TAKING A **ONE HEALTH** PERSPECTIVE TO **AMR**

HAI HEALTH ACTION INTERNATIONAL

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CONTENTS

1. ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR), dubbed the silent pandemic, is a major public- and animal health problem that complicates the treatment of infections and is associated with increased morbidity and mortality (WHO, 2021). An estimated 700,000 deaths globally were attributable to infections caused by antibiotic-resistant organisms, and this is expected to reach 10 million per year by 2050.[1] In the United States (US), AMR results in more than two million infections each year and is associated with approximately 23,000 deaths. In Europe, the European Centre for Disease Prevention and Control (ECDC) reported that almost two million people in the European Union (EU)/European Economic Area (EEA) are infected with antibiotic-resistant bacteria every year, leading to approximately 30,000 annual deaths.[2,3] The emergence and spread of resistant and multidrug-resistant (MDR) bacteria also have enormous implications for worldwide healthcare delivery and population health.[1]

From an economic perspective, it has been predicted that the morbidity and mortality from infections in which AMR is a factor could result in a reduction of 2% to 3.5% in global gross domestic product (GDP) in 2050, amounting to a loss of between 60 to 100 trillion USD.[1] In the US, the economic costs of AMR are substantial, estimated at 20 billion USD in excess medical spending each year.[4] Furthermore, according to the Centre for Disease Control and Prevention (CDC), AMR costs the US about 35 billion USD in loss of productivity annually.[5] It is further estimated that AMR costs the EU €1.5 billion per year in healthcare costs and productivity losses.[6]

Antimicrobials fulfil an essential infrastructural role in modern healthcare and food production systems and are therefore essential in our society. The use of antimicrobials in clinical medicine has decreased the burden of infectious diseases and facilitated complex medical interventions by enabling breakthroughs across the spectrum of clinical medicine, including safer childbirth, surgical procedures, organ transplantation, and advanced chemotherapy regimens. AMR threatens to impede and even reverse some of this progress.[1,4]

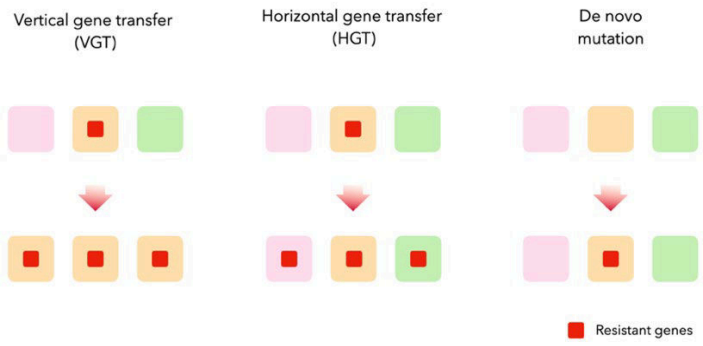
AMR occurs when microorganisms, including bacteria, viruses, fungi, and parasites, become able to adapt and grow in the presence of medications to which they were once susceptible.[5] AMR is on the rise due to a combination of factors. Primarily, AMR develops due to selective pressure on microorganisms as a result of exposure to antimicrobials. AMR is, however, not a recent adaptation, but an ancient bacterial trait. Recent work has uncovered resistance in ancient permafrost, isolated caves, and in human specimens preserved for hundreds of years.[7]

Nevertheless, indiscriminate, and extensive usage of antibiotics during the last 70 years has resulted in the selection and emergence of resistant pathogens against almost every antibiotic that has been created to date.[2]

Understanding the Problem

There are several mechanisms by which organisms can adapt and become resistant. A single mutation that confers AMR in a population under selective pressure can enable survival of an organism where all susceptible organisms are killed. That resistant organisms can continue to replicate, becoming the dominant variant.[1] This mechanism of inheritance of antibiotic resistance genes (ARGs) through bacterial reproduction is called vertical gene transfer (VGT). However, antibiotic resistance can also be transmitted through two other different routes: horizontal gene transfer (HGT), and de novo mutation.[9] HGT is the process of transferring ARGs between different bacterial cells; this is more likely to occur when ARGs are carried by mobile genetic elements (MGEs): a type of genetic material that can move around within a genome, or that can be transferred from one species or replicon to another. De novo mutations are single nucleotide polymorphisms (SNP), a variation at a single position in a DNA sequence, that occur due to low frequency errors arisen during DNA replication and proliferate under a selection pressure.[9] This type of mutation rarely occurs.

Figure 1. Antimicrobial resistance gene transfer mechanisms



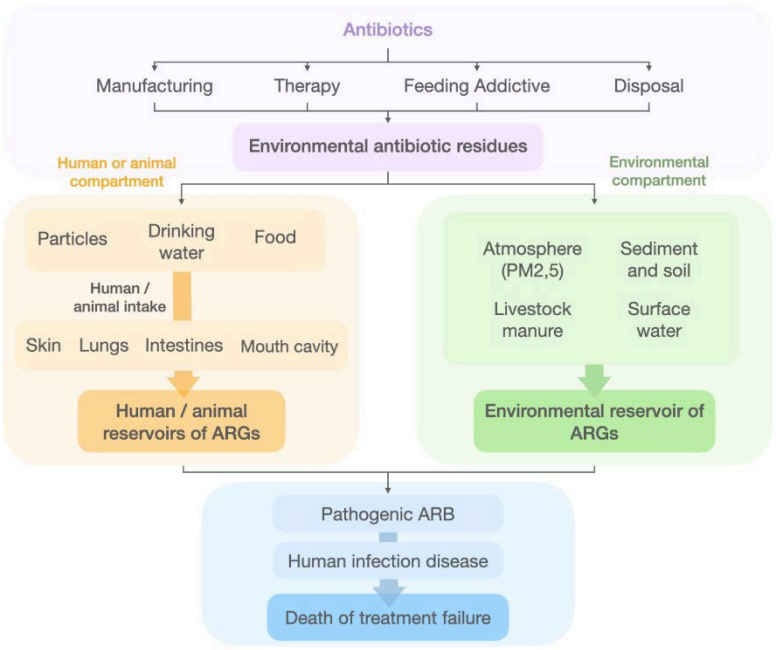
In VGT, gene transmission occurs from a cell to its daughters through replication; in HGT, a cell with resistance genes transmits its resistance genes to other bacteria, usually through MGEs; finally, through de novo mutation, a cell that previously had any resistance genes acquires them due to a random mutation.

Multiple drug resistant (MDR) organisms also need to be considered, since they are also exchanged between humans, animals and the environment. Infections caused by antibiotic resistant bacteria (ARB), especially those with MDR phenotype, are hard to treat due to reduced antibiotic efficacy, and result in higher medical costs due to prolonged hospital stays and increased morbidity and mortality.[7]

2. ONE HEALTH AND AMR

Antimicrobial resistance is influenced by bacterial, host, and environmental factors (Figure 2), including exposure to antimicrobials in clinical medicine, environmental waste, contamination, food production and animal husbandry, among others.[1, 2] Moreover, human activities in response to industrialisation drastically heightened the availability of antibiotic residues in food and the environment as, because of misuse of antibiotics, these residues are, ultimately, discharged into the environment, further fuelling the crisis.[10] Environmental antibiotic residues end up as human / animal or environmental reservoirs of ARGs, which can lead to pathogenic ARB. ARB can cause infectious diseases in humans, and death due to treatment failure at its worst. Hence, AMR must be dealt with from a perspective that addresses people, animals, and environment; the so called One Health approach.[1,11,12]

Figure 2. One-health perspective on antimicrobial resistance*



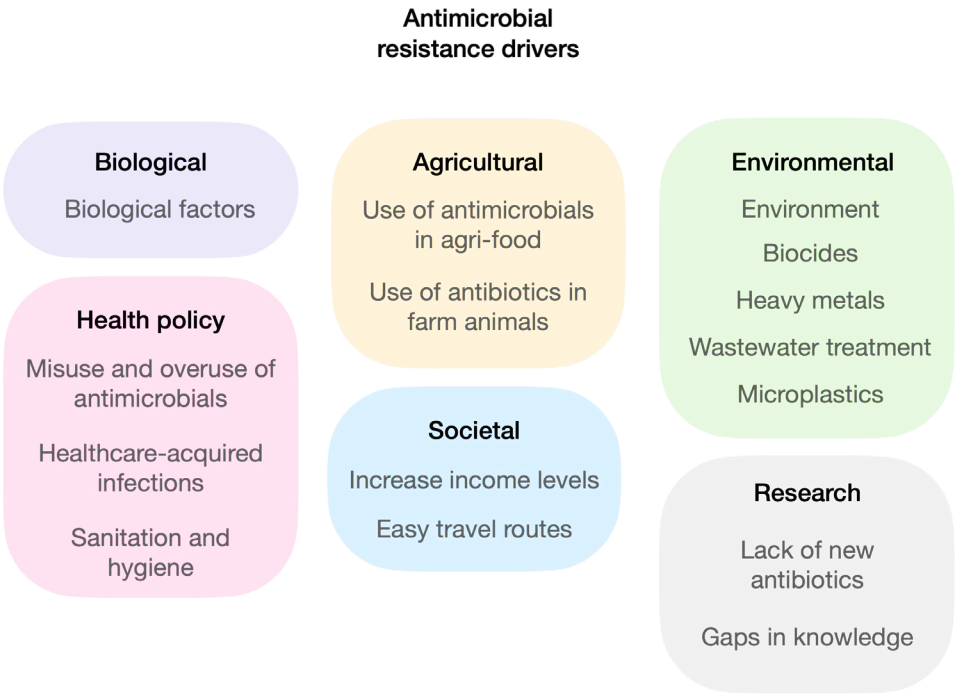
*Ben Y, Fu C, Hu M, Liu L, Wong MH, Zheng C. Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: A Review. Environmental Research. 2019;169:483–93. doi:10.1016/j.envres.2018.11.040

Currently, most of the approaches to tackle AMR are focused on reducing the consumption of antibiotics. However, a recent study analysing AMR and antibiotic consumption compared to potential contributing factors found that antibiotic consumption was not significantly associated with the antimicrobial resistance index. This suggests that reducing antibiotic consumption alone will not be sufficient to control AMR as the spread of resistant strains and resistance genes appear to be one of the dominant contributing factors.[7]

3. DRIVERS OF AMR

To better understand the complex system that drives antimicrobial resistance today, the main drivers have been grouped into six categories: biological drivers, agricultural drivers, environmental drivers, health policy, societal drivers, and research (see Figure 3). Each of the categories will be explained in detail below.

Figure 3. Drivers of antimicrobial resistance.



Biological Drivers

Biological factors

There are biological characteristics that aggravate AMR; such as heteroresistance and mutant prevention concentration. **Heteroresistance** is the resistance to certain antibiotics by a preexisting subpopulation of resistant cells, within a larger population of antimicrobial-susceptible microorganisms. This subpopulation of resistant cells can rapidly replicate in the presence of a given antibiotic, whereas the susceptible microorganisms are killed. **Mutant prevention concentration** represents a threshold above which the selective proliferation of resistant mutants is expected to occur only rarely, which can vary from one microorganism to another.[8]

Health Policy Drivers

Misuse and overuse of antimicrobials

Widespread AMR is mostly attributed to the selective pressure created by the overuse and misuse of antimicrobials in both humans and animals. Antimicrobials mainly stimulate the resistance mechanism of pathogens through HGT, which implies that ARGs can pass between different species of microorganisms.[2]

AMR varies between regions and countries, corresponding to the degree of antibiotic consumption.[10] In addition, in 2015 a positive association between consumption of antimicrobials and resistance in bacteria in humans and animals, as well as positive associations between antimicrobial consumption in animals and resistance in bacteria-infecting humans was found.[1,13]

Reducing antimicrobial use reduces selective pressure for resistant strains and therefore might benefit susceptible antimicrobial competitors. Reducing the current antibiotic use in hospitals (approximately 20%–30% of patients in the EU receive antibiotics during their hospitalisation) will lead to reductions in the prevalence of resistant strains, with an offsetting increase in sensitive strains.[14,15] One of the key tools to decrease antimicrobial use is antimicrobial stewardship to reduce overuse and ensure evidence-based antimicrobial use.

Healthcare-acquired infections

Hospitals, as well as healthcare workers and patients, can be a source of infection and transmission of AMR. Healthcare workers and a contaminated hospital environment are increasingly implicated in the transmission and persistence of multidrug-resistant (MDR) bacteria. Human healthcare infection, prevention and control (IPC) measures are key to prevent the transmission of AMR. IPC is a practical, evidence-based approach preventing patients and health workers from being harmed by avoidable infection, which requires constant action at all levels of the health system. Healthcare-acquired infection reduction needs to be multi-modal, with broad healthcare collaboration, and the strong support and accountability of all medical staff.[16] IPC effects all aspects of health care, including hand hygiene, surgical site infections, injection safety, antimicrobial resistance and how hospitals operate during and outside of emergencies.

Poor sanitation and hygiene

Poor sanitation and hygiene can increase healthcare-acquired infections, disease burden, hospitalisation time and costs, and contribute to the rise of AMR. Prolonged hospital stays and unhygienic medical conditions have proven to lead to the transmission of AMR.[2]

Hospitals and their materials can be the environmental reservoir for pathogens. Some bacteria can even survive in biofilms within hospital drains, toilets, and on equipment and other environmental niches which are difficult to access and clean.[16] Infection control via sanitation and hygiene does not equally affect resistant and sensitive strains of bacteria. Resistant strains rely more on hospital-based transmission for survival, meaning that nonspecific infection-control measures disproportionately reduce resistant infections.[15] Thus, infection prevention strategies to control AMR should include enhanced institutional investment in hand hygiene, hospital cleaning and disinfection, and the development of prescription guidelines and standards of care. For example, the implementation of hand hygiene policies can generate economic savings averaging 16 times the cost of their implementation.[17–20]

Agricultural Drivers

Poor use of antibiotics in farm animals

Animals receive far more antibiotics in terms of total mass compared to humans[21], and this is among the main causes of the spread of antimicrobial resistance.[8] It is responsible for the spread of resistant infections in both animals and humans.[7,21] The uses, types, and mode of actions of the antibiotics employed in agriculture and veterinary practice are closely related or the same as those in humans. The antibiotics may belong to the same general classes and function and act in similar ways. Therefore, AMR in agriculture also affects human antibiotics and their efficacy.[10]

Antibiotic consumption in cattle and poultry is expected to increase by 67% by 2030 in some low- and middle-income countries (LMICs).[2] In 2017, nearly 80% of antibiotics produced in the US were used in animal husbandry. Globally, it was estimated that each kilogram of meat harvested from cattle, chickens and pigs would lead to the consumption of 45 mg, 148 mg, and 172 mg of antimicrobials, respectively, which is expected to increase by 67% from 2010 to 2030.[7] Surplus calves and using antimicrobial compounds as growth promoters in animals have also been identified as risk factors for AMR spread.[2,22,23] Aquaculture was further confirmed as a source of ARG.[23]

Current livestock husbandry systems lead to relatively high levels of endemic disease. In the case of pigs and poultry, it is often uneconomic to provide treatment at the individual animal level, leading to the blanket treatment of groups of animals, normally delivered via the feed or water, which further aggravates the problem.[1] Moreover, 30% to 90% of antibiotics consumed by animals are released into manure and urine, leading to contamination in the environment with antibiotic-resistant bacteria. These resistant genes are then transferred to humans and other environments through the food supply and waste materials.[2]

Not only does the administration of antibiotics in food-producing animals facilitate AMR, it may also result in the presence of antibiotic residues in animal-derived products available for human consumption, having a negative impact on public health and food safety. These adverse impacts are also influenced by land use, contaminated water sources, national policies, national and international trade, animal demography, and interactions between the human populations, which will be explained in more in the following sections.[10]

Poor use of antimicrobials in agri-food

There is growing evidence regarding co-selection for AMR among bacteria exposed to non-antibiotic compounds used in the agricultural and food industry, such as biocides used as disinfectants, antiseptics and preservatives, and heavy metals that exist in nature and are used in agricultural production.[6] These have direct as well as indirect effects on the development of AMR in bacteria which can enter the food chain.[7] Moreover, the soil and water environment have been regarded as vital reservoirs and sources of AMR. This is especially the case when they are affected by agriculture. Recognising this, antimicrobial use in agriculture has been banned in almost every high-income country. However, antimicrobials are still being used in most LMICs.[10]

Although the role of agricultural antibiotic use and environmental antibiotic residues in promoting AMR remains difficult to quantify, the basic way in which such pressures likely act is to increase the proportion of resistant bacteria among those to which humans are eventually exposed. Reducing such use would likely shift human exposure towards susceptible flora, making antimicrobial-sensitive infections more likely. However, a better understanding of AMR development and transfer mechanisms might change this view.[15,21,24]

Environmental Drivers

Ecosystem

Spread of ARB and ARGs in the environment is now recognised as one of the top 10 global public health threats for humanity.[23] The ecosystem serves as a bridge for various compartments of animals to soil, water, sand, and sewage. Moreover, the environment acts as a reservoir to MGEs that interact and spread to other parts of the environment, or to human and animal hosts.[2] Hence, AMR transmission can be facilitated among humans, animals, and the environment via different routes.

Discharge of antibiotics into the environment occurs through different routes such as municipal- and hospital waste, animal husbandry, the manufacturing industry, runoff from agricultural fields containing livestock manure and landfill leachates. In addition, antibiotic residues are considered as persistent contaminants of the environment. Increased use of antibiotics generates robust selective pressure on natural microbial ecosystems and humans. Discharged antibiotics do not degrade and subsequently enter the groundwater or aquatic system during wastewater treatment processes. High levels of both AMR and/or ARGs have been detected in various wastewater samples, including municipal wastewater, sewage, influents and effluents of wastewater treatment plants, manure, and agricultural- and industrial wastewater, including samples from pharmaceutical sources.[2,7]

Antimicrobial resistance due to the irrational use of antimicrobials, the increased frequency of ARB, and mechanisms of AMR in the environment are now referred to as 'antibiotic resistance pollution'.[2]

Soil properties and cultivation conditions

Soil properties and cultivation conditions also need to be considered. Loamy soil is rich in nutrients, has more habitable pore-space, and retains moisture, so it is considered as creating beneficial conditions for microorganisms. The impact of **soil depth** on ARG spread is also important; topsoil and soil from deeper layers did not promote ARG spread, while the highest ARG level was observed at the depth of 10–15 cm. Obtained results are consistent with other studies and can be explained by natural microbe activity in the soil. Two more factors impacting ARG spread were **temperature** and **nutrient content**. High temperature (above 30℃) and high level of nutrients promoted ARG spread. To sum up, soil properties, soil depth and temperature are important factors for AMR spread in the environment. However, little attention is paid to soil properties as a factor for promoting AMR dissemination. Interestingly, the rhizosphere (a narrow region of soil or substrate that is directly influenced by root secretions) and some of its types were also shown to promote ARGs spread.[23]

Biocides

There is growing evidence regarding co-selection of AMR among bacteria exposed to biocides which are used as disinfectants, antiseptics, preservatives and various cationic heavy metals included in animal diets as nutritional supplements, growth promoters and therapeutic agents for livestock. However, a possible cross-resistance between biocides and antimicrobials is still controversial, and some studies have reported that there is no cross-resistance between biocides and antimicrobials.[7]

Heavy metals

Metals and antibiotic resistance mechanisms share some structural and functional similarities. Similar to antibiotics, some metals, which are commonly used in agricultural and aquacultural practices, have antibiotic properties. Like antimicrobials, metals are stressors that activate a variety of adaptive or protective responses in bacteria, and this can lead to co-regulation of metal and AMR, resulting in cross-resistance. Bacteria harbouring metal resistance genes have been reported to carry ARGs more frequently compared to those without metal resistance genes, which are often located on plasmids. Heavy metals facilitate AMR through HGT. Numerous studies have confirmed the correlation between elevated heavy metal concentrations and increased phenotypic or genotypic antibiotic resistance.[7,2,23]

Heavy metals can continue to exist in the environment and remain stable for prolonged periods, while most veterinary antimicrobial compounds can be metabolised and cleared from food-producing animals within weeks or months. This fact facilitates the development of resistances.[7] Considerable information is available regarding the toxicity and mobility of metal species in sediment, aquatic and soil ecosystems.[2,23] When heavy metals end up being transferred to the environment, they can cause AMR dissemination through co-selection. Co-selection of metal-driven antibiotic resistance in bacteria has been observed in many environments, such as marine environments, soil environments, manure, sediments or drinking water.[23]

Wastewater treatment

Over 80% of antibiotics consumed by humans or animals end up in faeces in wastewater treatment plants (WWTP).[23] WWTP can act as either a pathway for AMR spread or as a barrier to reduce the environmental release of AMR. A typical treatment plant integrates multiple engineering processes and multiple chemical factors, including disinfectants, metals, and various pharmaceuticals like antibiotics and other organic compounds. Chemical factors influence the transmission, expression and mobilisation of ARGs and drive the emergence, persistence, and proliferation of ARB. Wastewater (sewage) also provides a continuous input of ARGs, ARB, and highly diverse commensal and pathogenic bacteria from humans and animals into WWTPs. Together, those conditions create an ideal environment for the evolution of new and more complex microorganisms.[9] Once in contact with humans, ARG hosts can transfer ARGs to commensal bacteria and pathogens via HGT, even allowing bacteria to acquire both resistance and virulence at the same time.[9]

In addition, despite modern technologies and substantial removal of resistant bacteria from the water fraction, digested sludge or treated wastewater still contain heightened levels of ARB and ARGs. Using this material as biofertilizer on agricultural fields, for example, causes

AMR spread in the soil and aqueous systems. Moreover, research has also shown that direct application of animal manure to agricultural land introduces ARB and ARGs to the aqueous system.[24]

Microplastics

Recent research has indicated microplastic particles (MPs) as a new factor promoting antibiotic resistance spread. The presence of microbial communities on the plastic surfaces has been established for some time.[25] MPs have hydrophobic surfaces and are easily colonised by microbial biofilms. Moreover, the sorption process of antibiotics and heavy metals occurs on MPs. MPs were detected as a vector for the proliferation of heavy metal and antibiotic resistant bacteria, and HGT between microorganisms presented on microplastics was confirmed.

Societal Drivers

Increase in income levels

Global antibiotic use increased by 65% between 2000 and 2015.[26] This rise is predominantly because of overconsumption of antibiotics in LMICs, which is the direct result of rising incomes. The rise in GDP and increasing living standards in LMICs have shown to be positively correlated with antibiotic consumption. In addition, an increase in income levels in LMICs has led to an increase in animal protein consumption, which may require more antibiotics to be added to the food animals eat.[5]

Easy travel routes

Increasing globalisation also contributes to the development and spread of AMR. Population movement facilitates the spread of resistant infections from areas of high to low prevalence.[1] The modern and easy traveling routes for people, animals, and goods have proved to substantially contribute to the spread of antimicrobial resistance across the globe.[5]

There are multiple examples that demonstrate that national borders are no barrier for the spread of AMR. For example, since the 2011 EU directive on the application of patients' rights in cross-border healthcare, cross-border mobility of both patient and healthcare workers (HCWs) between Germany (DE) and The Netherlands (NL) has steadily increased. As a result of the increased cross-border patient and HCW mobility, AMR has also proven to spread in cross-border regions, like the EUREGIO (i.e., comprising communities of north-eastern NL and north-western DE).[27]

Research

Lack of new antibiotics

Since 1987, no new class of antibiotics has been discovered, and drug development has largely relied on structural changes to existing compounds. Furthermore, this lack of development of new antimicrobials in over three decades adds to the urgency of preserving the antimicrobial efficacy of currently available drugs.[1] Precisely because of the effort to limit antibiotic use, especially newer antibiotics, it is not an attractive market for the pharmaceutical industry. In other words, the financial outlook has made big pharma withdraw from antimicrobial development: antimicrobials do not present the same financial boon as drugs for chronic diseases, and the investment becomes even less attractive because of regulations that force large investments into the development process.[28]

Gaps in Knowledge

AMR has become a global threat, and filling the knowledge gaps is urgently needed to understand the potential role of selective agents in the evolutionary processes in the environment that lead to resistance. With a lack of new therapeutic agents to target resistant bacterial infections and without proper understanding of the role of environmental factors that promote AMR spread, any effort will be useless. It is increasingly important to understand the factors that contribute to the emergence of AMR so all the factors connected with AMR spread are considered rather than focusing only on one of them. There are not only limitations in population-based epidemiological studies of AMR, but also in individual-level data to assess individual patient outcomes in response to antimicrobial use.[1,2,23]

Some knowledge gaps require risk assessments in humans and animals. Assessment of knowledge gaps and modelling can support the identification of hotspots of antibiotic resistance emergence and dissemination, which would be helpful in finding the mitigation targets.[2] Further, well-designed, large-scale epidemiological and interdisciplinary research studies are needed to understand the relationship between AMR and distinct patterns of antimicrobial prescribing, consumption and dissemination of AMR in the environment. Genome-scale epidemiologic surveillance has also proven to be successful in identifying the impact of infection transmissions. These studies are needed to inform specific guidelines for AMR stewardship in humans as well as agricultural treatment practices. They are also critical for introducing new standards by the European Commission or governments of individual countries, concerning, for example, the use of antibiotics in veterinary medicine, agriculture or animal farming and methods of wastewater treatment.[1,23,21]

State of the art ARB identification technologies, such as metagenomic sequencing and fluorescence-activated cell sorting, have enriched ARG/ARB databases, unveiled keystone

species in AMR networks, and improved the resolution of AMR dissemination models. However, significant knowledge gaps have been identified in these settings. These include inconsistencies in ARG reporting units, lack of ARG/ARB monitoring surrogates, lack of a standardised protocol for determining ARG removal via wastewater treatments, and the inability to support appropriate risk assessment. This is due to a lack of standard monitoring targets and agreed threshold values, and paucity of information on the ARG-pathogen host relationship and risk management.[7]

4. CONCLUSION

Antimicrobials are an essential pillar of modern society. Antimicrobial resistance is a naturally occurring mechanism that can be slowed down gradually but not stopped completely because resistance is an inevitable consequence of the drug selective pressure. Therefore, the fight against resistance requires a global and complete One Health approach with a multisectoral collaboration from stakeholders; government, industry, professional societies, patient representatives, civil society and relevant expertise (infectious disease, epidemiology, IPC, microbiology, pharmacology, surveillance, environment, communications).

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