ONE HEALTH APPROACH: INVESTIGATING THE INTERPLAY OF ANTIBIOTIC RESISTANCE IN HUMANS, ANIMALS, AND THE ENVIRONMENT

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Abstract

Antimicrobial resistance (AMR) is a critical global health issue that poses a significant threat to public health, healthcare systems, the environment, and the economy. Despite several steps and various strategies taken in recent decades to address this issue, worldwide AMR trends show no indications of diminishing. Misuse and overuse of various antibacterial agents in the healthcare context, as well as in the agricultural, and aquaculture industries, are thought to be key contributors to the formation of antimicrobial resistance. Furthermore, spontaneous evolution, bacterial mutation, and the transmission of resistant genes via horizontal gene transfer are key factors in antimicrobial resistance. The environmental components of AMR are complicated, with dynamic interactions, cyclic interrelationships, complexity, and various causalities and dynamics in multidimensional media affecting global planetary and animal health. Understanding and managing the resistance challenge as a whole requires quantifying the routes and identifying the drivers and constraints for environmental development and transmission of antibiotic resistance. The current knowledge of the roles of the environment, particularly antibiotic pollution, in resistance development, and transmission, and as a mere mirror of the regional antibiotic resistance status are described in this chapter. We present a viewpoint on existing evidence, outline risk scenarios, and risk assessment, and ultimately recommend some risk-mitigation activities. The current level of information on the destiny of Antibiotic resistance and AMR genes, their spread, and the complexities of the AR phenomenon in connection to anthropogenic activities is insufficient. This chapter highlights current information on Antibiotic resistance in the environment, with a special emphasis on AR propagation in an anthropogenically changed environment and the associated environmental effects.

Keywords - Antibiotic resistant genes (ARG), antimicrobial resistance (AMR), LMICs, Climate Change (CC), WWTPs, landfill leachate (LL), Horizontal gene transfer.

1 Introduction

Global aquaculture production has grown significantly in recent years. Farmers expanded their cultural practices in response to the increasing demand from consumers for animal protein, and as a result, the disease load and spread have increased. In order to combat disease outbreaks, aquaculture farms ultimately rely their hands on antimicrobials or medications. The negative effects of extended antibiotic use include a rise in the development of antimicrobial resistance (AMR). When bacteria, viruses, fungi, and parasites evolve over a period and cease to respond to the medications that are intended to kill them, this phenomenon is known as antimicrobial resistance (AMR). Subsequently, it makes infections more difficult to cure and raises the possibility of disease spread, hazardous illness, and death. The present pace of spread is such that by 2050, an estimated 10 million people will die globally from resistant illnesses, with an associated economic cost of around £60 trillion (O'Neill, 2016). It is now commonly acknowledged as one of the biggest hazards to human and animal health. The worldwide conversation concerning the emergence of AMR has recently been dominated by attention to agricultural and public health centres. However, there has been increasing evidence that environmental factors play a candidate role, and they are important in the emergence, dissemination, and transmission of AMR, potentially reintroduction into humans and other animals. However, mounting data suggests that environmental variables play a more vital role in the origin, spread, and dissemination of AMR, especially from the aquatic environment back to humans and other animals. Pollutions caused by industrialization, modernization, and urbanization by anthropogenic activities encourage the development of AMR in the natural environment. The environmental spread of AMR can result in soil biodiversity loss, animal biodiversity loss and ecological loss, which can then increase the use of antimicrobials (negative feedback from distinctive usage) and aggravate the problem. Nonetheless, global antibiotic use has continuously grown over the last decades, owing to an increase in antibiotic use in both human medicine and other commercial sectors (Klein, E.Y et al., 2018). The usage of Antibiotics in cattle, for example, it has around reached 63,151 tons in 2010 and is expected to rise by 67% by 2030 (Van Boeckel, T.P et al. 2015). Even though there are practices being held on to curb the use of drugs and antimicrobials by proper management procedures and policies, the usage of antibiotics is cradling up in the world. Antimicrobials usage is also piling up in aquaculture, which is the fastest-growing food sector in the world due to intensive production (Henriksson, P.J.G et al., 2018). As a result, pharmaceutical-derived antibiotics are increasingly discovered at considerable levels in man-made ecosystems such as sewage and

wastewater treatment facilities (WWTPs) (Rizzo L et al., 2013). Furthermore, because antibiotic pollution is poorly regulated on a local and global basis, antibiotic compounds are increasingly discovered in terrestrial, freshwater, and marine habitats (Boy-Roura, M. et al., 2018). To limit the worldwide effect of AMR, more surveillance is required to develop epidemiological knowledge on AMR and inform aquaculture and fisheries actions.

2 The rise of Antimicrobial Resistance has greater consequences.

Antibiotics are essential for maintaining the health of people, animals, and plants (Hernando-Amado et al., 2019). Antimicrobials have a long history of being effective in the treatment or prevention of several infectious illnesses; nevertheless, their present efficacy is in jeopardy (Levy & Marshall, 2004). Antibiotic, antiviral, antiparasitic, and antifungal medications that used to be effective are no longer effective because of microorganisms acquiring resistance to antimicrobials (Allen et al., 2010; Topp et al., 2018; Graham et al., 2019; Murray et al., 2022). The WHO Global Report, which was published in April 2014 on AMR monitoring, showed the global breadth of this pandemic as well as the existence of large gaps in present and future surveillance. Antimicrobial resistance may influence people at every stage of life as well as the healthcare, veterinary, and agricultural industries. This makes it one of the most significant global public health problems. If the ecological effects of AMR and its worldwide impact are not addressed, mankind may one day return to a time when even simple infections might be fatal. Patients might suffer harm from second and third-line therapies for antibiotic-resistant infections because they prolong treatment and recovery by weeks or even months and have severe side effects, such as organ failure and multiple disorders. Thus, the public worry over antibiotic resistance would result in greater medical expenses, longer hospital stays, and more mortality in the last stage of the process. Likely the resistant microorganisms that thrive in the environment would pose a serious threat to the microbiome of the ecology, wildlife habitats, and plants. The entire food web that exists in the ecology would become utterly devastated. The World Bank predicts that by 2030, a phenomenal rise in AMR rates will have a particularly detrimental effect on low- and middle-income countries, undermining the development of vulnerable groups, escalating economic inequality, and increasing extreme poverty. According to recent estimates, that the 1.27 million deaths globally in 2019 were directly associated with drug-resistant diseases, whereas 4.95 million fatalities in 2019 were directly linked to bacterial AMR (including those directly related to AMR) (Murray et al., 2022). By 2050, it may cause up to 10 million deaths annually, which would be similar to the number of cancer deaths that year (O'Neill, 2016). An alarm is raised when food animals

exhibit resistance to the targeted illnesses. The most significant problems with public health and food safety are actually brought about by antibiotics' unanticipated effects on the bacteria that are usually found naturally in the gastrointestinal tracts of food animals (WHO 2000a, b). Antibiotic use by humans has effectively launched a massive experiment in evolutionary theory in almost every setting on Earth. In order to tackle AMR, the World Bank and AMR Global Leaders Group recommend integrating it into sustainable development strategies. Tools are needed to aid decision-makers in understanding the social and environmental factors behind AMR in LMICs and connecting it with other sustainable development issues. There exist different strategies for the detection of antimicrobial resistance in natural environments in order to combat the emerging race with Antibiotic-Resistant bacteria (ARB) (Fig 1).
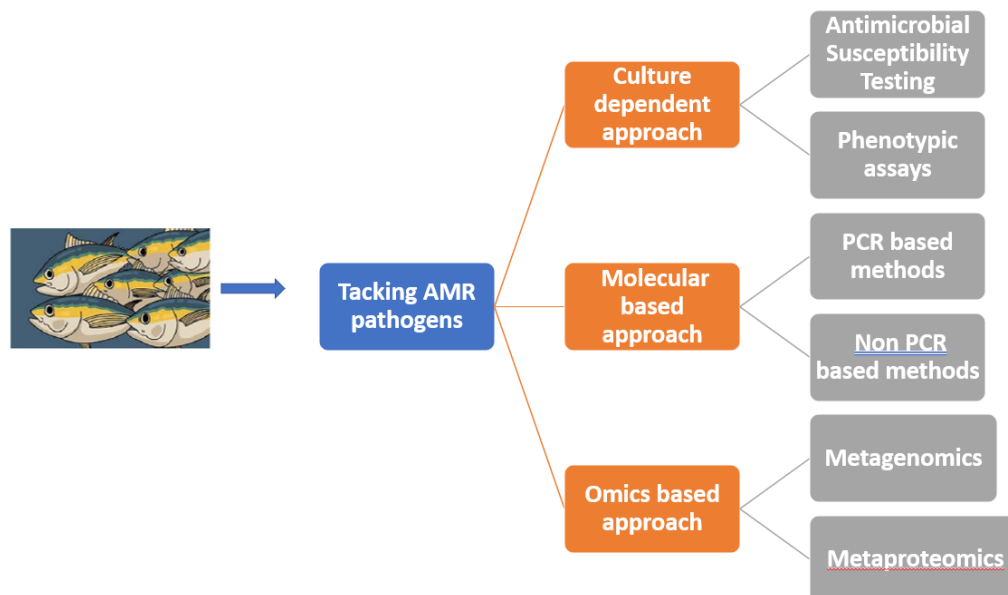
Fig 1 Different strategies for the detection of antimicrobial resistance

2.1 Antibiotics, antimicrobial resistance (AMR) and its concepts

A living organism, usually a bacterium, produces an antibiotic, a chemical substance that is toxic to other microbes. The term "antimicrobial" refers to anything that inhibits or kills microbial cells, such as antibiotics, antifungals, antivirals, and chemicals such as antiseptics. Antibiotics are unquestionably used by organisms in a complicated environment like soil to control the development of rival microorganisms. Soil microbes typically create antibiotics. Microorganisms called bacteria and fungi create antibiotics with a beneficial scope that can be used to cure or prevent illness. Antibiotics are substances produced by bacteria and other microorganisms as a regular part of their life in microbial communities. They are substances that may be found all over nature. The purpose of antibiotic antimicrobials is to treat bacterial

infections on or within the body. This distinguishes antibiotics from the other primary categories of antimicrobials that are now in use:

- Antiseptics are used to sterilize the surfaces of live tissue when there is a significant danger of infection, for example, during surgery.
- When used as disinfectants, bacteria work as non-selective antimicrobials to eliminate a wide range of pathogens. They are used to sanitize surfaces, including those in hospitals, laboratory surfaces and bio cabinet surfaces.

Parallel to this, bacteria from microbial communities are producing naturally occurring antibiotic resistance genes (ARG). Since there have been bacteria, there have also been ARG and antibiotics. A highly diverse collection of genes encoding antimicrobial resistance mechanisms to beta-lactam, tetracycline, and glycopeptide groups that are linked to modern bacterial pathogens, for example, have been exposed by the discovery of ancient DNA in 30,000-year-old permafrost sediments, highlighting the ancient origins of antibiotic resistance. Antibiotics are used globally in livestock to treat bacterial illnesses and/or to improve animal development in addition to being used in human medicine (Du and Liu, 2012). Worldwide antibiotic consumption has been estimated to be between 100 and 200 thousand tonnes annually (Wise, 2002; Kummerer, 2003), with roughly half of this quantity being used for veterinary purposes (Sarmah et al., 2006), even though information on antibiotic use is lacking in many nations.

In fact, microbes have more effects on people than just bacteria. Antifungals and antivirals, respectively, target viruses and fungi, which can both pose a threat to people. In contrast, antibiotics are only substances that target bacteria. Today's antibiotics are primarily made in laboratories, but they frequently take inspiration from elements that are found in nature. For example, some bacteria produce compounds that are specifically made to kill nearby bacteria in order to gain an edge while competing for food, water, or other limited resources. However, certain microbes can merely produce antibiotics only in a laboratory. Antibiotic overuse in animals has been found to be a key risk factor for the emergence of antimicrobial resistance (AMR), a growing threat to public health worldwide. Aquaculture could aid in the global spread of AMR because of its broad global trade and close closeness to the aquatic environment. It is now more crucial than ever to identify infectious disease outbreaks as soon as possible in order to put the required epidemiological controls in place to decrease their negative impacts as a result of the present SARS-CoV-2 pandemic (Oude Munnink et al., 2021).

Three main factors influence bacterial resistance to antibiotics: the absence of target molecules in the cell, the antibiotic compound being inactivated by enzymes, or the impermeability of the bacterial cell to the antibiotic molecule (e.g., due to the physicochemical characteristics of the molecules, the presence of efflux pumps, etc.). At least four well-known mechanisms that aid in bacterial drug resistance were,

(i) the inactivation or modification of the antibiotic.

(ii) an alteration in the antibiotic's target site that reduces its binding capacity.

(iii) the modification of metabolic pathways to circumvent the antibiotic effect.

(iv) the reduced intracellular antibiotic accumulation by decreasing the permeability and/or increasing the antibiotic's active efflux of the antibiotic.

Despite the fact that antimicrobial resistance (AMR) is a hidden pandemic, there are still many questions about how it has spread and developed.

2.2　The impacts of AMR on health, social and economic status on public

Furthermore, rising income levels in developing nations have resulted in a rise in animal protein consumption, which may require the inclusion of more antibiotics in the food animals ingest. The excessive utilization of antibiotics in poor nations, which is a direct outcome of growing wealth, is mostly to blame for the huge increase in worldwide antibiotic use (Chaw PS et al., 2018; Klein EY et al., 2018). In other words, the usage of antibiotics has been proven to positively correlate with both an increase in GDP and the standard of life in low- and middle-income countries (LMICs) (Dall C., 2018; Klein EY et al., 2018)

AMR may have a significant financial effect if left uncontrolled. According to the World Bank 2017, it may cause a 3.4 trillion-dollar yearly deficit in gross domestic product (GDP) over the following ten years and send 24 million additional people into extreme poverty. According to economic theory, AMR is an externality (i.e., an activity having an impact on third parties) originating from the use of antibiotics to treat illnesses. As a result, even though the patient or the doctor who prescribed the antibiotic may not initially notice the selection pressure and subsequent drug resistance caused by antimicrobial use, it will eventually have a negative social and economic impact on the community as a whole (Coast et al., 1996).

People can be cured of illnesses when they are curable with antimicrobials, and future transmission among the community can be easily stopped. Hundreds of millions of lives have

been saved as a result since these "miracle drugs" first became widely used more than 70 years ago. Antimicrobial resistance (AMR) is reducing the efficacy of medications in both developed and poor nations. The world will have to deal with a situation where numerous infectious illnesses have "no cure and no vaccine" if this tendency is allowed to continue unchecked.

However, the expensive effects of AMR on GDP would be greater in two ways: they would be seen over the whole simulation period (which lasts until 2050), and inequality between nations would rise since low-income countries would suffer the greatest gaps in economic development. AMR also makes societal injustices worse. Women, children, migrants, refugees, persons working in specific industries (such as agriculture or healthcare), those living in poverty, and those who are migrants or refugees may all be more susceptible to and/or exposed to drug-resistant diseases (WHO, 2007; Bhopal and Bhopal 2020; WHO et al., 2021). In addition, women are often in charge of collecting water in many nations, and the absence of access to water and sanitation on the property limits the amount of time women can devote to leisure, education, and income-generating activities while also increasing their vulnerability to gender-based violence (Travers et al., 2011; House et al., 2014; UNEP and International Union for Conservation of Nature (IUCN) 2018, p. 25). The common drivers of AMR are mentioned in Figure 1.
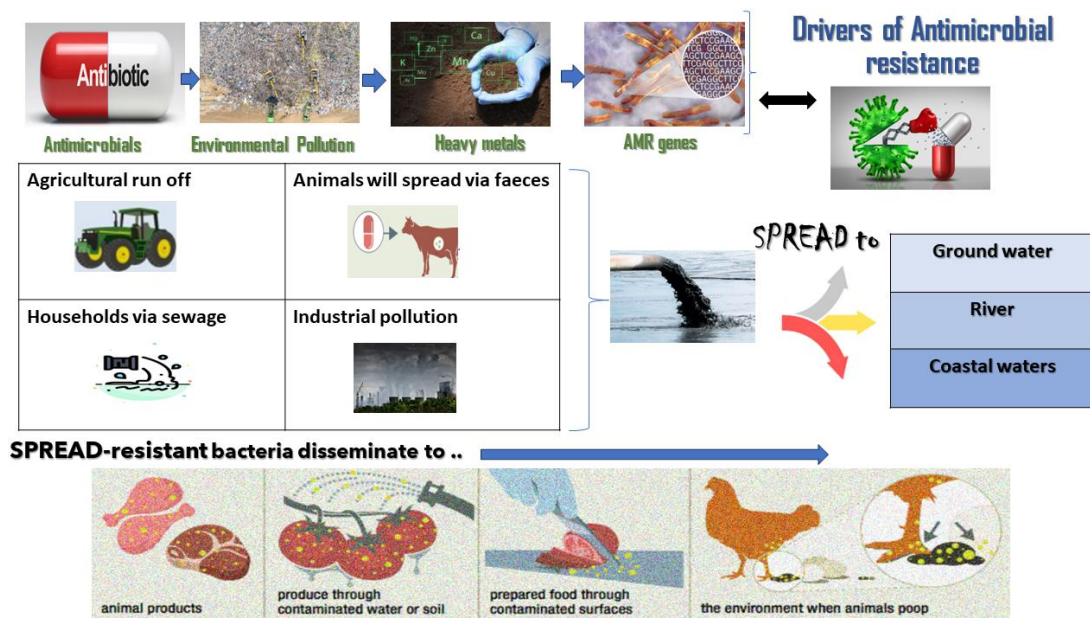
Fig 1 Drivers of AMR in the environment

To better focus policies and help the most vulnerable people and existing natural communities who still run the danger of being left behind, further research is needed on the implications and outcomes of resistance infections that vary by gender and age (WHO, 2018a).

3 AMR's environmental impacts

According to Cantón, González-Alba and Galán (2012) and Perry, Waglechner and Wright (2016), resistant microorganisms can cause other microorganisms (mainly bacteria) in water, soil, and air to develop resistance after encountering them. These microorganisms may have evolved in the environment over time or may have been introduced through human and/or animal waste streams. The AMR epidemic and the environment are inextricably intertwined. Antimicrobial contaminants, which have a detrimental effect on biodiversity and ecosystems, are also distributed by the environment and are a source of AMR microorganisms (UNEP, 2022). It is possible for resistance to emerge to antibiotics, fungicides, antiviral medications, parasiticides, some disinfectants (like triclosan, chlorine, and quaternary ammonium compounds), and other co-selecting medications (like metals like zinc and copper and biocides). These medications are released into the environment by human activity, poor sanitation, or contaminated land and water. Resistant microorganisms can spread and be transferred to people, animals, food animals, plants, and wildlife because of nature's many linkages (Graham et al., 2019; Larsson & Flach, 2022). Significant research and knowledge gaps must be filled to successfully track and control the development of AMR in the environment. ARG reporting unit discrepancies, a lack of consistent methodologies, monitoring goals, and established threshold values are a few of them (Berendonk TU. et al., 2015). Policymakers need to support the concepts and ideas of scientists if AMR in the environment is to be substantially reduced. In order to provide this assistance, more funding should be allocated to research, appropriate reduction objectives and measurements should be established, and multi-stakeholder collaboration should be encouraged through the creation of policies. Bacterial infections driven by multidrug-resistant or extensively drug-resistant organisms have become a grave problem in the environment and global biodiversity due to rising antimicrobial resistance and a thin new antibacterial pipeline.

3.1 AMR development in the environmental condition

Antibiotic resistance may evolve as a result of environmental factors and genetic makeup (Santos-Lopez A et al. 2019, Hughes D et al. 2017, Duro P et al. 2019, Bottery MJ et al. 2020). For instance, different genetic backgrounds can produce different levels of resistance

from the same AMR-causing mutation (Hughes D et al. 2017), and different evolutionary divergent strains of the same species can produce different levels of resistance as well as different mutational pathways that lead to resistance (Card KJ et al., 2019; Lamrabet O et al. 2019). As a result, adaptation to various environments may result in genetic variations that have an influence on the development of AMR. As an illustration, environmental bacteria, especially those that live in the soil, have developed while being exposed to natural antibiotics (presumably at relatively low doses). This is supported by the discovery that antibiotic resistance genes exist even in relatively pure habitats, including the deep ocean, Antarctic lakes, and Arctic permafrost (D'Costa VM et al., 2011).

Inland water sources are seen as a significant vehicle since not all transmission networks and links distribute AMR equally throughout the environment (Fondi et al., 2016). River sediments near wastewater sources might make selection, co-selection, and HGT more likely. Although other factors, such as the specific environmental sources and microorganisms that are carrying the ARGs, also are important to AMR fate in such locations (Quintela-Baluja et al., 2019; Wu et al. 2022), longer contact times between chemicals and wastewater with indigenous microorganisms increase the likelihood of AMR selection and transmission events (Kristiansson et al., 2011).

Contrarily, host-associated bacteria may have spent a considerable amount of time evolving in the absence of antibiotics, yet they are now often exposed to high antibiotic concentrations. The ways in which AMR develops and is maintained in strains from these various origins may be significantly impacted by these variances. There is potential for the formation and maintenance of AMR in the environment if genetic backgrounds that enable bacteria to live as free-living creatures have a high likelihood of evolving the trait and minimal associated fitness costs. This might have significant effects on ambient bacterial ecosystems and the ability of AMR genetic determinants to spread to bacteria that are host-associated and pathogenic.Both changes in a bacterium's native genome and the import of foreign DNA can result in antibiotic resistance. In humans or animals treated with antibiotics, mutations easily happen and become fixed. Pathogens seldom experience such a high selection pressure elsewhere. Additionally, the process is unaffected by the genetic reserve in other species.

For the majority of infections being located in environmental conditions, external factors are often less likely to make a significant contribution to the mutation-based evolution of resistance. Water, soil, and other habitats with highly varying ecological niches offer an

unequalled gene pool with a diversity that is significantly higher than that of the human and domestic animal microbiota with regard to the absorption of new resistance components 24,25. The environmental microbiome's extreme diversity, which offers a wide variety of genes that potentially could be acquired and used by pathogens to counteract the effect of antibiotics (Forsberg et al., 2012; Berglund et al., 2017; Dantas et al., 2008; Pawlowski et al., 2016; Berglund et al., 2020), is, in fact, its most striking characteristic. All kinds of licenced antibiotics—natural, semi-synthetic, or synthetic—have encountered resistance in at least some of the diseases they are intended to treat. This implies that, unless we start thinking profoundly differently about how antibiotics are constructed, external surroundings currently hold resistance elements for all antibiotics that will ever be developed.

Aquatic and terrestrial species may be negatively impacted by quaternary ammonium compounds, other biocides, and some heavy metals (such as zinc and copper) present in waste streams. When bacterial species have numerous genes that confer resistance to these substances and other antimicrobials, these compounds can provide a co-selective pressure (Wales & Davies, 2015). The presence of one drug may co-select for resistance of the other, even in its absence, when the resistance genes co-occur in the same microorganisms (Pal et al., 2015). As a result, it is typical in environmental systems for one antibiotic to co-select for resistance to other antimicrobials. For instance, zinc and copper are frequently added to animal feed as supplements for nutrition and disease prevention, and this may favour improved drug-resistant bacterial survival in environments containing metals, such as the gastrointestinal tract of animals fed these elements (Bearson et al., 2020).

3.2 Climate crisis

The consequences of CC on human health are deteriorating over time, as is their influence on public health, which impacts all physical, natural, social, and behavioral components (WHO, 2022). This deterioration is remarkably similar to that seen with AMR (Cars et al., 2008). As temperatures increase due to climate catastrophe, so does AMR in people, animals, plants, and the ecosystem (McGough, S.F 2020; MacFadden, D.R 2018). In fact, rising temperatures are closely connected to AMR, as they are associated with increasing bacterial growth rates (Pietikäinen, J.; et al., 2018) and horizontal gene transfer (Philipsborn, R et al., 2016). Although AMR is a natural phenomenon, "man-made" factors, such as the abuse and overuse of antibiotics in people, animals, and plants, are the primary causes of its growth and spread (WHO,2022). The transfer of resistance genes from animals to humans using whole genome sequencing (Harrison, E.M et al. 2013) underlines the necessity of global activities to

combat AMR across many sectors (such as human healthcare, agriculture, and the environment) (Pitchforth, E et al. 2022). Climate Change (CC) and AMR have frequently been contrasted because of their enormous scope, but these two problems are even more connected since CC may indirectly cause AMR (O'Neill, C.,2022). Since they affect people, animals, and the environment all at once, it makes it logical to treat them using the One Health approach. Numerous zoonotic microbes that have infected humans imply that there has been a long-standing connection between infectious diseases and global warming (Patz, J.A et al. 1996). For instance, when water systems' temperatures rise, infectious illnesses including Campylobacter, Salmonella, and Vibrio cholerae have returned due to bacteria's adaptation to warmer temperatures (Omazic A et al. 2019, Semenza et al. 2008). Due to the restricted alternatives for treating AMR infections, resistance rates for these bacteria will inevitably rise (Jobling, M.G. 2019; Lipp, E.K et al. 2002; Constantin de Magny, G et al. 2009). Uncertainty persists over the consequences of the re-emergence of pathogenic bacteria from CC, given the already diminished efficacy of several antibiotics (Laxminarayan, R et al., 2019). Therefore, managing "outbreaks" in all contexts requires early detection of infectious diseases associated with CC (Semenza et al., 2009).

Warmer temperatures have also been shown to influence heavy metals or biocides concentrations in soil and water, as well as their absorption by bacteria, activating AMR via co-resistance pathways (. Chen J et al., 2019; Coates-Marnane, J et al., 2016; Knapp et al., 2011; Seiler, C et al. 2012; Singer, A.C et al. 2016). According to Kusi 2022, the primary sources of AMR in surface waters include healthcare institutions, wastewater, agricultural settings, and foods, which may contain antibiotic residues, biocides, and heavy metals. Although CC might be regarded as an additional AMR driver in the aquatic environment (Kusi J et al. 2022), Its causal influence should be regarded with skepticisms (Kaba, H.E.J et al. 2021).

Similarly, intersectoral solutions may be successful in addressing the climate crisis, even if further research is required to determine whether the One Health strategy is sufficient to address CC (Zinsstag, J et al., 2018). One of these aspects has been the subject of the bulk of investigations to date. In order to better study the linkages between environmental changes and AMR from a One Health viewpoint, De Jongh and colleagues suggested using honeybees as a model organism (De Jongh, E.J et al. 2022). Environmental toxins, rising temperatures, and other CC-related variables might have a severe impact on honeybee health, leading to an increase in illnesses specific to honeybees and a reduction in the effectiveness of antibiotics in

treating infections (Regueira, M.S. et al. 2017; Prodˇelalová, J. et al. 2017; Runckel, C et al. 2011). The implementation of the synergy between partners in human, animal, and environmental health should thus be fostered by thorough research of the probable link between AMR and CC.CC and AMR are two of the most serious issues confronting the planet today. Both have been aggravated by human actions and can be alleviated by them. In an era of climate change, the burden of infectious illness might be decreased by concentrating on One Health methods that recognize how human health is inextricably linked to animals and the environment (Gudipati, S et al. 2020). According to "the 2022 report of the Lancet Countdown on Health and climate change," vulnerable persons (e.g., those over 65 years old and children under one-year-old) are more sensitive to the negative effects of heatwave days, a danger that is increased by the concurrent COVID-19 pandemic (Romanello, M et al 2022). At the same time, the climate crisis is having an impact on the spread of infectious illnesses, increasing the danger of emerging diseases and AMR.

3.3 Loss in biodiversity

Recent changes in soil microbial diversity brought on by human activity and climate change may have an impact on the spread of antibiotic-resistance genes in the environment (Zhu & Penuelas, 2020). The ecotoxicological impacts of antimicrobials on environmental microbiomes may also have an influence on larger ecosystem services, such as those linked to biogeochemical cycles and plant health (Brandt et al., 2015). Natural microbial communities play a significant role in ecosystem functioning. Even administering specific medicines to cattle can alter dung beetle microbiota, disrupting the crucial ecological service that dung beetles offer (Hammer et al., 2016). Antimicrobials may endanger the health of ecosystems, which is important for maintaining biodiversity and fully functioning ecosystems (Grenni et al., 2018; Banerji et al., 2019). In contrast, antimicrobial use can threaten to reduce microbial diversity (Chen, J. et al. 2019). Preservation of microbiological biodiversity is crucial to maintain a diverse molecular reservoir for future pharmaceutical discovery. High microbial diversity can act as a biological barrier to resist the spread of AMR (Chen, Q. et al. 2019). According to Neergheen-Bhujun et al. (2017), natural environment microbes have long been and will continue to be sources of pharmacological discoveries for health, disease prevention, and medical usage. Maintaining soil microbial diversity and understanding the forces that shape soil microbial diversity is essential in preserving this soil-borne legacy because soil biota is a crucial component of planetary health (Zhu et al., 2019; Zhu & Penuelas, 2020). According to Grenni, Ancona, and Barra Caracciolo (2018), Jorgensen et al. (2018), and Banerji et al. (2019),

changes in microbial diversity in natural environments are bioindicators of changes in ecosystem processes. Few studies have looked at how the microbes carrying these ARGs persist and interact with other microbial species in their surroundings, despite human activities like the production of wastewater elevating ARGs in affected environments (Rodriguez-Mozaz et al., 2015; Bengtsson-Palme et al., 2018; Smalla et al., 2018; Banerji et al., 2019). Although the effects of antibiotic use and pollution on ecosystem services and biodiversity loss are becoming more apparent, there is still very little proof that AMR causes consequences to biodiversity loss.

3.4   Pollution as a driving force in AMR spread

Although the (more ancient) evolution of ARGs was likely aided by the natural production of antibiotic molecules, this is not the cause of the rapid evolution and spread of resistance factors across strains, species, and environments that we have seen since the discovery of antibiotics as therapeutic agents. Antibiotics generated by environmental microbes are widely distributed, however, they mostly function on a microscale, limiting exposure because it is typical for concentrations to fall off quickly surrounding the generating organisms. On the other hand, synthetic antibiotics operate on a much larger scale and are frequently linked to selection forces that affect entire microbial populations. Antibiotics are released into the environment through human and domestic animal excretions (urine and faeces), improper handling and/or disposal of leftover medications, aquaculture contamination, plant production contamination, and waste streams from antibiotic production. Utilization and excretion of antibiotics result in the most extensive emissions and very possibly the majority of antibiotics that are emitted. However, exposure levels through this method are always constrained by factors including the fraction of the population taking the antibiotic at any particular moment, the dosages utilized, and human or domestic animal metabolism.

Antimicrobial resistance genes are becoming more widely acknowledged as emerging pollutants, and polluted environments can act as sources of AMR. The prevalence of AMR is correlated with anthropogenic inputs (Pruden et al., 2006; Sanderson et al., 2016; UNEP, 2017). The release of biological AMR pollutants resulting from the leakage of both treated and untreated human and animal excreta into the environment is particularly concerning. Pollution issues are exacerbated by the discharge of chemical wastes, such as those from pharmaceutical manufacturers and the disposal of unwanted and outdated antimicrobials.

3.5 Accumulation of Antibiotic Pollution and Toxicity in Larger Organisms.

Antibiotics influence the health profile of living organisms and the microbial community in the environment. With the aid of several standard clinical experiments and reports regarding pharmacology, knowledge regarding the side effects caused by antibiotics on humans and animals has been well delineated. On the contrary, it is also claimed that insignificant antibiotic levels in the ecology do not pose any health hazard to human beings. But continuous exposure to minimal doses of antibiotics over a period of time may lead to adverse health effects for humans by the process accumulation through food and drinking water. Examples include the detection of quinolones and macrolides in chlorinated water used for drinking and the recent detection of triclosan (an antimicrobial agent in soap, detergents, soaps etc.) in breast milk, urine and human serum exerting a variety of unknown health risks. Reports reveal that 75% of the population in the United States is prone to triclosan exposure via certain consumer products being used daily. The toxicity range in humans has been well elucidated, but scarce information is found regarding the toxic levels in the lower organisms. Under lab conditions, even the least concentration of erythromycin and streptomycin had a negative impact on the behavior and survival of artemia as well as in *Daphnia magna.* In addition, the major drawback is the exposure of antibiotics to UV rays in lab circumstances leads to negative impacts by increasing its effectiveness. This leads to antibiotic toxicity among vertebrates. The pollution caused due to antibiotics in aquatic environments has a chronic effect on aquatic organisms. For instance, the concentration of macrolides in sub-inhibitory doses in zebrafish leads to edema in the yolk sac and aliments in the swim bladder. Exposure of quinolone, tetracycline and sulphonamide to other fishes also yields similar effects. Additionally, metabolites of quinolones persist in the body through the process of bioaccumulation, leading to long-term toxicity. Aquatic pollution that is least investigated is known to have a negative impact on aquatic organisms. Amphibians, when exposed to tetracycline, reduce the growth rate and lead to malformation. Disruption of physiological factors by antibiotics can potentially interfere with changes in the expression of genes. It is understood that the majority of antibiotics, independent of their receptors and mechanisms of action, are known to cause significant activation of transcription in bacteria and in several multicellular organisms, even at low doses. Kim, along with his fellow researchers, discovered that exposure to tetracycline had an influence on carbohydrate and protein metabolism as well as affecting the stress response mechanism in *Daphnia magna*. Also, even in the absence of tetracycline, alterations in the gene transcription might persist over several generations.

The tremendously context-specific impact of antibiotic contamination poses a significant public health concern (Danner et al., 2019). Antimicrobial compounds have wide applications in the field of aquaculture, human medicine, agriculture, and livestock. However, significant amounts of active molecules are being excreted from numerous sources into the environment after exposure to antibiotics Factors like the type of antimicrobial drug, host organism, formulation and route of administration determine the unmetabolized concentration of antimicrobials excreted via urine and feces of animals and humans (Kümmerer & Henninger, 2003; Giguère et al., 2013). Inappropriate wastewater treatment leads to exposure to contaminated waters resulting in the development of consumption and excretion cycles (WEF 2021).

The role of the transmitting agent in the environment still remains unclear. Certain diseases (such as *Vibrio* spp. Or *Legionella* spp.) flourishes well in the environment than humans or any animal host. Growth difference in resistant and non-resistant strains after exposure to subacute levels of antibiotics is known to develop an infection with higher affinity in humans or animal hosts. Opportunities of environmental transmission by resistant and non-resistant strains are greatly influenced by environmental variables like oxygen, temperature, competition, predation, and nutrients.

4   Antimicrobial resistance in the Aquatic environment

The recent outbreak of the SARS-CoV-2 pandemic has led to the development of rapid diagnostics assays in order to minimize the harmful effects (Oude Munnink et al., 2021). Antimicrobial resistance (AMR) is a hidden epidemic, yet there are still several unanswered concerns regarding how it has spread and evolved. A comprehensive strategy including all ecosystem niches is urgently needed to understand how antimicrobials and antimicrobial resistance genes (ARGs) originated, maintained, and transmitted (Da Silva et al., 2020). The importance of aquatic ecosystems as the final destination for the discharge of effluents from wastewater treatment facilities (WWTPs) or the direct disposal of sewage of human or animal origin (Zheng et al., 2021; Miłobedzka et al., 2022), runoff from agricultural lands (Buta et al., 2021) and several human activities makes them crucial for understanding how the AMR develops and spreads globally.

Over the past few decades, aquaculture has had the greatest rate of growth in the food sector, with the production of proteins on a worldwide scale expected to increase from 10% to 50% by 2030. The prophylactic use of antibiotics has also become increasingly prevalent as

aquaculture practices have become more intense. These farming systems have been referred to as "genetic reactors" because they allow AMR genes to recombine, exposing ambient bacteria to antimicrobials. AMR genes from aquaculture facilities are released into the environment through fish products, waste products that are utilized as fertilizer and direct sediment runoff. Antimicrobial usage in aquaculture has decreased in "high-income countries" (HICs) in recent years, while it has increased in middle- and low-income nations (MICs, LICs). Effective environmental risk assessment (ERA) methodologies, each with their own advantages and disadvantages, need to be framed for monitoring the spread of AMR. Some of the approved antibiotics that has been used in aquaculture systems are mentioned in the table 1

Table 1 List of antibiotics that have been approved for use in aquaculture.

Approved Antibiotics	Action regarding Disease aspects	Route of administration
Chloramine T	For the control of mortality in bacterial gill disease associated with *Flavobacterium spp.*; columnar is disease associated with *Flavobacterium columnare.*	**Immersion**
Oxytetracycline hydrochloride (Terramycin 343®; Tetroxy® 343)	Used in finfish fry and fingerlings' skeletal markings	**Immersion**
Florfenicol (Aquaflor®)	For the control of mortality in catfish due to enteric septicemia of catfish associated with *Edwardsiella ictaluri*; freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum*; furunculosis associated with *Aeromonas salmonicida*.	**Medicated Articles/Feeds**
Oxytetracycline dihydrate (Terramycin® 100; Terramycin® 200)	• For the control of ulcer disease caused by Hemophilus piscium, furunculosis caused by *Aeromonas salmonicida*, bacterial hemorrhagic septicemia caused	**Medicated Articles/Feeds**

	by *Aeromonas liquefaciens* and pseudomonas disease in salmonids. • For the control of bacterial hemorrhagic septicemia caused by Aeromonas hydrophila and pseudomonas disease in catfish. • For the control of gaffkemia caused by *Aerococcus viridans*	
Sulfadimethoxine/ormeto prim (Romet®-30)	• For the control of furunculosis in salmonids (trout and salmon) caused by *Aeromonas salmonicida* • For the control of bacterial infections in catfish caused by *Edwardsiella ictaluri* (enteric septicemia of catfish).	**Medicated Articles/Feeds**

Major environmental contaminants that have been linked with the spread of AMR profiles in bacterial populations include antimicrobials, pesticides, heavy metals, microplastics, antimicrobials and crude oil. Microplastics, for instance, have the ability to absorb pollutants like heavy metals and antibiotics used in ponds used for aquaculture. Microbial communities being subjected to pressure (i.e., antibiotics) on microplastic surfaces leading to alterations in the chromosomes that improve resistance. Additionally, bacteria may create dense multi-species biofilms on microplastics, which makes it easier for bacteria to transmit AMR genes horizontally or vertically, with the latter including mobile genetic components like class 1 integrons. This is extremely important because the movement of microplastics by the water flow might transfer bacteria with wide AMR profiles to new environments. The Projected Antimicrobial use in aquaculture, as mentioned by Scar et al.,2020 from the year 2017 to 2030 is estimated to be in a voluminous and increasing manner, with China topping the list, Table 1.

Table 2 Projected Antimicrobial use in aquaculture (2017 to 2030)

Country	2017	Projected (2030)
China	57.90%	55.90%
India	11.30%	Remains the same
Indonesia	8.60%	10.10%
Vietnam	5%	5.20%

4.1 Water – rivers, lakes, and sediments

According to Pruden et al. (2006), river and lake sediments can be a temporary source of AMR that rapidly assembles resistance genes and microbes, chemical contaminants and MGEs that have been accumulated in transit (Lu & Lu, 2020). These areas become "new" sources for AMR dissemination due to the deposited material, which may have different resistant microbial hosts than the initial sources due to transformation. In situ, AMR development and transmission can also take place in sediment. For extended periods of time, sediments can be pseudo-static, slowly collecting AMR from polluted water and other sources. However, during severe weather, they turn into sources and remobilize AMR in large numbers into the surrounding environment. The first investigation to show a gradient in the magnitudes of ARGs in water and sediment as there were more WWTPs and runoff from agriculture inputs to the river involved the Cache-La Poudre River, which rises from a pristine source in the Rocky Mountains (Pruden et al., 2006). Studies on the Almendares River in Cuba revealed that over 98% of related ARGs are carried downstream during the rainy season (Knapp et al., 2012), even though untreated wastewater discharges occur year-round and build near wastewater outflows in the dry season (Graham et al., 2011). Similar occurrences have been observed in other places, such as the Ganges, during the summer's monsoon washes deposited silt downstream containing resistant genes and microbes (Ahammad et al., 2014). ARGs in downstream lake sediments mirrored upstream river sediments in a river-lake continuity in China, showing that AMR spread with sediment movement (Chen et al., 2020). Genetic signatures (ARGs) in sediments of rivers mimicked upstream wastewater sources, suggesting that the AMR that was present in the river and lake likely spread in a sequence of stages from human waste sources to the river and lake. AMR diversity increased throughout sediment movement, but interestingly, ARG concentrations did not significantly increase. This suggests that in situ microbial growth was low, but the AMR potentiated ARGs between human and environmental microorganisms. Strong correlations between wastewater treatment facilities and the prevalence of AMR in sediments were found in watershed scale research conducted in the River Thames by Amos et al., with the size, type, and proximity of the treatment facility being the most important predictors of AMR levels in sediments.

4.2 Antimicrobial resistance in marine environments

In contrast to freshwater and wastewater ecosystems, marine habitats have different occurrence mechanisms for ARB and ARG. Marine habitats are home to 28% of ARGs, as per a survey by Hatosy and Martiny in 2015.The coastal runoff of the ARBs from the agricultural

environment is the main cause of the increasing prevalence of AMR in the marine environment. Additionally, human activities are discharging direct antibiotic residues into marine systems. For instance, the usage of 363.4 tons of antibiotics by Chilean marine salmonid farms alone in 2016 may have acted as a selective pressure for the formation of AR in marine habitats (Miranda et al., 2018). The same ARGs were found in the intestines of Baltic Sea farm fish and farm sediments based on metagenomics studies; the use of antibiotics during the hatching and rearing of juvenile fish or the fish's acquisition of the ARGs from marine microorganisms in the farms are two potential explanations for the observation. (Rosenfeld and Zobell, 1947; Baam et al., 1966; Miranda et al., 2018; Tortorella et al., 2018). It is unable to completely rule out the possibility of a bidirectional transmission of ARGs between aquatic ecosystems and people. Studies employing both culture-dependent and culture-independent methods indicate the prevalence of ARB and worldwide contamination of aquatic habitats, including open oceans (Shimizu et al., 2013; Hatosy & Martiny, 2015; Segura et al., 2015; Fekadu et al., 2019). Bacteria in the natural aquatic environment can produce AR as a result of induced mutagenesis at low antibiotic concentrations (Kohanski et al., 2010). Even if the proportion of resistant mutants is quite low, the prolonged presence of antimicrobials could accelerate the selection of ARBs over generations (Gullberg et al., 2011). As a result, aquatic habitats should be taken into consideration as a key to the development and dissemination of ARGs and ARBs.

4.3   Involvement of anthropogenic activities in AMR spread.

Treatment procedures for wastewater do not entirely remove antibiotics, thereby increasing the amount of antibiotics in aquaculture systems. The reported amount of many antibiotics in surface water ranges from 0.001 to 484 g/L globally. Unused antibiotics, which should be returned for safe disposal, are frequently combined with other garbage, and end up in landfills, where their presence is identified in landfill leachate (LL) (Wang, Y. et al. 2022, Wu, D et al. 2022). The purification of LL in conjunction with municipal wastewater at wastewater treatment facilities (WWTPs) is a common method of managing LL produced in landfills (Wang J.Y et al., 2020). Furthermore, wastewater transported to WWTPs has been discovered to include antibacterial compounds, which are employed in the treatment of humans and animals and are frequently released to the environment in an unmodified state (Chen, Y et al., 2020). The use of antibiotics in aquatic environments is linked to an increase in the number of antimicrobial-resistant bacteria (ARB) and the emergence of resistance genes in all forms of natural water bodies. HGT (horizontal gene transfer) and genetic modification in bacteria are influenced by sub-inhibitory doses of antibiotics in aquatic environments. As a result, a number

of diseases have developed resistance to the most potent medicines, and it is unclear how quickly new antibiotic-resistant microorganisms emerge. Resistance-developing microorganisms disseminate resistance genes in the environment and transmit them to the following generation. Antibiotics and antibiotic resistance might potentially be deposited in surface waters. Recreational activities in some surface waters that contain antimicrobial resistance genes (ARGs) raise the possibility of human exposure to organisms with resistance.

The anthropogenic environment and all of its objects have a direct impact on the existence of antibiotics as well as the propagation of ARB and ARGs in the environment. Municipal infrastructure facilities, such as WWTPs and landfills, but also biogas plants and agriculture, including plant and animal production, are important reservoirs of antibiotics, ARBs, and ARGs. Anthropogenic activity allows a large pool of antimicrobials to enter the environment, resulting in unregulated use by humans and animals, as well as incorrect disposal of unneeded medications. Incomplete antibiotic metabolism and the fact that antibiotics permeate multiple environments add to selection pressure, allowing for an expansion in the ARG pool among microbes.

Numerous studies show that ARGs are ubiquitous in a variety of anthropogenic contexts, with a wide range of occurrences. Mobile genetic elements (MGEs) and HGT processes, which occur in a variety of contexts, particularly those at WWTPs, play an important role in the transmission of ARGs. Antibiotics, as well as ARB and ARGs, are released into the aquatic environment in conjunction with discharged treated wastewater and LL, as well as through surface runoff from arable fields and agricultural buildings. Furthermore, the soil environment is frequently supplemented with these micropollutants as a result of fields being fertilized with stabilized waste from municipal facilities and the agricultural industry.

Escherichia coli from the river Yamuna (India), a heavily polluted river that gets a significant amount of human impact from urban and animal sources, was examined by Singh et al. They found that the isolates had strong AMR profiles, emphasizing the presence of class I integrons and of ESBLs of the CTX-M-15 type. According to research done in Ireland by Sala-Comorera et al in 2021 different watercourse discharges have a significant impact on the abundance of AMR in both bacterial and bacteriophage fractions in marine waters. This could expose users to fecal pollution and raise their risk of coming into contact with ARGs. The extent to which AMR is required to truly pose a threat to the ecosystem is a further unanswered topic regarding its presence in the environment. In the end, Pallares-Vega et al. demonstrated

how ecological factors may prevent conjugative plasmid transmission from gut bacteria once they have been released into the environment by several in vitro experiments. Their findings emphasize the prospect that plasmid transmission by fecal microbes may occur in aquatic environments despite various existing environmental circumstances.

5   Impact of AMR on the food chain

Food is an effective means to transmit harmful germs and AMR degradation. Notably, a rise in AMRB in food would be harmful to people's health. It may be difficult to properly comprehend the extent to which AMR is transmitted around the world through the food supply. Throughout the whole farm-to-fork chain, AMRB has the potential to contaminate food supplies. Foods that are being served to consumers raw or undercooked are likely to retain the AMRB that contaminates items at the farm level. AMRB are direct contact with infected animals or biological components (such as urine, feces, blood, semen, and saliva) and indirect contact with food.

The food supply chain is another key area in the One Health paradigm for comprehending the spread and evolution of AMR since it links environmental sources of bacteria with humans. The study by Montero et al. examined ESBL-producing E. coli found in Ecuadorian fruits, vegetables, and irrigation waters. ARG quantification, physicochemical analysis, and network plots based on 16S rRNA metagenomics were also used in the paper by Cheng et al. to investigate sediments from aquaculture farms in China. Their findings offer proof for comprehending the environmental dangers connected to aquaculture methods. On the other hand, Ye et al. demonstrated that reactive oxygen species (ROS) have a role in bacterial resistance and sensitivity to ceftazidime in *Edwardsiella tarda*, a significant pathogen in aquaculture. Due to the inactivation of the pyruvate cycle, they observed less ROS generation in ceftazidime-resistant *E. tarda* than in a susceptible strain. Their research also identifies a novel mechanism, pyruvate cycle stimulation by $Fe3+$, which boosts ROS generation.

6   AMR's perspective

This brief serves as an example of how eliminating AMR in the environment will necessitate a diverse strategy due to its wide-ranging environmental impacts. Measures for preventing, reducing, and remediation will need to be created and put into place at all phases of the spread of AMR in the surroundings, from detecting exposure sources to getting AMR out of food and water supplies. By examining present environmental changes that trigger and encourage the growth of AMR, microbiologists play a critical role in the fight against AMR in

the environment. Additionally, they are pioneers in the creation of novel methods for detecting, diagnosing, and reducing AMR from all environmental sources. The best-known example that can be stated is that, in terms of epidemiological monitoring, outbreak identification, and infection management, whole-genome sequencing (WGS) of bacterial pathogens seems promising. WGS is being used by scientists, especially microbiologists, to identify Staphylococcus aureus strains that are most likely to develop antibiotic resistance while being treated. Using antibiotic adjuvants, they have also utilized this ground-breaking method to stop or slow down the emergence of resistance. Similarly, bacteriophages, viruses that infect bacteria, have potential benefits for both agricultural productivity and animals. Since they can selectively target bacteria without harming the host microbiome, they provide a possible replacement for antibiotics and growth hormones.

A number of molecular tactics and strategies have been developed over the past few decades to combat AMR in the environment, including the creation of sensitive and precise diagnostics for bacterial and viral illnesses (to help reduce unnecessarily overusing antibiotics), gene-editing technology, DNA and mRNA vaccines and recently developed, CRISPR technology. To make sure that solutions are practical and long-lasting, all of these advancements have required multifaceted, multi-stakeholder collaboration and investment. Since pathogens are always changing, these treatments will need to stay up or be changed. Therefore, it is crucial that public policy recognizes the importance of AMR in the environment and aids in scientists' attempts to completely eradicate AMR in the environment.

Microbes constantly evolve techniques to circumvent the technology and inventions that humans are continually developing to lessen the effects of AMR. Since these microorganisms will never stop evolving, scientists are constantly creating new technologies that are critically important for the quick identification of these resistant, always-evolving microbes and for directing their focused and timely removal from the surrounding environment.

Nanotechnology is another emerging area that has several applications across many industries. Nanomaterials were primarily created via physical and chemical processes since this technology has its roots in both science and engineering. However, experts in microbiology have attempted significant attempts to create a more sustainable method of producing these nanomaterials utilizing various bacteria that is both economical and environmentally friendly. Without giving up on their efforts, microbiologists have developed ways to completely eradicate these AMR microbes concerning the environment by using these microbe-mediated

nanomaterials to detect them in the environment, particularly from food and water sources. It's interesting to note that some of these microorganisms were employed to create nanoparticles that were isolated from their natural habitat.

Microbe-mediated nanomaterials differ from traditional antibiotics, in that they target several locations in these resistant microorganisms. This makes them a viable weapon that, if used effectively, might put an abrupt end to AMR in the environment. In order to combat the worldwide threat of AMR in our environment, it is advised that significant energy be directed into scaling up this promising and sustainable technology or innovations.

7   Policy Approaches to Tackle Antibiotic Pollution and ABR

Managing the social and economic consequences of the antibiotic pollution and resistance dilemma is a global issue due to the situation's enormity and the estimated 700,000 annual fatalities caused by antibiotic resistance worldwide. This multi-sector problem is frequently addressed using "The One Health model," which unites the concerns of environmental, animal, and human health. The World Health Assembly implemented a global action plan in 2015 to address the antibiotic pollution and resistance crisis on a global scale, providing the framework for individual national action plans to create rules and regulations to fight ABR and antibiotic pollution in general. We will provide an overview of current national action plans and strategies in the section that follows in relation to recognized hotspots of antibiotic contamination and ABR development. Few contrasts national action plans against AMR aimed at a few sample regions and nations within them: Europe., the South-East Asian region (case study: India) and the Pan-American region (case study: Canada). Antimicrobial Resistance (AMR) and Antibiotic pollution policies have been developed in the Pan-American area to address the overuse of antibiotics in the health and agricultural sectors, while other exposure sources have received far less attention. Canada volunteered for multi-sectoral assistance for the execution of the WHO Global Action Plan on ABR and participated in international efforts to combat antibiotic contamination and ABR. "Taking Attempts Against Antibiotic Resistance and Antibiotic Use: A Pan-Canadian Framework for Action" emphasizes the following three themes: surveillance, management, and innovation. Antibiotic resistance is a serious issue in the South-East Asian region due to widespread and inappropriate antibiotic usage, yet there are no systematic monitoring mechanisms in action. Antibiotic misuse is caused by relatively unsecured rules, an inadequate level of awareness, an elevated prevalence of medication oneself brought about by easy access to antibiotics without a prescription, and a

lack of knowledge about how to use antibiotics properly. Improper medicinal prescription also contributes to ABR increase in a particular area owing to inconsistencies in diagnostics, consumer demands and incentives from drug manufacturers. Additionally, this area includes the majority of the nations with antibiotic production facilities which is a significant contributor to antibiotic contamination leading to AMR. India in recent times begun tracking antibiotic contamination and creating ABR rules in response. For instance, in order to encourage antibiotic stewardship, India's medical societies issued a set of national guidelines in 2012. The primary recommendations were then integrated into the 2017 National Action Plan on Antimicrobial Resistance, which was based on the WHO Global Plan.

In order to spot emerging threats or evolving trends in the use of antibiotics and ABR in agriculture, particularly in animal production settings India, Canada, and other Asian and European member states established and strengthened surveillance systems. These countries are now emphasizing the promotion of the responsible use of antibiotics in animal healthcare. In this regard, the use of antibiotics as growth promoters in animals for human consumption as well as livestock, has been entirely prohibited by the EU since 2006. As of February 2018, a more stringent regulatory framework for medications for animals and medicated feeds has been put in place in Canada. This framework includes making it easier to get alternatives and promoting the implementation of better practices to lessen the usage of antibiotics. For instance, farmers in Canada are now obliged to obtain veterinarian prescriptions for antibiotics, and the labels of veterinary medicines also include comments on responsible usage in addition to the removal of claims about medicated feed and growth enhancement. Despite the fact that there are few laws prohibiting the use of antibiotics for non-therapeutic purposes, India is one of the top five countries in the world that use antibiotics in the food and animal industry. As antibiotics are widely used as growth promoters, only a few regulations are being followed.

Antibiotics in aquaculture may only be used to combat disease, not to boost growth, according to regulations in Canada, India, and Europe. Because many infections affecting farmed fish may now be controlled using vaccinations, the amount of antibiotics used in aquaculture in these countries should be considerably decreased, lowering the danger of ARB and ARG environmental transmission. Furthermore, veterinarians in Canada as well EU, must prescribe the minimal quantity of antibiotics required to treat farmed fish. Despite regulatory frameworks, antibiotic abuse persists in the Indian aquaculture business, with multi-drug resistance bacteria found in more than two-thirds of aquaculture samples. Policies were implemented in all three regions to raise awareness of ABR and the risks of over-prescription

of antibiotics in human medicine, encouraging stewardship in patients and healthcare professionals and promoting improved standards in the welfare of people by avoiding unnecessary use and prescription of antibiotics to cure illnesses. Health Canada, for example, is in the process of recommending that drug sponsors change their product labelling with a special focus on when and how to use antibiotics, therefore encouraging the use of the appropriate antimicrobials for each therapy. With an emphasis on the need for more evidence on the impact of industrial pollution by pharmaceutical companies, as described in the EU action plan and with no mention of the topic in the Canadian National Action Plan, there are currently no procedures in place to regulate the suppliers in the pharmaceutical industry to ensure that antibiotics are not released into the surrounding waterways during production. Given that India is one of the world's major producers of antibiotics, the National Action Plan of India is one of the first plans to announce the intention to establish regulations that control antibiotic residues in industrial effluents.

8 Conclusion

The continuous abuse, misuse, and unregulated pollution of the environment by antimicrobials is turning the AMR problem into a worldwide health disaster. To address the AMR problem, new rules need to be implemented that restrict the release of antimicrobial residues into the environment and promote adequate monitoring to reduce their buildup and prompt removal. To establish effective control tactics, further studies are needed to understand the magnitude and molecular foundations of AMR development and ARG transfer to other pathogenic bacteria. The public's participation in the local management and disposal of antimicrobials and AMB remains a viable area of collaboration and policy development to control the AMR epidemic, as it might foster both a sense of responsibility and awareness. The complex commonalities between AMR and CC should be deeply investigated from a One Health perspective.

In addition to contributing to the spread of antibiotic resistance, antibiotic pollution has the potential to negatively impact human and ecological health. On the one hand, antibiotic contamination is likely to be highly disruptive in aquatic settings, where it might hinder ecosystem functioning and have an influence on creatures exposed throughout their life cycle. Antibiotics in the environment and in animals, on the other hand, may have an influence on human health. While the effect of such exposure on people is uncertain, epidemiological studies show that long-term antibiotic exposure may contribute to chronic diseases such as obesity,

diabetes, and asthma. As a result, it is critical to assess the total impact of antibiotic contamination on individuals and the environment. Moving from data collection to more interpretive studies will assist in the development of effective policies based on the study. Current policy plans are centered on monitoring, but the magnitude of the situation necessitates more forward-thinking measures. Understanding antibiotic pollution and resistance as part of a "One Health Approach" may assist in the development of more societal participation and, eventually, more efficient policies. Such regulations must assess the direct hazards of transmission posed by specific polluted settings while also accounting for the complex patterns of inter-environmental transmissions that may occur.

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Declarations

Competing Interests

9   References

O'Neill J (2016) Tackling drug-resistant infections globally: final report and recommendations. Review on Antimicrobial Resistance: 84 pp. https://doi.org/10.1016/j.jpha.2015.11.005.

Hernando-Amado, S., Coque, T.M., Baquero, F. and Martínez, J.L. (2019). Defining and combating antibiotic resistance from one health and global health perspectives. Nature Microbiology 4(9), 1432–1442. https://doi.org/10.1038/s41564-019-0503-9.

Levy, S.B. and Marshall, B. (2004). Antibacterial resistance worldwide: causes, challenges and responses. Nature Medicine 10(12S), S122–S129. https://doi.org/10.1038/nm1145

Graham, D.W., Olivares-Rieumont, S., Knapp, C.W., Lima, L., Werner, D. and Bowen, E. (2011). Antibiotic resistance gene abundances associated with waste discharges to the Almendares River near Havana, Cuba. Environmental Science and Technology 45(2), 418–424. https://doi.org/10.1021/es102473z.

Allen, H.K., Donato, J., Wang, H.H., Cloud-Hansen, K.A., Davies, J. and Handelsman, J. (2010). Call of the wild: antibiotic resistance genes in natural environments. Nature Reviews Microbiology 8(4), 251–259. https://doi.org/10.1038/nrmicro2312.

Topp, E., Larsson, D.G.J., Miller, D.N., Van den Eede, C. and Virta, M.P.J. (2018). Antimicrobial resistance and the environment: assessment of advances, gaps and recommendations for

agriculture, aquaculture and pharmaceutical manufacturing. FEMS Microbiology Ecology 94(3). https://doi.org/10.1093/femsec/fix185.

Murray, C.J.L., Ikuta, K.S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Naghavi, M. et al. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet 399(10325), 629-655. https://doi.org/10.1016/s0140-6736(21)02724-0.

World Health Organization (2021a). Antimicrobial resistance: Key facts, 17 November. https://www.who.int/newsroom/fact-sheets/detail/antimicrobial-resistance. Accessed 11 November 2022.

Oude Munnink, B. B., Worp, N., Nieuwenhuijse, D. F., Sikkema, R. S., Haagmans, B., Fouchier, R. A. M., et al. (2021). The next phase of SARS-CoV-2 surveillance: real-time molecular epidemiology. Nat. Med. 27, 1518–1524. doi: 10.1038/s41591-021-01472-w

Travers, K., Khosla, P. and Dhar, S. (eds.) (2011). Gender and Essential Services in Low-income Communities: Report on the Findings of the Action Research Project Women's Rights and Access to Water and Sanitation in Asian Cities. Montréal: Women in Cities International. https://www.academia.edu/63022716/Gender_and_essential_services_in_ low_income_communities_report_on_the_findings_of_the_action_research_project_Wo men_s_Rights_and_Access_ to_Water_and_Sanitation_in_Asian_Cities_.

House, S., Ferron, S., Sommer, M. and Cavill, S. (2014). Violence, Gender & WASH: A Practitioner's Toolkit – Making Water, Sanitation and Hygiene Safer Through Improved Programming and Services. London: Sanitation and Hygiene Applied Research for Equity. https://www.susana.org/_resources/documents/default/3-2098-7-1414164920.pdf

World Health Organization (2018a). Tackling Antimicrobial Resistance (AMR) Together. Working Paper 5.0: Enhancing the Focus on Gender and Equity. https://www.who.int/antimicrobial-resistance/national-action-plans/ AMRGenderEquityGuidance-Sept2018.pd

Graham, D.W., Bergeron, G., Bourassa, M.W., Dickson, J., Gomes, F., Howe, A. et al. (2019). Complexities in understanding antimicrobial resistance across domesticated animal, human, and environmental systems. Annals of the New York Academy of Sciences 1441(1), 17–30. https://doi.org/10.1111/nyas.14036

Larsson, D.G.J. and Flach, C.-F. (2022). Antibiotic resistance in the environment. Nature Reviews Microbiology 20, 257–269. https://doi.org/10.1038/s41579-021-00649-x

Berendonk TU, Manaia CM, Merlin C, Fatta-kassinos D, Cytryn E, Walsh F et al. Tackling antibiotic resistance: the environmental framework. Nature Reviews Microbiology 2015; 13, 310–317

Fondi, M., Karkman, A., Tamminen, M. V., Bosi, E., Virta, M., Fani, R., Alm, E., et al. (2016). "Every gene is everywhere but the environment selects": global geolocalization of gene sharing in environmental samples through network analysis. Genome Biology and Evolution 8(5), 1388–1400. https://doi.org/10.1093/gbe/evw077.

Bhopal, S.S., and Bhopal, R. (2020). Sex differential in COVID-19 mortality varies markedly by age. The Lancet, 396(10250), 532–533. https://doi.org/10.1016/S0140-6736(20)31748-7.

World Health Organization (2007). Addressing Sex and Gender in Epidemic-Prone Infectious Diseases. https://apps.who.int/iris/handle/10665/43644

Kristiansson, E., Fick, J., Janzon, A., Grabic, R., Rutgersson, C., Weijdegård, B., et al. (2011). Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. PLoS ONE 6(2). https://doi.org/10.1371/journal.pone.0017038.

Wu, D., Zhao, J. Su, Y. Yang, M. Dolfing, J. Graham, D.W. et al. (2022). Explaining the resistomes in a megacity's water supply catchment: Roles of microbial assembly-dominant taxa, niched environments and pathogenic bacteria. Water Research 228. https://doi.org/10.1016/j.watres.2022.

Quintela-Baluja, M., Abouelnaga, M., Romalde, J., Su, J.Q., Yu, Y., Gomez-Lopez, M. et al. (2019). Spatial ecology of a wastewater network defines the antibiotic resistance genes in downstream receiving waters. Water Research 162, 347–357. https://doi.org/10.1016/j.watres.2019.06.075.

Santos-Lopez A, Marshall CW, Scribner MR, Snyder DJ, Cooper VS. Evolutionary pathways to antibiotic resistance are dependent upon environmental structure and bacterial lifestyle. eLife 2019; 8, e47612

Hughes D, Andersson DI. Evolutionary trajectories to antibiotic resistance. Annual Review of Microbiology 2017; 71, 579–596

Durão P, Balbontín R, Gordo I. Evolutionary mechanisms shaping the maintenance of antibiotic resistance. Trends in Microbiology 2018; 26, 677–691

Bottery MJ, Pitchford JW, Friman V. Ecology and evolution of antimicrobial resistance in bacterial communities. The ISME Journal 2020; 15, 939–948.

Card KJ, LaBar T, Gomez JB, Lenski RE. Historical contingency in the evolution of antibiotic resistance after decades of relaxed selection. PLoS Biology 2019; 17, e3000397

Lamrabet O, Martin M, Lenski RE, Schneider D. Changes in intrinsic antibiotic susceptibility during a long-term evolution experiment with Escherichia coli. mBio 2019; 10(2), e00189–19

Card KJ, Jordan JA, Lenski RE. Idiosyncratic variation in the fitness costs of tetracycline-resistance mutations in Escherichia coli. Evolution 2021; 75, 1230–1238

D'Costa VM, King CE, Kalan L, Morar M, Sung WW, Schwarz C, et al. Antibiotic resistance is ancient. Nature 2011; 477(7365), 457–61

Nesme J, Cécillon S, O.Delmont T, Monier J, Vogel TM, Simonet P et al. Large-scale metagenomic-based study of antibiotic resistance in the environment. Current Biology 2014; 24, 1096–1100

Forsberg, K. J. et al. The shared antibiotic resistome of soil bacteria and human pathogens. Science 337, 1107–1111 (2012).

Berglund, F. et al. Identification of 76 novel B1 metallo-beta-lactamases through large-scale screening of genomic and metagenomic data. Microbiome 5, 134 (2017).

Dantas, G., Sommer, M. O. A., Oluwasegun, R. D. & Church, G. M. Bacteria subsisting on antibiotics. Science 320, 100–103 (2008).

Berglund, F. et al. Comprehensive screening of genomic and metagenomic data reveals a large diversity of tetracycline resistance genes. Microb. Genomics https://doi.org/10.1099/mgen.0.000455 (2020).

Pawlowski, A. C. et al. A diverse intrinsic antibiotic resistome from a cave bacterium. Nat. Commun. 7, 13803 (2016)

Wales, A.D. and Davies, R.H. (2015). Co-selection of resistance to antibiotics, biocides and heavy metals, and its relevance to foodborne pathogens. Antibiotics 4(4), 567–604. https://doi.org/10.3390/antibiotics4040567.

Pal, C., Bengtsson-Palme, J., Kristiansson, E. and Larsson, D.G.J. (2015). Co-occurrence of resistance genes to antibiotics, biocides and metals reveals novel insights into their co-selection potential. BMC Genomics 16(1), 1–14. https://doi.org/10.1186/s12864-015-2153-5.

Bearson, B.L., Trachsel, J.M., Shippy, D.C., Sivasankaran, S.K., Kerr, B.J., Loving, C.L. et al. (2020). The role of Salmonella genomic island 4 in metal tolerance of Salmonella enterica serovar i 4,[5],12:i:- pork outbreak isolate USDA15WA-1. Genes 11(11), 1291. https://doi.org/10.3390/genes11111291.

World Health Organization (WHO). Strategic Priorities on Antimicrobial Resistance. Available online: https://apps.who.int/iris/ bitstream/handle/10665/351719/9789240041387-eng.pdf (accessed on 1 November 2022)

Harrison, E.M.; Paterson, G.K.; Holden, M.T.; Larsen, J.; Stegger, M.; Larsen, A.R.; Petersen, A.; Skov, R.L.; Christensen, J.M.; Bak Zeuthen, A.; et al. Whole genome sequencing identifies zoonotic transmission of MRSA isolates with the novel mecA homologue mecC. EMBO Mol. Med. 2013, 5, 509–515. [CrossRef] [PubMed]

Pitchforth, E.; Smith, E.; Taylor, J.; Davies, S.; Ali, G.C.; d'Angelo, C. Global action on antimicrobial resistance: Lessons from the history of climate change and tobacco control policy. BMJ Glob. Health 2022, 7, e009283. [CrossRef] [PubMed

O'Neill, C. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations; HM Government: London, UK, 2016. Available online:https://amrreview.org/sites/default/files/160518_Final%20paper_with%20cover.pdf (accessed on 1 November 2022).

Patz, J.A.; Epstein, P.R.; Burke, T.A.; Balbus, J.M. Global climate change and emerging infectious diseases. JAMA 1996, 275, 217–223. [CrossRef] [PubMed]

Almeida, A.P.; Gonçalves, Y.M.; Novo, M.T.; Sousa, C.A.; Melim, M.; Grácio, A.J. Vector monitoring of Aedes aegypti in the Autonomous Region of Madeira, Portugal. Euro Surveill. 2007, 12, E071115.071116. [CrossRef]

Omazic, A.; Bylund, H.; Boqvist, S.; Högberg, A.; Björkman, C.; Tryland, M.; Evengård, B.; Koch, A.; Berggren, C.; Malogolovkin, A.; et al. Identifying climate-sensitive infectious

diseases in animals and humans in Northern regions. Acta Vet. Scand. 2019, 61, 53. [CrossRef] [PubMed]

Semenza, J.C.; Menne, B. Climate change and infectious diseases in Europe. Lancet Infect. Dis. 2009, 9, 365–375. [CrossRef] [PubMed]

Jobling, M.G. Trust but Verify: Uncorroborated Assemblies of Plasmid Genomes from Next-Generation Sequencing Data Are Likely Spurious. Microb. Drug Resist. 2019, 25, 1521–1524. [CrossRef]

Lipp, E.K.; Huq, A.; Colwell, R.R. Effects of global climate on infectious disease: The cholera model. Clin. Microbiol. Rev. 2002, 15, 757–770. [CrossRef] [PubMed]

Constantin de Magny, G.; Colwell, R.R. Cholera and climate: A demonstrated relationship. Trans. Am. Clin. Climatol. Assoc. 2009, 120, 119–128.

Laxminarayan, R.; Duse, A.; Wattal, C.; Zaidi, A.K.; Wertheim, H.F.; Sumpradit, N.; Vlieghe, E.; Hara, G.L.; Gould, I.M.; Goossens, H.; et al. Antibiotic resistance-the need for global solutions. Lancet Infect. Dis. 2013, 13, 1057–1098. [CrossRef]

Zinsstag, J.; Crump, L.; Schelling, E.; Hattendorf, J.; Maidane, Y.O.; Ali, K.O.; Muhummed, A.; Umer, A.A.; Aliyi, F.; Nooh, F.; et al. Climate change and One Health. FEMS Microbiol. Lett. 2018, 365, fny085. [CrossRef] [PubMed]

Woolhouse, M.; Ward, M.; van Bunnik, B.; Farrar, J. Antimicrobial resistance in humans, livestock and the wider environment. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2015, 370, 20140083. [CrossRef] [PubMed

Cleaveland, S.; Sharp, J.; Abela-Ridder, B.; Allan, K.J.; Buza, J.; Crump, J.A.; Davis, A.; Del Rio Vilas, V.J.; de Glanville, W.A.; Kazwala, R.R.; et al. One Health contributions towards more effective and equitable approaches to health in low- and middleincome countries. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2017, 372, 20160168. [CrossRef

De Jongh, E.J.; Harper, S.L.; Yamamoto, S.S.; Wright, C.J.; Wilkinson, C.W.; Ghosh, S.; Otto, S.J.G. One Health, One Hive: A scoping review of honey bees, climate change, pollutants, and antimicrobial resistance. PLoS ONE 2022, 17, e0242393. [CrossRef

Regueira, M.S.; Tintino, S.R.; da Silva, A.R.P.; Costa, M.D.S.; Boligon, A.A.; Matias, E.F.F.; de Queiroz Balbino, V.; Menezes, I.R.A.; Melo Coutinho, H.D. Seasonal variation of Brazilian red propolis: Antibacterial activity, synergistic effect and phytochemical screening. Food Chem. Toxicol. 2017, 107, 572–580. [CrossRef]

Proďelalová, J.; Malenovská, H.; Moutelíková, R.; Tiťera, D. Virucides in apiculture: Persistence of surrogate enterovirus under simulated field conditions. Pest Manag. Sci. 2017, 73, 2544–2549. [CrossRef]

c.; Flenniken, M.L.; Engel, J.C.; Ruby, J.G.; Ganem, D.; Andino, R.; DeRisi, J.L. Temporal analysis of the honey bee microbiome reveals four novel viruses and seasonal prevalence of known viruses, Nosema, and Crithidia. PLoS ONE 2011, 6, e20656. [CrossRef] [PubMed]

Zhu, Y.G. and Penuelas, J. (2020). Changes in the environmental microbiome in the anthropocene. Global Change Biology 26(6), 3175–3177. https://doi.org/10.1111/gcb.15086.

Brandt, K.K., Amézquita, A., Backhaus, T., Boxall, A., Coors, A., Heberer, T. et al. (2015). Ecotoxicological assessment of antibiotics: A call for improved consideration of microorganisms. Environment International. 85, 189–205. https://doi.org/10.1016/j.envint.2015.09.013

Hammer, T.J., Fierer, N., Hardwick, B., Simojoki, A., Slade, E., Taponen, J., Viljanen, H. and Roslin, T. (2016). Treating cattle with antibiotics affects greenhouse gas emissions, and microbiota in dung and dung beetles. Proceedings of the Royal Society B: Biological Sciences 283(1831), 1–7. https://doi.org/10.1098/rspb.2016.0150.

Grenni, P., Ancona, V. and Barra Caracciolo, A. (2018). Ecological effects of antibiotics on natural ecosystems: a review. Microchemical Journal 136, 25–39. https://doi.org/10.1016/j.microc.2017.02.006

Banerji, A., Jahne, M., Herrmann, M., Brinkman, N. and Keely, S. (2019). Bringing community ecology to bear on the issue of antimicrobial resistance. Frontiers in Microbiology 10. https://doi.org/10.3389/fmicb.2019.02626

Chen, Q.L., An, X.L., Zheng, B.X., Gillings, M., Peñuelas, J., Cui, L., Su, J.Q. and Zhu, Y.G. (2019). Loss of soil microbial diversity exacerbates spread of antibiotic resistance. Soil Ecology Letters 1(1–2), 3–13. https://doi.org/10.1007/ s42832-019-0011-0

Chen, J., McIlroy, S.E., Archana, A., Baker, D.M. and Panagiotou, G. (2019). A pollution gradient contributes to the taxonomic, functional, and resistome diversity of microbial communities in marine sediments. Microbiome, 7(1), 104. https://doi.org/10.1186/s40168-019-0714-6

Neergheen-Bhujun, V., Awan, A.T., Baran, Y., Bunnefeld, N., Chan, K., dela Cruz, T.E. et al. (2017). Biodiversity, drug discovery, and the future of global health: introducing the biodiversity to biomedicine consortium, a call to action. Journal of Global Health 7(2), 1–5. https://doi.org/10.7189/jogh.07.020304.

Zhu, Y.G., Zhao, Y., Zhu, D., Gillings, M., Penuelas, J., Ok, Y.S. et al. (2019). Soil biota, antimicrobial resistance and planetary health. Environment International 131(105059), 1-7. https://doi.org/10.1016/j.envint.2019.105059.

Zhu, Y.G. and Penuelas, J. (2020). Changes in the environmental microbiome in the anthropocene. Global Change Biology 26(6), 3175–3177. https://doi.org/10.1111/gcb.15086.

Grenni, P., Ancona, V. and Barra Caracciolo, A. (2018). Ecological effects of antibiotics on natural ecosystems: a review. Microchemical Journal 136, 25–39. https://doi.org/10.1016/j.microc.2017.02.006.

Jørgensen, P.S., Wernli, D., Folke, C. and Carroll, S.P. (2017). Changing antibiotic resistance: sustainability transformation to a pro-microbial planet. Current Opinion in Environment Sustainability 25, 66–76. https://doi.org/10.1016/j.cosust.2017.07.008

Rodriguez-Mozaz, S., Chamorro, S., Marti, E., Huerta, B., Gros, M., Sànchez-Melsió, A. et al. (2015). Occurrence of antibiotics and antibiotic resistance genes in hospital and urban

wastewaters and their impact on the receiving river. Water Research 69, 234–242. https://doi.org/10.1016/j.watres.2014.11.021.

Bengtsson-Palme, J., Kristiansson, E. and Larsson, D.G.J. (2018). Environmental factors influencing the development and spread of antibiotic resistance. Federation of European Microbiological Societies Microbiology Reviews 42(1), 68–80. https://doi.org/10.1093/femsre/fux053

Smalla, K., Cook, K., Djordjevic, S.P., Klümper, U. and Gillings, M. (2018). Environmental dimensions of antibiotic resistance: assessment of basic science gaps. FEMS Microbiology Ecology 94(12), 1–6. https://doi.org/10.1093/ femsec/fiy195.

Cabello, F. C. et al. Antimicrobial use in aquaculture re-examined: its relevance to antimicrobial resistance and to animal and human health. Environ. Microbiol. 15, 1917–1942 (2013).

Cabello, F. C., Godfrey, H. P., Buschmann, A. H. & Dölz, H. J. Aquaculture as yet another environmental gateway to the development and globalisation of antimicrobial resistance. Lancet Infect. Dis. 16, e127–e133 (2016).

Taylor, P. & Reeder, R. Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors. CABI Agric. Biosci. https://doi.org/10.1186/s43170-020-00001-y (2020).

Larsson, D. G. J. Pollution from drug manufacturing: review and perspectives. Philos. Trans. R. Soc. B Biol. Sci. 369, 20130571 (2014).

Larsson, D. G. J., De Pedro, C. & Paxeus, N. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J. Hazard. Mater. 148, 751–755 (2007).

Milaković, M. et al. Pollution from azithromycinmanufacturing promotes macrolide-resistance gene propagation and induces spatial and seasonal bacterial community shifts in receiving river sediments. Environ. Int. 123, 501–511 (2019).

Bielen, A. et al. Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. Water Res. 126, 79–87 (2017).

Fick, J. et al. Contamination of surface, ground, and drinking water from pharmaceutical production. Environ. Toxicol. Chem. 28, 2522–2527 (2009)

Pruden, A., Pei, R., Storteboom, H. and Carlson, K.H. (2006). Antibiotic resistance genes as emerging contaminants: studies in northern Colorado. Environmental Science and Technology 40(23), 7445-7450. https://doi.org/10.1021/ es060413l.

Sanderson, H., Fricker, C., Brown, R.S., Majury, A. and Liss, S.N. (2016). Antibiotic resistance genes as an emerging environmental contaminant. Environmental Reviews 24(2), 205–218. https://doi.org/10.1139/er-2015-0069.

United Nations Conference on Trade and Development (2017). Review of Maritime Transport: 2017. Geneva: United Nations. https://unctad.org/system/files/official-document/rmt2017_en.pdf

Cunha, B.A. Antibiotic side effects. Med. Clin. N. Am. 2001, 85, 149–185. [CrossRef]

Mojica, E.-R.E.; Aga, D.S. Antibiotics Pollution in Soil and Water: Potential Ecological and Human Health Issues. In Encyclopedia of Environmental Health; Elsevier: Burlington, NJ, USA, 2011; pp. 97–110.