

Review

Antimicrobial Resistance in the Environment: Review of the Selected Resistance Drivers and Public Health Concerns

Nikola Puvaca^{1*}, Jelena Vapa Tankosić², Svetlana Ignjatijević², Marko Carić² and Radivoj Prodanović¹

¹ Department of Engineering Management in Biotechnology, Faculty of Economics and Engineering Management in Novi Sad, University Business Academy in Novi Sad, Cvečarska 2, 21000 Novi Sad, Serbia

² Department of Business Economics and Finance, Faculty of Economics and Engineering Management in Novi Sad, University Business Academy in Novi Sad, Cvečarska 2, 21000 Novi Sad, Serbia

* Correspondence: nikola.puvaca@fimek.edu.rs

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Abstract: Antimicrobial resistance (AMR) is a growing global epidemic due to the improper overuse of antimicrobials in the agriculture, veterinary, and medical sectors. Antimicrobial-resistant genes (ARGs) spread primarily through the environment, which is becoming a growing concern among researchers and stakeholders. Antibiotic-resistant bacteria and their ARGs are spread by various factors, such as the use of antimicrobial drugs in health care, agriculture and livestock, and the environment, as well as the release of antibiotic residue. Through various routes and hotspots such as hospital wastewater, agricultural waste, and wastewater treatment plants, resistant microorganisms, and their resistance genes enter the soil, air, water, and sediments. It is important to identify high-risk environments that cause the evolution of resistance and its spread around the world if global mitigation strategies are to be effective. As a result, infection control, sanitation, access to clean water, antimicrobials, diagnostics, travel, and migration are all factors impacting AMR transmission. Through various mechanisms, this review discusses AMR as a global concern and how environmental factors may contribute to the spread of antibiotic-resistant bacteria.

Keywords: AMR; water; antibiotics; drugs; drinking water; wastewater.

1. Introduction

In the 21st century, antimicrobial resistance (AMR) has become a serious global concern in humans, animals, and the environment. Veterinary, medical, and agricultural sectors overuse antibiotics, which may be contributing to AMR globally [1]. Injudicious sale of antibiotics over-the-counter, improper sanitation, and discharge of non-metabolized antibiotics or their residues through faeces and manure and industrial effluents into the environment have worsened the problem. There is a considerable relationship between these contributing factors and the environmental spread of AMR [2]. Infections with multidrug-resistant microbial pathogens lead to a high number of annual deaths worldwide [3]. If an effective action plan is not implemented, the annual death rate is expected to reach 10 million deaths per year by 2050, more than the deaths caused by cancer [4]. Across continents, antibiotic consumption in cattle and poultry has soared to unprecedented levels and is expected to increase by 67% by 2030 in rapidly polluting and developing countries. The growing global issue of AMR has also significantly contributed to the world's economic healthcare load. Despite the difficulty in measuring the global cost of antibiotic

resistance, it is undeniable that AMR imposes a significant financial burden [5]. It is detrimental to the health of humans and animals when antibiotics are misused or abused [6]. Antibiotics are well known to stimulate the resistance mechanism of pathogens through horizontal gene transfer [7]. Currently, microbial resistance to third-generation cephalosporins, carbapenems, and polymyxins is increasing rapidly. The evolution of resistance in bacteria is a natural process. The development of resistance occurs genetically either by mutation or the acquisition of new resistance genes through genetic exchange mechanisms [8]. Resistance of bacterial pathogens to third-generation cephalosporins is related to the acquisition of extended-spectrum β -lactamase (ESBL) genes. According to one estimate, around 14% of the global human population is colonized by ESBL-producing enteric bacteria and it is growing at a rate of 5.4% annually [9]. There are rising concerns about the last group of β -lactam (carbapenem) and polymyxin (colistin) antibiotics that possess broad-spectrum activity against Gram-negative bacteria [10]. Non-antibiotic antimicrobial compounds prevalent in environmental samples are also responsible for the selection of resistance.

Using antimicrobials for animal production at subtherapeutic doses provides bacteria with an ideal environment to fix resistance genes [11]. Contaminated foodstuffs or the environment can transmit resistance genes to the human gut microbiota. Prolonged hospital stays and unhygienic medical conditions lead to the transmission of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) [12]. Outrageous use of antimicrobial compounds as growth promoters in poultry or livestock is another important cause of resistance transmission to humans through animal products. The most common resistant pathogens in this category are *Campylobacter* spp., *Salmonella* spp., and food-borne *Escherichia coli* [1]. Recent reports suggest that AMR action plans lack a necessary element of involving all environmental regulators and risk assessments to enhance the efficacy of existing antimicrobials for future applications [13]. Throughout this review, we provide a brief overview of the epidemiology of AMR in human and veterinary practices, as well as the environmental drivers that contribute to AMR development. Combatting AMR-related issues might be improved by examining these factors.

2. AMR in Human and Veterinary Practices

There are a variety of environments where antimicrobial compounds are used, including hospitals, intensive care units, outpatient clinics, and food animal farms, increasing the risk of resistance emergence. The discovery and development of antibiotics for combating infectious diseases is the biggest advancement in the history. However, indiscriminate and extensive usage of antibiotics during the last seven decades has resulted in the selection and emergence of resistant pathogens against almost every antibiotic that has been launched to date [14]. In clinical practice, penicillin resistance was identified in *Streptococcus pneumoniae* and *S. aureus* in 1940, which demonstrated the presence of previous penicillin resistance mechanisms in the natural environment before its clinical use. Likewise, after the introduction of methicillin, semi-synthetic penicillin, for treating infections by penicillin-resistant *S. aureus*, a methicillin resistance mechanism was also recorded in strains of MRSA. *S. aureus* is closely associated with humans as it is a nasal commensal in around 30% of the population and causes a skin infection known as boils [15]. Recently, MRSA has become a major community-acquired pathogen with enhanced virulence and transmission characteristics to become a serious nosocomial pathogen [16]. Antibiotic-resistant Gram-negative bacteria, mainly members of the Enterobacteriaceae family, have been increasingly reported in hospital wastewater [17]. These reports describe that the use of almost every antibiotic eventually results in the development of resistant strains, proving the extreme flexibility, hostility, and wide-range adaptability of the bacterial genome. The use in food animals of antibiotics that are structurally similar to agents used for humans exacerbates antibiotic-resistant bacteria of public health concern. Enteric antibiotic-resistant bacteria are excreted in faeces and can disseminate in the environment and possibly enter other livestock and farm workers [18,19]. Resistant bacteria and mobile genetic elements may enter human food from different animal sources, as all processing stages contain abundant resistant bacteria and resistance genes. Members of the Enterobacteriaceae

are frequently distributed in livestock and on retail meat, including opportunistic pathogens such as *Escherichia* and *Klebsiella* spp. [20,21]. These pathogens as well commonly causes clinical urinary tract infections and bloodstream infections in patients [22].

Some ARGs found in foodborne pathogens have also been identified in humans, thus confirming the risk of consuming animal products colonized by resistant bacteria [23,24]. The increase in food-animal consumption with the rising economies of low-income and middle-income countries will probably increase antibiotic consumption until it exceeds the present-day limit of high-income countries. The Organization for Economic Cooperation and Development (OECD) has suggested that antimicrobial usage in food animals will rise from 63 151 tons in 2010 to 105 596 tons by 2030 [25]. The average annual global consumption of antibiotics in producing 1 kg of different meats is 172 mg/kg for pork meat, 148 mg/kg for chicken, and 45 mg/kg for beef [26]. This consumption is speculated to double in Brazil, Russia, India, China, and South Africa (BRICS) because of the increasing requirement for antibiotics to maintain animal health and productivity [27].

3. Antibiotics as Drivers of Resistance and their Transmission Pathways into the Environment

There are well-characterized classes of resistance-driving compounds or drivers that confer AMR [28], including antimicrobials such as antibacterial, antifungal, antiviral, and antiparasitic drugs; heavy metals; and biocides, mainly surfactants, and disinfectants. Resistance to natural compounds (plant-derived) and xenobiotics (hexane, toluene, and octanol) have also been reported to select resistance genes. Co-selection of resistance genes has been reported for hazardous chemicals such as solvents, biocides, heavy metals, and antibiotics [29]. There are two different means of co-selection such as co-resistance, where a selection of one gene supports the selection of another gene that usually does not offer a selective advantage to the compound of interest; and cross-resistance, where one resistance gene protects against a range of toxic chemicals. The major transmission pathways of these drivers in the environment include industrial and municipal wastewater, sewage sludge, and the spreading of animal manure and aquaculture systems [30].

In addition to treating various human infectious diseases, antibiotics are also commonly used in aquaculture and livestock farming [31]. Since penicillin was discovered, they have played a significant role in the treatment of various infectious diseases. Multidrug-resistant pathogens such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* may grow in niches where other bacteria cannot survive and may also disturb the host microbiota [32]. Antibiotic misuse and overuse result in the selection of resistant strains. An estimated 50% of antibiotic prescriptions have been suggested to be inappropriate [33]. In many countries outside of Europe and North America, non-prescription use of antibiotics is still common, accounting for 19% of total consumption and even up to 100% in some cases. Approximately 20–30% of European patients receive antibiotics during their hospitalization, and hospital effluents are hotspots for horizontal gene transfer, which can facilitate the interspecies and intraspecies transfer of antibiotic resistance determinants and virulence factors. The existence of mobile genetic elements facilitates horizontal gene transfer, which can efficiently contribute to the acquisition, maintenance, and spreading of ARGs within bacterial communities [34]. Evaluation of ARGs in clinical and environmental settings should be the first step in tackling the rapidly growing resistance to antibiotics.

Veterinary medicines were intended to minimize animal infections but are currently used as prophylactic agents, feed additives, and growth promoters. Antibiotic residues have been identified in food-animal products such as chicken, meat, and milk [35,36]. According to the sale and distribution of antimicrobials in food-producing animals, consumption of medically important antimicrobial drugs has increased by 9% from 2017 to 2018 [37]. The year 2018 was the second lowest year with a 21% decrease in antimicrobial consumption since the first year of the report (2009) and a 38% decrease compared with the peak year of sales and distribution (2015). Similar to humans, 30–90% of antibiotics consumed in animals are released into manure and urine [38]. Due to the high rate of antibiotics on animal farms, a high concentration of antibiotic residues in farm waste

contaminates the environment with antibiotic-resistant bacteria [39]. This situation further facilitates the selection and transfer of antibiotic resistance genes within the microbial community of an environment. These resistance genes are transferred to humans and other environments through food supply and waste materials [2]. *E. coli* O157:H7 and *Salmonella* spp. have been detected in manure, compost, soil, and water samples [40]. The rigorous use of antimicrobials in veterinary and medical fields has resulted in high AMR through the exertion of selection pressure against antimicrobial agents. Some of the commonly used antibiotics in food animals for prophylactic purposes along with their negative impacts on animal and human health are listed in Table 1.

Table 1. Common antibiotics and their effects on humans and animals.

Antibiotic	Target organs or product	Effects on health
Amoxicillin	Raw milk and eggs	Carcinogenic and mutagenic
Moxifloxacin	Poultry and cattle meat	Allergic reaction, phototoxic effects on skin and ligament fissures
Sulfisoxazole	Raw milk	Carcinogenicity and allergic reactions
Oxytetracycline	Raw milk, kidneys, liver and muscles of cattle and poultry	Carcinogenicity and cytotoxicity in broiler chicken bone marrow
Tetracycline	Liver and muscles of poultry, and kidneys of cattle	Primary and permanent tooth discolouration in children and infants, nephrotoxicity, carcinogenicity, hepatotoxicity and alteration of the normal intestinal microflora, hyperpigmentation of skin exposed to the sun, acidosis in proximal and distal renal tubules

AMR transmission can be distributed among humans, animals, and the environment via different routes [41]. The ecosystem serves as a bridge for various compartments of animals to soil to water to sand, and sewage. The environment acts as a reservoir to mix mobile genetic elements that interact and spread to human and animal hosts. Discharge of antibiotics occurs through several routes such as municipal and hospital waste, animal husbandry, the manufacturing industry, runoff from agricultural fields containing livestock manure, and landfill leachates of antibiotic discharge [42]. The half-life of antibiotics ranges from hours to hundreds of days but antibiotic residues are considered persistent contaminants in the environment.

Increased use of antibiotics generates robust selective pressure on natural microbial ecosystems and humans [43]. Similar to other pharmaceutical products, unused or expired antibiotics are thrown in the garbage that cannot degrade and enter the groundwater or aquatic system during the wastewater treatment process. A very limited concentration of these disposed of antibiotics can promote selective pressure either by horizontal gene transfer or modifying target sites. Primarily, such resistance genes originate from the gastrointestinal tract of humans. Similarly, 70% of Gram-positive and 65% of Gram-negative bacterial isolates from a natural cave microbiome contained multiple active antibiotic resistance genes, suggesting that multiple resistance is an environmental standard instead of an exceptional response to elevated anthropogenic antibiotic stress [44]. Resistance genes have also been found in 30000 to 50000 years old samples of permafrost but comparatively, there is a clear spike in the abundance of resistance genes in recent environmental samples. Higher levels both of antibiotic-resistant bacteria and ARGs have been detected in various wastewater samples including municipal wastewater, sewage, and influents and effluents of wastewater treatment plants. Likewise, high levels of AMR have been identified in agricultural and industrial wastewater, including samples from pharmaceutical sources [45]. Increased rates of ARGs have been identified in pharmaceutical wastewater associated with the rate of clinically important antibiotic drugs that are used during different treatment stages and are subsequently released into the environment. Hospitals and other healthcare facilities are essential

sources of antimicrobial waste generation either indirectly by patient secretions or directly as discarded medicines [46]. Recent studies have demonstrated the presence of novel ARGs, enriched in activated sludge and effluent wastewater, that confer resistance to multiple antibiotics including aminoglycosides, fluoroquinolones, and β -lactams [47,48]. Activated sludge has been found to possess ESBL-producing *E. coli*, MRSA, and vancomycin-resistant enterococci containing *vanA* and *mecA* genes conferring resistance to vancomycin and β -lactams, respectively [48]. India and China are the largest contributors to the global rise of AMR, therefore strict surveillance is urgently required.

In contrast to clinical microorganisms, antibiotic-producing environmental microorganisms display a higher level of intrinsic resistance that appears to be independent of selective pressure [49]. As environmental microbes are becoming more resistant to human pathogens, the risk of them spreading intrinsic resistance to human-adapted pathogens is becoming more important. There is now a term for antibiotic resistance pollution, which refers to the greater frequency of antibiotic-resistant bacteria as well as mechanisms of antibiotic resistance in the environment caused by the irrational use of antibiotics [50].

4. Influence of AMR on Public Health

The indiscriminate release of antibiotics into the environment is creating an economic burden on the global healthcare system. The European Centre for Disease Prevention and Control (ECDC) reported that almost two million people in the EU/EEA get infected with antibiotic-resistant bacteria every year leading to approximately 25000 annual deaths [51]. As a result of AMR, chronic infections occur, treatments are delayed, and resistance is transmitted from one species to another [52]. Multiple clinical problems have been attributed to antimicrobial resistance and multidrug-resistant infections in healthcare [53]. Currently, there should be more attention paid to the extensive consumption of antibiotics and the risk assessment of antibiotic residues on human health. The hazard assessment of drug-resistant bacteria should include four main domains, including identification of hazards, exposure assessment, characterization of risk, and the dose-response relationship. Human antibiotic resistance is believed to develop from antibiotic residues in the environment altering the microbiome of the human gut and causing the emergence of resistant bacteria. ARGs and antibiotic-resistant bacteria may also develop in the environment as a result of selective pressure on the environment's microbiome [45].

Investigation between the usage of antibiotics on farms and human health risk is a complex process. Because of epidemiological factors, AMR does not follow a simple model for pathogen emergence. The individual contribution of different antimicrobial drugs to the overall burden of AMR is still not clear.

5. Aspects of Antimicrobial Concentrations that are Ecologically Relevant

In clinical settings, minimum inhibitory concentrations (MIC) refer to concentrations needed to inhibit or kill a target pathogen. Microorganisms cannot survive if the concentration at which a resistance gene offers a selective advantage to its host is higher than the MIC. When applied to more realistic scenarios involving multiple species and multiple chemicals, the minimal concentration of the chemical (MSC) has a different meaning than when it is determined in the laboratory for any microorganism and chemical pair [54]. There is ongoing research to identify MSCs for more complex systems, which might provide more insight into the ecological importance of low antibiotic concentrations. Many biological and physicochemical factors influence the MSC. Microorganisms resistant to antibiotics can co-occur with microorganisms sensitive to antibiotics due to heterogeneous concentrations of antibiotics due to differential partitioning into soil pores, sediment, biofilms, and organic matter [55]. When microorganisms are exposed to weakly selective sub-lethal antibiotic concentrations within a matrix, more common and frequent mutations confer a small

effect [56]. In addition, these accumulated small mutations in the population are further aided by their proximity to higher or lower concentrations of resistance-driving chemicals.

6. Conclusions

The environment can act as a reservoir of antibiotic-resistant bacteria and ARGs or as an arena for the evolution of resistance. The susceptibility of bacteria to antibiotics can be increased in wild animals as well as in livestock. Therefore, it is the most common route of transmission of resistant bacteria associated with faecal matter in water, sewage infrastructure, or organic fertilizers. Foodstuffs of animal origin may also be considered a potential source of exposure to multidrug-resistant enteric pathogens. There must be a well-established model system for risk assessment of infections and deaths resulting from exposure to antibiotic resistance arising from environmental antibiotic residues. All relevant decision-makers must be aware of the AMR threat and should apply the regulatory frameworks in agriculture, pharmaceutical manufacturing, and aquaculture to minimize the development of antibiotic resistance. Developed and developing countries facing various challenges must be cognisant to develop policies and research networks for the mitigation of AMR. In the future, we may be able to achieve a deeper understanding of the associated risks through the development of methods with increased sensitivity towards rare resistance determinants without cultivation, as well as improved culture technique capabilities.

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