# Antimicrobial resistance in the light of One Health strategy

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**Abstract:** Antimicrobial resistance (AMR) is recognised as a major healthcare problem rapidly spreading across the world. The global rise of highly resistant bacteria is well documented and closely linked to the increasing mobility of people, animals, and goods. Indeed, World Health Organization published its first-ever list of antibiotic-resistant "priority pathogens" which consists of 12 bacteria that pose the greatest threat to human health. If we do not find proactive strategies to slow down the spread of drug resistance, it is estimated that by 2050, 10 million lives per year and a cumulative 100 trillion USD of economic output will be at risk due to the rise of drug-resistant infections.

The major drivers of AMR are the misuse and overuse of antimicrobial agents in both humans and animals, plus environmental pollution. Moreover, over the past three decades, it has become increasingly obvious that the majority of the novel, emerging zoonotic infectious diseases originate in animals, particularly wildlife, and that human activities, such as changes to ecosystems and land use, intensification of agriculture, urbanization, and international travel and trade, are the main drivers of their emergence. In this regard, combating AMR and emerging infections requires a One Health approach because it depends on the interrelationship between animals, people, and the environment. Recently, a novel concept to tackle AMR named "One health genomics", was proposed. Accordingly, the Global Antimicrobial Resistance and Use Surveillance System established by the World Health Organization strongly suggests using whole-genome sequencing for surveillance of AMR to add important, policy-relevant information for AMR surveillance, to better inform strategies to tackle AMR, and to enhance the overall surveillance capacity. Implementation of the "One health genomics" could provide an in-depth insight into the AMR landscape of a region, microbial composition across different sample sources, the genetic relatedness of the circulating multidrug-resistant bacteria, and differences in resistome profiles of interconnected sectors.

In conclusion, the implementation of the One Health concept, as an integrated and unifying approach against AMR is of utmost importance at both national and global levels.

**Keywords:** One-health concept; antimicrobial resistance; multidrug-resistant bacteria; antimicrobial resistance genes; infection control

## 1. Introduction

### 1.1. Antimicrobial resistance

The phenomenon of antimicrobial resistance (AMR) is a natural process whereby microorganisms, such as bacteria, viruses, fungi, and parasites evolve in such a way as to withstand the action of antimicrobial agents. The pressure that antimicrobials put on pathogens is responsible for the selection of resistant strains (Fair & Tor, 2014).

With at least 700,000 deaths per year globally, AMR is recognised as a major healthcare issue rapidly spreading across the world (O'Neill, 2016). A recent Global resistance report predicts that if nothing is done, the figure might increase drastically and exceed 10 million deaths annually by 2050 (O'Neill, 2016). Infection caused by antimicrobial-resistant pathogens leads to prolonged hospital admissions and treatment failures, increasing healthcare-related costs (Prestinaci *et al.,* 2015). Moreover, the COVID-19 pandemic has exacerbated the ongoing AMR global crisis due to the increased use of antibiotics during the treatment of COVID-19 patients, disruption of infection prevention and

control practices in the overwhelming healthcare systems, and shifts of human and financial resources away from surveillance and responding to AMR threats. In addition, secondary bacterial infections caused by multidrug-resistant (MDR) bacteria have caused more COVID-19 deaths among severe and critically ill patients.

Resistance can be classified into two groups: intrinsic resistance and acquired resistance. While intrinsic resistant microorganisms refer to those that do not have the target for the antimicrobial agent, acquired resistance refers to an originally susceptible microorganism that acquires a mechanism that allows them to evade the action of the antimicrobial. Microorganisms can develop AMR either by mutations or by the acquisition of external antimicrobial resistance genes through horizontal gene transfer of mobile genetic elements (MGEs) carrying AMR genes. The latter mechanism contributes significantly to the rapid spread of resistance genes and the emergence of phenotypic drug resistance, especially in hospital settings.

### 1.2. Circulation of multidrug-resistant bacteria

During the last decade, healthcare professionals have started to face novel atypical challenges in the treatment of severe infections in critically ill patients due to the selection and transmission of multidrug-resistant (MDR) bacteria, i.e., strains resistant to at least one agent in three or more antimicrobial categories (Magiorakos *et al.*, 2012). World Health Organization (WHO) published its first-ever list of antibiotic-resistant "priority pathogens" which consists of 12 bacteria that pose the greatest threat to human health (Taconelli, 2020).

This list was created to guide and encourage research and development of new antibiotics as part of WHO's efforts to combat the growing antimicrobial resistance around the world. The extensive list highlights in particular the threat of MDR Gram-negative bacteria. Pathogens are classified as critical, high, and medium based on mortality, level of resistance, and treatability. The WHO global priority list of pathogens ranks extended spectrum β-lactamase (ESBL) *Enterobacterales*, carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) in the highest priority category (i.e., critical). Although several mechanisms account for the resistance to carbapenems, the production of carbapenem-hydrolyzing enzymes encoded by horizontally transferable genes is of utmost importance. Interestingly, the Indian subcontinent and the Balkan regions are considered the main reservoirs of globally emerging New Delhi Metallo-β-Lactamases (NDM), an enzyme hydrolyzing a broad range of β-lactam antibiotics, including carbapenems, which are considered as the last resort antibiotics with proven efficacy to ESBL-producing *Enterobacterales* (Livermore *et al.*, 2011). Important

**Table 1.** World Health Organization priority pathogens list (Tacconelli, 2018)

| Pathogen | Resistance |
|---|---|
| **PRIORITY 1: CRITICAL** | |
| *Acinetobacter baumannii* | Carbapenem - resistant |
| *Pseudomonas aeruginosa* | Carbapenem - resistant |
| *Enterobacteriaceae* | Carbapenem – resistant, 3$^{rd}$ generation cephalosporin-resistant |
| **PRIORITY 1: HIGH** | |
| *Enterococcus faecium* | Vancomycin - resistant |
| *Staphylococcus aureus* | Methicillin-resistant, vancomycin intermediate and resistant |
| *Helicobacter pylori* | Claritromycin-resistant |
| *Campylobacter* | Fluoroquinolone-resistant |
| *Salmonella species* | Fluoroquinolone-resistant |
| *Neisseria gonorrhoeae* | 3$^{rd}$ generation cephalosporin-resistant, fluoroquinolone-resistant |
| **PRIORITY 1: MEDIUM** | |
| *Streptococcus pneumoniae* | Penicillin-non-susceptible |
| *Haemophilus influenzae* | Ampicillin-resistant |
| *Shigella species* | Fluoroquinolone-resistant |

bacterial pathogens also included in the group ES-KAPEE, an acronym introduced to designate a group of bacteria that successfully escape the action of antibiotics: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *P. aeruginosa*, *Enterobacter* species, and *Escherichia coli* (Ruekit *et al.*, 2022). Although MDR bacteria are concerning causative agents of healthcare-associated infections (HCAI), reports suggest that animals, food products, and aquatic environments may also constitute significant reservoirs of these bacteria and resistance genes (Wyres *et al.*, 2018; Lepuschitz *et al.*, 2019). The intensive use of antimicrobials in farming may promote the fixation of AMR genes in bacteria, which may be zoonotic or capable of transferring these genes to human-adapted pathogens or human gut microbiota via direct contact, food, or the environment. Of major concern is the mass medication of animals with antimicrobials that are critically important for humans, i.e., third-generation cephalosporins and fluoroquinolones, as well as the long-term, in-feed use of medically important antimicrobials, such as colistin and tetracyclines, for growth promotion (Argudin *et al.*, 2017). Indeed, several studies have indicated that typical nosocomial resistances linked to ESBL and carbapenemases are emerging in Gram-negative bacteria from animals (Dahms *et al.*, 2015; Michael *et al.*, 2015). Also, colistin-resistant *Enterobacterales*, pathogens untreatable with regular antibiotics, might emerge as the result of the potential spread of plasmid-mediated mobile colistin resistance (*mcr*) genes from the animal sector to humans (Liu *et al.*, 2016). Therefore, agriculture and food-producing animals represent a significant pool of resistance genes for humans, whereas research on them should be strategic research Project in agriculture, food, and environmental microbiology, contributing to public health.

Water is a crucial environmental setting and one of Earth's most important bacterial habitats. The main sources of contamination in the aquatic environment are various genetic reactors, i.e., human/animal microbiota, hospitals, large-scale animal farming, wastewater, hospitals, and soil, where bacteria mix and interact through genetic exchange and recombination (Baquero *et al.*, 2008). Surface waters, in particular, seem to play a key role in this spread, serving both as habitats and as transport systems for MDR bacteria (Falgenhauer *et al.*, 2019). To date, many studies have highlighted wastewater as a hotspot for the dissemination of ARGs into the environment (Zhang *et al.*, 2015; Gundogdu *et al.*, 2013; Mokracka *et al.*, 2012). Another important public health concern is the potential effect of antibiotics in the aquatic environment regarding their potential influence on potable water quality and global human health. The significant existence of antibiotics in the environment, especially in aquatic ecosystems, can be attributed to multiple factors, including the production of active pharmaceutical ingredients, the excretion of residues after usage, and the discarding of unused medicines from medicinal practices, laboratories, factories, residential, and commercial institutes (Kemper, 2008). As a consequence, aquatic biota became exposed to unprecedented antibiotic selection pressures, contributing to the rapid resistance development we face today. Furthermore, antibiotic traces in potable water and food can lead to antibiotic-induced microbiome depletion and selective pressure on the human microbiome, which might serve as a reservoir for ARGs. By horizontal gene transfer, such resistance determinants may be transferred to pathogenic bacteria compromising antibiotic treatment and the outcome. Although previous scientific literature reports the presence of antibiotics in surface waters and studies focused on genes involved in AMR, mechanisms leading to the selection and acquisition of resistance determinants by bacterial strains, as well as ARG maintenance in aquatic environments, remain unclear. At a policy level, no safety threshold values or standardised guidelines on the environmental risk assessment of antibiotics currently exist, which is largely due to insufficient data on environmentally relevant concentrations (Niegowska *et al.*, 2021). At the European level, the amended Water Framework Directive includes the Watch List program, which aims to gather good data quality for substances contaminating waterbodies to determine the risk they may pose to aquatic environments (Niegowska *et al.*, 2021).

Antimicrobial resistance in humans, animals, and the environment is depicted in Figure 2.

### 1.3. Antimicrobials use in humans, animals, and plants

Although ARGs existed in nature before the discovery of antibiotics, the emergence and spread of AMR in pathogenic strains occurred in response to the development and use of these agents. Cumulating reports indicate that antimicrobial misuse and abuse in human, animal, and environmental sectors, as well as the spread of resistant bacteria and resistance determinants within and between these sectors, are the main drivers of AMR (Holmes *et al.*, 2015).

Antimicrobials are used for various purposes (therapeutic, prophylactic, and development promoters) and play an important role in animal production. Some antimicrobials used in humans and animals (tetracycline, triazoles, and streptomycin) are used for prophylaxis and treatment against bacteria that cause plant infections (Sundin *et al.*,
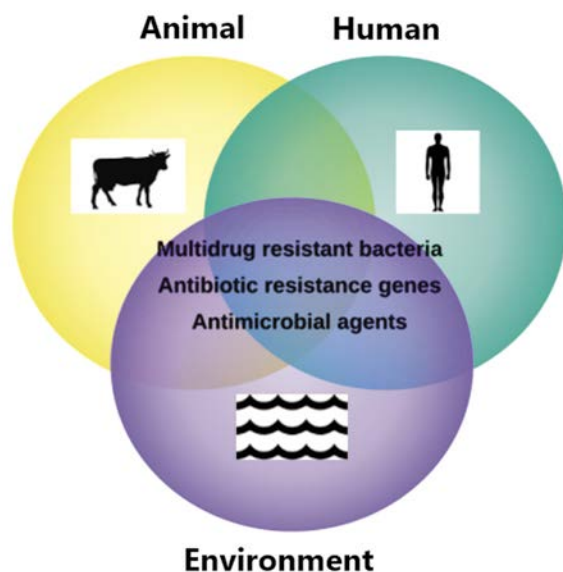
**Figure 2.** Antimicrobial resistance in humans, animals and environment

2018). There are some classes of antimicrobials for human use only (carbapenems) and others for animal use only (flavophospholipol and ionophores) (Wall *et al.*, 2016; Van Boeckel *et al.*, 2015). The application of antibiotics in veterinary settings is different between food-producing animals and pets, where the prescription of antibiotics is generally comparable to those in humans (McEwen & Collignon, 2018). Antibiotics in poultry are often administered to the whole group through water or feed without any clinical indications for preventive purposes.

Some antibiotics were used for decades before resistance developed, while others developed resistance in a much shorter period of time. Antibiotics with a slow development of resistance, especially vancomycin, are valued for their enduring ability to treat infections.

In 2019, the WHO identified 32 antimicrobial agents in hospital development, of which only six were classified as innovative. The world's health systems are being impacted by the lack of antimicrobials. Accordingly, antibiotics play an important role in controlling bacterial pathogens, but decreasing their usage is vital because of the emergence of resistant pathogens and transmissible ARGs. Recent studies have enabled us to understand the gene exchange and pathogen interactions in various One Health niches, which is important for the development of alternative antibiotic approaches, such as the use of bacteriophages. Additionally, vaccines in both human and veterinary medicines, also play an important role in controlling ABR as they reduce the need for antibiotic therapy**.**

## 2. One Health approach to combat antimicrobial resistance

### 2.1. Historical perspective of One health concept

One Health is an approach that acknowledges that human health is closely connected to the health of animals and our shared environment. Although the phrase "One Health" is relatively new, the concept has long been recognized on a national and international level. The pioneers in this field include the following persons:

- Rudolf Virchow recognized the link between human and animal health and introduced the term "zoonosis," which encompasses the relationship between human and animal health.
- William Osler had a deep interest in the linkages between human and veterinary medicine
- James H. Steele was responsible for the official inclusion of veterinarians into the US Public Health Service and in 1947, he founded the Veterinary Public Health Division at CDC, which led to rapid advances in the control and prevention of zoonotic diseases both in the United States and internationally.
- Calvin Schwabe coined the term "One Medicine" and spent a lifetime practicing and teaching the principles of One Health (Schwabe, 1964).

### 2.2. A modern perspective of One Health

On September 29, 2004, the Wildlife Conservation Society published the 12 Manhattan principles and formed the basis of the "One Health, One World" concept. In 2007, the One Health approach is recommended for pandemic preparedness. One Health becomes a recommended approach and a political reality in 2008.

Although the epidemiology of AMR at the human-animal-water interface is invariably complex, ARGs' diversity and the evolvability of antibiotic resistance particularly depend on control of the flow of active antimicrobials, bacterial populations, and genetically based biological information along different genetic reactors, i.e., hospital settings, farm animals, and water sources. Due to the multidisciplinary nature of the issue, an integrative "One Health" concept is best suited to address the existing and emerging threats of AMR as well as to understand how human behaviour, environmental degradation, and antibacterial usage in animals lead to AMR transmission (One Health Initiative, 2017). However, the interdisciplinary, intersectoral, and multi-institutional "One Health" approach to fight clinically-relevant MDR organisms, has not been

effectively implemented in many countries. The understanding of genetic relatedness between MDR organisms from hospital settings, animal and water sources, will contribute to the further strengthening of the national control of drug-resistant diseases. In light of that, it is known that the distribution of resistant bacteria in clinical settings is acceptably well-documented on a global scale. Contrary to this, the distribution and evidence of MDR bacteria in the environment are hardly based on qualitative data.

**Table 2.** Goals of the national strategies concerning antimicrobial resistance

| | |
|---|---|
| 1. | A prudent use of antibiotics, especially broad-spectrum antibiotics and critically important antibiotics, to reduce the incidence of AMR |
| 2. | Greater efforts to prevent infections by improving hygiene and utilizing vaccines more effectively and promote alternatives to antibiotics. |
| 3. | Knowledge enhancement based on sound scientific knowledge to improve targeted measures. |
| 4. | National and international surveillance systems on AMR in all three sectors must be implemented. |
| 5. | Information and guidance on resistance and transmission. |
| 6. | An active international cooperation to minimise the development of antibiotic resistance and support the implementation of international strategies and action plans. |

*2.3. Genomic approach*

Traditional microbiological methods such as culturing bacterial pathogens and sequencing isolates require additional logistics and may not be practical in the field. Therefore, The Global Antimicrobial Resistance and Use Surveillance System (GLASS) established by the WHO strongly suggests using whole-genome sequencing (WGS) for surveillance of AMR to add important, policy-relevant information for AMR surveillance, to better inform strategies to tackle AMR, and to enhance the overall surveillance capacity (WHO, 2020).

Implementation of the "One health genomics", as a novel concept to tackle AMR, could provide an in-depth genomic insight into the AMR landscape of a region, microbial composition across different sample sources, the genetic relatedness of the circulating

MDR bacteria, and differences in resistome profiles of interconnected sectors. State-of-the-art technologies, such as a sequence-based approach to studying genomes from a mixed microbial community known as metagenomics is being applied to understand and decipher the complexity of AMR in different niches of One health sector. Moreover, an integrative genomic approach enables scientists to elucidate hotspots of AMR and transmission routes of ARGs, the ARGs diversity, as well as the relatedness between MDR microorganisms from different environmental compartments, which could enable the detection of the most important environmental point sources of ARGs. A novel genomic approach could serve as the most optimal tool to achieve the above-mentioned goals.

## 3. Conclusion

In conclusion, supporting and implementing a "one health" approach is critical to combating AMR. This necessitates accelerating global development, innovating to ensure the future, collaborating for more effective action, investing in long-term solutions, and enhancing global governance and accountability. The rise of AMR can be reduced when antibiotics are used only for treatment, rarely for prophylaxis, and never as growth promoters. Success will require strict and efficient control of the types and amounts of antimicrobials used, monitoring, reporting, and controlling the proliferation of resistant microorganisms that spread to the environment.

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