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RECENT DEVELOPMENTS IN ANTIBIOTIC CONTAMINATION OF ANIMAL PRODUCTS, SOIL, AND WATER WORLDWIDE – A REVIEW

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Abstract

Antimicrobial resistance (AMR), facilitated by antibiotic consumption, remains one of the biggest threats to global health and food security. The burgeoning AMR has an estimated forecast of 10 million deaths and 100 trillion USD economic losses annually worldwide by 2050 if no urgent actions are taken. The indiscriminate use of antibiotics in food animal production plays an expressive role in the AMR crisis. This paper compiles information regarding antibiotics and AMR in animals, animal-derived products, and agriculture-impacted environment. A holistic approach is needed to mitigate the burden of AMR within the context of human-animal-environment. Currently there are few approaches to this problem such as nanotechnology, anaerobic digestion, biochar composting, and alternatives to antibiotic treatments (like herbal plant extracts, probiotics, vaccines, enzymes, and antimicrobial peptides) have been developed. However, there are gaps in knowledge about AMR and areas for improvement are obvious. There is no clear path to put an end to the persistent trends of AMR. Despite the trends for stricter regulation on the use of antibiotics worldwide, they find their way into food animal production, water, and soil as a result of misuses in many countries. We need to acknowledge the antibiotic contamination and/or AMR as a silent pandemic, and we are challenged to adopt a global approach to reducing and improving their use.

Key words: agriculture, antimicrobial resistance, food safety, food-producing animals, integrated surveillance

Antimicrobials (a diverse array of chemical substances that are produced naturally, semi-synthetically, and synthetically*)* are wildly used in agri-food sector to eliminate or inhibit the growth of microorganisms (Okaiyeto et al., 2024; Wu-Wu et al., 2023; Ghimpețeanu et al., 2022; Bacanli et al., 2019). Globally, the intensification of food animals (such as cattle, poultry and pigs) production, not only as a source of food but also a source of income, resulted in the uncontrolled upsurge in the application of antimicrobials (Xu et al., 2022; Hedman et al., 2020). The residues of these substances can subsequently contaminate the animal products (i.e. meat, milk, and dairy products), soil, water, and plants contribute to the emergence and spread of antimicrobial resistance (AMR) and foodborne-disease outbreaks (Al Amin et al., 2020; Huygens et al., 2021; Ghimpețeanu et al., 2022). AMR is currently a critical multifaceted and complex global public health issue to be addressed by the scientific community since it is associated with the emergence and dissemination of antibiotic-resistant genes (ARGs) among humans, animals, and the environment results in severe infections and diseases that are difficult to treat (Okaiyeto et al., 2024; Al Amin et al., 2020).

AMR figures are a major threat for public health and food safety, as it can lead to drug toxicity, immunopathological diseases, carcinogenicity, allergic reactions, and drug sensitization, amongst others. So, the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), and the World Organization for Animal Health (OIE) issued a joint alert and developed a global program within the concept of "One World, One Health", which began to be applied in the different member countries of these organizations, based on the knowledge of the profound changes in the interactions between people, animals, plants, and the environment studied in the first decade of this century (Jimenez et al., 2023; Helmy et al., 2023; Zinsstag et al., 2021). The amount of antibiotics used in human medicine (728 tons/year in 2018) and animal medicine (471 tons/year in 2018) globally are known, but the amount of antibiotics reaching the environment is still unknown (Haenni et al., 2022). The evolution and AMR of different antibiotics are shown in Figure 1. It has been estimated that an AMR-related problem will cause 300 million human deaths globally along with 100 trillion USD financial losses and 11% fall in livestock productions by 2050 (Al Amin et al., 2020).

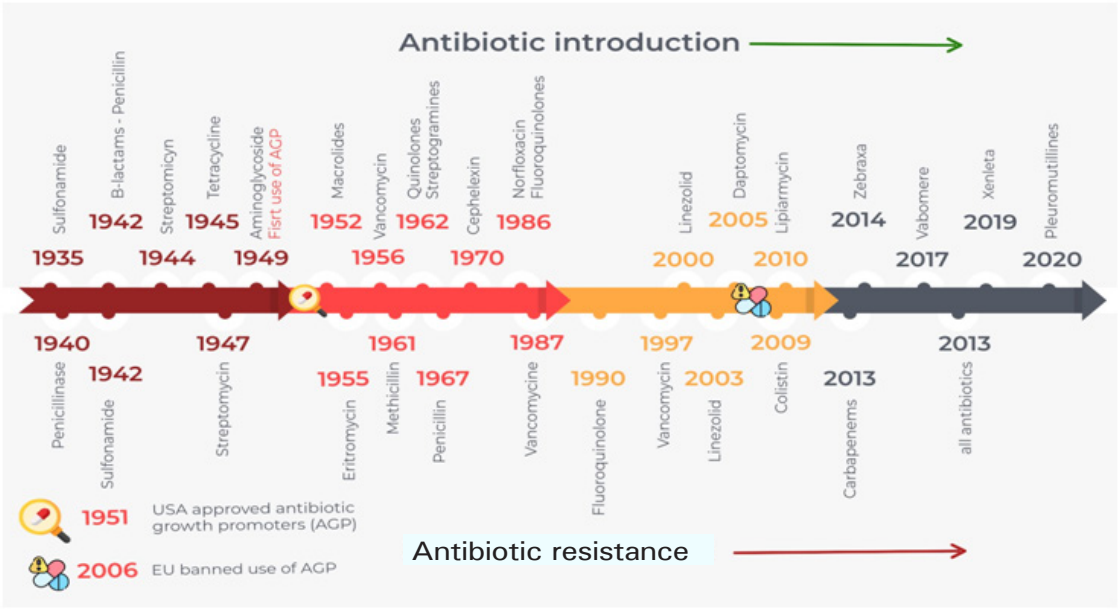


Figure 1. Timeline of the key antimicrobial discoveries and the subsequent emergence of AMR strains (adapted from: Helmy et al., 2023; Gonzalez Ronquillo and Hernandez, 2017)

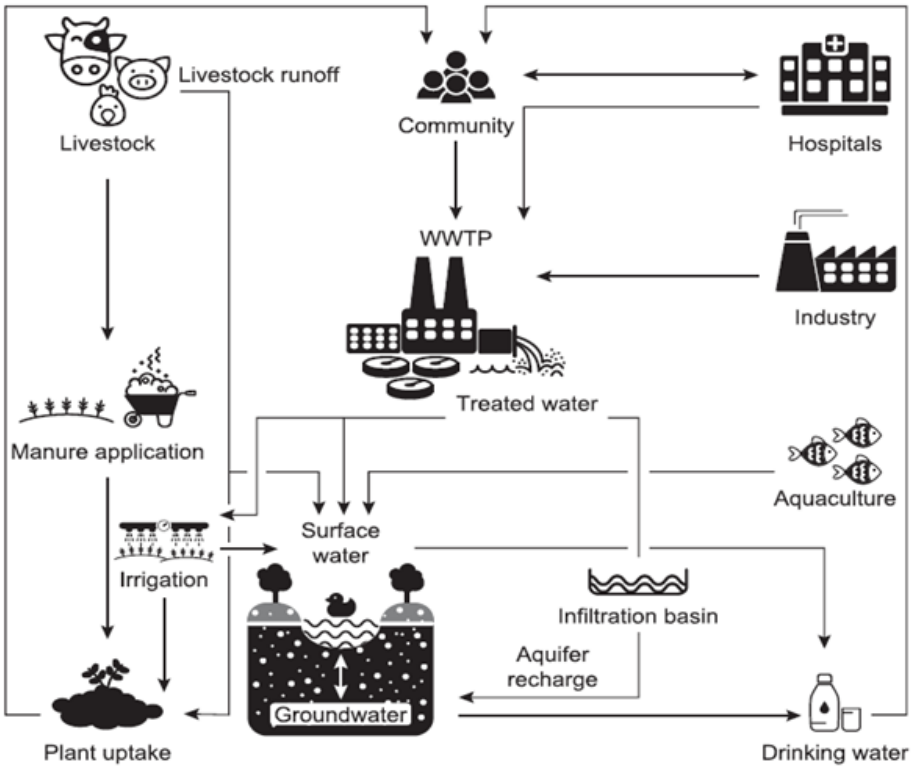


Figure 2. Schematic diagram of how antibiotic contaminants can end up in the human food systems (adapted from: Manaia et al., 2022)

AMR is a consequence of the selective pressure of antimicrobials, although sometimes these agents also promote resistance by favoring the emergence of subsequently selected mutations. Multiple studies indicate a link between antimicrobial use (AMU) and the emergence of resistance (Ghimpețeanu et al., 2022; Helmy et al., 2023). Moreover, the association between AMR infections in humans and antimicrobial use in agriculture is complex, but well documented (Figure 2; Hedman et al., 2020). Globally, over 70% of antimicrobials produced on Earth are used in food-animal production (Hedman et al., 2020; Manaia et al., 2022). It has been also shown that

a substantial part of the resistance burden in humans is attributable to antimicrobial use in the food-animal production chain, primarily for disease prevention and growth promotion (Xu et al., 2022; Ghimpețeanu et al., 2022). In addition, there is growing awareness that the application of antimicrobials in food animals may contribute to the emergence of resistance to antibiotics commonly utilized in human medicine, primarily due to the similarity of molecules belonging to the same antibiotic classes that are used in both human and veterinary medicine (Helmy et al., 2023; Huygens et al., 2021; Bennani et al., 2020). The antibiotics administered to food-producing animals can disseminate to humans through multiple direct and/or indirect routes. Consumption and handling of contaminated food is the main direct route of exposure (Manyi-Loh et al., 2018), while environmental exposure considered the main indirect route (Al Amin et al., 2020; Manaia et al., 2022). Remarkably, 90% of the antibiotics administered to food-producing animals are excreted in their active form in the urine and feces and ultimately dispersed through soil, groundwater, and surface runoff in the environment (Zinsstag et al., 2021; Manyi-Loh et al., 2018). The present overview assembles the current information about antibiotic contamination in agriculture-impacted environment. Specifically, we intend to update the applications and implications of antibiotics in food animal, soil, and water. This study includes an analysis how they end up in the environment causing antibiotic pollution, and their consequential effects of antibiotic residues on public health. We also highlight the gaps in knowledge that should constitute a basis for the development of policies to control or limit the impact of AMR in the world.

Antibiotic in animal products

The growing demand for food animal products is driving the need to optimize livestock production. According to the UN population prospects, the world's population is expected to grow by 34% to reach 9.1 billion by 2050. In addition, more than 70% of the world's population will be urban by 2050, with changes in lifestyles and food consumption patterns. In the same way, there is a combination of rising incomes and dietary diversification with a decline in the proportion and consumption of cereals and an increase in the consumption of meat, dairy products and fish in developing countries (FAO, 2009). The controversy surrounding the use of antimicrobials in animals and its potential adverse impact on human health was first initiated by the release of Swann report in the United Kingdom in 1969, leading to the publication of numerous reports addressing the issue (Table 1) (Torres et al., 2021).

Table 1. Timelines on the use of antimicrobials in food animals and their implications on public health

Year	Report
1969	Swann Committee Report – Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine
1969	National Academy of Sciences – The Use of Drugs in Feed Animals
1977	U.S. General Accounting Office Report – Need to Establish Safety and Effectiveness of Antibiotics Used in Animal Feeds
1980	Institute of Medicine Report – The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds
1981	Council for Agricultural Science and Technology – Antibiotics in Animal Feeds
1989	Institute of Medicine Report – Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed
1995	American Society for Microbiology Task Force Report
1997	World Health Organization – The Medical Impact of the Use of Antimicrobials in Food Animals
1998	World Health Organization – Fluoroquinolone Use in Food Animals
1998	Ministry of Agriculture, Fisheries, and Food – A Review of Antimicrobial Resistance in the Food Chain
1998	National Research Council – Use of Drugs in Food Animals: Benefits and Risk
1999	U.S. General Accounting Office Report – The Agricultural Use of Antibiotics and Its Implications for Human Health
2001	EU SCAN Report – Opinion of the Scientific Committee on Animal Nutrition on the Criteria for Assessing the Safety of Microorganisms Resistant to Antibiotics of Human Clinical and Veterinary Importance.
2002	The FAAIR Report – The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences.
2015	World Health Organization – Global action plan on antimicrobial resistance.
2016	The Food and Agriculture Organization of the United Nations (FAO) – The FAO Action Plan on Antimicrobial Resistance 2016–2020.
2016	World Organization for Animal Health (OIE) – The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials
2018	International Consultation Group on Antimicrobial Resistance (IACG). Surveillance and Monitoring for Antimicrobial Use and Resistance – IACG.
2020	European Centre for Disease Prevention and Control (ECDC) –The European Surveillance System Antimicrobial Consumption (AMC) Reporting Protocol 2020

Table 2. Antibiotic residues in the different animal-derived products

Antibiotic residue	Concentration	Sample	Consequences in humans/animals	Country	Reference
Oxytetracycline		Chicken	Carcinogenic and cytotoxic substances in chicken bones. Presence of residues cause technological challenges during milk processing.	Tanzania	Kimeria et al. (2015)
	2604.1±703.7 µg/kg	Muscle			
	3434.4±604.4 µg/kg	Liver			
	3533.1±803.6 µg/kg	Kidney			
		Beef		Nigeria	Olufemi and Agboola (2009)
	51.8±90.53 µg/kg	Muscle			
	372.7±366.8 µg/kg	Liver			
	1197.7±718.9 µg/kg	Kidney			
		Cattle		Ethiopia	Bedada et al. (2012)
	15.92–108.34 µg/kg	Muscle			
	99.02–112.53 µg/kg	Kidney			
Enrofloxacin	0.73 and 2.57 µg/kg	Chicken tissues	Allergic hypersensitivity reactions or toxic effects, (photo-toxic skin reactions, chondrotoxic) and tendon rupture	Iran	Tavakoli et al. (2015)
Chloramphenicol	1.34 and 13.9 µg/kg		Bone marrow toxicity, optic neuropathy, brain abscess		
Penicillin	0.87 and 1.3 µg/kg	Calves' muscles	Allergy, affect starter cultures to produce fermented milk product		
Oxytetracycline	3.5 and 4.61 µg/kg		Carcinogenicity, cytotoxicity in the bones of broiler chickens		
Quinolones	30.81–0.45 µg/kg	Chicken	Allergic hypersensitivity reactions or toxic effects (photo-toxic skin reactions, chondrotoxic) and tendon rupture	Turkey	Er et al. (2013)
	6.64–1.11 µg/kg	Beef			
Tetracyclines		Chicken	Teeth discoloration in children and infants, allergic reactions, and teratogenicity during the first trimester of pregnancy, nephrotoxicity, carcinogenic, hepatotoxicity, and disturbance of the normal microflora of the intestines. It equally causes skin hyperpigmentation of areas exposed to the sun, proximal and distal renal tubular acidosis, hypersensitivity reactions	Egypt	Salama et al. (2013)
	124–5812 µg/kg	Breast			
	107–6010 µg/kg	Thigh			
	103 to 8148 µg/kg	Liver			
		Chicken		Cameroon	Guetiya-Wadoum et al. (2016)
	150±30 µg/kg	Liver			
	62.4±15.3 µg/kg	Muscle			
		Beef		Kenya	Muriuki et al. (2001)
	50–845 µg/kg	Kidney			
	50–573 µg/kg	Liver			
	23–560 µg/kg	Muscle			
Amoxicillin	9.8–56.16 µg/kg	Milk	Carcinogenic, teratogenic, and mutagenic effects	Bangla-desh	Chowdhury et al. (2015)
	10.46–48.8 µg/kg	Eggs			
Sulfonamides	16.28 µg/kg	Raw milk	Carcinogenicity, allergic reactions	China	Zheng et al. (2013)
	23.25 µg/kg		Allergic hypersensitivity reactions or toxic effects (photo-toxic skin reactions, chondrotoxic) and tendon rupture		
Oxytetracycline	199.6±46 ng/g	Beef	Carcinogenicity, allergic reactions	Zambia	Nchima et al. (2017)
Sulfamethazine	86.5±8.7 ng/g				
Penicillin G	15.22±0.61 µg/L	Fresh milk	Allergy (hypersensitivity reaction) ranging from mild skin rash to life-threatening anaphylaxis	Nigeria	Olatoye et al. (2016)
	7.60±0.60 µg/L	Cheese			
	8.24±0.50 µg/L	Fermented milk			
Sulfonamides		Chicken	Carcinogenic potential and mild skin rash to severe toxi-derma, epidermal toxic necrolysis, blood dyscrasias	Malaysia	Cheong et al. (2010)
	0.08–0.193 µg/g	Liver			
	0.006–0.062 µg/g	Breast			

The total antimicrobials application in food animal production amounted to approximately 131,109 metric tons in 2013 and the figure is projected to reach 200,235 metric tons by 2030 (Zinsstag et al., 2021; Vidovic and Vidovic, 2020). Consumption of antimicrobials varies significantly between countries, with a reported range of 8 mg/population correction unit (PCU) in Norway to an alarmingly high 318 mg/PCU in China. In the United States, it is estimated that approximately 70% of antimicrobials used to treat human infections are also employed in food animals. Similar patterns are also exhibited across 30 European countries. While information from developing countries is limited, empirical evidence suggests that the excessive use of antimicrobials in food animals is a pressing concern (Okaiyeto et al., 2024; Pokharel et al., 2020).

Antibiotic administration is a main strategy in the livestock industry, serving as a key tool to enhance animal performance, improve the efficiency of conversion of natural resources to food, and meet the escalating demand for animal products (Gonzalez Ronquillo and Hernandez, 2017). Antibiotics are used in animals for three main purposes: therapeutic use against infectious diseases, prophylactic use to prevent infectious animal diseases, and as feed additives to improve feed utilization and animal production (Fischer et al., 2011). A significant proportion of antibiotics used in veterinary medicine are used in food-producing animals. For example, in the US up to 80% of all antibiotics are used in livestock, where they are widely used as growth promoters. The main problems associated with the misuse of antibiotics are the presence of potentially harmful residues in meat and other animal products, and the associated contamination of soil and water (Manaia et al., 2022; Xu et al., 2022). Therefore, organizations such as the World Health Organization (WHO) have proposed a ban on the use of antibiotics as growth promoters, arguing that their use leads to various human health and environmental problems (Bengtsson-Palme et al., 2018).

Ideally, no animal derived product should be consumed unless there is a complete absence of residual amounts of administered drugs. Nevertheless, the intriguing fact is that there are constant detectable levels of residues, identified via the help of markedly improved analytical methods. However, antibiotics have been reported to accumulate and form residues at varying concentrations in the tissues and organs of food animals, as presented in Table 2. It has been well established (Bennani et al., 2021; Torres et al., 2021; Xu et al., 2022) that antibiotics used in food-producing animals can spread to humans through various direct and/or indirect routes (Vishnuraj et al., 2016; Bennani et al., 2020). In this context, food animal producers are expected to adhere to and implement the right dosages of the antibiotics and observe the associated withdrawal periods (clearance or depletion time; the length of time required for an animal to metabolize the administered antibiotics under normal condition) before slaughter and marketing, in order to prevent the presence of excessive drug residues in animal products (Manyi-Loh et al., 2018).

Techniques of measurements and limits

The most widely used method for the detection of antibiotic residues in animal-based foodstuffs is the microbial inhibition method that was first introduced by Myers (1964). This method is not only cost-effective but also able to detect multiple antibiotics simultaneously in a single test run (Vishnuraj et al., 2016). Microbial inhibition tests can be performed in either tube or plate format, with the tube test being the preferred method for detecting residues in milk samples, and the plate test has been the primary format for screening antibiotic residues in slaughter animals (Vishnuraj et al., 2016).

The European Union (EU) has established the four plates test (EU4pt) as a standard method for screening meat products for antibiotic residues (Tang and Gillevet, 2003). However, due to the laborious nature of the test and the increased likelihood of false positives with kidney samples, an alternative one plate test has been developed (Vishnuraj et al., 2016). Another screening method for detecting antibiotic residues in chicken meat and poultry has been proposed by Johnston et al. (1981). This method involves inserting a cotton swab into the meat or poultry tissue to absorb tissue fluid; this test has been shown to have equivalent sensitivity to conventional methods for detecting antibiotics such as chlortetracycline, oxytetracycline, tetracycline, erythromycin, neomycin, penicillin, streptomycin, and tylosin (Johnston et al., 1981). Shareef et al. (2009) utilized thin layer chromatography (TLC) to detect antibiotic residues in stored poultry products and discovered that 52% of all the samples evaluated tested positive for at least one antibiotic.

Currently, regulatory agencies require the antibiotic residue detection methods that possess high throughput, rapidity, reliability, and sensitivity, and can even process solid samples (Vishnuraj et al., 2016). Immunoassays and biosensors have gained significant attention in this context, owing to their advantages over traditional microbial assays (Cháfer-Pericás et al., 2010). Biosensors offer the potential for automation, *in situ* analysis, and the development of numerous commercial detection kits. These systems typically consist of two fundamental components: a transducing device and a recognition element. The benefits of biosensors include their capability to detect non-polar molecules, high specificity, and real-time applicability for industrial purposes. However, limitations include the susceptibility to biosensor contamination and the inability to heat sterilizes those (Cháfer-Pericás et al., 2010). Enzyme-linked immunosorbent assay (ELISA) is a widely employed method for detecting antibiotic residues in various tissue samples (Vishnuraj et al., 2016; Cháfer-Pericás et al., 2010). ELISA-based techniques offer several advantages, including high sensitivity, broad specificity, and the ability to handle a large number of small-volume samples in a relatively short period. However, the major limitations of this test are its expense and

the fact that detection is not real-time (Vishnuraj et al., 2016). Liquid chromatography–mass spectrometry (LC–MS) coupling is another effective and sensitive system for detecting antibiotic residues. Different methods of LC–MS include electrospray ionization sources, direct injection methods, and mobile phases. Mass spectrometry operates on the principle of mass-to-charge ratio (Cháfer-Pericás et al., 2010). Maximum residue limits (MRLs) of antimicrobial and analytic techniques from animal products are described in Table 3.

Table 3. Maximum residue limits (MRLs) of antimicrobial and analytic techniques from animal products

Substance	Chemical group	Animals	Tissue	MRL (µg/kg)	Analytical method
1	2	3	4	5	6
Amoxicillin	β-lactams	Cattle, Sheep, pig and fish	Muscle, fillet, kidney, fat, liver	50	LC–MS, MS
Amoxicillin	β-lactams	Cattle and sheep	Milk	4	LC–MS, MS
Ampicillin	β-lactams	Fish	Muscle, fillet	50	LC–MS
Benzylpenicillin	β-lactams	Cattle and pig	Muscle	50	LC–MS, MS
Procainebenzylpenicillin	β-lactams	Chicken, cattle, and pig	Muscle, liver, and kidney	50	LC–MS, MS
Benzylpenicillin	β-lactams	Cattle	Milk	4	LC–MS, MS
Ceftiofur	Cephalosporins	Cattle and pig	Muscle	1000	LC–MS, MS
Ceftiofur	Cephalosporins	Cattle and pig	Liver and fat	2000	LC–MS, MS
Ceftiofur	Cephalosporins	Cattle and pig	Kidney	6000	LC–MS, MS
Ceftiofur	Cephalosporins	Cattle	Milk	100	LC–MS, MS
Chlortetracycline	Tetracyclines	Cattle, pig, poultry and sheep	Muscle	200	GC–MS
Oxytetracycline	Tetracyclines	Fish, giant prawn	Muscle	20	GC–MS LC–MS
Chlortetracycline	Tetracyclines	Cattle, pig, poultry, and sheep	Liver	600	GC–MS
Chlortetracycline	Tetracyclines	Cattle, pig, poultry, and sheep	Kidney	1200	GC–MS
Chlortetracycline	Tetracyclines	Cattle and sheep	Milk	100	GC–MS
Chlortetracycline	Tetracyclines	Poultry	Eggs	400	GC–MS
Colistin	Polypeptide Polimixin	Cattle, sheep, goat, pig, chicken, turkey, and rabbit	Muscle, liver and fat	150	LC–MS/MS
Colistin	Polypeptide Polimixin	Cattle, sheep, goat, pig, chicken, turkey, and rabbit	Kidney	200	LC–MS/MS
Colistin	Polypeptide Polimixin	Cattle and sheep	Milk	50	LC–MS/MS
Colistin	Polypeptide Polimixin	Chicken	Eggs	300	LC–MS/MS
Danofloxacin	Fluoroquinolone	Cattle, chicken, and pig	Muscle	200	LC–MS/MS
Danofloxacin	Fluoroquinolone	Cattle, chicken, and pig	Liver and kidney	400	LC–MS/MS
Danofloxacin	Fluoroquinolone	Cattle, chicken, and pig	Fat	100	LC–MS/MS
Dihydrostreptomycin/ Streptomycin	Aminoglycosides	Cattle, chicken, pig, and sheep	Muscle, liver and fat	600	LC–MS
Dihydrostreptomycin/ Streptomycin	Aminoglycosides	Cattle, chicken, pig, and sheep	Kidney	1000	LC–MS
Dihydrostreptomycin/ Streptomycin	Aminoglycosides	Cattle and sheep	Milk	200	LC–MS
Erythromycin	Macrolides	Chicken and turkey	Muscle, liver, kidney, and fat	100	LC–MS
Erythromycin	Macrolides	Chicken	Eggs	50	LC–MS
Flumequine	Quinolones	Cattle, chicken, pig, sheep, and trout	Muscle	500	LC–MS
Flumequine	Quinolones	Cattle, chicken, pig, and sheep	Liver	500	LC–MS
Flumequine	Quinolones	Cattle, chicken, pig, and sheep	Kidney	3000	LC–MS
Flumequine	Quinolones	Cattle, chicken, pig, and sheep	Fat	1000	LC–MS
Gentamicin	Aminoglycosides	Cattle and pig	Muscle	100	LC–MS, MS
Gentamicin	Aminoglycosides	Cattle and pig	Liver	2000	LC–MS, MS
Gentamicin	Aminoglycosides	Cattle and pig	Kidney	5000	LC–MS, MS

Table 3 – contd.

Substance	Chemical group	Animals	Tissue	MRL (μg/kg)	Analytical method
1	2	3	4	5	6
Gentamicin	Aminoglycosides	Cattle and pig	Fat	100	LC–MS, MS
Gentamicin	Aminoglycosides	Cattle	Milk	200	LC–MS, MS
Haquinol	Quinolones	Swine	Muscle	40	LC–MS
Haquinol	Quinolones	Swine	Skin plus fat	350	LC–MS
Haquinol	Quinolones	Swine	Liver	500	LC–MS
Haquinol	Quinolones	Swine	Kidney	9000	LC–MS
Lincomycin	Macrolides	Cattle	Milk	150	LC–MS/MS
Lincomycin	Macrolides	Chicken and pig	Muscle	200	LC–MS/MS
Lincomycin	Macrolides	Chicken and pig	Liver and kidney	500	LC–MS/MS
Lincomycin	Macrolides	Chicken and pig	Fat	100	LC–MS/MS
Monensin	Ionophores	Cattle, sheep, goats, chicken, turkey, and quail	Muscle and kidney	10	LC–MS
Monensin	Ionophores	Cattle	Liver	100	LC–MS
Monensin	Ionophores	Cattle, sheep, goats, chicken, turkey, and quail	Fat	100	LC–MS
Monensin	Ionophores	Cattle	Milk	2	LC–MS
Monensin	Ionophores	Sheep and goats	Liver	20	LC–MS
Monensin	Ionophores	Chicken, turkey, and quail	Liver	10	LC–MS
Narasin	Ionophores	Cattle, chicken, and pig	Muscle, kidney	15	LC–MS
Narasin	Ionophores	Cattle, chicken, and pig	Liver	50	LC–MS
Narasin	Ionophores	Cattle, chicken, and pig	Fat	50	LC–MS
Neomycin	Aminoglycosides	Cattle, chicken, duck, goat, pig, sheep, and turkey	Muscle, kidney, and fat	500	LC–MS
Neomycin	Aminoglycosides	Cattle, chicken, duck, goat, pig, sheep, and turkey	Kidney	10000	LC–MS
Neomycin	Aminoglycosides	Cattle	Milk	1500	LC–MS
Neomycin	Aminoglycosides	Chicken	Eggs	500	LC–MS
Pirlimycin	Lincosamides	Cattle	Muscle, fat and milk	100	LC–MS/MS
Pirlimycin	Lincosamides	Cattle	Liver	1000	LC–MS/MS
Pirlimycin	Lincosamides	Cattle	Kidney	400	LC–MS/MS
Sarafloxacin	Quinolones	Chicken and turkey	Muscle	10	LC–MS/MS
Sarafloxacin	Quinolones	Chicken and turkey	Liver and kidney	80	LC–MS/MS
Sarafloxacin	Quinolones	Chicken and turkey	Fat	20	LC–MS/MS
Spectinomycin	Aminoglycosides	Cattle, chicken, pig and sheep	Muscle	500	LC–MS
Spectinomycin	Aminoglycosides	Cattle, chicken, pig and sheep	Liver and fat	2000	LC–MS
Spectinomycin	Aminoglycosides	Cattle, chicken, pig and sheep	Kidney	5000	LC–MS
Spectinomycin	Aminoglycosides	Cattle	Milk	200	LC–MS
Spectinomycin	Aminoglycosides	Chicken	Eggs	600	LC–MS
Spiramycin	Macrolides	Cattle, chicken, and pig	Muscle and liver	300	LC–MS/MS
Spiramycin	Macrolides	Cattle and pig	Kidney	200	LC–MS/MS
Spiramycin	Macrolides	Cattle, chicken, and pig	Fat	800	LC–MS/MS
Spiramycin	Macrolides	Cattle	Milk	25	LC–MS/MS
Spiramycin	Macrolides	Chicken	Kidney	100	LC–MS/MS
Sulfadimidine	Sulfonamides	Cattle	Milk	100	LC–MS/MS
Sulfadimidine	Sulfonamides	Not specified	Muscle, liver, kidney	100	LC–MS/MS
Sulfadimidine	Sulfonamides	Not specified	Fat	1000	LC–MS/MS
Tilmicosin	Macrolides	Cattle, pig, sheep, and turkey	Muscle	300	LC–MS/MS
Tilmicosin	Macrolides	Cattle and sheep	Liver	100	LC–MS/MS
Tilmicosin	Macrolides	Cattle and sheep	Kidney	150	LC–MS/MS

Table 3 – contd.

Substance	Chemical group	Animals	Tissue	MRL (μg/kg)	Analytical method
1	2	3	4	5	6
Tilmicosin	Macrolides	Cattle, pig, and sheep	Fat	2400	LC–MS/MS
Tilmicosin	Macrolides	Chicken	Muscle	600	LC–MS/MS
Tilmicosin	Macrolides	Chicken	Liver	250	LC–MS/MS
Tilmicosin	Macrolides	Chicken	Kidney	1500	LC–MS/MS
Tilmicosin	Macrolides	Chicken and turkey	Skin/fat	1000	LC–MS/MS
Tilmicosin	Macrolides	Pig	Liver	1200	LC–MS/MS
Tilmicosin	Macrolides	Pig	Kidney	1400	LC–MS/MS
Tilmicosin	Macrolides	Turkey	Kidney	1200	LC–MS/MS
Tilmicosin	Macrolides	Turkey	Liver	1400	LC–MS/MS
Tylosin	Macrolides	Cattle, pig, and chicken	Muscle, liver, kidney and fat	100	LC–MS/MS
Tylosin	Macrolides	Cattle	Milk	100	LC–MS/MS
Tylosin	Macrolides	Chicken	Eggs	300	LC–MS/MS

GC, gas chromatography; GC–MS, gas chromatography–mass spectrometry; LC, liquid chromatography; LC–MS, liquid chromatography–mass spectrometry; LC–MS/MS, liquid chromatography–tandem mass spectrometry.

Antibiotic in soil

The soil is a complex ecosystem characterized by a unique biodiversity that encompasses a wide range of species abundance, diversity, and functional roles, thus it can be one of the main reservoirs of antimicrobial resistance genes (ARGs) (Manyi-Loh et al., 2018; Nesme et al., 2014). It has been well established that the abundance and the mobility of antibiotic-resistant bacteria in the soil is mainly due to the application of manure from intensive livestock farming, the use of wastewater (black or grey water) for the irrigation, and the use of antibiotics to treat crop diseases (Manyi-Loh et al., 2018). It has been reported that 40 to 90% of the antibiotics in manure are released into the environment and even composting cannot completely reduce the high levels of antibiotics present in the soil (Gou et al., 2018; Tien et al., 2017). The interaction of indigenous soil microorganisms with manure bacteria helps the spread of mobile genetic elements (MGE), better known as horizontal transfer, generating a divergence and selection of ARGs in the agroecosystem (Gillings et al., 2015). As already mentioned, fields are fertilized with manure from different livestock species, with pig and cattle manure being the most used (Huygens et al., 2022). The extent of antibiotic residues in the soil resulting from manure application will depend on the type of manure (species of animals and the type of farming system) used. Also, quantity varies upon manure management practices, which themselves differ based on factors such as herd size, animal type, farm operations, and the production stage of the animals (Manyi-Loh et al., 2018). In soils fertilized with pig and bovine slurry the main antibiotic residues found are flumequine, doxycycline, oxytetracycline, lincomycin, and sulfadiazine (Huygens et al., 2021; Van den Meersche et al., 2020), which have half-lives ranging from 226 to 8 days with flumequine being the most found due to its longer half-life in the environment (Berendsen et al., 2021).

Another one of the most common antibiotics in soils are tetracyclines, even without their presence in the manure used for fertilization (Berendsen et al., 2021; Conde-Cid et al., 2020). This is attributed to the fact that *Streptomyces rimosus* can produce them naturally, but there is a lack of information on the subject. In contrast, the lowest concentration was for sulfadiazine and lincomycin (Berendsen et al., 2021), which may be due to its structure, since it has fewer functional groups (only aniline and amide groups), which decreases its affinity for the soil. This may be attributed to its structure, specifically the presence of only two functional groups, namely aniline and amide, which limits its affinity for soil. In addition, its adsorption capacity depends on the organic carbon content (the higher carbon content resulting in the greater adsorption) (Conde-Cid et al., 2020). It is currently known that the three pathways for the existence and divergence of ARGs in soils receiving organic manure are by direct introduction of ARGs transported by manure, by intrinsic enrichment of ARGs in soils, or by horizontal transfer of ARG genes provided by MGEs as mentioned above (Zhang et al., 2021).

Techniques of measurements and limits

In recent years antibiotic resistant bacteria have been isolated from soil samples, e.g. from sulfonamides and tetracyclines (Schmitt et al., 2006; Walsh et al., 2011), resulting in a risk to human health. The duration of antibiotic residues in soil varies according to soil type and the physicochemical properties of the antibiotic (Berendsen et al., 2021) (Table 4). Van den Meersche et al. (2020) detected the presence of 9 ARGs (tet(B), tet(L), tet(M), tet(O), tet(Q), tet(W), erm(B), erm(F), and sul2) in soils fertilized with pig slurry, which remained for 5 to 7 months in crop soils (until harvest time) and then disappeared. The most found ARGs in soil or slurry are erm(M), erm(B), erm(F), and sul2 (Van den Meersche et al., 2020; Zhang et al., 2021).

Table 4. Limit of detection (LOD) and limit of quantification (LOQ) and concentration for antibiotic resistance selection in soil

Antibiotics	Excretion rate (%)	Source and residual levels	Soil sample and concentration (μg/kg)	LOD (μg/kg)	LOQ (μg/kg)	PNEC soil (μg/kg)	Reference
1	2	3	4	5	6	7	8
Amoxicillin	10–20			18.2	–		Huygens et al. (2021)
Ampicillin	60			5.4	17.9		Huygens et al. (2021)
Ciprofloxacin			Livestock farm (0.1–30 μg/kg)	5.0	16.6	27–310	Cycoń et al. (2019); Bengtsson-Palme and Larsson (2016)
Chlortetracycline	65	Pig manure (46 mg/kg)	Vegetable farmland (31 μg/kg)	10.3	30.5		Huygens et al. (2021)
		Dairy cow feces (0.6–2 mg/kg)	Field adjacent to composting facility (0.3–0.9 μg/kg)				Kuppusamy et al. (2018)
		Chicken feces (0.5–3 mg/kg)	Agricultural field fertilized with poultry or cattle manure (70–100 μg/kg)				Kuppusamy et al. (2018)
		Pond water (0.6 μg/L)	Field fertilized with cattle manure (<1 μg/kg)				Kuppusamy et al. 2018
		Animal wastewater (0.4–1 μg/L)	Agricultural soils under long-term swine effluent application (2–140 μg/kg)				Kuppusamy et al. 2018
		Animal farm-effluent (0.5–4 μg/L)					Kuppusamy et al. (2018)
		Pig manure (119 μg/L)					Kuppusamy et al. (2018)
Chloramphenicol			Livestock farm (0.1–15 μg/kg)	1.5	–		Kuppusamy et al. (2018)
Difloxacin	90			3.3	10.9		Huygens et al. (2021)
Doxycycline		Animal wastewater (0.6–40 μg/L)					Kuppusamy et al. (2018)
Enrofloxacin		Dairy cow feces (0.4–4 mg/kg)		4.4	14.7	0.03–359	Huygens et al. (2021)
		Chicken feces (0.3–15 mg/kg)					Kuppusamy et al. (2018)
		Pig manure (33 mg/kg)					Kuppusamy et al. (2018)
Erythromycin	5–10		Vegetable farmland (99 μg/kg)	5.6	18.5		Huygens et al., 2021
			Agricultural field fertilized with poultry or cattle manure (20–70 μg/kg)				Kuppusamy et al. (2018)
Lincomycin			Livestock farm (0.1–12 μg/kg)	2.6	8.7	4–420	Mehrtens et al. (2021); Bengtsson-Palme and Larsson (2016)
Norfloxacin			Vegetable farmland (62 μg/kg)	15.0	50.1		Huygens et al. (2021)
Oxytetracycline	21	Pig manure (29 mg/kg)	Vegetable farmland (10 μg/kg)	7.1		200–500	Huygens et al. (2021
		Pig feces (0.7–56 mg/kg)	Field adjacent to composting facility (2–4 μg/kg)				Kuppusamy et al. (2018)
		Dairy cow feces (0.2–56 mg/kg)					Kuppusamy et al. (2018)
		Pond water (6.9 μg/L)					Kuppusamy et al. (2018)
		Animal wastewater (9–73 μg/L)					Kuppusamy et al. (2018)
		Pig manure (59 mg/kg)					Kuppusamy et al. (2018)

Table 4 – contd.

1	2	3	4	5	6	7	8
Ofloxacin	90		Livestock farm (0.6–16 µg/kg)				Kuppusamy et al. (2018)
Pefloxacin			Livestock farm (1.2–25 µg/kg)				Kuppusamy et al. (2018)
Streptomycin	66						Kuppusamy et al. (2018)
Sulfamethazine	90	Animal wastewater (2.3–211 µg/L)	Vegetable farmland (6 µg/kg)	4.8	16.0		Huygens et al. (2021)
		Animal farm- effluent (0.8–169 µg/L)					Kuppusamy et al. (2018)
		Pig farm dust (0.3 mg/kg)	Pig farm (0.7 µg/kg)				Kuppusamy et al. (2018)
Sulfachloropyridazine		Slurry from pig farm (703 µg/L)	Agricultural field fertilized with poultry or cattle manure. (40–100 µg/kg)	6.2	18.8		Huygens et al. (2021)
Sulfadimidine		Pig manure (20 mg/kg)	Field adjacent to composting facility (20–28 µg/kg)				Kuppusamy et al. (2018)
		Chicken and turkey dung (91 mg/kg)	Pig farm (0.7 µg/kg)				Kuppusamy et al. (2018)
Sulfadoxine		Animal wastewater (0.3–0.6 µg/L)		5.0	16.6		Huygens et al. (2021)
		Animal farm-effluent (0.08–0.1 µg/L)					Kuppusamy et al. (2018)
Sulfamethoxazole		Animal farm-effluent (0.2–0.6 µg/L)	Wastewater irrigated field (16–90 µg/kg)	3.9	13.1	22–224	Huygens et al. (2021)
		Pig manure (9990 µg/kg)	Vegetable farmland (24 µg/kg)				Kuppusamy et al. (2018)
Sulfathiazole			Agricultural field fertilized with poultry or cattle manure. (50–100 µg/kg)				Kuppusamy et al. (2018)
Sulfameter			Vegetable farmland (51 µg/kg)				Kuppusamy et al. (2018)
Sulfamonomethoxine		Pig feces (0.1–4 mg/kg)					Kuppusamy et al. (2018)
		Pig manure (4 mg/kg)					Kuppusamy et al. 2018
Sulfonamides	15					10	Huygens et al. (2021)
Sulfadiazine			Agricultural field (0.9–3 µg/kg)	6.6		84,000	Huygens et al. (2021)
Tetracycline	75–80	Pig manure (23 mg/kg)	Vegetable farmland (44 µg/kg)	5.6	18.6	15	Huygens et al. (2021)
		Pig feces (0.3–30 mg/kg)	Agricultural field (199 µg/kg)				Kuppusamy et al. (2018)
		Dairy cow feces (0.4–2 mg/kg)	Field adjacent to composting facility. (0.8–3 µg/kg)				Kuppusamy et al. (2018)
		Chicken feces (0.5–4 mg/kg)					Kuppusamy et al. (2018)
		Animal farm-effluent (0.5–6 µg/L)					Kuppusamy et al. (2018)
Tylosin	50–100	Pig manure (12 µg/kg)	Agricultural field (2–6 µg/kg)	2.9	9.8	22–689,920	Huygens et al. (2021)
		Pig farm dust (12 mg/kg)					Kuppusamy et al. (2018)
Thiamphenicol				9.1			Huygens et al. (2021)

Predicted concentration for antibiotic resistance selection in soil (PNECsoil). Detection the antibiotics tested using UHPLC–MS/MS.

The amount and presence of ARGs in soil or slurry is given even by the type and amount of bacteria present in the gut of the animals (Gram-negative or Gram-positive). For example, tet(B) and tet(L) come from encoding Gram-negative efflux bonbons and tet(M) can be found in both Gram-positive and Gram-negative bacteria (Chee-Sanford et al., 2009). One factor to consider that influences the amount of ARGs present in the soil is the depth of the soil, as it has been reported that the deeper the soil, the less ARGs have been found (Huygens et al., 2022), when using manure (0–10 cm depth), which may be due to a lower microbial density. However, the use of slurry suggests the presence of ARGs may be present at a greater depth and affect the upper 2 layers (15–30 cm depth) (Huygens et al., 2022).

Antibiotic in water

Water is a crucial habitat for bacteria on earth, serving as a primary natural way for the dispersal of microorganisms between various environmental compartments and/or aquatic ecosystems, as well as between humans and other animals (Manyi-Loh et al., 2018). The microbial aquatic environment encompasses a range of water types, including surface and ground waters, drinking water, tap water, and wastewater. The bacterial communities present in these waters exhibit complex and variable composition patterns that are influenced by a combination of temporal and spatial factors, including physicochemical and biotic variables, such as environmental stressors and nutrient availability (Manyi-Loh et al., 2018). A recent review (Maghsodian et al., 2022) on the presence of antibiotics in aquatic environments highlights that the fluoroquinolones and sulfonamides had the highest concentrations in water. Li et al. (2019) evaluated the concentration of antibiotics in rivers in China, among different classes of antibiotics. Sulfonamides generally dominated in river water (39.8–65.7%) of the total concentrations, quinolones were the second dominant group of antibiotics (10.9–30.0%), followed by macrolides (7.17–20.3%). Hernandez et al. (2019) sampled in the Antarctic Sea and found ciprofloxacin, clindamycin, and trimethoprim, these compounds were also found in wastewater, illustrating that wastewater discharges lead to seawater contamination; the most widespread antibiotic in seawater was ciprofloxacin, in concentrations ranging from 4 to 218 ng/L (mean 48 ng/L), clindamycin and trimethoprim were found in very low concentrations (below 0.1 ng/L). Moreover, Yang et al. (2018) conducted a comprehensive review of the presence of antibiotics in lakes worldwide and found that a total of 57 antibiotics were present, with sulfamethoxazole, sulfamerazine, sulfameter, tetracycline, oxytetracycline, erythromycin, and roxithromycin being the most common in both water and sediment samples. Regarding groundwater, López-Serna et al. (2013) assessed the presence of the antibiotic in groundwater of Spain and reported that 72 different pharmaceutical active products were detected in underground water of Barcelona city. Similarly, Mahmood et al. (2019) found a high concentration of ciprofloxacin (1.270 µg L), levofloxacin (0.177 µg L), and amoxicillin (1.50 µg L) in potable water in Baghdad city, Iraq. Bilal et al. (2020) have provided an up-to-date data on the impact of antibiotic contamination in water sources, including surface water, groundwater, and seawater, on human health, microbiomes, and various aqueous environment systems.

Table 5. Antimicrobial concentration and characteristics of sea water, river water, and wastewater samples

Substance	Chemical group	Concentration (ng/l)	Type of water*
1	2	3	4
Ampicillin	β-lactams	83.75 (22.13)	Wastewater
	β-lactams	215.6 (29.8)	East China Sea
	Macrolides	33.6 (14.8)	East China Sea
Amoxicillin	Penicillin	1.50 µg/L	Groundwater
Azithromycin	Macrolides	990.0 (N.D.)	River
Azithromycin	Macrolides	221.90 (149.85)	Wastewater
Cefalexin	Cephalosporins	99.79 (86.98)	Wastewater
	Tetracyclines	2.5 (2.0)	East China Sea
Chlortetracycline	Tetracyclines	6.0 (N.D.)	River
Ciprofloxacin	Quinolones	48.0 (N.D)	Antarctic Sea
Ciprofloxacin	Quinolones	4–218	Antarctic Sea
Ciprofloxacin	Quinolones	1.27 µg/L	Groundwater
Ciprofloxacin	Quinolones	342.0 (335.84)	River
Ciprofloxacin	Quinolones	234.77 (157.7)	Wastewater
Clarithromycin	Macrolides	47.0 (65.05)	River
Clarithromycin	Macrolides	104.48 (94.67)	Wastewater
Clindamycin	Lincosamides	0.1 (N.D)	Antarctic Sea
Clindamycin	Lincosamides	11.5 (12.02)	River
Clindamycin	Lincosamides	62.89 (38.06)	Wastewater

Table 5 – contd.

1	2	3	4
Enrofloxacin	Quinolones	69.4 (N.D.)	Wastewater
Erythromycin	Macrolides	65.0 (21.21)	River
Levofloxacin	Quinolones	29.0 (N.D.)	River
Levofloxacin	Quinolones	0.177 μg/L	Groundwater
Metronidazole	Nitroimidazoles	330.0 (N.D.)	River
Metronidazole	Nitroimidazoles	49.51 (34.27)	Wastewater
	Quinolones	54.2 (48.9)	East China Sea
Nalidixic acid	Quinolones	37.8 (17.68)	Wastewater
Norfloxacin	Quinolones	1,116.5 (1,419.16)	River
Ofloxacin	Quinolones	1,270 (N.D.)	River
Ofloxacin	Quinolones	107.77 (87.63)	Wastewater
Orbifloxacyn	Quinolones	6.6 (0.14)	Wastewater
Oxytetracycline	Tetracyclines	6.0 (N.D.)	River
Roxithromycin	Macrolides	70.0 (N.D.)	River
	Sulfonamides	39.3 (15.2)	East China Sea
Sulfadiazine	Sulfonamides	260.0 (N.D.)	River
Sulfamethazine	Sulfonamides	4.0 (N.D.)	River
Sulfamethoxazole	Sulfonamides	397.25 (670.53)	River
Sulfamethoxazole	Sulfonamides	44.59 (33.38)	Wastewater
Sulfamethoxazole	Sulfonamides	26.75 (N.D.)	Lake water
Sulfapyridine	Sulfonamides	73.47 (48.66)	Wastewater
Tetracycline	Tetracyclines	16 (N.D.)	River
Tetracycline	Tetracyclines	111.16 (79.90)	Wastewater
Tetracycline	Tetracyclines	280–540	Drinking water
Tetracycline	Tetracyclines	2.11–9.23	Sea water
Tetracycline	Tetracyclines	17–30	Lake water
Trimethoprim	Diaminopyrimidines	181.5 (153.44)	River
Trimethoprim	Diaminopyrimidines	115.23 (54.84)	Wastewater

Overall, the aquatic environment has been reported to be the origin and reservoir of antibiotic-resistant bacteria and resistance genes (Huddleston, 2014; Cabello, 2006; Sørum, 2006; Mirzaei et al., 2022). Table 5 and Figure 3 compile information on antimicrobial concentration and characteristics of water samples. Among the adverse effects of antibiotics in water bodies is the accumulation of these chemical components in aquatic organisms to human consumption. In this sense, antibiotics have a strong inhibitory effect on the enteric bacterial community of human intestinal microorganisms. However, the main concern about antibiotic contamination of the aquatic environment is the transfer of antibiotic resistance. The antibiotics released into water bodies exert a selective pressure on the microbial community, resulting in the spread of drug-resistant bacteria. According to Huddleston (2014), the transfer of antibiotic resistance genes acquired by humans from the environment (food, soil, etc.) to gut microbes leads to an increase in gut microbial resistance.

As regards veterinary activities, the unrestricted use of antibiotics in aquaculture is of particular concern due to the rapid transfer of antibiotic resistance (Cabello, 2006). Although aquaculture shares several characteristics in the use of antibiotics with other livestock activities, the high concentration of normal and pathogenic bacteria of humans and animals in water environments and aquatic sediments facilitates and accelerates the transfer of antibiotic resistance (Cabello, 2006; Sørum, 2005; Li et al., 2019). However, antibiotic resistance is not the only problem associated with the release of antibiotics into the aquatic environment (Sørum, 2005; Fajardo et al., 2008). Several studies show that very low concentrations of antibiotics in aquatic environments can have biological activities such as signaling (like-hormone effect) and affect chloroplast replication, folate biosynthesis, fatty acid synthesis, and sterol biosynthesis (Fajardo et al., 2008).

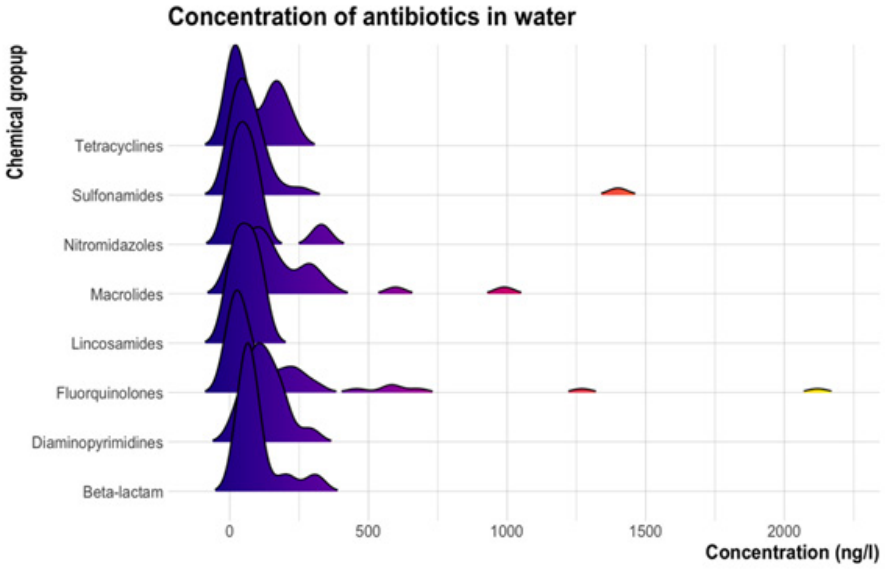


Figure 3. Concentration of antibiotics in water according to the chemical group (Rodriguez-Mozaz et al., 2020; Grenni, 2022)

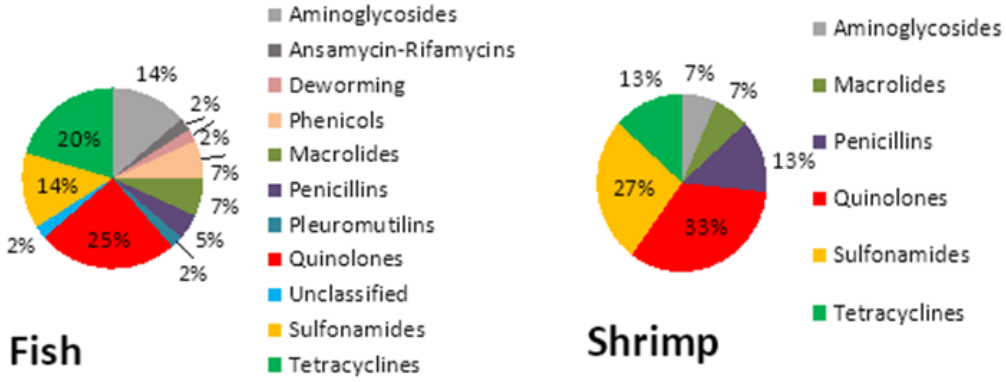


Figure 4. Concentration of antibiotic residues in fish and shrimp (adapted from Robles-Jimenez et al., 2021)

It is important to note that antibiotics are affecting essential fish functions (swimming speed and feeding behavior), even at relatively low steroid concentrations. It has now been mentioned that even non-steroidal anti-inflammatory drugs (NSAIDs) can affect gene expression functions as well as the activities of several metabolic enzymes (Mikula et al., 2024). In previous studies (Robles-Jimenez et al., 2021), it has been mentioned that quinolones (25% and 33%), and sulfonamides (14 and 27%) are the antibiotic residues that have been found with the highest prevalence in fish and shrimp (Figure 4). Fluoroquinolones can develop disabling and potentially permanent side effects in tendons, muscles, joints, nerves, and central nervous system (Robles-Jimenez et al., 2021). The route that antibiotics follow to cause these problems in farmed fish is as follows; regularly, fish feed contains antibiotics, reaching the fish intestine where it is an optimal site for the selection of resistant bacteria. Subsequently, in fish feces, the bacteria are dispersed in the water column or sediments stimulating mutagenesis or horizontal gene transfer (Bojarski et al., 2020).

Mechanism of antimicrobial resistance (AMR)

Prior to discussing the key issues regarding AMR in the animal food sector, it is essential to define the concept of resistance, as it is integral to grasping the underlying principles and consequences of the phenomenon (Vidovic and Vidovic, 2020; Manaia et al., 2022). Bacteria can acquire antibiotic resistance by different routes, e.g. from farms, hospitals, or from patients (animals, humans) that are mostly prone to transfer antimicrobial resistance (Cantas et al., 2013). The ability of bacteria with antimicrobial resistance genes to survive in hostile environments and transfer

easily from one host to another in diverse ecosystems (soil, water, air, host) is what makes them most dangerous (Boerlin and Reid-Smith, 2008). It has now been reported that when bacteria are in a suitable environment, they can multiply every 12 min (e.g. *Escherichia coli)* and can increase their survival by up to 50% in humid environments (*Pseudomonas putida*, *Serratia marcescens*, and *Alcaligenes faecalis*) (Werkneh and Islam, 2023).

Antimicrobial resistance in bacteria is mainly due to transformation, transduction, and conjugation that occur in the process of horizontal gene transfer (Ahmad et al., 2021). The AMR mechanism can be better understood by looking at Figure 5 (A, B), which shows the entire process that a bacterium undergoes in order to acquire microbial resistance. Responsible for moving ARGs from one host to another are transposons (transposable elements) via plasmids, which are mobile DNA sequences that are interconnected with bacterial chromosomal DNA or plasmids (Venter et al., 2017), a process that is common for certain bacteria (*Acinetobacter* spp.) (Haenni et al., 2022).

The conjugative processes of gene transfer are not the same in Gram-positive and Gram-negative bacteria. Gram-positive bacteria exchange genetic material by mating (Vittecoq et al., 2016).

Figure 5. (A)

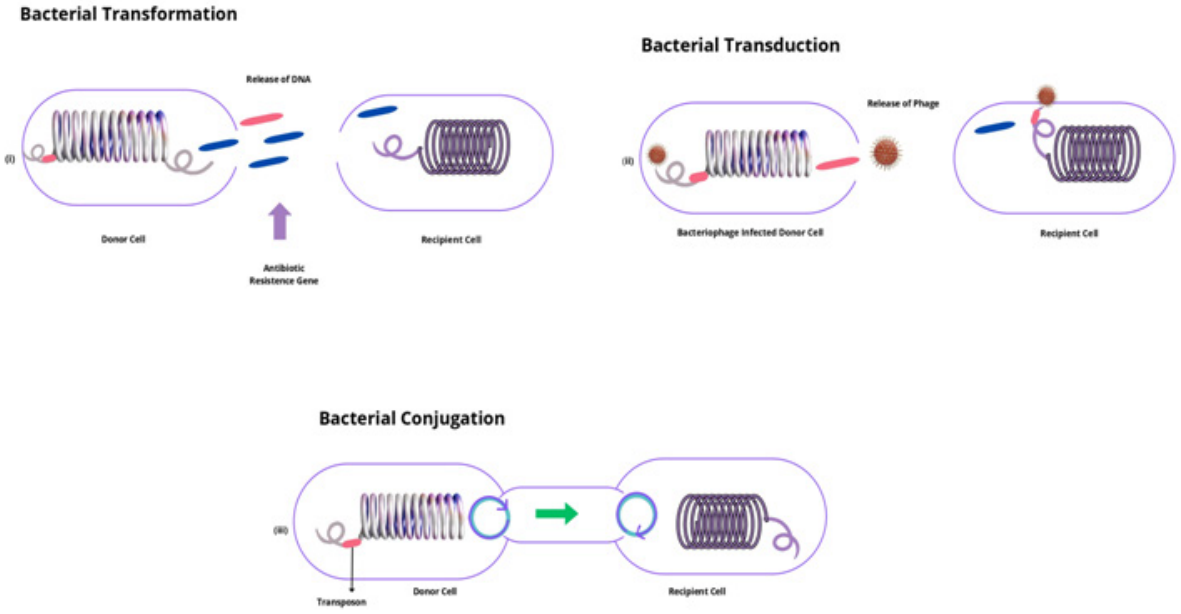


Figure 5. (B)

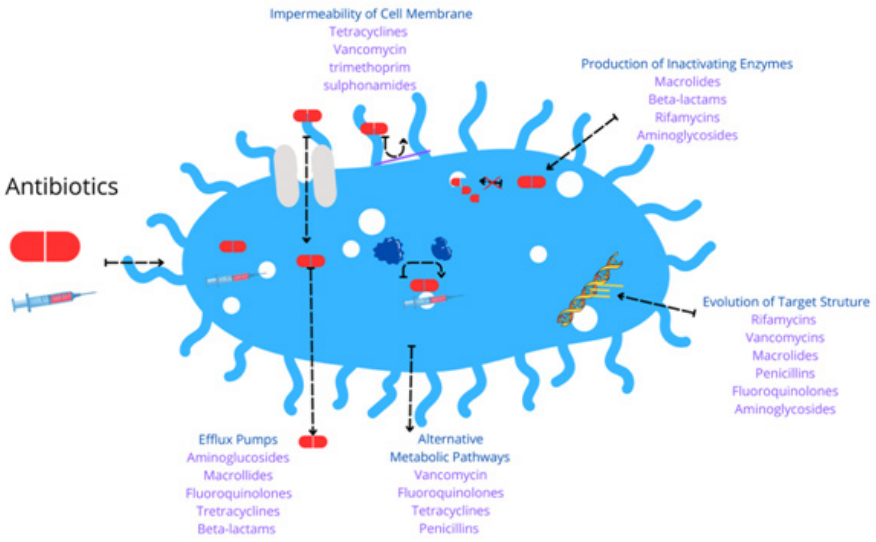


Figure 5. Bacterial gene transformation methods and resistance mechanism. A) Three methods of bacterial genetic material exchange: (I) Transformation (II) Transduction (III) Conjugation, B) Five mechanisms of bacterial resistance to antibiotics (modified from Werkneh and Islam, 2023)

Table 6. Bacteria with antibiotic resistant genes

Bacteria	Genes	Animal species	Reference
Campylobacter spp.	FlaA, CadF, CeuE, ErmB	Sheep, cattle and poultry, wet surfaces	Anampa-Diego et al (2020); Palomino-Camargo et al. (2014)
Salmonella	NDM-1	Gram-negative bacilli	De la Fuente et al. (2007)
	OgdH	Poultry, sheep, cattle, and pigs	Palomino-Camargo et al. (2014)
E. coli	NDM-1	Sheep	Pérez Vázquez et al. (2019)
	Wzx, wzy, UidA, lacC	Domestic animal and human feces	Jimenez-Mejia et.al. (2017); Palomino-Camargo et al. (2014)
Klebsiella pneumoniae	NDM-1	Sheep	Pérez Vázquez et al. (2019)
Listeria spp.	CadC, PrfA	Cattle, sheep, dogs, cats, and humans	Pombinho et al. (2020)
E. coli	blaCTX-M-1	Red deer	Alonso et al. (2016)
E. coli	NDM-5	Dairy cows	He et al. (2017)
Enterococcus spp.	pAD1	Food of animal origin	Schell et al. (2014)

Several genes associated with antimicrobial resistance have been identified in a wide range of Gram-positive and Gram-negative bacteria, which can be identified by multiplex PCR (Table 6).

Approaches to combat with the emergence of AMR in animal, soil, and water settings

There is an urgent need to develop new strategies to better control the emergence and spread of AMR, particularly resistance to clinical antibiotics used in human medicine (Xu et al., 2022). Tackling AMR requires a comprehensive approach that involves several interconnected strategies. In this sense, the priority actions have been well documented (Mudenda et al., 2023; Wu-Wu et al., 2023) that include reinforcing industrial and academic research, regulating the antimicrobial market, monitoring usage, and enhancing awareness and education among healthcare professionals, agricultural workers, and the general public. Moreover, since antimicrobials serve as critical production factors in food animal production, it is crucial to consider substitution possibilities between antimicrobials and other production factors (Vidovic and Vidovic, 2020; Xu et al., 2022). On the other hand, previous researches established that addressing AMR is hampered by various challenges including: insufficient human resources for AMR management, financial constraints, limited surveillance of antimicrobial use and AMR, inadequate data sharing capabilities, lack of awareness and understanding of AMR among healthcare professionals and the public, inadequate disease diagnostic facilities, behavioral issues related to prescribing, dispensing, and use of antimicrobials, and limited capacity building and effective implementation of AMR policies (Mudenda et al., 2023). In the EU, the use of antimicrobials in agriculture has been restricted since the 1960s. Sweden, Norway, and Denmark pioneered the phase-out of antimicrobial use as growth promoters, and by 2006, all EU countries had followed suit (Pokharel et al., 2020). The WHO Global Action Plan aims to optimize antimicrobial use in animal health, while FAO action plan focuses on surveillance, governance, and best practices. The OIE backs these initiatives (Helmy et al., 2023; Zinsstag et al., 2021). Despite universal acknowledgment of the necessity to combat antimicrobial resistance (AMR), progress towards a "One Health" approach remains slow (Pokharel et al., 2020).

Over the past decade, there has been increasing global interest in engineered metal nanoparticles (NPs) due to their high and prolonged toxicity to microorganisms. The antimicrobial properties of NPs are attributed to their large surface area-to-volume ratio, which enhances their reactivity and produces reactive oxygen species (ROS) (Vidovic and Vidovic, 2020). Certain types of metal NPs demonstrate broad-spectrum antimicrobial activity without harmful effects on humans. However, advanced technology is required to fully utilize their potential. For instance, zinc-doped copper oxide NPs have shown promising results against multidrug-resistant (MDR) bacteria, resulting in a six-log reduction in both *Escherichia coli* and *Staphylococcus aureus* strains after a brief 10-minute exposure (Soni et al., 2010). The application of bacteriophages is another field of interests for facing with AMR. These viruses target bacteria and can be employed against human, animal, or zoonotic pathogens. Two commercially available bacteriophage products, ListShield™ and Listex™ P100, have received approval as food preservatives (PhageGuard, 2019). Research has demonstrated that Listex™ P100 can effectively diminish *Listeria monocytogenes* populations by 5-logs within a 24-hour period at ambient temperature. Additionally, it can break down *L. monocytogenes* biofilms on stainless steel surfaces after 24 hours at 20°C. However, shorter exposure durations lead to reduced efficacy. Notably, Listex™ P100 has been shown to decrease *L. monocytogenes* counts on fresh catfish fillets by over 1 $\log_{10}$ following 30 minutes of contact (Vidovic and Vidovic, 2020; Soni et al., 2010).

Bacteriocins, peptides or proteins synthesized by ribosomes that possess antimicrobial qualities, nowadays serve as a viable substitute for conventional antibio-

tics (Silva et al., 2018). These molecules exhibit unique mechanisms of action, such as bactericidal or bacteriostatic effects, and can target various cellular processes, including peptidoglycan synthesis, lipid II binding, and central metabolic pathways. Lactic acid bacteria (LAB) are notable producers of bacteriocins, and research has demonstrated their efficacy against foodborne pathogens. Nisin, a commercially approved bacteriocin, has been shown to reduce *L. monocytogenes* biofilms by 3.5 logs over 48 hours. While there exists a vast array of bacteriocins, with over 230 different variants produced by LAB alone, only a select few have undergone thorough testing (Silva et al., 2018; Vidovic and Vidovic, 2020). However, detailed researches are required to assess the efficiency of bacteriocins and bacteriophage therapy against multiple pathogens under different conditions. This will help establish the full potential of either bacteriocins and/or bacteriophages as a biological intervention technology against the emergence and spread of antimicrobial-resistant bacteria, as well as their capability to combat human and zoonotic pathogens.

The study of AMR has been focused on humans, however, given the afore mentioned interaction, the scientific community, with the support of these organizations, is focusing on the knowledge of the traceability of resistant bacteria in different hosts. Currently, there are already databases where the amount of antibiotic contamination in some parts of the world can be known (Table 7), but more information on AMR is needed, which is why it is so important to know methods for detecting genes in bacteria.

Molecular tools can be applied to study N by identifying resistance genes, as well as markers such as the ^{15}N isotope and microbiological techniques such as minimum inhibitory concentration (MIC) assisted by UV spectrophotometry and flow cytometry.

N is increasingly seen as a biomarker for monitoring the role of metabolism in disease and a variety of other problems. This marker can be used to monitor the behavior of alternative solutions against infections such as probiotics, including the study of the traceability of antimicrobial resistant bacteria. A major obstacle for such experiments is the lack of established and standardized protocols and the unavailability of available protocols, ^{15}N NMR reference spectra to identify N-containing metabolites.

Isotopic analyses are now of considerable importance for food certification, plant, and animal physiology. Indeed, the natural nitrogen isotope composition (δ15N) is extremely useful for examining metabolic pathways of N nutrition involving isotope fractionations. However, δ15N analysis of amino acid N is not straightforward and involves specific derivatization procedures to produce volatile derivatives that can be analyzed by gas chromatography coupled to isotope ratio mass spectrometry (GC-C-IRMS).

The excessive use of antibiotics in agriculture has contributed to the growing problem of antibiotic resistance (Ahmad et al., 2021; Al Amin et al., 2020; Vishnuraj et al., 2016). To address this issue, measures should be taken to educate farmers and the public about the proper use of antibiotics and the risks of overusing them. Veterinarians should also be involved in the prescription and monitoring of antibiotics in animal farming. Additionally, the government should provide subsidies to farmers, particularly those in rural areas, to encourage the use of regular, proper, and efficient veterinarian services (Venter et al., 2017; Zinsstag et al., 2021; Ghimpețeanu et al., 2022). The use of antibiotics without prescription and proper supervision should be avoided, and veterinary officers and pharmacists should adhere to strict policies governing antibiotic prescriptions. Routine surveillance and analysis of antibiotic residues in foods of animal origin should also be conducted before they are consumed by humans. Finally, policy makers should implement regulations to enforce the legitimate purchase and use of antibiotics in animal farming, taking into account the varying consumption patterns and production systems between countries (Manyi-Loh et al., 2018; Xu et al., 2022).

Concluding remarks

The emergence and spread of AMR is a complex and multifaceted challenge that affects not only humans but also animals and the environment. Agricultural intensification is a significant contributor to the emergence of AMR and the increasing of the overall resistance. So, a holistic approach is necessary to mitigate the burden of AMR and ARGs within human, animal, and environment (Vidovic and Vidovic, 2020). Currently, national veterinary service standards fail to meet international benchmarks. Access to trained veterinarian services can

Table 7. Antibiotic monitoring websites

Name	Description	Website
ADES	Groundwater database	ades.eaufrance.fr
METEOFRANCE	French weather database	meteofrance.com
NAIADES	Continental water database	naiades.eaufrance.fr
QUADRIGE	Coastal water database	quadrige.eaufrance.fr
PIREN	Database on the hydrographic network of the Seine River	piren-seine.fr
SIPIBEL	Surface water, groundwater, wastewater database	graie.org/sipibel
SOKARST	Network of karst groundwater monitors	sokarst.org

substantially improve diagnostic capability, treatment, and prescribed food animal antibiotic use. Investment in animal production and veterinary services is essential in two-part, to: (1) Provide early detection and diagnostics of AMR, thereby enabling the implementation of effective biosecurity and biocontamination measures, and (2) Strengthen food animal production and veterinary systems, which is critical for stabilizing economies, ensuring food security and safety, and minimizing exposure to AMR and pathogenic microorganisms (Forman et al., 2012).

As emphasized by OIE, robust veterinary systems are vital for achieving these goals. By effective veterinary system, not only will the burden of AMR be reduced, but also the prevalence of other infectious diseases will be simultaneously diminished (Maron et al., 2013; Vidovic and Vidovic, 2020). Many countries have already established veterinary oversight mechanisms to regulate animal production, slaughter, food processing, product distribution, retail store inspections, and foodborne and occupational disease exposure surveillance programs (Manyi-Loh et al., 2018; Pokharel et al., 2020). Enhancing the capacity of veterinary services within food animal systems through capital and training investments could further fortify global food safety, which is not only a matter of animal and public health concerns, but also a factor in maintaining market feasibility for international trade partners.

Effective veterinary services play a crucial role in promoting public health through partnerships with human medical services, adopting a "One Health" framework. This multifaceted strategy surveillance endeavors across human, animal, and environment, yielding benefits for both human and animal health. The recent pandemics, such as COVID-19 (SARS-CoV-2), influenza A (H1N1), and West Nile virus (WNV), have underscored the importance of public health intervention at the human-animal interface to prevent zoonotic transmission and protect human populations (Maron et al., 2013).

Recently, a few different methods, such as nanotechnology, anaerobic digestion, biochar composting, etc., have been developed to minimize AMR and ARGs (Vidovic and Vidovic, 2020; Xu et al., 2022). Also, promising alternatives to conventional antibiotic treatments such as herbal plant extracts, probiotics, vaccines, enzymes, and antimicrobial peptides (short peptides, 15–20 amino acids, with a complex mechanism of action, which are harder to counter than those of antibiotic drugs) are introduced that make the development of AMR difficult (Xu et al., 2022; Wu-Wu et al., 2023). It has been also documented that the search for alternatives to traditional antibiotics, such as antimicrobial peptides and targeted therapies using bacteriocins, may help to reduce the advance of antibiotic resistance by providing safer, more environmentally friendly options for disease control (Wu-Wu et al., 2023).

Furthermore, a better understanding of the evolution of AMR is crucial to guide cutting-edge interventions. The establishment of research infrastructures and tracking systems (e.g., laboratory networks) is critical to collect data for decision-making and share information on AMR globally. Similarly, advanced molecular tools for identifying ARGs and bacterial hosts are necessary to elucidate transmission dynamics and the evolution of AMR at the human-livestock-environment interface. Despite the decline in antibiotic use in livestock and the growing trend of "antibiotic-free" farms, the persistence of multidrug-resistant bacteria in these animals remains a pressing global concern. The efficacy of reducing antimicrobial use in controlling AMR has been proposed due to studies demonstrating that AMR imposes a fitness cost, slowing down bacterial growth rates and virulence. Nonetheless, bacteria are developing compensatory adaptations that mitigate the cost of AMR, potentially rendering reductions in antibiotic use ineffectual in the short term for poultry farms previously exposed to antibiotics. Nevertheless, the implementation of AMU bans in high-income countries has led to a decrease in resistance levels in the long term (Bengtsson-Palme et al., 2018).

The array of antimicrobial use in food animal husbandry is rapidly declining, even as they remain indispensable for maintaining animal health, rural livelihoods, and public well-being. A meticulous assessment of antibiotic usage in the context of intensive poultry farming may help curtail the spread of drug resistance. Veterinary medical interventions should focus on areas where resistance is already manifesting. Embracing sustainable livestock management practices could also contribute to containing the rise of resistance. Moreover, there is a pressing need for nearly all nations to enhance their stewardship of antimicrobials as part of their commitment to fostering biosafety and biosecurity. The future research endeavors should concentrate on creating integrated strategies and technological solutions that thoroughly address human-animal-environment contamination, thereby diminishing the transmission and spread of AMR. Although this goal may seem challenging, advancements in high-throughput analytical methods, multi-omics approaches, and machine-learning tools can provide valuable insights to minimize pollution. Furthermore, improvements in waste management practices on a global scale, and the rational use of antibiotics in livestock production, may offer more immediate benefits.

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