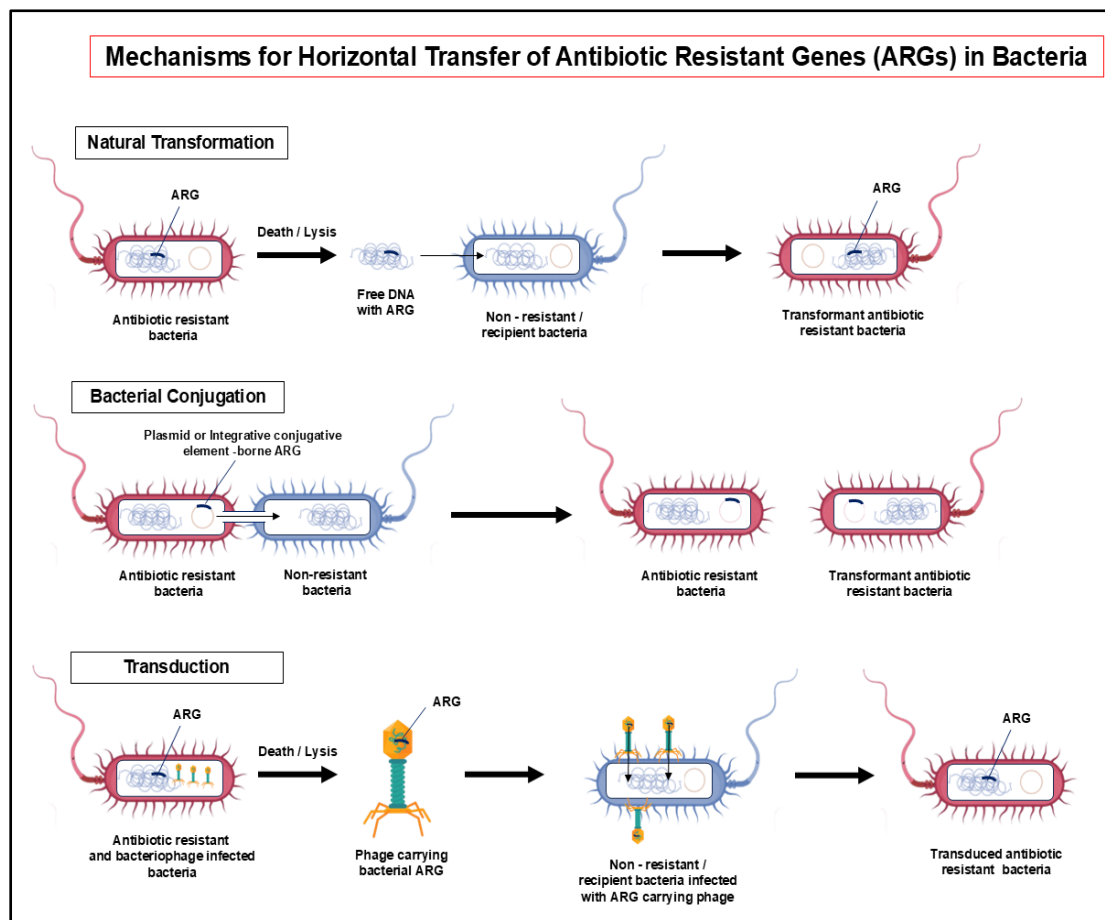


Figure 2: Horizontal gene transfer mechanisms: Conjugation by plasmids, transformation by extracellular DNA, and bacteriophage-mediated transduction, facilitate the spread of antibiotic resistance genes among bacterial populations. Illustration was prepared by using CorelDraw Graphics suite software (version 2022)

2.2.3. Horizontal transfer of ARGs via Integrative conjugative elements (ICEs)

Integrative conjugative elements (ICEs) are MGE that can integrate, self-replicate and conjugate. These elements, present in proteobacteria and firmicutes, aid in spreading antibiotic resistance genes in addition to plasmids (Che et al., 2019). It was discovered Tn916-like Integrative conjugative element (ICE) confers resistance to vancomycin and tetracycline in bacterial genera like *Streptococcus*, *Staphylococcus*, and *Enterococcus* (Sansevere et al., 2017).

2.2.4. Horizontal transfer of ARGs by transduction

Several metagenomic studies indicate that phages can carry ARGs (Figure 2) (Balcazar, 2014). Phage DNA carrying β -lactamases and a penicillin-binding protein have been reported in sewage and river water samples. Further, many ARGs from the phage DNA can be transferred to susceptible *E. coli* strains, resulting in ampicillin resistance development (Colomer-Lluch et al., 2011). Such studies underline the importance of phages in the horizontal transfer of genes. Investigating the importance of phages in developing effective strategies and mitigating the emergence and spread of antibiotic resistance should be a priority.

3. ROLE OF ENVIRONMENTAL COMPONENTS IN WIDE SPREADING OF ARGs

ARGs have been found to thrive in and spread via natural environmental factors (e.g., both ground and surface water sources, sediments, soil, and uninhabited areas) and man-made environments (e.g., farms, hospitals, and water treatment systems) (Figure 3) (Blake et al., 2021).

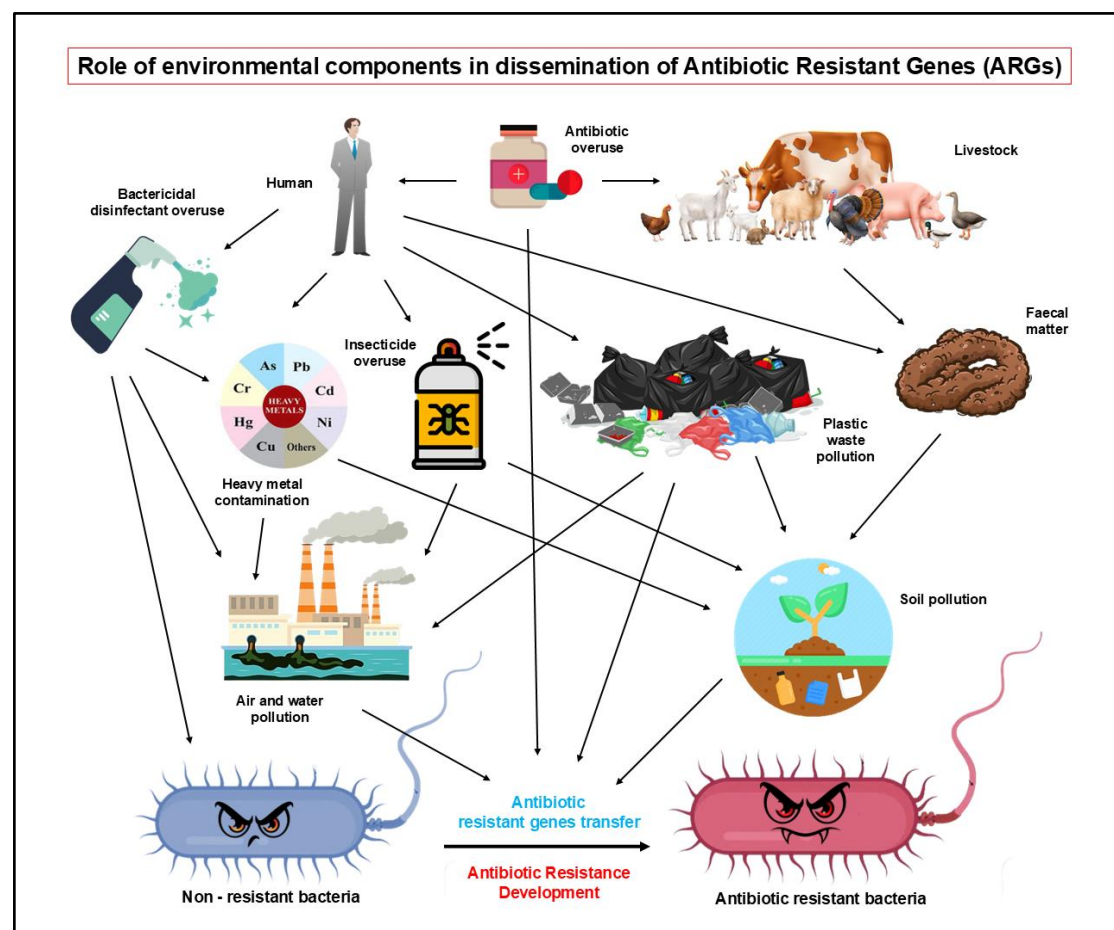


Figure 3: Role of Environmental Components in the Spread of Antibiotic Resistance Genes. This figure highlights how the overuse of bactericidal disinfectants and antibiotics in humans and livestock, combined with plastic waste pollution, fosters the emergence of antibiotic-resistant bacteria. Contaminated environments can convert non-resistant bacteria into antibiotic-resistant strains through gene transfer, exacerbating the public health crisis of antibiotic resistance. Illustration was prepared by using CorelDraw Graphics suite software (version 2022)

3.1. Air

Multiple studies report the presence of genes resistant to lactams, macrolides, tetracyclines, vancomycin, sulphonamides, and quinolones in air (Li et al., 2021), suggesting possible airborne ARG transmission. Table 2 gives an overview of various multidrug-resistant airborne pathogens.

Table 2: An overview of various multidrug-resistant airborne pathogens

Multidrug resistant Airborne Pathogen	Description	Drugs to which the MDR strain has developed resistance
<i>Mycobacterium tuberculosis</i>	A bacterium that causes tuberculosis (TB).	Isoniazid and Rifampicin.
<i>Staphylococcus aureus</i> (MRSA)	Methicillin-resistant <i>Staphylococcus aureus</i> is a bacterium that causes various infections.	Methicillin and other beta-lactam antibiotics.
<i>Pseudomonas aeruginosa</i>	A common, respiratory infections causing, hospital-acquired pathogen	Multiple antibiotics, making treatment challenging.
<i>Klebsiella pneumoniae</i>	A bacterium responsible for respiratory and urinary tract infections.	Various antibiotics, including carbapenems.
<i>Acinetobacter baumannii</i>	An opportunistic pathogen commonly detected in healthcare settings.	Multiple antibiotics, including carbapenems.
<i>Escherichia coli</i> (ESBL)	Extended-spectrum beta-lactamase (ESBL)-producing <i>E. coli</i> strains	broad range of beta-lactam antibiotics, including cephalosporins.
<i>Aspergillus fumigatus</i>	A fungus responsible for respiratory and systemic infections.	Azole antifungal drugs.
<i>Candida auris</i>	An emerging multidrug-resistant yeast that can cause bloodstream and invasive infections.	Multiple antifungal agents.

3.1.1. Outdoor transmission

The 16S rRNA gene sequencing and high-throughput quantitative PCR (HT-qPCR) studies confirmed ARGs can become airborne via particulate matter, dust, and human airways in a hospital (Zhen-Chao et al., 2021). Further, airborne ARB can be blown freely with the wind from one place to another (Madsen et al., 2018; Brągoszewska et al., 2018).

3.1.2. Indoor transmission

Studies indicate a build-up of resistome in various air-conditioned indoor environments. Unchecked usage of antibiotics and the aerosolisation of clinical waste in hospitals have been major contributors to the enrichment of airborne AMR in hospitals. Several genera of pathogens like *Enterococcus*, *Streptococcus*, *Micrococcus*, and *Staphylococci* etc. have been reported to thrive under such conditions (Li et al., 2021). These hospital-associated pathogens (HAPs) have been implicated in several Hospital-associated infections (HAIs). Further, the medical equipment used by healthcare professionals can enhance the rate of ARG transmission e.g.; stethoscopes, coats, touching the patients, and sitting with the patients

(Monegro et al., 2020). There is always a high risk of aerosol-associated ARG transfer which comes under airborne transfer of ARGs (Zhao et al., 2021). The airborne ARG transfer may occur in an indoor environment or outdoors but comparatively indoor airborne ARG transfer is faster and more contagious since maximum population reside in small spaces (Pal et al., 2016). ARGs spread in indoor environments through inhalation and exhalation too. Studies indicate that individuals living mostly indoor life are more prone to the airborne microbiome followed by the ARBs resistome (Dohmen et al., 2017).

ARGs can be transmitted on a local scale through aerosols after the detection of tetracycline resistance genes, tet (X) and tet (W) in indoor and outdoor environments of animal breeding houses and human residences. Airborne dust and similar particles harbor ARGs that enter living systems via inhalation or ingestion and easily spread via natural air circulation (Dohmen et al., 2017). Outdoor haze environments show maximum concentration of ARG, and hospitals shows maximum concentration and diversity of ARG (Wang et al., 2018). Correlation studies between increasing temperature and population density to antibiotic resistance showed that a 10 °C increase in temperature was associated with an elevated antibiotic resistance in common pathogens *E. coli*, and *Klebsiella. Pneumoniae*, and *S. aureus* by 4.2%, 2.2%, and 2.7%, respectively; an increase in population density by 25,900 persons per km² was associated with 6% increase in antibiotic resistance for *K. pneumoniae* and 3% for *E. coli* (MacFadden et al., 2018).

3.2. Soil

Millions of microbes dwell in soil in association with other microbial communities. Contamination of soil with antibiotics due to waste discharge, improper fertilizer application, wastewater irrigation, and animal feeding activities may drive bacteria towards acquisition and retention of ARGs. Often, higher concentrations of antibiotics are found in manure-amended soils than sewage water irrigated soils (Bengtsson-Palme et al., 2018). Manure from livestock, particularly animals treated with antibiotics, often contains significant quantities of unmetabolised antibiotics introduced directly into soils. In comparison, sewage water, sourced from a larger and more diffuse human population, undergoes treatment processes that degrade or dilute antibiotics before being used for irrigation. It is estimated that an average to the maximum amount (30-90%) of antibiotics implemented for human or animal use are not metabolised completely and instead excreted via faeces which then get mixed up during soil irrigation, the wastewater treatment processes, as well as through manure application (Wang et al., 2018). Three commonly used herbicides—glyphosate, glufosinate, and dicamba increase antibiotic resistance genes (ARGs) and MGEs prevalence in soil microbiomes with no changes in the abundance, diversity, and composition of bacterial communities (Liao et al., 2021).

Also, the antibiotic resistance transmission among humans via food chains increases after fertilising soil with animal manure. A study carried out a five-field experiment with anaerobic agricultural soil unamended (BS-) and amended (BS+) with biogas slurry (8–18 years) and characterised the action of ARBs and MGEs. The study reflected the notion of the increase in tetracycline in soil due to the long-term application of biogas slurry. This effect increased the predominance of ARBs and mainly the transposase gene (*Tn916/1545*) and ARGs-associated bacteria suggesting the higher preserving capacity of anaerobic soil for ARBs and exogenous microorganisms. Thus, the researchers implicated the positive role of anaerobic soil in mitigating the harmful effects of ARBs in farmland environments (Xue et al., 2021). Different clinically relevant pathogens and commensal bacteria acquire resistance over time owing to the continual selection pressure via increased antibiotic abuse. The soil ecosystem is a vast repository of ARB and MGE, both intrinsic and acquired ARGs especially perturbed and graded by human activities (Wang et al., 2021). Soil resistome and its interconnected

environments are largely affected by agricultural practices and farming practices that restructure and shapeshift the intrinsic properties of soil.

3.3. Water

Aquatic environments are considered key channels for AMR transmission of ARB and ARG. The application of several chemical fertilisers in farms contributes to the creation of ARB and ARG and leachates from such farms as a result of irrigation (Chopyk et al., 2020; Bougnom et al., 2020). ARG and ARB accumulate in soil and can migrate deep into the earth to contaminate groundwater (Huang et al., 2013). Groundwater is a major source of water for many people and could be a potential cause of antibiotic resistance spread to all living beings (Sun et al., 2017). Phytoplankton-zooplankton communities (PZCs) could be the mode of ARG transfer as they harbored large amounts of ARGs (Xue et al., 2021).

Biofilms on water surface/extracellular matrices, provide an efficient mechanism to microorganisms against disinfectants, and antibiotics. Biofilms can adsorb a variety of pollutants such as metals, antibiotics, industrial dyes, etc. and provide a binding site for ARB and aid in their transmission. Pollutants adsorbed on biofilms can stimulate ARG selection and HGT (Huang et al., 2014). A study on role of antibiotic resistance transmission via biofilm detachment in drinking water pipe systems, showed that the amount of elevated ARB concentration in tap water due to the detachment of biofilms harboring these bacteria by disinfectants, further enhancing antibiotic resistance mutation rate (Zhang et al., 2018a). The interconnectivity of food chains among plants and animals provides prominent evidence of bacterial transfer. Interestingly, this transfer between species is also applicable to plants sharing their bacterial microbiome with humans along with the resistant genetic material that gets pooled within the bacteria themselves. Post harvest, vegetables have also been tested for the frequency of occurrence of resistant bacterial strains (Olaimat & Holley, 2012). Determinant-resistant bacteria which include *Coliform* and *Clostridium perfringence* have also been detected in vegetables like tomato, cucumber, pepper, and carrot (Beuchat, 1996). The addition of food preservatives, disinfectants, and decontaminants as antimicrobial agents at every stage is a routine practice in food processing before distribution. This too can potentially exacerbate antibiotic resistance. The need of the hour is to curb the overuse of antibiotics and to develop comprehensive strategies to limit their application. Resistant *Enterococci* species need to be monitored among the class of plant-based food products (Jasiak & Amund, 2021). In a study, 270 food samples were tested, out of which 72 showed enterococcal isolates. The researchers reported a high level of resistance towards aminoglycosides shown by the majority of strains with the most frequent ARG being the *ant (6')-Ia* (Chajęcka-Wierzchowska et al., 2021). Characterisation of a popular street food, *Phuchka*, revealed the sensitivity and resistance of *Staphylococcus* spp. and *E. coli* to gentamicin ciprofloxacin and ampicillin respectively (Hasan et al., 2021). Livestock-based bacteria and food-borne pathogens develop antibiotics-induced resistance in livestock (Zwe et al., 2018). Genetic material uptake through contaminated surfaces confers resistance in bacteria. The food processing environment and the transport-associated activities elevates high cross-contamination probability. Furthermore, surroundings comprising animal sustenance before slaughter has shown to harbor antibiotic-resistant *Salmonella* families (Hedman et al., 2020). The wide group of resistant organisms can then get transferred via a contamination source before the process of slaughtering (Hudson et al., 2017). Food-borne bacteria commonly detected in food can repeatedly become resistant to tetracycline and can configure resistance genes into their genomes. Multi-drug resistance in food-borne pathogens is majorly translated with the misuse and overuse of antibiotics which are generally applied to prevent diseases and promote healthy growth (Xiong et al., 2019; Sharma et al., 2019). A high probability of ARBs entering and stably growing into the food system and getting detected in

raw or ready-to-eat food is always a possibility. However, it is extremely difficult to trace their survival rates and changes in their growth (Perez-Rodriguez & Taban, 2019). Mobilised colistin resistance (MCR-1) resistance carrying gene has also been detected in *E. coli* present in meat and vegetable samples (Ghafur et al., 2019).

Gene abundance is most affected by environmental factors that alter the bacterial community succession. The 21st century marks AMR in living biota as a global threat. The problem is itself serious due to unnecessary demand, and sale of antibiotics over the counter, along with their poor disposal practices after use (Guinovart et al., 2018; Auta et al., 2019; Sharma et al., 2021). The non-metabolised antibiotic effluents, the use of faeces/manure in agriculture, and the release of industrial effluents into the environment are the reasons for threatening situations. Uncontrolled AMR affects healthcare and causes a high financial burden. Human, animal, and environmental microbiota are at risk of exposure to antibiotic resistance also due to pollution and adverse climate changes (Burnham, 2021). Bacteria present in the animal's digestive system undergo considerable high selection pressures and maintain ARGs due to the widely common use of antibiotics in veterinary medicine and animal husbandry. As a result, resistant strains thrive in their chance of relative abundance and develop different ARGs to different kinds of antibiotics (Jian et al., 2021). The physiology and intrinsic characteristics of bacteria determine their resistance mechanisms towards a certain antibiotic. A well-established stress response system comes into action where the bacteria use their survival strategy to express and suppress their genes.

The ecosystem balance of the microbial community is altered significantly owing to the haphazard use of antibiotics and rapid spread of antibiotic-resistant organisms which ultimately contaminate the environment (Llor & Bjerrum, 2014; Letten et al., 2021; Hubeny et al., 2021). The development of resistance is caused by the major contributors residing in the natural environment as well as those that comprise the socio-behavioural aspects. Antibiotics when accumulated, lay down the field for the growth of resistant bacterial strains, usually in association with soil, food, and water further complicating the assessment of the consumption rate and associated public health risks (Davies et al., 2019; Zainab et al., 2020). Along the same line, it is difficult to estimate the pharmaceutical compound concentration in long exposure areas (Bungau et al., 2018). For bacteria, AR is a natural response because they develop resistance genes towards antimicrobials. Development of antibiotic resistance is inappropriately caused by the abusive use of antibiotics that drive the selection pressure in bacteria. Bacteria sensitive towards antibiotics then become resistant, although not reacting to the antimicrobial action (Zaha et al., 2019).

3.4. ARBs may also spread through faecal matter

Antibiotic-resistance genes have their origin in the environment; albeit, mainly within the host that ARB are selected (Manai, 2017). As a result, these bacteria can spread through both human and animal faeces. If these faeces are not disposed of properly, there is a considerable risk of transmission of both antibiotic-resistance genes and bacteria. Human faeces contain 23 times more ARGs than river water (Zhen-Chao et al., 2018). Antibiotic concentrations at sites of pharmaceutical waste dumps may facilitate the resistance development in bacteria. Such sites can contribute to the spread and transmission of both ARGs and ARBs. Poultry and livestock are the primary sources and hotspots of ARGs and their development and spread. Despite the fact that manure is a well-established organic fertiliser that is rich in nutrients, it nonetheless facilitates ARG distribution in edible crops and arable soil, consequently impacting humans and animal health (de Araújo et al., 2020).

Enterobacterial diseases caused by resistant gram-negative bacteria are known to be cured by the therapeutic use of colistin which is characterised under the list of most critically important

antibiotics according to WHO for use in human medicine besides amoxicillin (Wongsuvan et al., 2018). ARB rise under selection pressures created by the leftover or residual environmental antibiotics, most of which are regularly detected in manure samples. Poultry samples have been observed to contain unusually high levels of multiple drug resistance (MDR) bacteria, especially those of the *Enterobacteriaceae*. The faecal microbiome and the remnants possess various enteric bacteria and other potentially pathogenic bacteria containing ARGs which are known to stimulate their development and maintenance by the unlikely high use of antibiotics in dairy cattle. Through these processes, acquired resistance of ARGs in additional amounts can pose great risk for humans through the spread of these pathogenic bacteria (Zalewska et al., 2021). Tetracycline is prescribed widely for treating diseases of the skin, respiratory system, and gastrointestinal tract in cattle. Hence, rapid transfer of tetracycline resistance is inevitable because tetracycline ARGs are often located on MGE (Leclercq et al., 2016). Human faeces samples, in healthy conditions, carries bacteria with beta-lactamases genes and exhibit beta-lactam resistance in 49 strains of bacteria (Vázquez-López et al., 2021).

4. FACTORS INFLUENCING ARG TRANSFER

4.1. Environmental pollutants

Pollutants such as heavy metals, nanoparticles, and organic compounds like fertilizers are present in the environment and can contaminate air, water, and soil (Lipczynska-Kochany, 2018; Weithmann et al., 2018; Rahman & Singh, 2019; Madhav et al., 2020; Sall et al., 2020; Shakoor et al., 2020). Several pollutants influence the horizontal transfer of ARGs (Riaz et al., 2020). Heavy metals (e.g., Cr (VI), Zn (II), and Ag (I) facilitate HGT by inducing reactive oxygen species (ROS) production, which increases membrane permeability. These have been shown to enhance the transfer of ARG between *E. coli* (Zhang et al., 2018b). A strong correlation between metal ion concentration and ARG enrichment has been demonstrated by several studies (Zhang et al., 2018c; Ohore et al., 2019). Further, in the environment ARGs can be selected without the presence of antibiotics but with presence of metals (Knapp et al., 2017). Similarly, metal nanoparticles also spread through the environment and enhance the conjugation-mediated transfer of ARGs (Qiu et al., 2015; Wang et al., 2018). Non-antibiotic anti-microbial (NAAM) too are widely used and persistent biocidal agents, with a high propensity of diffusion. Triclosan, a NAAM, has been reported to trigger resistance in microorganisms via the oxidative effect of ROS (Lu et al., 2018). NAAMs chlorhexidine digluconate and triclosan elevates the transmission of ARGs at sub-minimum inhibitory concentrations (MIC) (Jutkina et al., 2018). Nitrogen and phosphorus nutrients in farms and landfills increase the ARG development and their widespread (You et al., 2018). The pollutants in the environment influence the survival of bacteria thereby mediating changes in the ARG flux.

4.2. Consumption of antibiotics

Improper and abusive usage of antibiotics in humans and animals is a major cause of antimicrobial resistance (AMR). Antibiotics are a primary form of treatment for bacterial infections. A large number of antibiotics and disinfectants were overused to control and treat COVID-19 infections due to the lack of effective treatment procedures. This overuse was particularly common in cases where COVID-19 led to inflammation and other associated disorders according to WHO (Elsayed et al., 2021; Gupta et al., 2021).

Researchers have evaluated the ARGs and ARBs occurrence frequency in humans and animals' gut (McInnes et al., 2020; Serwecińska, 2020; Sun et al., 2020). A study assessed ARGs in gut microbiota post-consumption of antibiotics for 14 days. The results confirmed a

significantly high abundance of ARGs in the gut microbiome (Zhu et al., 2018). Antibiotic resistance can be aggravated by antibiotic overuse during prescription for bacterial co-infections, especially where the patients do not clearly show symptoms of infection (Chang et al., 2019; Van de Maat et al., 2019; Blaser et al., 2021; Vaughn et al., 2021).

In social and zoological circles, antibiotics such as β -lactams, lincomycin, and tetracycline are extensively used in pets and animal farms to promote growth (Alagawany et al., 2018). Apart from the vaccination and antibiotic usage in aquaculture, phage therapy and prevention of biofilm formation have taken centre stage in the administration of antibiotics (Kraemer et al., 2018). Similarly, the poultry sector employs antibiotics for disease prevention, treatment and growth promotion. The inadvertent and continual employment of different classes of antibiotics has arisen a new era of resistance and cross-resistance in bacteria, as a result of which several therapies and formulations have lost their therapeutic benefits and efficiency.

4.3. Use of biocidal agents as surface cleaner

Bacterial environments are flat-out influenced and altered by various chemical agents. As per the current regulatory guidelines, public cleaning with disinfectants, particularly for touch surfaces is carried out routinely and because of these biocidal agents, there is continuous selective pressure and bacterial tolerance increases with time (CDC, 2021; WHO, 2020) (Mc Carlie et al., 2020). Bacterial resistance and tolerance that emerged among communities, especially of human transfer, are some of the major risk factors in healthcare. Precisely, the interactions between closely packed urban communities and their surroundings lead to a rise in antimicrobial-resistant pathogens (Chen et al., 2021). Transfer of microorganisms from inanimate surfaces like floors, doorknobs, and toilet seats is a close link of contamination to indoor human settings. In a six-month study where an occupant's hand shared 84% of genes with those present on a kitchen countertop. Bacterial tolerance due to exposure to biocidal agents and antibiotics is distinguished as acquired and intrinsic. Among the different classes of bacteria, the most tolerant species include bacterial spores, mycobacteria, Gram-negative bacteria, and Gram-positive bacteria (Lax et al., 2014). Furthermore, antimicrobial stress by biocidal agents has the potential to alter the gene structure of bacteria through mutations or differential gene expression and subsequently, their increased tolerance (Mc Carlie et al., 2020).

4.4. Wastewater discharge practices

A study of comparison among industrial sludge, wetland sludge, and sediment samples contaminated with pharmaceutical discharge, confirmed the enrichment and distribution of ARGs and their associated resistance. The researchers exemplified the mitigation practices of AMR that occurs via pharmaceutical industries' effluent discharge which is the major link for AMR intervention (Bombaywala et al., 2021). Additionally, the release of antibiotics used for disease prophylaxis and other animal operations into wastewater treatment plants as well as sewage treatment plants occurs in partially metabolised forms, and because of this these plants and the livestock manure pose a high risk for the spread of AMR. Eventually, they become a source of water pollution and public health safety concerns (Deshmukh et al., 2016; Dafale et al., 2020; de Araújo, 2020). Studies carried out on ARBs and ARGs have confirmed the wastewater and sewage plants to be a prime nexus for ARBs and ARGs distribution in animals and humans (Yadav & Kapley, 2019; Xia et al., 2019). The existing bacterial population in untreated sewage is easily able to cultivate HGT events due to the high density of rich nutrients and sub-MIC range of antibiotics (Bengtsson-Palme et al., 2018). Antimicrobial resistance genes (ARGs) are highly transmitted via the several microbial communities that are commonly found in wastewater treatment plants (Turolla et al., 2018). The composition and field features of pharmaceutical products serve their conversion and

dispersal leading to their biotic or abiotic degradation in soil, water, etc., and a loss of action causing harm. Wastewater harbours antimicrobials as they can exist in hydrophilic forms (Huang et al., 2018; Akhil et al., 2021; Cheng et al., 2020; Langbehn et al., 2021). High deposition of various pharmaceutical products in fat tissues of animals also occurs due to them being lipid-soluble and finally entering the food chain. Antibiotics present in the environment in water, soil, plants, meat, and fish accumulate in the form of pharmaceutical products, anticancer drugs, hormones, and antimycotics and pose a serious threat to human health (Yamaguchi et al., 2017; Nelson et al. 2019). Several factors such as demographic distribution, weather, socioeconomic use, consumption, and conduct of communities with antibiotic use, consumption, and dispersal give rise to areal disturbance as well. Antibiotics are prescribed keeping in view the various seasonal aspects, such as temperature, precipitation, and humidity. Antibiotics are routinely prescribed for diarrhea and skin infections in the summer and rainy season while for the common cold and respiratory problems in winter. Surface and groundwater are henceforth affected by the accumulation of antibiotic waste which is usually inappropriately dumped. The class of antibiotics such as ciprofloxacin, azithromycin, and clarithromycin are known to be present in high amounts where azithromycin and clarithromycin specifically in contaminated aquatic environments lay down more risk for organisms like algae, fish, etc. (Tong et al., 2020). The high exercise of antibiotic exposure also creates consequences of serious pollution among geographical factors since contaminated settings easily pave the way to infection in turn increasing bacterial resistance towards antimicrobials used to counteract those infections (Aydin et al., 2019). Table 3 presents a summary of the various environmental factors influencing the spread of ARGs.

Table 3: Overview of the role of environmental factors in the spread of ARGs

Environmental factor	Role in Antibiotic Resistance Genes (ARG) Spread
Air	Acts as a source and disseminator of ARGs
Soil	Serves as a reservoir of ARGs, antibiotics promote resistant strains
Water	Serves as a reservoir and disseminator of ARGs
Natural Reservoirs	Acts as a reservoir for Antibiotic resistance genes
Horizontal Gene Transfer	Allows transfer of genes between bacteria
Selective Pressure	Selective pressure can be generated by antibiotics, evolutionary forces and other agencies resulting in ARGs
Biofilm	Allows genetic exchange including that of ARGs
Climate Change	Promotes environmental conditions aiding in spread of ARGs
Anthropogenic Activities	Antibiotics abuse affects spread of ARGs
International trade and travel	Serves as a platform for global exchange of ARGs

5. POLICY RECOMMENDATIONS TO CONTROL ENVIRONMENTAL AMR

The environmental load of antimicrobial-resistant microbes is a global issue; however, the degree of contamination greatly differs from region to region. As a part of shared

responsibility, it is important to have a global approach incorporating interventions that are relevant for a particular area. Local situation of a particular country or region should be assessed to determine an action plan that is both beneficial and feasible, and enlist factors that prove as risks to public health. It is desirable to have a well-established model system in place for risk assessment of infections and deaths arising from exposure to antibiotic resistance from environmental antibiotic residues (Ahmed et al., 2024). Key factors include implementing 'One Health' approach for antibiotic administration that emphasises the interconnectedness of human, animal, and environmental health, promoting responsible use of antibiotics to prevent AMR across all sectors. The creation of health policies for antibiotic administration under the One Health approach would promote responsible antibiotic use, surveillance of AMR, and would minimize misuse and ensure sustainability. (Samreen et al., 2021). This strategy could be highly effective in tracking and mitigating the effects of environmental antibiotic residue exposure on humans, thereby reducing associated health risks. Many European nations have taken steps to minimise antibiotic resistance through responsible use of antimicrobial drugs. Recently, the FDA has announced plans to address AMR issues. Countries that have implemented integrated national strategies have successfully tackled AMR. Key priorities for tackling AMR in human health involve preventing infections that could lead to the misuse of antimicrobials, guaranteeing universal access to quality diagnostics and suitable treatment for infections, and promoting strategic information and innovation. This includes monitoring AMR and antimicrobial use, as well as investing in research and development for new vaccines, diagnostics, and medications (WHO, 2023).

6. STRATEGIES FOR MITIGATING ANTIBIOTIC RESISTANCE

Mitigating antibiotic resistance in bacteria is a complex global challenge. To address this, we must reduce the overuse and misuse of antibiotics in human medicine and agriculture. Implementing stricter regulations, public health campaigns and surveillance systems is crucial. Improved infection control practices, vaccination programs, and strengthening healthcare infrastructure are equally important in controlling outbreaks of resistant infections.

Developing new antibiotics is crucial, but the process is time-consuming and expensive. Consequently, there is an urgent need to explore alternative therapies. One such promising approach is the use of bacteriophages—viruses that specifically infect bacteria—and antimicrobial peptides, both of which offer potential as treatments for infections caused by resistant bacteria (Wang et al., 2024). Advances in biotechnology, such as the CRISPR-Cas system, provide another innovative solution. This gene-editing tool can precisely target and disable antibiotic-resistance genes in bacterial populations, potentially restoring the efficacy of existing antibiotics (Duan et al., 2021; Montazeri et al., 2024). Combining CRISPR-based therapies with traditional antibiotic treatments could significantly reduce the spread of resistant strains and prolong the lifespan of current drugs.

Environmental management is crucial in curbing antibiotic resistance. Antibiotic residues and resistant bacteria can enter natural ecosystems through wastewater and agricultural runoff, leading to a cycle of resistance. Treating wastewater, managing organic waste effectively, and monitoring environmental hotspots are essential steps (Wang et al., 2024).

7. CONCLUSION

The study of mobilome, resistome, microbial pangenome, and parvome may help understand antibiotic resistance spread. Transmission of AMR is alarming in regions with inadequate waste management. Techniques to remove antibiotics from sewage discharges and understand resistance gene transfer are needed. Monitoring antibiotic residue levels in the environment and human exposure is crucial. A holistic strategy integrating responsible antibiotic use,

infection control, therapeutic innovation, and environmental stewardship is essential to tackle antibiotic resistance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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