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ANTIBIOTICS AND ANTIBIOTIC RESISTANT BACTERIA IN ENVIRONMENT: RISKS AND CONSEQUENCES TO PUBLIC HEALTH

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Abstract. Antibiotics are significant microbial compounds that are commonly utilized to treat bacterial illnesses. Their use began in the early twentieth century, and there have been numerous antibiotics created worldwide since then. Antibiotics saved millions of lives and increased plant productivity because of their benefits in human and animal medicine and plant agriculture. However, its broad use has had major environmental repercussions, including buildup in agricultural ecosystems and the food chain, as well as wastewater and sewage sludge. Antibiotics are overused in animal agriculture and the veterinary sector in comparison to human use, and this overuse is linked to antibiotics leaching into the environment via feces and urine, posing a high risk of antibiotic contamination in manure and the transmission of antibiotic-resistant genes.

The accumulation of antibiotics resulted in the creation of antibiotic-resistant bacteria, which entered the food chain. The majority of them are human pathogenic bacteria from a variety of genera, including Escherichia, Salmonella, Shigella, Listeria, and Campylobacter. These bacteria have antibiotic resistance genes and can cause serious health issues in humans. Antibiotics, such as tetracyclines, β-lactams, quinolones, macrolides, and sulfonamide, have been found in activated sludge, raw sewage, digested sludge, and treated effluents. Conventional wastewater treatment plants are not equipped to remove them. According to the literature, some bacteria found in agricultural ecosystems, food chains, and effluents may be multidrug resistant, which could have major ramifications for human health. This report summarizes the hazards and implications of antibiotic use and the occurrence of antibiotic-resistant microorganisms in the environment.

Keywords: antibiotic, antibiotic resistance bacteria, food chain, public health

1. Introduction

Antibiotics, microbial-derived chemicals that limit microbial development [1], are one of the most important inventions of the twentieth century [2], with widespread use in human medicine and agricultural productivity [3]. Selman Waksman and his associates coined the word "antibiotics" to describe substances capable of inhibiting microbial development [4]. These medicinal chemicals have saved human lives from infectious diseases throughout history [5]. Antibiotics were introduced in hospital procedures in the 1940s due to their great efficacy in pathogen eradication [6], and a wide range of antibiotics have been created and used since then, particularly during the 1940s and 1960s during the golden era of antibiotic use [7].

Because of the global increase in antibiotic use [8, 9] and antibiotic occurrence in diverse settings [10, 11], many countries have advocated proper antibiotic usage and reduction. In addition to the benefits, antibiotic use has been linked to an increase in antimicrobial resistance (AMR) and the emergence of antibiotic resistant bacteria (ARB) in a variety of environments [12], including aquatic ecosystems [13], soils [14], sewage sludge [15], the food chain [16], and so on.

In this paper, we summarized the origins, dangers, and threats that antibiotics and ARB pose to environmental quality and public health. Furthermore, this study emphasizes the relevance of methods in addressing AMR.

2. Origin of antibiotics and ARB in environment

Mouldy bread and therapeutic soil are the most ancient examples of antibiotic use from the middle of the second millennium BC [17]. During the Anglo-Saxon period (10th century), "Bald's Lechbook," a collection of medicinal writings, had recipes for combinations with probable antibacterial properties [18]. However, the credit for developing antimicrobial compounds goes to Paul Ehrlich, who synthesized salvarsan and neo-salvarsan around the turn of the twentieth century [19], and Alexander Fleming, who found penicillin in 1929 [20]. There have been numerous antibiotics created since ancient times [21], as showed in Figure 1.

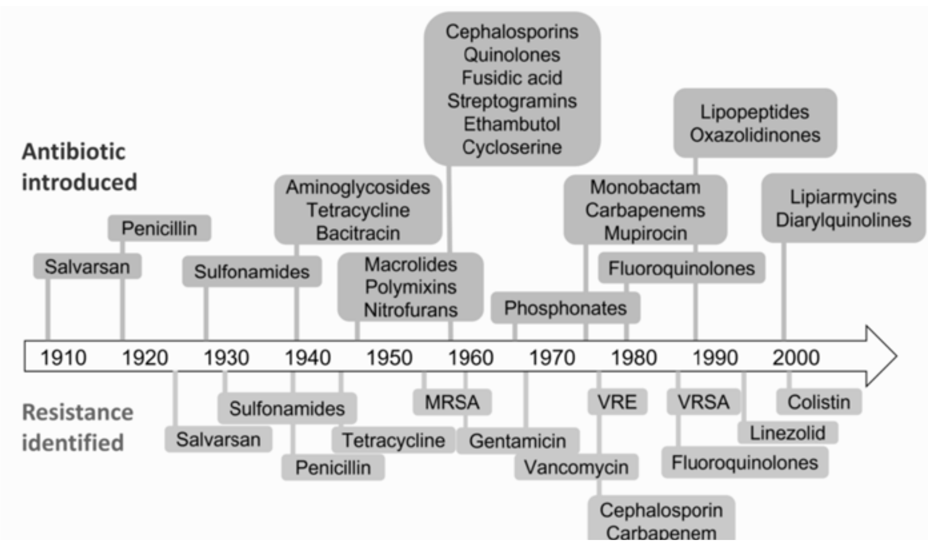

Figure 1. Development of antibiotics and antibiotic resistance in twentieth century (adopted from Salam et al. [22])

Antibiotics are produced as a result of metabolic activity in some bacteria, actinomycetes, and fungi; because of their benefits, antibiotics are widely utilized in human medicine and have saved millions of lives worldwide [23]. Antibiotics improve animal performance, enhance food safety, prevent illnesses, and save lives [24]. However, multiple studies have found that antibiotics are overused in animal agriculture and the veterinary sector when compared to human use [25]. Given that over billion tons of antibiotics have been synthesized since 1940 [26, 27], it is clear that this overuse is associated with antibiotics leaching into the environment via feces and urine [28], an increase in bacterial resistance to antibiotics, and the occurrence of risks to human health [29]. Bacterial resistance develops when bacteria are exposed to lower antibiotic concentrations than those with inhibitory or microbicide effects; these bacteria gain an advantage over other bacteria and become prevalent in a certain ecosystem [30]. ARB and resistance genes spread throughout the ecosystem by a series of phases [31]: gene movement within the genome, gene relocation, horizontal gene transfer, and physical transfer of bacteria to humans and/or animals. These bacteria can cause severe health problems in humans [32]. According to the CDC [33], antibiotic resistance causes more than 2.8 million infections and over 35,000 deaths in the United States each year. Some of ARBs and their resistance to various antibiotics are presented in the Table 1.

Table 1. ARBs and their resistance to antibiotics

ARB species	Resistance	Reference
Campylobacter spp.	fluoroquinolone	[34]
	macrolide	[35]
	erythromycin	[36]
Enterococcus spp.	amynoglycoside	[37]
	erythromycin, tetracycline	[38]
Escherichia coli	fluoroquinolone	[39]
	sulfonamide	[40]
	polymyxin	[41]
Listeria spp.	macrolide	[42]
	tetracycline	[43]
Salmonella spp.	β-lactams	[44]
	chloramphenicol, amynoglycoside	[45]
	colistin	[46]
Shigella spp.	β-lactams	[47]
	ampicilin, chloramphenicol	[48]

Due to overuse and improper practices in agriculture, and excretion by living organisms, antibiotics can be detected in all environments, as well as in wastewater treatment plants. Thus, antibiotics and ARB levels in agriculture, the food chain, and sewage sludge will be discussed further in the text.

3. Antibiotics and ARB in agricultural production: sources and consequences

Antibiotics are commonly used in plant and animal production [49], but their usage is restricted in several countries [50]. Antibiotics promote plant development and prevent infections [51]. Vidaver [52] stated that foliar spraying is the most common way for antibiotic use, while Batuman et al. [53] indicated that streptomycine and oxytetracycline are the most commonly used antibiotics in crop production. EPA allowed the use of these two antibiotics and kasugamycin in plant production [54], but with necessity of bacterial resistance monitoring. Fortunatelly, Williams-Nguyen et al. [55] revealed that use of antibiotics in crop cultivation is lower compared with human or animal treatment.

Antibiotics are used in animal agriculture to prevent disease and promote welfare [56]. Antibiotics are widely utilized in animal production [57]; however, 25 to 75% of the antibiotics used are not absorbed by the animal digestive tract and end up in the feces [58]. Depending on the species, several antibiotics might be employed in animal production (see Table 2).

Table 2. Antibiotics used in animal production

Type of animal	Antibiotics	Reference
swine	tetracyclines, macrolides	[59]
	benzylpenicillins	[60]
	amoxicillin	[61]
chicken	tetracycline, bacitracin, tylosin, salinomycin, virginiamycin, bambermycin	[62]
	colistin and fosfomycin	[63]
cattle	oxytetracycline, penicillin, streptomycin	[64]
	β-lactams, tetracyclines, aminoglycosides	[65]

Antibiotics accumulate in urine and/or feces [3], posing a high danger of antibiotic contamination in manure and the transmission of antibiotic-resistant genes [66]. The usage of this manure may alter the variety and organization of the microbial population in soil [67]. Popowska et al. [68] found that agricultural soils have a greater diversity of ARB species than forest soils. It is clear that the existence of antibiotic resistance genes in soil is determined by a variety of factors, including soil structure [69], the use of organic fertilizers [70], pH value, and salinity [71]. Heavy metals, on the other hand, infiltrate agricultural soils through agrochemical application (pesticides, mineral fertilizers), causing antibiotic resistance to develop and bacterial susceptibility to antibiotics to decrease [72]. These bacteria, once introduced into the food chain, produce serious diseases in humans [73].

3.1 Antibiotics and ARB in food chain

Antibiotic resistance has emerged as a global environmental issue as a result of its widespread usage in human treatment and agricultural productivity. Antibiotics may enter the food chain through a variety of routes after being released from crop fields, farms, and hospitals [74]. In any keys, Zhu et al. [75] and Wu et al. [76] identified agricultural soil, manure, and wastewater as "hot spots" of antibiotic presence in the environment. Antibiotic pollution of the environment, including residues and antibiotic resistance genes, can result in the presence of ARB in a variety of items such as fruits, vegetables, water, and feed, with major effects for human health [77].

Table 3 contains several examples of antibiotics found in feed, whereas Table 4 shows the incidence of ARB in the food chain.

Table 3. Occurence of antibiotics in feed

Type of feed	Detected antibiotic(s)	Reference
Capsicum annuum, Cucumis melo, Solanum melongena	sulfadiazine, sulfamethizole, tetracycline, doxycicline etc.	[78]
Lactuca sativa, Solanum lycopersicum, Brassica oleracea, Vicia faba	benzyl pyrimidines, fluoroquinolones, sulfonamides	[79]
milk	β-lactams, tetracycline, sulfonamides	[80]
beaf meat	oxytetracycline	[81]
hen eggs	enrofloxacin, sulfonamides, florfenicol	[82]
fish	clarithromycin, roxithromycin	[83]

Table 4. Occurence of ARB in feed and food chain

Type of feed	ARB detection and specifics	Reference
Cucumis sativus, Solanum lycopersicum, Citrullus lanatus	36 from 53 isolates were resistant to 5 of 8 antibiotics	[84]
fish and seafood	ARB isolates were resistant to gentamicin, chloramphenicol and tetracycline	[85]
spring onion	β-lactam-producing Shigella sonnei	[86]
irrigation and surface water	detection of multiresistant E. coli isolates	[12]

ready-to-eat vegetables	76.92 % of bacterial isolates were resistant to at least 5 antibiotics and 44.23% to over 10 antibiotics	[87]
potable water, meat, cheese, work surfaces	Gram negative bacteria: >50% of resistance to the 55% of the tested antibiotics; Gram positive bacteria: >50% of resistance towards 14% of antibiotics	[88]

4. Antibiotics and ARB in sewage sludge

Conventional wastewater treatment plants (WWTPs) are not specifically equipped to get rid of antibiotics; instead, these hydrophobic compounds are partially or fully adsorbed onto organic matter and solids within sludge, where they can accumulate over time [89]. Multiple classes of antibiotics including, tetracyclines, β-lactams, quinolones, macrolides and sulfonamide, have been frequently reported in activated sludge, raw sewage, digested sludge, and treated effluents [90]. Table 5 illustrates the prevalence of representative antibiotics from these classes in selected WWTPs of the globe. The persistence of antibiotics in sludge exerts selective pressure on microbial communities, facilitating the emergence and proliferation of resistant behavior among bacteria. Resistance is expressed through various mechanisms, including enzymatic degradation of antibiotics, modification of target binding sites, or reduced uptake of the pharmaceutical substance [90].

Table 5. Global occurrence of antibiotics in sewage treatment plant effluents (adapted from Samrot et al., [90])

Antibiotics	Concentration range (ng/L)	Wastewater treatment plant location
Cefalexin, Trimethoprim, Ciprofloxacin, Ofloxacin, Tetracycline, Sulfapyridine, Sulfamethoxazole, Azithromycin, Pipemidic Acid, Clindamycin	4.7-597.5	Portugal
Tetracycline, Trimethoprim, Sulfamethoxazole, Macrolides	40-550	USA
Ofloxacin, Norfloxacin, Cefalexin, Erythromycin, Sulfamethoxazole, Trimethoprim	5-7870	Hong Kong
Ciprofloxacin, Levofloxacin, Amoxicillin	60-1500	Iraq

Ampicillin, Ciprofloxacin, Gatifloxacin, Sparfloxacin, Cefuroxime	140-12,680	India
Metronidazole, Erythromycin, Ofloxacin, Trimethoprim, Azithromycin	0.11-0.22	South Africa
Tetracycline, Carbamazepine, Sulfadiazine, Trimethoprim, Clarithromycin, Roxithromycin	50-1069	Finland
Sulfapyridine, Azithromycin, Clarithromycin, Sulfamethoxazole	90-570	Switzerland
Clindamycin, Doxycycline, Azithromycin, Ciprofloxacin	41-422	Germany
Sulfamethoxazole, Clindamycin, Azithromycin, Ciprofloxacin	65-7494	Spain

The aforementioned traits are often acquired via spontaneous genetic mutations that generate antibiotic resistance genes, which can subsequently spread among microbial populations through horizontal gene transfer. For example, point mutations in ribosomal proteins have been shown to confer resistance to aminoglycosides, tetracyclines, and macrolides [91]. Furthermore, the agricultural application and disposal of sewage sludge in landfills introduces ARB and their related genes into terrestrial and aquatic ecosystems, increasing the risk of transmission to humans and other biota. Thus, WWTPs and their sludge systems represent critical hotspots for the evolution, enrichment, and propagation of ARB into the environment [92]. Notably, wastewater treatment process has been linked to the selective proliferation and development of multi-drug resistance (resistance to >3 antibiotics) in *Acinetobacter* spp. [93], underscoring the serious implications for public health.

5. Conclusion

The presence of drugs and antibiotic resistant microorganisms in the environment is a big global issue. This study summarizes the origins of antibiotics in diverse habitats, as well as the presence and prevalence of antibiotic-resistant bacteria in agricultural production, the food chain, and sewage sludge. Future initiatives will focus on ways for removing antibiotic-resistant microorganisms as well as the description of antibiotic alternatives in agriculture and health.

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