Chapter 1
Entry Routes of Antibiotics and Antimicrobial Resistance in the Environment

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Abstract This chapter describes the current knowledge about the entry routes of antibiotics and antimicrobial resistance in the environment. It starts with an overview of the most important entry routes being wastewater and sludge from urban wastewater treatment plants, and natural fertilizers like pig slurry and cow manure and fertilizer from poultry farming. These sites are referred to as hotspots for antibiotic resistance genes (ARGs) and antibiotic resistance bacteria (ARB), including bacteria pathogenic for humans and animals, also those mentioned on the WHO priority list of global priority pathogens and of antibiotic-resistant bacteria. All these entry routes, manure, wastewater, and aquacultures, are characterized in terms of general sources of antibiotics, ARB, and ARGs. We also analyze the European Surveillance of Veterinary Antimicrobial Consumption report on the sale of antibacterials for veterinary. Furthermore, the EU guidelines to reduce the sales of veterinary antimicrobials across Europe under the umbrella of the EU One-Health Action Plan against Antimicrobial Resistance are mentioned. In the last section we point the need to develop and standardize the guidelines and method protocols for surveillance of AMR which need to be practicable, comparable, simple, and cost-effective so that they can be applied globally.

Keywords Entry routes · Antibiotics · Antimicrobial resistance · Environment

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1.1 Introduction

Antibiotics and antimicrobial resistance (AMR) can enter the environment through very many different routes, the most important being wastewater and sludge from urban wastewater treatment plants (WWTPs), and natural fertilizers like pig slurry and cow manure and fertilizer from poultry farming. These sites are referred to as hotspots for antibiotic resistance genes (ARGs) and antibiotic resistance bacteria (ARB), including bacteria pathogenic for humans and animals. In many cases, these are multidrug-resistant (MDR) strains, where ARGs are frequently carried on mobile genetic elements, notably plasmids and transposons, that can be transferred by different mechanisms of horizontal gene transfer (HGT) not only among bacteria of the same species, but also among different species. In the following sections, we present current knowledge on antibiotics and antimicrobial resistance entry routes in the environment, and finally we present a scheme of general sources of antibiotics ARB and ARGs and degradation mechanisms of antibiotics in the environment, in an attempt to better understand the complexity of the problem of dissemination of AMR.

1.2 Characterization of Entry Routes

The entry routes of antibiotics and AMR are mainly connected with the excretion of animal urine and feces (manure) from agriculture, where a large fraction of antimicrobial agents can be released into the environment in an active form. Another source represents WWTPs, where both sludge and treated wastewater are major pathways. For example, when sewage sludge is used as fertilizer or to condition soil, or when treated wastewater is reused for irrigating arable fields, the remaining antibiotics and ARB that are reservoirs of ARGs are introduced into the environment (Krzeminski et al. 2019). Finally, the third pathway is aquaculture, where antibiotics provided with a feed are frequently overused. Perhaps of lesser importance for AMR, there are also communal rubbish dumps; however in this case a leachate from a municipal solid waste is a real threat to environmental pollution by antibiotics and other drugs that are thrown into the household rubbish bins. The presence of antibiotics in the environment creates a selective pressure, which promotes the spread of AMR among bacteria, especially with a high potential of resistance genes located on mobile genetic elements (MGEs). This, in turn, may lead to the selection of resistant strains, which are also capable of moving between different environments (including people's microbiome and the hospital environment), thereby creating the potential for the movement of ARGs and associated MGEs (further covered in Chap. 14 on the fate of ARB and their AMR genes within the environment). Considering the above, it seems extremely important to develop effective methods of wastewater, water, and soil treatment to reduce spread and proliferation of AMR in the environment.

1.2.1 Manure

Manure is characterized by a rich chemical composition and contains, among others, compounds sometimes unavailable in mineral fertilizers. The advantage of manure is also that it slowly decomposes and does not cause soil salinity. Manure provides plants with basic nutrients such as nitrogen, phosphorus, and potassium. In addition, it also contains calcium, magnesium, boron, and iron, which are sometimes unavailable in mineral fertilizers (Szogi et al. 2015; Burton and Turner 2003). Manure spread and excavated with soil (optimally at a depth of 15–20 cm) also affects the humus formation. Manure types due to their origin:

Bovine manure—used on different soils, but it is recommended for sandy substrates in which nutrients are quickly washed away. It contains fewer nutrients, but is more abundant in potassium. The bovine manure contains an average of 0.9% N; 0.5% P_2O_5; 1.2% K_2O; 1.2% CaO, and 0.2% MgO at a water content of 34%.

Horse manure—causes rapid heating of the soil which is not always a beneficial process. It can be used on heavy and light soils. Horse manure contains an average of 0.7% N; 0.3% P_2O_5; 0.8% K_2O; at a water content of 55%.

Pig manure—a good solution for sandy substrates in the cultivation of plants that produce a large amount of green matter. It is nitrogen rich. The liquid manure is a mixture of animal manure and water. It is created in the non-bedding of swine as a by-product and waste product. Among the compounds included in its composition, it is possible to distinguish compounds that are mainly a solid fraction, for example, organic compounds and phosphorus compounds, as well as components of the liquid fraction, such as nitrogen compounds and minerals in the form of sodium, potassium, and magnesium oxides. However, the content of these substances depends on the method of breeding and feeding of pigs. Pig manure contains an average of 1.1% N, 0.6% P_2O_5, 0.7% K_2O, 0.4% CaO, and 0.2% MgO at a water content of 88% (Jørgensen and Jensen 2009).

Poultry manure—usually used as an additive to other fertilizers or a component of a compost prism. It contains a very large amount of nitrogen and its use may lead to a risk of overfertilizing the plants. It is usually recommended to dilute it and/or mix with other natural fertilizers. Poultry manure is used for fertilizing soils and for the production of various types of organic substrate, e.g., for growing mushrooms. The chemical composition of this fertilizer varies depending on the species. The chicken manure contains an average of 2.8% N, 1.2% P_2O_5, 1.4% K_2O, 2.4% CaO, and 0.7% MgO at a water content of 56%. Manure of waterfowl (duck and goose) contains 0.5–1.0% N, 0.5–1.4% P_2O_5, 0.6–0.9% K_2O, 0.8–1.6% CaO, and 0.2–0.3% MgO at a water content of 30%. Nitrogen in bird manure is predominantly in the form of uric acid, which quickly decomposes into ammonia. Poultry manure is recommended in doses of 10–15 t/ha, for the same plants and at the same times as traditional manure.

Natural fertilizers like manure can be harmful to health. Therefore, in the countries of the European Union, the rules for introducing these products for sale and use have been specified. Permission for introduction of fertilizer or other means is issued by the minister competent for agriculture. Before being placed on the market, organic fertilizers must be carefully tested in terms of both fertilizer value and safety for humans, animals, and the environment.

Organic and organic-mineral fertilizers are subject to physicochemical and biological research. Physicochemical tests determine the content of organic matter, nitrogen, phosphorus, magnesium, and heavy metals in fertilizers. In addition to organic matter and heavy metals, the scope of fertilizer testing depends on the manufacturer's declaration. Biological examinations are aimed at excluding the presence of *Salmonella* and live parasitic eggs from *Ascaris* spp., *Trichuris* spp., and *Toxocara* spp.

The biological impurities introduced together with organic fertilizers into the environment include bacteria, viruses, fungi, and invasive forms of parasites, mainly intestinal. It is also known that the survival time of pathogenic organisms in the soil is from several days to even 10 years, and on plants from several days to 1 year.

The chemical composition of natural fertilizers is variable and depends on the species, age, direction of use and way of feeding animals, as well as the storage conditions of fertilizers.

In order to use natural fertilizers rationally and in accordance with the regulations, it is necessary to determine the permissible and optimal dose of fertilizers. The permissible dose is that in which the amount of nitrogen carried in does not exceed 170 kg N/ha. The optimum dose, depending on the nutritional requirements of the plants and soil availability, may be lower than the acceptable dose. When using natural fertilizers frequently and in high doses, particular attention should be paid to the abundance of soils in phosphorus, the excessive accumulation of which may pose a threat to the aquatic environment. Manure is not active enough to fully replace fast-acting mineral fertilizers, but it can significantly reduce expenditures on the total cost of fertilizers, because it is the cheapest of all known fertilizers. Liquid manure differs from manure not only in physical values but also in chemical composition and fertilizing action. In contrast to manure, it is a liquid fertilizer, more aggressive, and thus faster affecting the soil. In addition, its use by plants is very fast, which results from the fact that most fertilizer substances are in a mineral form, e.g., nitrogen from slurry is much better used by plants than from manure. Liquid manure is a mixture of feces and urine as well as water from washing up the stands. It is created in rooms adapted to keep animals without mulch. The content of fertilizing ingredients in slurry depends on the species and age of the animals and how they are used, the type of feeding, the degree of dilution, water, etc.

It should be remembered, however, that the aforementioned fertilizers are the essence of fertilization in so-called organic farming, whose aim is to maintain or increase the fertility and biological activity of the soil and create optimal conditions for the development of plants.

In manure, antibiotics from a wide range of classes are detected in the highest levels (Hu et al. 2010; Jechalke et al. 2014; Kemper et al. 2008; Lathers 2001; Marshall and Levy 2011; Sarmah et al. 2006). The second environment with high concentration of antibiotics are soils fertilized with manure, where antibiotics are washed off with groundwater from the soil and move forward (Anjum and Krakat

2015; De La Torre et al. 2012; Williams-Nguyen et al. 2016). Also veterinary medicine were antibiotics of the same classes as in human treatment are or have been used, carries the danger of the emergence and spread of AMR (Heuer et al. 2009; Martínez 2009). This phenomenon is particularly serious in the case of the pathogens transmitted via food, e.g., *Campylobacter jejuni*, *Escherichia coli*, *Salmonella*, and *Enterococcus faecium*. The same strains may hence colonize animals and humans, yet resistance genes disseminate easily between closely related species. This creates a serious threat of extensive antibiotic and/or resistance gene dissemination (Ding and He 2010; Popowska et al. 2010, 2012; Mąka et al. 2015a, b, 2018). Since January 1, 2006, antibiotics should not be used as growth promoters (http://europa.eu). Until 2006, 90% of antibiotics used in agriculture had been destined for growth stimulation and only 10% for fighting bacterial diseases. Statistical data indicate that in the last 50 years over one million of tons of antibiotics were introduced into the environment, 50% derived from veterinary medicine and agriculture (Allen et al. 2010). Despite the existence of legal acts regulating the use of antibiotics in veterinary medicine and animal husbandry, medically important antibiotics are still routinely used for livestock (Cantas et al. 2013). Many publications report the association between antibiotics (of 24 antibiotics used in animal and/or human medicine) and bacterial AMR of *Escherichia coli*, *Enterococcus faecalis,* and *Enterococcus faecium* in liquid pig manure used as fertilizer. Reported concentrations of antibiotics in manure are from residual levels to commonly 1–10 mg/kg or mg/L, yet concentrations of more than 50 mg/kg were also reported (Hölzel et al. 2010; Massé et al. 2014). A summary of the findings is presented in Table 1.1.

The levels of antibiotics found in manure might seem generally low, but the production of manure is on a big scale: in Europe, pigs and cows are reported to jointly produce 1.27 billion tonnes of manure per year. The consolidated data from 30 EU/EEA countries shows that more than 8300 tonnes of active ingredients were sold for use in animals in 2015 alone (EMA/ESVAC 2017; ECDC/EFSA/EMA 2017). In agricultural land where farm manures (both solid manures and slurries) are applied, it is estimated that, antimicrobials are being released into the environment in the region of kilograms per hectare per year (Kemper 2008). An example of the use of fertilizers on a large scale is the United Kingdom, where about 96 million tonnes of farm manures (both solid manures and slurries) are applied to agricultural land (Defra 2010). This is a real threat of environmental contamination with antibiotics used in livestock. The final concentration of antibiotics in manure and then in the agriculture soil is the resultant of various processes, among others, antibiotic metabolism and degradation processes. Some antibiotics bind strongly to soil and sediments, which contributes to their persistence as they become inaccessible to degradation (Kumar et al. 2005; Kühne et al. 2000; Rabølle and Spliid 2000; Sengelov et al. 2003). The rate of degradation of antimicrobials in the environment is dependent on a range of conditions, for example: antibiotic concentration, chemical structure of the compound, composition and structure and sorption properties of soil, pH, temperature, availability of oxygen and microorganisms that support biodegradation (Kümmerer 2004, 2009a, b). The application of manure to land poses a threat to contamination of the aquatic environment including surrounding surface

Table 1.1 Concentration of antibiotics in manure from global sources (Massé et al. 2014)

Class of antibiotic	Antibiotic	Source	Concentration	Reference
Ionophorous	Monensin	Beef manure stockpile	120 mg/kg	Dolliver et al. (2008)
Macrolide	Tylosin	Fresh calf manure	0.11 mg/kg	Jacobsen and Halling-Sørensen (2006)
		Beef manure stockpile	8.1 mg/kg	Dolliver et al. (2008)
Sulfonamide	Sulfadiazine	Swine manure	7.1 mg/L	Chen et al. (2012)
	Sulfonamides	Swine manure	2 mg/kg DM	Jacobsen and Halling-Sørensen (2006)
Tetracycline	Chlortetracycline	Swine manure	764.4 mg/L	Pan et al. (2011)
		Swine manure	139 mg/L	Chen et al. (2012)
		Swine manure storage lagoon	1 mg/L	Campagnolo et al. (2002)
		Beef manure stockpile	6.6 mg/kg	Dolliver et al. (2008)
	Doxycycline	Swine manure	37 mg/L	Chen et al. (2012)
	Oxytetracycline	Swine manure	354 mg/L	Chen et al. (2012)
		Manure	136 mg/L	Martínez-Carballo et al. (2007)
		Cow manure	0.5–200 mg/L	Ince et al. (2013)
		Fresh calf manure	10 mg/kg	De Liguoro et al. (2003)
	Tetracycline	Swine manure	98 mg/L	Chen et al. (2012)

water and groundwater. The antibiotic concentrations reported in aquatic environments are less than 10 μg/L (Kümmerer 2009a, b), which, however, taking into account the phenomenon of promoting antibiotic resistance in sub-lethal concentrations, creates a serious risk of antibiotic resistance spread (Andersson and Hughes 2014; Cairns et al. 2017; Friman et al. 2015; Händel et al. 2013).

Manure is also the reservoir of AMR and ARGs, and thus poses a risk for animal or human health (Marshall and Levy 2011; Storteboom et al. 2007; Thanner et al. 2016). It has been shown that manure is a "hot spot" of ARB, which carrying ARGs on mobile genetic elements (MG) and via horizontal gene transfer (HGT) these ARGs can be transferred to the soil bacteria (Cytryn et al., 2017; Binh et al. 2008; Fahrenfeld et al. 2014; Wolters et al. 2014). ARB are also found in meat, generating a real risk of pathogen infections in human. Examples are *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing or AmpC beta-lactamase-producing *Escherichia coli*, and *Enterococcus faecalis* (Endimiani et al. 2012; EU 2015; Overesch et al. 2013; Schmidt et al. 2015; Vogt et al. 2014). These bacteria were included on the WHO priority list on February 2017, the first ever list of global priority pathogens (global PPL) and of antibiotic-resistant bacteria. Totally, 12 families of bacteria identified as posing the greatest threat to human health were mentioned (Table 1.2). These bacteria were grouped into three classes in the order of risk: I—critical, II—high, and III—medium priority. Due to the high

Table 1.2 WHO global PPL of antibiotic-resistant bacteria (WHO 2017)

Classification	Antibiotic resistant
Priority 1: Critical	
Acinetobacter baumannii	Carbapenem-resistant
Pseudomonas aeruginosa	Carbapenem-resistant
Enterobacteriaceae	Carbapenem-resistant, ESBL-producing
Priority 2: High	
Enterococcus faecium	Vancomycin-resistant
Staphylococcus aureus	Methicillin-resistant, vancomycin-intermediate and resistant
Helicobacter pylori	Clarithromycin-resistant
Campylobacter spp.	Fluoroquinolone-resistant
Salmonellae	Fluoroquinolone-resistant
Neisseria gonorrhoeae	Cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: Medium	
Streptococcus pneumoniae	Penicillin-non-susceptible
Haemophilus influenzae	Ampicillin-resistant
Shigella spp.	Fluoroquinolone-resistant

level of resistance among these bacteria and the presence of MDR strains, new antimicrobial agents targeting this priority list of pathogens are needed. According to the WHO "The list was drawn up in a bid to guide and promote research and development (R&D) of new antibiotics, as part of WHO's efforts to address growing global resistance to antimicrobial medicines." It is important to realize that R&D of new antibiotics is not enough and cannot solve the problem. It is equally important to use better prevention of infections and appropriate use of existing antibiotics in humans and animals.

The European Medicines Agency (EMA) published on 15th October 2018, the eighth ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) report on the sale of antibacterials for veterinary use in 2016 (EMA/ESVAC 2018). On average, sales of antibacterial agents for veterinary use in the EU decreased by 20% between 2011 and 2016. Sixteen countries experienced a reduction of 9–58%. Not all countries, however, experienced such a reduction as six countries experienced an increase of 8–68%. What can be a reason for satisfaction, the sale of critical substances, which are antibacterial substances that are important for public health, amounted to 0.21 mg/PCU, 2.70 mg/PCU, and 6.62 mg/PCU, respectively, for third and fourth generation cephalosporins, fluoroquinolones, and polymyxins. The data shows there was a drop of almost 40% in sales of polymyxins for veterinary use. This class includes colistin, which is used as a last resort treatment in patients with bacterial infections resistant to other antibiotics. Sales of third and fourth generation cephalosporins decreased by 15.4%, while sales of quinolones declined by 13.6%.

This continues the downward trend seen over the last few years and confirms that EU guidance and national campaigns promoting prudent use of antibiotics in animals to fight antimicrobial resistance are having a positive effect. Reduction in sales is the result of combined efforts of the European Commission, EMA, EU Member States, veterinarians, farmers, and other actors in the livestock sector. EU guidance together with national campaigns for prudent use of antibiotics in animals, sales targets, and restriction of use of some antimicrobials in food-producing animals are among the actions implemented to reduce the sales of veterinary antimicrobials across Europe under the umbrella of the EU One-Health Action Plan against Antimicrobial Resistance (EU 2017; WHO—http://www.who.int/features/qa/one-health/en/). Actions to reduce the emergence and spread of AMR are also carried out.

The results of studies on AMR in soil fertilized with manure indicate that the spread of manure leads to a temporary increase in the occurrence of AMR in the manure-amended soil (Bengtsson-Palme et al. 2018; Kumar et al. 2018; Scott et al. 2018). Thus, the use of manure in agriculture contributes to the global dissemination of AMR in the environment (Heuer et al. 2011a, b; Jensen et al. 2002; Sengelov et al. 2003). Therefore, a matter of high importance is the right manure treatment strategies to reduce or eliminate the risk of the release of antibiotics and ARGs from manures to the environment. More information on AMR and ARGs in natural fertilizers is provided in Chap. 6: "Antimicrobial/antibiotic resistance gene due to manure and agricultural waste applications," and on treatment technologies for removal of antibiotics, ARB, and ARGs is posted in Chap. 19.

1.2.2 Wastewater Treatment Plants (WWTPs)

WWTPs where sewage is collected and then treated serve an essential role in the protection of human and environmental health. WWTPs therefore meet the principles outlined in the WHO concept—One-Health approach. Unfortunately, traditional WWTPs are designed to remove conventional pollutants, including organic matter, suspended solids, and nutrients like nitrogen and phosphorus. In many cases traditional WWTPs are effective in eliminating some pathogens but are not designed for the removal of antibiotics or ARGs (Agga et al. 2015; Manaia et al. 2018; Novo et al. 2013; Krzeminski et al. 2020; Pruden et al. 2013; Schwermer et al. 2018). Together with sewage to WWTPs enter antibiotic residues from different sources (hospital, pharmaceutical industry, and household) and other co-selecting factors, such as chemical pollutants (e.g., pesticides), heavy metals, and disinfectants/surfactants. Sewage microbiota is mainly composed of human commensal bacteria, which is mixed with bacteria that may be colonizing the sewage system (Cai et al. 2014; Shchegolkova et al. 2016; Wang et al. 2014). The ARB fraction in sewage may reach more than 50%, mainly in a given group: enterobacteria or enterococci (Manaia et al. 2016; Rizzo et al. 2013). Considering the very good conditions for bacterial growth in a bioreactor system such as WWTPs, the presence of these abovementioned factors causes selection pressure and the phenomenon of co-selection, which in turn promotes horizontal gene transfer (Di Cesare et al. 2016;

Schlüter et al. 2007). Besides, the mobile genetic elements (MGEs) are in fact postulated as important vectors of ARGs between bacterial strains (Dröge et al. 2000; Kim et al. 2014; Marano and Cytryn 2017; Perry and Wright 2013; Szczepanowski et al. 2009).

Analysis of the effectiveness of removing various antibiotics from wastewater in WWTPs showed that removal is achieved mainly via chemical treatment and/or bio-adsorption onto particulates, and subsequent physical separation from municipal wastewater. The removal is not a result of biological degradation, which is relatively less effective in removing antibiotics from the municipal wastewater (Michael et al. 2013). For some antibiotics such as sulfonamides like sulfamethoxazole and quinolones like norfloxacin and ciprofloxacin the detected abundance in the effluent still remained high, ranging at concentrations of 119–544 ng/L, 24–175 ng/L, and 11–168 ng/L, respectively (Senta et al. 2013). Generally, at least 56 antibiotics belonging to six different classes have been widely detected at nanogram per-liter to microgram per-liter levels in sewage of East Asia, North America, Europe, and Australia (Zhang and Li 2011). Many studies have shown the occurrence of chemical contaminants including antibiotic residues and their uncontrolled emission in the environment, which contributes to the proliferation of ARB and their associated genes, especially ARGs (Berendonk et al. 2015; Berglund et al. 2015; Manaia 2017; Manaia et al. 2016; Michael et al. 2013; Rizzo et al. 2013). The results of numerous studies indicate that WWTPs are "hot spots" of ARGs and ARB (Baquero et al. 2008; Michael et al. 2013; Piotrowska et al. 2017a; Zhang et al. 2009a; b). Depending on the treatment technology used and the sources of sewage coming to a WWTP (hospital, municipal effluent), the variability of diverse ARB including multidrug-resistant (MDR) strains of clinically relevant bacteria and ARGs for important antibiotics in medicine and veterinary medicine (B-lactams, macrolides, sulfonamides, fluoroquinolones and tetracyclines) are observed (Hong et al. 2013; Michael et al. 2013; Rizzo et al. 2013). For example, β-lactamase genes (https://www.lahey.org) belonging to the AmpC, ESBL, KPC, and NDM groups have been found in bacteria in wastewater (Amador et al. 2015; Gatica et al. 2016; Khan and Parvez 2014; Picão et al. 2013; Piotrowska et al. 2017a; Varela et al. 2016; Zhang et al. 2009a, b). A study of Chen and Zhang (2013) using QPCR methods found that tetracycline resistance genes (e.g., tetA, tetB, tetC, tetD, tetE, tetG, tetK, tetL, tetM, tetO, tetP, tetS, tetX) were present in the activated sludge sampled from 15 WWTPs at different geographical locations. Others indicated the ARGs are widespread in the effluent, for example: sulfonamide resistance genes (sul1 and sul2); erythromycin resistance genes (ermB, ermF); and vancomycin resistance gene (vanA) (Bockelmann et al. 2009; Burch et al. 2013; Chen and Zhang 2013; Fahrenfeld et al. 2013; Negreanu et al. 2012; Zhang et al. 2009a, b). ARBs found at different stages of the treatment process in municipal WWTPs belong mainly to *Acinetobacter* spp., and to enterococci and *Enterobacteriaceae*, which includes those mentioned in the list of global priority pathogens list (Table 1.2). Analysis of the results published showed that many of the enterococci and *Enterobacteriaceae* were resistant to more than one antibiotic (Ferreira da Silva et al. 2006, 2007). In addition, it has been shown that for some bacteria of *Escherichia*, *Shigella* and *Klebsiella* spp. resistant to more than two antibiotics increased from an average 11% in the raw wastewater to 21% in the treated wastewater. Similarly, the collective proportion of these *Enterobacteriaceae* which were resistant to three antibiotics increased from 5.5 to 14.1% in the treated wastewater. This observation further suggested that the conventional municipal wastewater treatment scheme does not effectively remove viable *Enterobacteriaceae* that are resistant to antibiotics. Goldstein et al. (2012) reported evidence for the presence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the effluent of four U.S. WWTPs. Likewise, bacteria resistant to clinically important antibiotics, including ciprofloxacin and vancomycin, have been found in the activated sludge (Nagulapally et al. 2009). Since many similar examples can be given, the effluent of WWTPs, if not purified sufficiently, poses a threat to public health (Hong et al. 2013; Walsh et al. 2011). To analyze ARB and ARGs different approaches are used: targeted (culture-based and quantitative PCR) and non-targeted like metagenomics. However, it should be remembered that depending on the type of environment, less than 1–10% of bacteria can be culturable (Vaz-Moreira et al. 2013). That is why it seems that the combination of culture-based methods with culture-independent approaches may be the ideal way to explore the environmental resistome (Li et al. 2015; Port et al. 2014; Yang et al. 2014).

Water scarcity is a global issue, especially in certain regions like Africa, the Middle East, southern Europe, as well as the western states of America. Thus, in these regions irrigation with treated wastewater is likely an important entry route of antibiotics into soil ecosystems. Multiple studies point out the presence of ARGs and ARB in wastewater effluent (Auerbach et al. 2007; LaPara et al. 2011; Manaia et al. 2010; Munir et al. 2011; Piotrowska and Popowska 2015; Piotrowska et al. 2017a). Unfortunately, the effects of antibiotics introduced into the soil on ARGs or ARB levels in soil has been little explored (Negreanu et al. 2012; McLain and Williams 2014). Antibiotics transferred into the soil may also affect the microorganisms and other biota inhabiting the niche and also the different processes in soil (Aga et al. 2016; Majewsky et al. 2014; Williams-Nguyen et al. 2016).

1.2.3 Aquaculture

Aquacultures are an intensively developing, fastest-growing food industry in the world. Continuous intensification of fish farming, increasing the risk of disease, has resulted in the widespread application of antibiotics treatment (Bostock et al. 2010). Consequently, the occurrence of ARGs in commercially available fish meals has been reported. Han et al. (2017) found 132 AMR genes in fishmeal from Russia and from China and these resistance genes were also isolated from sediment bacteria. Hence in aquacultures, where antibiotics are used as feed additives, the number of strains non-susceptible to antibiotics is many times greater (Baquero et al. 2008). The type and amount of use of antibiotics in aquaculture depends on farming practices, different local and national regulations and government enforcement ability. However, in many countries that are major aquaculture producers, regulation and enforcement is very weak and, it seems that inadequate. In aquaculture, antibiotics are used in range: from 1 g in Norway to 700 g in Vietnam per metric ton of production (Defoirdt et al. 2011). The low use of antibiotics in Norway is a results of a national strategy to substitute antibiotic treatment with vaccinations. The antibiotics officially approved for use in the treatment and prophylaxis of cultured aquatic animals belongs to several classes and their representatives are: oxytetracycline, florfenicol, sarafloxacin, erythromycin, sulfonamides with trimethoprim or ormethoprim (Serrano 2005; Kümmerer 2009a). The literature data indicate that up to 75 percent of antibiotics used in aquaculture may be released to the surrounding environment and the presence of antibacterial compounds strongly disturbs the microbiome composition. The application of antimicrobials affects targeted pathogens as well as a wide variety of environmental bacteria, resulting in selection of AMR strains. The presence of AMR strains increases the risk of HGT to potential human pathogens (Zhang et al. 2009a, b). Some antibiotics in aqueous medium are not biodegradable and accumulate, e.g., by the process of adsorption on solid surfaces including bottom sediments or silt (Kümmerer 2004, 2009b). As research indicates, a minimum of 75% of antibiotics added to the feed of farmed fish enters the aquatic environment and accumulate in sediments (Lalumera et al. 2004). In the review article by Caruso (2016), there are many examples of research work on AMR and HGT in aquacultures. Generally, till now ARGs have been described in bacteria responsible for fish diseases, such as *Aeromonas hydrophila, Aeromonas salmonicida, Edwardsiella tarda, Edwardsiella icttaluri, Vibrio anguillarum, Vibrio salmonicida, Pasteurella piscida, Yersinia ruckeri,* or *Piscirickettsia salmonis* (Serrano 2005; Henríquez et al. 2016). Two bacterial genera have been found in aquacultures with a high frequency: *Aeromonas* spp. and *Vibrio* spp. What is interesting, bacteria of the genus *Aeromonas* isolated from fish ponds exhibit resistance to multiple antibiotics, and the resistance genes for these therapeutics are primarily located on plasmids and integrons (Baquero et al. 2008; Piotrowska and Popowska 2014, 2015; Piotrowska et al. 2017b). What is very important, since some of the *Aeromonas* strains also cause disease in humans and become the same specific vector that connects both environments, they may transfer MGEs carrying resistance genes to pathogenic or opportunistic bacteria in the human microbiome. These data clearly indicate that aquacultures are a reservoir of antibiotic resistance genes, and therefore pose a great risk to the health and life of humans (Agersø and Petersen 2007; Cabello et al. 2013; Furushita et al. 2003; Kemper 2008; Miranda et al. 2018). The significantly greater percentage of an aquaculture's strains are non-susceptible to tetracycline, streptomycin, and erythromycin, but the resistance mechanism against those antibiotics has been explained in only 50% of the resistant isolates. Literature data indicates that the dominant mechanisms of tetracycline and erythromycin resistance are: efflux pumps, ribosomal protection, or enzymatic modification of rRNA (Miranda et al. 2003; Muziasari et al. 2014; Patterson et al. 2007; Piotrowska et al. 2017b; Tamminen et al. 2010). The latter is dominant in the streptomycin-resistant aquatic isolates (Mohapatra et al. 2008). Quinolone, florfenicol, flumequine, ampicillin, or oxolinic acid-resistant strains are found with lesser frequency in aquaculture (Miranda et al. 2018; Su et al. 2011). On the contrary, bacteria resistant to gentamicin, kanamycin, flumequine, and enrofloxacin have been reported to account for a low percentage of the total of the isolates (Miranda and Zemelman 2002). Very often, specific ARGs are detected simultaneously during the analysis of fish farm effluents. The results of the research of coastal aquaculture located in South Korea revealed 22 ARGs encoding tetracycline resistance (tetA, tetB, tetD, tetE, tetG, tetH, tetM, tetQ, tetX, tetZ, tetBP), sulfonamide resistance (sul1, sul2), quinolone resistance (qnrD, qnrS, aac(60)-Ib-cr), b-lactams resistance (blaTEM, blaCTX, blaSHV), macrolide resistance (ermC), florfenicol resistance (floR), and multidrug resistance (oqxA) and a class 1 integrons-integrase gene (intI1) were quantified (qPCR) (Jang et al. 2018). The same ARGs have been found in the commercial fish and seafood (Ryu et al. 2012) which already creates real threats to human health. Yang et al. (2013) detected with metagenomic method 58 genes codifying for resistance against 11 antibiotics. Many of these genes are located on MGE with more than 90% similarity with transposons and plasmids described for human pathogens, which suggests the possibility of occurrence of mobility of these ARGs to human pathogenic bacteria (Yang et al. 2013; Chen et al. 2018) or the potential risk of the ARGs spreading to other environments (Muziasari et al. 2017). The AMR strain from fish farms have been detected in nearly all key countries responsible for the production of farmed fish: United States (Seyfried et al. 2010), Pakistan and Tanzania (Shah et al. 2012), Australia (Akinbowale et al. 2006), China (Su et al. 2011), and Chile (Miranda et al. 2018).

It seems obvious that the overuse of antibiotics in aquaculture, especially prophylactic use, must be stopped. Antibiotics should be used only to treat diagnosed bacterial diseases. However, the question how to do it effectively, remains unanswered. It seems that the best solution would be to change food-safety regulations that set maximum residue limits or the use of special aquaculture ecolabeling schemes. For example, in Norway, veterinarians, fish farmers, and feed producers are legally obligated to report antibiotics use and prescriptions to a government agency. Due to such strict regulations, this data is made publicly available. In Norway, such data show a 99% reduction in antibiotic use in the Norwegian salmon industry since the early 1980s (Taranger et al. 2015). Therefore, implementation of legal obligation to report antibiotics use in food animals to a government agency in all countries is urgently needed. This approach will enable meaningful comparisons between species, countries, and over time of application. It is only on the basis of such aggregate data will it be possible to demonstrate any reduction or change in antibiotics use. Another very interesting approach is introduction of the farm level certification system (https://www.asc-aqua.org/). It is known that, only 5% of farmed seafood is currently certified, but its market share is growing because of consumer awareness about this framework. It is also extremely important to raise the awareness of fish farmers and veterinarians regarding the use of medically important antimicrobial drugs in food-animal production, and the public health risks associated with antibiotic resistance. “At a joint aquaculture and agriculture industry roundtable discussion in Oxford, UK, in May 2014, participants including vets, food scientists, farmers, and representatives of the food and animal health industries agreed that the development of a ‘replace, reduce, refine’ strategy could help drive the responsible use of antibiotics in food-producing animals" (Taranger et al. 2015). At the same time, the Aquaculture Stewardship Council (ASC) recommends development of alternative treatments and vaccines (https://www.asc-aqua.org/). There are a lot of methods capable of removing antibiotics from aquaculture systems: physical, chemical, and biological methods including adsorption, biodegradation, disinfection, membrane separation, hydrolysis, photolysis, and volatilization (Chuah et al. 2016; Feng et al. 2016). The use of the "One Health approach" seems to be extremely important in the case of aquacultures, because this framework recognizes the interconnectedness of aquaculture production and human health especially in the aspect of linkage between antibiotic use in aquaculture and AMR pathogenic bacteria in humans.

1.2.4 Airborne ARGs

In recent years, the interest in the potential spread of airborne ARGs has increased. So far, scientists have been able to demonstrate ARGs in air samples collected from places around WWTPs, for example, they detected sul2 and class 1 integrase (Li et al. 2016). Similar research was carried out in the vicinity of composting plant, cattle feed yards, metro station, and hospital, where ARGs were detected in the airborne particulate matter (PM) (Hu et al., 2018; Gao et al. 2014, 2018; McEachran et al. 2015; Zhou and Wang 2013). In addition, mexF was found in airborne samples collected from sludge and animal feces (Yang et al. 2018).

These studies indicate the main threat to human respiratory tract infections as well as the possibility of transferring ARGs to other places as a result of rainfall and thus the possibility of threatening water or soil ecosystems (Ahmed et al. 2018).

Li et al. (2018) studied 39 ARG subtypes coding resistance to seven common classes of antibiotics (aminoglycosides, β-lactams, macrolides, sulfonamides, tetracyclines, quinolones, and vancomycins) and two MGE genes (tnpA encoding transposase and intI1 encoding integrase class I), which were screened by a high-throughput real-time qPCR platform. The study samples were total PM across 19 world cities, sampled and grouped by year (2004, 2009, 2014), and by season. The obtained results allowed for the detection of 30 ARG subtypes and from all the cities the highest richness (up to 18 subtypes) of airborne ARGs was found in Beijing, compared with Bandung where only 5 subtypes of ARGs were found. The most frequent genes were resistance genes to β-lactams (blaTEM was found to be most abundant) and quinolones (qepA), followed by macrolide, tetracycline, sulfonamide, aminoglycoside, and vancomycin. The highest abundance of β-lactam resistance genes was detected in San Francisco in contrast to Johannesburg, Zurich, and Hong Kong. In each of 19 cities except Melbourne intI gene was detected, and the TnA gene was determined in only 4 cities, with the largest amount being in Beijing. It is worth noting that in general these two genes, blaTEM and qepA, as well as the class 1 integron-integrase gene, IntI1, are widespread across various external environments such as sediment, water, soil, and wastewater/sludge (Pal et al. 2016). As is known, MGEs are associated with HGT and therefore may be responsible for the dissemination of detected ARGs, which already poses a health risk (Xie et al. 2018).

Li et al. (2018) also analyzed the bacterial communities associated with the airborne ARGs detected for 19 cities. Fifty most abundant bacterial genera were detected, among others *Corynebacterium, Albirhodobacter*, *Burkholderia*, *Escherichia/Shigella*, *Brevundimonas*, *Streptococcus*, *Delftia*, *Serratia*, *Lactobacillus*, *Mathanosarcina*, *Bacillus*, *Raoultella*, *Acinetobacter,* or *Pseudomonas*; among them also pathogenic bacteria for humans and animals. In other work, 69 air samples were collected every 4 h continuously, both day and night, over 6 days in Beijing. Not only was the blaTEM gene detected but also the multidrug-resistant NDM-1 gene and vanB gene. In addition, increase in the abundance of ARGs in the more polluted air, as well as of MGEs tnpA and intI1, was also observed. Of the ARGs detected, the sul3 gene proved to be the most widespread among the culturable *Bacillus* isolates in the air (Zhang et al. 2019).

Although the evidence of the studies carried out so far on airborne ARGs is not sufficient to specify their public health impact and to determine the real risk to public health, the results definitely indicate the need for redefining our current air quality standards. Consequently, studies on the dissemination of ARB and ARGs require global research to demonstrate their importance for public health.

1.3 Mutual Interactions: A Conceptual Model for Understanding Entry Routes of Antibiotics, ARB, and ARGs

As comprehensively explored above, the scope and dynamics of ARB and ARGs in each of the entry routs are determined by many factors. The main ones may include: a natural, for each entry route, microbiome and resistome (biodiversity); the abundance and diversity of ARGs and ARB introduced within the different environments; the ability to mobilize genes and the ability of bacteria to survive and replicate in different ecosystems (horizontal and vertical transfer); the scope and intensity of selective pressure (i.e., presence of residual antibiotic compounds, heavy metals, biocides or detergents); and environmental conditions (e.g., temperature, moisture, pH, amount of rainfall, availability of organic matter, nutrients). In addition, there are also mutual interactions between all entry routes that can generate, through dust and air-borne aerosols, new threats of the dissemination of ARB and ARGs to humans, animals, or food. According to the One Health approach, we can additionally superimpose the transfer of AMR between people, animals, animals and humans, which complicates this scheme even further.

A conceptual model that summarizes the various factors, conditions, and interactions that impact ARB and ARGs transfer is shown in Fig. 1.1. This model is not complete and, depending on the specificity of place and climate, other factors involved in the dissemination of ARB and ARGs, such as flies, river and lake waters can probably be of importance.

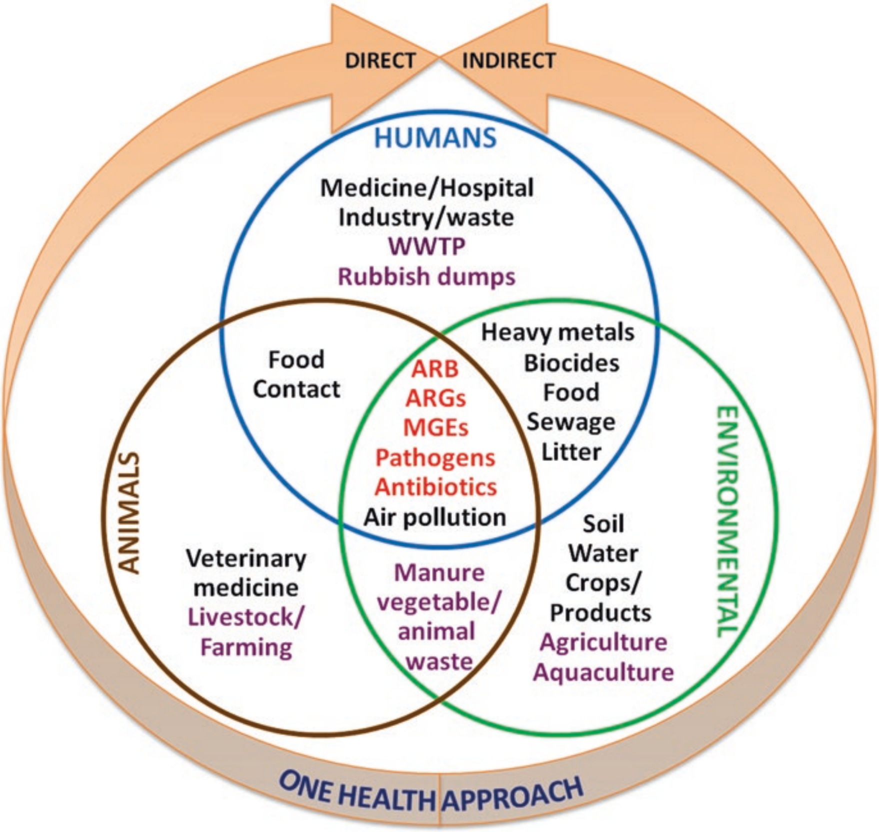

Fig. 1.1 A conceptual model, according to the One Health approach, that summarizes the interactions that impact the dissemination of antibiotics, ARB, and ARGs transfer

1.4 Summary and Perspectives

Antibiotics, ARB, and ARGs are widespread in the environment, not only in the clinical one but also in the natural one. Yet, it is difficult to clearly identify what constitutes the greatest threat to humans and animals. It is known that in the natural environment, as a result of the presence of subminimal inhibitory concentrations of antibiotics, new resistance mechanisms or resistance genes encoded on mobile genetic elements can be propagated through horizontal gene transfer. Therefore, antibiotic pressure does not eliminate as many bacteria as in a clinical environment. When high concentrations of antibiotics are used, only a single selected bacterial strain resistant to one or, more often, many antibiotics survives. In addition, in the natural environment there are co-selection mechanisms associated with resistance to heavy metals and biocides, which are also widespread in the environment. The resistance determinants for metals and biocides can be co-localized to the same

MGEs as antibiotic resistance genes, which mean that even in the absence of an antibiotic in the environment, a specific MGE is maintained and disseminated. However, WWTPs seem to be the most dangerous of the entry routes for resistant pathogenic bacteria, including MDR strains. Since the human feces are the main sources of pathogenic bacteria, the risk of human fecal contamination should not be neglected. There is definitely a greater risk of the transfer of resistance genes between pathogens in the human microbiome than the transfer of the same genes from environmental bacteria. On the other hand, there are probably more possibilities in the environment for the creation of new antibiotic resistance mechanisms and horizontal transfer events that lead to the phenomenon of co-selection.

After the antibiotics were used globally on a huge scale in the last few decades, their use as growth stimulators was prohibited in Europe. Nevertheless, their massive use in agriculture and animal husbandry in India and China makes it impossible to eliminate the problem of antibiotic resistance. Even though in many countries outside Europe there are antibiotic protection programs dedicated to the clinical environment, ARB do not recognize borders. Unfortunately, there are no regulations to monitor the problem of ARB dissemination in the environment and the main route of antibiotics, ARB, and ARGs, or use of WWTP sludge as natural fertilizers without proper treatment in agriculture. Furthermore, chemical plant protection products in agriculture as well as widespread environmental pollution with toxic compounds such as xenobiotics is also important contributing factor. All this causes the reduction of the proper microflora in a given environment, creating the niche for opportunistic and pathogenic bacteria. However, there is still insufficient knowledge about the barriers to the spread of antibiotic resistance in the environment and the importance of biodiversity in this process.

It is also necessary to develop and standardize the guidelines and method protocols for the surveillance of AMR, allowing to estimate precise values of the abundance of ARB and ARGs in WWTP discharges and to determine the fate of ARBs and ARGs. Such guidelines and protocols need to be practicable, comparable, simple, and cost-effective so that they can be applied globally.

However, to effectively limit the spread of ARB and ARGs via environmental pathways it is necessary to develop and implement new policies and regulations, which should be used globally and not locally. It should also be mentioned that the development of effective treatment strategies for removal of antibiotics, ARB, and ARGs is also extremely important.

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