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Popular Article

Development of Antibiotic Resistance in The Soil Microbes

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Abstract:

Antibiotic resistance is an emerging threat to public health and it is becoming more challenging to overcome this menace. There are several key drivers for developing antibiotic resistance, apart from the consumption of antibiotics. It is a complex process that includes overt selection pressure imposed on microbial communities due to the excessive use of antimicrobials in human, animal, and agriculture sectors. The soil environment is critical in the epidemiology and transmission of antibiotic resistance. Antibiotic resistomes are found in soil. The resistome consists of an accumulation of antibiotic-resistance genes in pathogenic, antibiotic-producing, and non-pathogenic commensal bacteria in the environment. The emergence of antibiotic-resistance genes in the soil is a global problem and soil is a major reservoir of resistance genes. As animal, human, and environmental health are interconnected, antimicrobial resistance has been prioritized under one health umbrella. It is essential to distinguish clinically relevant antibiotic resistance genes present in the soil, their coexistence, and further transmission into the human food chain.

Introduction:

The World Health Organization (WHO) in 1948 defined health as a "state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being. Human health is largely influenced by the environment and interconnected with several biotic and abiotic elements of the ecosystem, including plants, animals, and microbes. Nowadays the new field of health is gaining momentum known as Planetary Health. It is defined as "the achievement of the highest attainable standard of health, well-being, and equity worldwide through judicious attention to human systems-political, economic, and social,

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that shape the future of humanity and the Earth's natural systems that define the safe environmental limits within which humanity can flourish" (Whitmee *et al.,* 2015). It is relatively a new field examining the links between human health and the natural environment. Soil is a critical component of the planetary health system as most of our food is derived from soil. Soil is considered as the soul of infinite life. However, soil also acts as a major reservoir for antimicrobial resistance (AMR). It harbors abundant microbes and the microbial diversity of soil varies from region to region and also depends on the type of soil. Soils across the globe are one of the largest reservoirs of antibiotic resistance genes (ARGs) and researchers have enlightened our understanding of the ecology and global distribution of the environmental soils and antibiotic resistomes (Delgado-Baquerizo *et al.,* 2022). "Antibiotic resistome" is defined as "a collection of all the ARGs and their precursors in pathogenic and nonpathogenic bacteria.

AMR a Global Problem:

The WHO has declared AMR as one of the 10 global public health threats facing humanity. It is estimated that by 2050 more people may die from infections with multidrug-resistant bacteria or pan-resistant bacteria than from cancer. It is an alarming problem and resistant traits are rapidly spreading across the globe. According to the joint FAO/WHO expert meeting on foodborne antimicrobial resistance, different kinds of foods may act as a vehicle for the transmission of resistant microbes. Potentially, high levels of resistant microbes can be found in animal and plant-origin foods if the agricultural environment is abundant with microbes harboring ARGs. Systematic analysis on the global burden of bacterial antimicrobial resistance estimated that 4·95 million deaths were associated with bacterial AMR in 2019, including 1·27 million deaths attributable to bacterial AMR. The six leading pathogens for deaths associated with resistance identified were *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa.* Methicillin-resistant *S. aureus* was responsible for more than 100,000 deaths attributable to AMR in 2019 (Antimicrobial Resistance Collaborators, 2022). Antimicrobial agents are used for therapeutic purposes in animal and human medicine. However, they have also been heavily used in animal production systems as a growth promoter. Of the known antibiotics consumed by humans and animals, over 30%-90% are excreted through urine and feces. They are finally leached into the soil through polluted water, sewage, wastewater used for agriculture fields, and manure as a fertilizer. Global human antibiotic consumption increased by 65% between 2000 and 2015. In 2017, an estimated 93309 tonnes of antibiotics were sold for use in food-producing animals globally. However, the World Organization for Animal Health (WOAH) recently released a landmark report showing encouraging progress in combatting antimicrobial resistance.

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Global antimicrobial use in animals has declined by 13% in 3 years. As the global authority on animal health, WOAH has been collecting information on the use of antimicrobials in animals since 2015.

Soil As a Reservoir of Resistomes:

Soil is one of the important components of a healthy ecosystem, and is a complex mixture of minerals and organic matter providing nutrients and energy. The biophysical functions of soil are diverse and include nutrient cycling, filtering and buffering, stability and support, promotion of biodiversity, carbon sequestration, etc. The soil's microbial diversity is abundant and plays an important role in the biogeochemical cycle. It has been estimated that one gram of soil may contain over 2000- 50000 microbial species and between 100 million to 1 billion bacteria. The microbial diversity of rich soil is predominated by bacteria followed by fungi, viruses, archaea, algae, and protozoa. Bacteria and fungi are involved in nearly all ecological processes that impact soil and plants (Wang *et al.,* 2024). Soil microorganisms increase soil fertility by breaking down organic matter and minerals. Although soil microbes are very significant in maintaining the soil-plant ecosystem, continuous selection pressure on soil bacteria has increased the diversity and abundance of ARGs, hastening the spread of ARGs in various environmental settings.

The continuous release of antibiotics into the environment is of great concern due to their limited degradation in the environment. The release of increasing amounts of antibiotics into waters and soils creates a potential threat to all microorganisms in these environments. The presence of antibiotic residues in soil alters the overall microbial biomass of a particular soil. The concentrations of antibiotic residues in manure, sewage sludge, biosolids, and soil depend on the type of drug, its metabolism in animals, and the duration of treatment. For example, tetracyclines are the most frequently reported antibiotic residues in animal manure (Cycoń *et al.,* 2019). Intrinsic type of resistance is also found in soil as it is a natural source of antibiotics and thus antibiotic resistance. However, the unwarranted use of antibiotics in livestock, poultry, and humans has created selection pressure on the microbes and led to the development of AMR. It has also impacted the diversity and prevalence of antimicrobial resistance in soil environments that are polluted by wastewater and livestock manure containing residues (Zhu *et al.,* 2019). Soil easily accepts antibiotics like many other environmental pollutants. The external pressure of antibiotics and other pollutants can promote the proliferation and occurrence of antibiotic-resistant bacteria and antibiotic-resistance genes in soil. For example, multidrug-resistant strains of *E. coli* isolated from soil were found to harbor ARGs encoding streptomycin, spectinomycin, tetracycline, sulfonamide, and tetracyclines ARGs detected in soils across the globe.

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Transmission Routes:

There are two ways *viz.* horizontal gene transfer and vertical gene transfer by which soil ARGs are spread. Genes that can confer resistance to relevant antibiotics are referred to as antibiotic-resistance genes. As a result of the increased transmission and abundance of these genes in humans, food-producing animals, and domestic animals, clinically relevant ARGs are now considered to be emerging environmental contaminants (Shi *et al.,* 2023). Corresponding reasons for the development of antibiotic resistance in bacterial communities vary and may be divided into genetic and non-inherited resistance. Bacteria typically use two major genetic strategies to combat the action of antibiotics, i.e. genetic mutation mutations, and acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT). Worldwide observations have shown that HGT can widely occur in the soil environment. Genetic resistance is further classified as intrinsic and acquired resistance. In the bacterial genome, the natural existence of certain genes generates a resistant phenotype called intrinsic resistance. Acquired resistance is due to spontaneous chromosomal mutations or ARGs gained through HGTs. These resistant traits are further transferred from a bacterial species to the progeny and the mechanism is called vertical gene transfer. Non-inherited resistance is not acquired through horizontal or vertical transfer of ARGs but through behaviors such as collaboration between groups. Cooperative resistance, a population-based survival strategy that adapts to high antibiotic stress through the cooperation of multiple resistant bacterial species, is a typical non-inherited resistance (Hu *et al.,* 2022). There are three pathways through which bacterial mobile genetic elements are transmitted *viz.* extracellular DNA-mediated transformation, plasmid-mediated conjugation, and phage-mediated transduction. The process of acquiring DNA by competent bacteria from outside is known as transformation. It does not require physical contact between the donor and recipient bacterial cells. However, only competent bacteria can obtain extracellular DNA. Conjugation is a process by which the plasmid or chromosome carrying ARGs enters the bacteria through the fimbriae of donor bacteria. In transduction, ARGs are transferred from one bacterium to another through bacteriophages.

Detection of ARGs in The Soil Environment:

Researchers across the globe have identified the persistence of antibiotic-resistant bacteria and ARGs in different environments including soil. Due to the massive use of antibiotics, several habitats are under threat leading to the evolutionary changes in the bacterial resistome.

Several resistant bacteria and ARGs originating from hospitals, processing plants, abattoirs, animal farms, wastewater treatment plants, lagoons, etc. keep on accumulating in the soil, and water bodies. Zhuang *et al.* (2021) revealed seven major antibiotic families and their respective ARG subtypes in different habitats on six continents. ARGs belonging to multidrug, glycopeptide, and β-lactam families were most common in hospitals, and sulfonamide and tetracycline families were common in reports from farms, WWTPs, water, and soil. Liu *et al.* (2016) investigated if antibiotic residues excreted from treated animals can contribute to the persistence of resistant bacteria in agricultural environments. It was documented that the administration of ceftiofur, a third-generation cephalosporin, resulted in a ~ 3-log increase in ceftiofur-resistant *E. coli* found in the feces and pen soils by day 10. Treatment with therapeutic doses of ceftiofur or florfenicol resulted in 2–3 log g^{-1} more bacteria than the estimated ID_{50} (2.83 CFU g^{-1}), consistent with a soil-borne reservoir emerging after antibiotic treatment that can contribute to the long-term persistence of antibiotic resistance in animal agriculture. Osbiston *et al.* (2020) estimated levels of antibiotic-resistant bacteria that can survive inhibitory concentrations of chloramphenicol, erythromycin, and vancomycin, in soil samples collected from Great Britain. A significant difference in the level of resistant bacteria was found in agricultural land compared to urban or semi-natural sites. The results also showed that resistance levels to vancomycin and chloramphenicol in the agricultural and urban soils were significantly higher than those for erythromycin. Li *et al.* (2022) studied the occurrence and proliferation of antibiotic resistance in wastewater treatment plants (WWTPs) and documented the existence of multi-resistant bacteria, including *Enterobacteriaceae, Pseudomonas aeruginosa,* and *E. coli* in various processes of WWTPs. Klimkaitė *et al.* (2023) studied antibiotic-resistant *Stenotrophomonas maltophilia* and *Chryseobacterium* species isolated from agricultural soils for ARGs. Their findings indicate that soil microorganisms possess a diversity of ARG variants, which could potentially be transferred to the clinical setting. They find novel variants of aminoglycoside and β-lactam resistance genes, with β-lactamases isolated from the *Chryseobacterium* spp. He *et al.* (2020) stated that antibiotic resistance genes can confer resistance to nine major classes of antibiotics namely tetracyclines (*tet*), sulfonamides (*sul*), *β*-lactams (*bla*), macrolide-lincosamid-streptogramin B (*erm*), aminoglycosides (*aac*), FCA (fluoroquinolone, quinolone, florfenicol, chloramphenicol, and amphenicol) (*fca*), colistin (*mcr*), vancomycin (*van*) and multidrug (*mdr*). The most frequently detected ARG classes in livestock waste are *tet*, *sul*, *erm*, *fca*, and *bla*.

Approaches for Mitigation:

Human and animal fecal matter can carry antimicrobial-resistant microbes and the environment may become contaminated with antimicrobials and antimicrobial-resistant microbes when it is not properly handled. Thus, implementing basic hygiene, and sanitation strategies is mandatory. The connection between waste, antimicrobials, and resistant microbes in the environment, and its impact on human health, is not well understood. Quantifying the AMR pathways and identifying their drivers for environmental evolution and transmission are key components to understanding and managing the current AMR crisis (Larsson and Flach, 2022). Application of concepts of planetary health to track the movement of ARGs between different environmental compartments, including soil, water, food, and air has been advocated (Zhu *et al.,* 2019). Several environmental contaminants including human and veterinary drug residues are polluting the environment. Conventional livestock waste treatment processes do not completely remove ARGs, and anaerobic digestion and biochar addition could be beneficial. More holistic approaches are recommended to prevent environmental pollution from unregulated and neglected pollutants. Li *et al.* (2024) advised increased funding for research, development of advanced detection technologies, establishment of standardized methods, adoption of precautionary regulations, enhanced public awareness and education, cross-sectoral collaboration, and integration of scientific research into policy-making for reducing environmental contaminants.

What Can be Done?

When antimicrobials are used in food animals, the animal manure can carry both antimicrobials and resistant bacteria. It is not known how long resistant microbes remain in manure and, subsequently, in the environment. Environmental pollution by waste generated from pharmaceutical manufacturing plants, hospitals, wastewater treatment plants, untreated human wastes, waste and runoff from aquaculture, livestock, and plant-based food production and processing facilities are among the major contributors. Despite current knowledge gaps, actions can be taken to minimize the risk of AMR in the environment.

Certain approaches include,

(1) Protecting water from contamination with residues,

(2) Reducing the need for antimicrobial use through improved animal health and hygiene practices in the animal agriculture system.

(3) Effective treatment of wastes to reduce and eliminate residual antimicrobials.

(4) Animal manure might be treated before it is used as fertilizer (e.g., composting). If used properly, treatments can be effective in reducing environmental exposure to AMR.

(5) Research on determining the magnitude of the direct and indirect public health costs posed by environmental contamination with antimicrobial residues, AMR organisms, and ARGs.

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