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Antimicrobial pharmaceuticals in the aquatic environment - occurrence and environmental implications

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ABSTRACT

The environmental occurrence of antimicrobial pharmaceuticals and antibiotic resistant bacteria and antibiotic resistant genes has become a global phenomenon and a multifaceted threat. Integrated actions of many parties are needed to prevent further aggravation of the problem. Well-directed actions require clear understanding of the problem, which can be ensured by frequent revaluation of the existing knowledge and disseminating it among relevant audiences. The goal of this review paper is to discuss the occurrence and abundance of antimicrobial pharmaceuticals in the aquatic environment in context of adverse effects caused directly by these substances and the threat associated with the antibiotics resistance phenomenon. Several classes of antimicrobial pharmaceuticals (aminoglycosides, β-lactams, glycopeptides, macrolides, fluoroquinolones, sulfonamides and trimethoprim, tetracyclines) have been selected to illustrate their sources, environmental abundance, degradation routes (transformation products) and environmental implications including their ecotoxic effect and the spread of antibiotic resistance within the compartments of the aquatic environment and wastewater treatment plants. Wastewater treatment plants are indeed the main source responsible for the prevalence of these factors in the aquatic environment, since predominantly the plants have not been designed to retain antimicrobial pharmaceuticals. In order to limit the prevalence of these impurities into the environment, better source control is recommended as well as the establishment of stricter environmental quality standards. Counteracting all the above-mentioned threats requires to undertake integrated activities based on cooperation of professionals and scientists from various fields of science or industry, such as environmental sciences, medicine, veterinary, pharmacology, chemical engineering and others.

1. Introduction

The discovery of antimicrobial pharmaceuticals (APs) is regarded as one of the most significant achievements of the 20th century, which together with improved hygiene and vaccination programs revolutionized both human and veterinary medicine (Carvalho and Santos, 2016; Berkner et al., 2014). For decades, antibiotics have been widely prescribed for the treatment of infectious diseases in humans and animals. Moreover, antibiotics are used at a global scale in livestock to increase meat production by preventing infections and promoting growth (Cycoń et al., 2019).

The most frequently applied antimicrobials in all European countries were beta-lactams and among them the most popular subclass were penicillins, whose consumption was ranging from 36% (Germany) to 71% (Slovenia) of the total consumption in out-of-hospital conditions (ECDC, 2018). For example, in the European countries, the average total consumption (including community and hospital sector) of antimicrobial pharmaceuticals for systemic use is estimated at 23.4 defined

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daily doses (DDD) per 1000 inhabitants per day, ranging from 11.0 in the Netherlands to 34.1 in Spain (ECDC, 2018). The data from 27 European countries, including 25 EU Member States and two EEA countries (Iceland and Norway), indicated that approximately 90% of antibacterial pharmaceuticals consumption refer to the consumption outside of hospital (i.e. in the community).

The global consumption of antibacterial drugs is directly reflected in their presence in various compartments of the environment, including the aquatic environment. It is estimated that annually a few thousand tons of antimicrobials and their transformation products are introduced to the environment (Ji et al., 2012; Harnisz et al., 2015a). It should be noted, that in the environment, antimicrobials (i.e. natural antibiotics) can occur naturally, but the anthropogenic source of pollution is predominant. Because of the latter these substances can be classified as xenobiotics. There are many pathways of introducing the antimicrobials to the aquatic environment (Michael et al., 2013; Kümmerer, 2009a). The pollution of surface waters, groundwater and even drinking water with APs can originate from point sources and non-point sources (Barbosa et al., 2016). Wastewater treatment plants (WWTPs) are very often indicated to be the main point source of antimicrobials pollution. In the WWTPs, APs may predominantly undergo transformation, biodegradation or sorption onto the activated sludge and precipitation, depending on the technology used in a WWTP and also on the physical, chemical and biochemical properties of a given compound (Ternes and Joss, 2006). However, in most cases such a treatment does not completely eliminate (mineralize) these substances, so in result they can still be detected in the treated wastewater (Loos et al., 2013; Michael et al., 2013). Further degradation of APs is possible, however it is a major challenge because of varying efficiency, significant investment and operation cost and need for intensive maintenance (Sochacki et al., 2018). Discharge of conventionally treated wastewater results in release of APs into the aquatic environment compartments, including streams, rivers, lakes, and the marine environment (Moldovan, 2006; Lapworth et al., 2012). These compounds can also reach soil and groundwater when water reclamation for irrigation purposes is taking place. In result, the APs can potentially accumulate in soils, be taken up crops or leach into groundwater (Shenker et al., 2011). The non-point sources of antimicrobials in the aquatic environment are: the runoff or drainage waters from agriculture and livestock areas (human or veterinary APs introduced onto the fields with manure or in reclaimed wastewater), uncontrolled landfills leachates and other types of leaching and drain flows (Barbosa et al., 2016; Vymazal and Březinová, 2015). The veterinary drugs can constitute the main source of AP pollution in the agricultural areas or in the catchments dominated with agricultural activity. An estimated 5393 tons of antibiotics went into the production of veterinary pharmaceuticals in the European Union in 2004 (Kools et al., 2008). Veterinary pharmaceuticals can spread in the environment in different pathways. The most significant sources of veterinary drugs are farms and aquacultures, but also inappropriate disposal of used containers and unused drugs or livestock feed. Application of high amount of veterinary pharmaceuticals in reared livestock is the main source of drugs to terrestrial environment (Bártíková et al., 2016; Knäbel et al., 2016).

The average concentrations of selected APs in various compartments of aquatic environment range between few ng/L to few μg/L (Barbosa et al., 2016; Kümmerer, 2009a; Krzeminski et al., 2019; Loos et al., 2013; Michael et al., 2013). The occurrence of antimicrobial pharmaceuticals in the aquatic environment poses a serious problem for living organisms that inhabit this environment. First of all, because the APs are designed to exert specific biological activities and their action can cause an immediate effect (acute toxicity) towards the organisms (Loos et al., 2013; Kümmerer, 2009a). Secondly, long-term exposure of the antimicrobials towards living organisms even in sub-inhibitory concentrations can be associated with chronic toxicity (Bengtsson-Palme and Larsson, 2016). APs and their transformation products entering the environment can also affect the evolution of the bacterial community structure which play a significant role in the ecosystem (Grenni et al., 2018; Rede et al., 2019). However, little is currently known about the potential ecotoxicological and ecological impact of APs in aquatic ecosystems (Carvalho and Santos, 2016).

Another problem related to the release of antimicrobial agents into the aquatic environment is related to the development of antibiotic resistant bacteria (ARB) and environmental occurrence of antibiotic resistance genes (ARGs) (Kümmerer, 2009b; Kumar et al., 2019). Antibiotic resistance poses a global threat to human and animal health, with many bacterial species having developed some form of resistance to antimicrobial agents. However, it turned out that bacteria are able to develop resistance, not just as the consequence of mutations towards the targets antibiotics, but also by acquiring genes conferring resistance to antimicrobials (Munita and Arias, 2016). Due to this, a growing number of infections are becoming harder to treat as the antibiotics used to cure them become less effective. Antibiotic resistance leads also to higher medical costs and increased mortality (World Health Organization (WHO), 2018). Antimicrobial resistance (AMR) causes an estimated 700,000 deaths annually worldwide, and each country is potentially affected by this problem. If no proper action is taken, their number could grow to 10 million per year by 2050 (O'Neill, 2016). Of course, the spread of AMR does not only have an environmental aspect - there are many different factors affecting the scale of this phenomenon. However, guided by the principles given in the "One Health European Joint Programme", environmental considerations should also be taken into account, which can also play a significant role in a better understanding and preventing the AMR phenomenon (Destoumieux-Garzón et al., 2018; Margalida et al., 2014).

ARB have the capacity to survive or self-replicate in the environment regardless of the presence of residues of antimicrobial agents. However, it should be emphasized that the treated wastewaters have the potential to offer ideal conditions for ARB development such as the abundance of nutrients and/or higher probability of cell-to-cell interactions aided by the presence of antimicrobials residues and other favorable conditions (Berendonk et al., 2015). All those factors are believed to enhance the chances of survival or even proliferation of ARB thus contributing to the spread of ARGs in the environment (Michael et al., 2013; Krzeminski et al., 2019).

Due to the multiple threat that could be caused by occurrence of the antimicrobial pharmaceuticals in the environment, many countries have already introduced the obligation to monitor such type of pollution in the aquatic environment. For example, EU Commission has established a watch list of substances for Union-wide monitoring in the field of water policy. On the first watch list three antibiotics were included (apart from other groups of contaminants), namely the following macrolides: erythromycin, clarithromycin, azithromycin (EU Decision, 2015/495 of March 20, 2015). These macrolides antibiotics remained on the second watch list (EU Decision, 2018/840 of June 5, 2018), but additionally amoxicillin and ciprofloxacin have been added to the list. The substances included in the EU watch list are selected "from amongst those for which the information available indicates that they may pose a significant risk, at Union level, to or via the aquatic environment, but for which monitoring data are insufficient to come to a conclusion on the actual risk posed "(EU Decision, 2018/840 of June 5, 2018). Including a substance on the watch list means that with regard to it the data on its presence in the aquatic environment, covering all EU countries, should be collected and verified. This means that the list includes substances whose occurrence in the environment creates a potential risk for humans and living organisms, but the knowledge about this risk is not sufficient. The watch list is verified and reviewed every two years. It is also assumed that the information received as a result of monitoring in the environment of substances includes in the watch list will enable to establish of Environmental Quality Standards (EQS) for all European Union countries for substances of which such standards have not yet been established.

The goal of this review paper is to discuss the occurrence and

Table 1
Major classes of antimicrobial agents and their representative substances selected for this review as the special concern antimicrobials.

Class	Representative substances
Aminoglycosides	streptomycin, gentamicin, amikacin
β-lactams	amoxicillin, penicillin, cefuroxime
Glycopeptides	vancomycin
Macrolides	azithromycin, clarithromycin, tylosin, erythromycin
Fluoroquinolones	ciprofloxacin, levofloxacin, ofloxacin, norfloxacin
Sulfonamides and trimethoprim	sulfamethoxazole, sulfapirydyne, sulfamethazine, trimethoprim
Tetracyclines	doxycycline, oxytetracycline, tetracycline

abundance of APs in the aquatic environment in context of adverse effects caused directly by these substances and the threat associated with the AMR phenomenon. In this review, the relevant classes of APs and their representative substances that raise special concern are discussed (Table 1).

2. Occurrence, persistence and pseudo-persistence of antimicrobials in the aquatic environment

2.1. Occurrence of antimicrobial pharmaceuticals in the aquatic environment

Table 2 summarizes the information on occurrence of the target antimicrobial agents in surface water and groundwater as the compartments of the aquatic environment, and in the raw and treated wastewater and in drinking water. Depending on the class of compounds, their presence can be found in all matrices of the aquatic environment. The physico-chemical properties of the discussed antimicrobials are presented in Supplementary Information (SI, section S1). The highest concentrations were observed for the wastewater and the surface wasters, which are usually the recipients of the treated and, still in many cases, for untreated wastewater and discharges of various types and origins. The presence of antimicrobials in the aquatic environment poses a problem in the context of partial closure of water cycles and reuse of treated wastewater for different purposes (Ternes and Joss, 2006). Generally, in the European countries, treated wastewater is mostly used for irrigation purposes, but it can also be used for other urban or environmental applications (Carvalho and Santos, 2016). One such application is groundwater replenishment to compensate for prolonged drought periods (Carvalho and Santos, 2016). These substances may also enter the groundwater via infiltration or bank filtration from surface water and/or via leaching from the soil. As it was mentioned above, the groundwater is frequently used as a source of drinking water. Admittedly, reliable toxicological studies on long term consumption of drinking water containing low concentrations of selected antimicrobial agents are not available, however, the continuous impact of even such low concentrations on humans and animals is still being discussed by scientists (Carvalho and Santos, 2016; Kümmerer, 2009a; Michael et al., 2013; Rizzo et al., 2013; Ternes and Joss, 2006).

2.1.1. Aminoglycosides

Among the discussed substances, aminoglycosides were found to be present in raw and treated wastewater, and also in seawater. Their highest concentration in marine waters was observed for streptomycin (3400 ng/L). Of all aminoglycosides, only gentamicin was present in the groundwater. This is particularly important in the context of the use of groundwater as a source of drinking water, because default methods of water purification do not ensure a complete removal of pharmaceutical substances. Nevertheless, no aminoglycoside has been identified in drinking water. In the case of aminoglycosides, effluents from hospitals and wastewater from factories producing these drugs play a relatively important role as their input into the aquatic environment (Löffler and Ternes, 2003; Tahrani et al., 2015). In order to prevent the spread of this type of pollutants in the environment, more effective methods of their decay should be introduced at the level of internal installations designed for this purpose.

2.1.2. β-lactams

Despite the high consumption of β-lactams, penicillin G and V were detected only in several raw wastewater samples (Harrabi et al., 2018; Michael et al., 2013), probably because of their chemical instability. β-lactams are known to be rather unstable due to the hydrolysis of the β-lactam ring in the environmental conditions. The hydrolysis of the β-lactam ring may occur due to physico-chemical interactions (e.g. occurrence of transition metals such as zinc and copper may catalyze this reaction), but also due to the action of beta-lactamase-containing bacteria that are widespread in the environment. It is also assumed that these substances are relatively well biodegradable in conventional WWTPs (about 90%), however, the residual part can reach the environment i an unchanged form (Michael et al., 2013). Representatives of synthetic derivatives of penicillin as amoxicillin and next generation of β-lactams as cefuroxime are much more stable and therefore more often detected in both hospital effluents and raw wastewater. It was also proved that substances such as amoxicillin and penicillin G showed low recovery rates (between 20 and 30%) in all water samples (hospital, wastewater and surface water), which is the main limitation for the analysis of those compounds (Gros et al., 2013).

2.1.3. Glycopeptides and macrolides

From the class of glycopeptides, basically only vancomycin was identified in the aquatic environment. This substance is mainly used to treat life-threatening infections by Gram-positive bacteria being unresponsive to other antibiotics. Due to its physico-chemical properties, this substance is relatively resistant to degradation in conventional WWTPs (removal between 5 and 52%) (Li and Zhang, 2011; Zuccato et al., 2010), therefore, its presence was confirmed in surface water as well as in groundwater (Szekeres et al., 2018; Zuccato et al., 2010).

Macrolides are substances that are widely found in various compartments of the aquatic environment. Some substances from this group, i.e. erythromycin, clarithromycin and azithromycin have been included in the first EU watch list and, after its revisions, also in the second EU watch list. Based on the report from the review of the first EU watch list, it can be stated that the most frequently detected substance (among the macrolides included) is clarithromycin. Its quantification frequency in 2792 surface water samples (from 24 European countries) was equal to 58.8% (Loos et al., 2018). In the case of azithromycin, its quantification frequency in European surface water was equal to 17.1% (Loos et al., 2018). The lowest quantification frequency was observed for erythromycin (8.4%) (Loos et al., 2018). However, it should be mentioned that erythromycin can be also present as its main human metabolite, the dehydrated product with an apparent loss of one molecule of water, this is, erythromycin-H_2O (Michael et al., 2013; Ternes and Joss, 2006). The susceptibility to the biodegradation of the main metabolite of erythromycin in conventional WWTPs generally varies between 10-26% (Göbel et al., 2007; Li and Zhang, 2011), wherein the information on the decay of the parent compound in WWTPs varies significantly from 0% to complete removal (100%) (Michael et al., 2013). It should also be noted that the removal of macrolides which is observed in conventional WWTPs may be a result of a sorption of these compounds on activated sludge flocs and not directly from their biodegradation. This is mainly due to the physico-chemical properties of macrolides - all of these substances are characterized by a high value of log Kow parameter (higher than 3) (SI, Tab. S1), which increases the affinity of these substances for sorption on the activated sludge. Among the discussed macrolides, only erythromycin and tylosin were also detectable in drinking water samples. The presence of tylosin in drinking water most likely results from the contact of

Table 2
Occurrence of the antibiotics in various compartments of the aquatic environment.

Class/compound	Concentration range, ng/L				
	Raw wastewater	Treated wastewater	Surface water	Groundwater	Drinking water
Aminoglycosides					
Streptomycin	nd-2700(Tahrani et al., 2015)	nd-1200 (Tahrani et al., 2015)	nd-3400 (seawater) (Tahrani et al., 2015	n.a.	n.a.
Gentamycin	nd-1600 (Tahrani et al., 2015) 14400-19100 (pharmaceutical company) (Tahrani et al., 2015) 400-7600 (hospital eff.) (Löffler and Ternes, 2003)	nd-500 (Tahrani et al., 2015)	nd-1400 (seawater) (Tahrani et al., 2015)	nd.-21 (Szekeres et al., 2018)	n.a.
Amikacin	nd-2300 (Tahrani et al., 2015)	nd-1000 (Tahrani et al., 2015)	nd-1200 (seawater) (Tahrani et al., 2015)	n.a.	n.a.
β-lactams					
Amoxicillin	nd-33800 (Azanu et al., 2018; Proia et al., 2018) nd-164 effluent from pharm. factory (Thai et al., 2018) 2.0–57.0 (hospital effluent) (Azanu et al., 2018; Thai et al., 2018)	nd-116400 (Azanu et al., 2018; Proia et al., 2018; Palli et al., 2019; Gros et al., 2013)	nd-2,7 (rivers) (Azanu et al., 2018) nd-1,3 (irrigation canals (Azanu et al., 2018) nd-40 aquaculture (Thai et al., 2018)	n.a.	n.a.
Penicillin G	nd-29 (Gros et al., 2013; Michael et al., 2013)	nd (Gros et al., 2013)	nd (Gros et al., 2013)	n.a.	n.a.
Penicillin V	nd-160 (Gros et al., 2013; Michael et al., 2013)	20 (Michael et al., 2013)	n.a.	n.a.	n.a.
Cefuroxime	49-24380 (Ribeiro et al., 2018) nd-7860 effluent from pharm. factory (Thai et al., 2018) nd-246 hospital effluent (Thai et al., 2018)	nd (Gros et al., 2013)	nd (aquaculture) (Thai et al., 2018)	n.a.	n.a.
Glycopeptides					
Vancomycin	nd.-61 (Li and Zhang, 2011; Zuccato et al., 2010)	nd-40 (Li and Zhang, 2011; Zuccato et al., 2010)	0.44–11.69 (river) (Zuccato et al., 2010)	nd-153.38 (Szekeres et al., 2018)	n.a.
Macrolides					
Azithromycin	1083 (Lara-Martín et al., 2014)	0-380 (Al Aukidy et al., 2012; Lara-Martín et al., 2014)	240 (Gibs et al., 2013)	nd (Cabeza et al., 2012)	n.a.
Clarithromycin	nd- 122 (Lara-Martín et al., 2014; Watkinson et al., 2009)	8-460 (Al Aukidy et al., 2012; Gracia-Lor et al., 2011; Lara-Martín et al., 2014)	75-91 (McArdell et al., 2003; Gracia-Lor et al., 2011)	nd - 154 (Cabeza et al., 2012)	n.a.
Tylosin	55-180 (Yang et al., 2006; Watkinson et al., 2007)	nd. −3400 (McArdell et al., 2003; Hernando et al., 2006; Watkinson et al., 2009)	2-280 (Wang et al., 2011; Kleywegt et al., 2011; Hernando et al., 2006)	n.a.	< MDL (Wang et al., 2011) 1.7 (Zuccato et al., 2000) 31 (Kleywegt et al., 2011)
Erythromycin	9-249 (Tylová et al., 2013)	nd-886 (Gracia-Lor et al., 2011; Tylová et al., 2013; Hernando et al., 2006)	24-145 (Gracia-Lor et al., 2011; Gibs et al., 2013; Kleywegt et al., 2011)	nd-568 (Szekeres et al., 2018)	155 (Kleywegt et al., 2011)
Fluoroquinolones					
Ciprofloxacin	0.82–6453 (Dong et al., 2016; Östman et al., 2017; Tran et al., 2016)	0.4–920 (Dong et al., 2016; Rossmann et al., 2014) 1400-26000 (hospital effluent) (Verlicchi et al., 2012)	14.9–21.3 (river) (Castrignanò et al., 2018) nd −115 (lake) (Ding et al., 2017; Tran et al., 2019)	nd-323.7 (Cabeza et al., 2012; López-Serna et al., 2013; Ma et al., 2015)	0.82–6453 (Dong et al., 2016; Östman et al., 2017; Tran et al., 2016)
Levofloxacin	5 -2247 (Golovko et al., 2014; Oertel et al., 2018; Rossmann et al., 2014)	4- 836 (Birošová et al., 2014; Golovko et al., 2014; Rossmann et al., 2014)	< MDL-10.5 (river/lake) (Guruge et al., 2019)	n.a.	5 -2247 (Golovko et al., 2014; Oertel et al., 2018; Rossmann et al., 2014)
Ofloxacin	11.1–1330 (Birošová et al., 2014; Dong et al., 2016; Golovko et al., 2014)	0.3–527 (Dong et al., 2016; Golovko et al., 2014) 23-510 (hospital effluent) (Verlicchi et al., 2012)	nd-6.4 (river) (Hu et al., 2018) nd-9700 (lake) (Nageswara Rao et al., 2008; Tang et al., 2015)	nd −503 (López-Serna et al., 2013; Ma et al., 2015)	11.1–1330 (Birošová et al., 2014; Dong et al., 2016; Golovko et al., 2014)
Norfloxacin	< LOQ-5411 (Dong et al., 2016; Östman et al., 2017) 450- 2200 (hospital wastewater: 2% of	0.2–628 (Dong et al., 2016; He and Blaney, 2015)	nd −39 (river) (He et al., 2015; Hu et al., 2018) 3-518 (lake) (Tran et al., 2019)	nd −367 (López-Serna et al., 2013; Ma et al., 2015; Teijon et al., 2010)	< LOQ-5411 (Dong et al., 2016; Östman et al., 2017) 450-2200 (hospital wastewater: 2% of

(*continued on next page*)

Table 2 (*continued*)

Class/compound	Concentration range, ng/L				
	Raw wastewater	Treated wastewater	Surface water	Groundwater	Drinking water
	the influent hydraulic load) (Verlicchi et al., 2012)	3300-37000 (hospital effluent) (Verlicchi et al., 2012)			the influent hydraulic load) (Verlicchi et al., 2012)
Sulfonamides and trimethoprim					
Sulfamethoxazole (and N^4-AcSMX)	52-2000 (Göbel et al., 2007; Hirsch et al., 1999; Zuccato et al., 2010); (850–1600 N^4-SMX) Göbel et al. (2005)	0.6–1147 (Göbel et al., 2005; Hanna et al., 2018; Loos et al., 2013); nd.-150 (N^4-SMX) Göbel et al. (2005)	0.3–360.0 (river) (Hanna et al., 2018; Managaki et al., 2007) 612-4330 (city canal) (Hoa et al., 2011)	nd-470 (Hirsch et al., 1999)	0.3–18.6 (Hanna et al., 2018; Ye et al., 2007)
Sulfapirydyne	60-230 (Göbel et al., 2005, 2007)	0.4–230 (Göbel et al., 2007; Hanna et al., 2018)	0.2–3.1 (river) (De Jesus Gaffney et al., 2015; Hanna et al., 2018)	< 2.5 (De Jesus Gaffney et al., 2015)	0.05–0.5 (De Jesus Gaffney et al., 2015; Hanna et al., 2018)
Sulfamethazine	nd-4010 (Li and Zhang, 2011; Choi et al., 2007) 97230 (agriculture wastewater) (Choi et al., 2007)	nd (Li and Zhang, 2011; Choi et al., 2007) nd. (agriculture wastewater) (Choi et al., 2007)	15-28 (river) (Managaki et al., 2007) 16.1–328 (city canal) (Hoa et al., 2011; Managaki et al., 2007)	nd-220 (De Jesus Gaffney et al., 2015; Hirsch et al., 1999)	76-220 (Batt et al., 2007)
Trimethoprim	100-4300 (Li and Zhang, 2011; Göbel et al., 2007; Watkinson et al., 2009)	65-800 (Loos et al., 2013; Li and Zhang, 2011; Göbel et al., 2005)	7.0–19 (river) (Managaki et al., 2007) 23-1808 (city canal) (Hoa et al., 2011)	nd-730.19 (Hirsch et al., 1999; Szekeres et al., 2018)	nd (Ye et al., 2007; Watkinson et al., 2009)
Tetracyclines					
Doxycycline	1.8–264 (Azanu et al., 2018; Hanna et al., 2018) 24-120 hospital wastewater (Azanu et al., 2018)	14-49 (Azanu et al., 2018) < LOQ (Palli et al., 2019)	1.9–68 (river) (Azanu et al., 2018; Hanna et al., 2018; Li et al., 2014) 9.4–25 (irrigation canal) (Azanu et al., 2018) nd-39.7 (lake) Ding et al., 2017)	n.a.	< LOQ (Hanna et al., 2018) 0.21–1650 (food production farm) (Gbylik-Sikorska et al., 2015)
Oxytetracycline	4.3–233 (Azanu et al., 2018) 75-1487 (hospital effluent) (Azanu et al., 2018; Wang et al., 2018a)	2.4–24 (Azanu et al., 2018)	3-26 (river) (Azanu et al., 2018; Li et al., 2014) 2.2–9.2 (irrigation canal (Azanu et al., 2018)	n.a.	nd (food production farm) (Gbylik-Sikorska et al., 2015)
Tetracycline	58-1960 (Azanu et al., 2018; Proia et al., 2018) 13-1598 (hospital effluent) (Azanu et al., 2018; Wang et al., 2018a; Proia et al., 2018)	220-1290 (Proia et al., 2018)	14.05 (river) (Li et al., 2014)	n.a.	nd (food production farm) (Gbylik-Sikorska et al., 2015)

nd – not detected; n.a. – not available; LOQ – limit of quantification.

drinking water sources with waste and/or leachates from agricultural activities (Kleywegt et al., 2011).

2.1.4. Fluoroquinolones

It is estimated that in human medicine the consumption of fluoroquinolones is 7% of the total consumption of antimicrobials (Szymańska et al., 2019). Relatively high consumption of these drugs, but also their hydrophilic properties, cause that fluoroquinolones are identified in all compartments of the aquatic environment. The removal efficiency of these substances at the conventional WWTP, depending on the substance, varies from 56% (ofloxacin) to 90% (ciprofloxacin) (Michael et al., 2013). However, it is assumed that the main process in removing these substances from wastewater is sorption onto activated sludge, despite the low values of the log Kow parameter (< 1) (SI, Table S1) (Golet et al., 2003). It should be noted that the prediction of the affinity for sorption onto the sludge based on the value of log Kow is mainly possible for non-polar compounds. In the case of polar compounds (or charged compounds) it is not always correct and can lead to an underestimation of the importance of sorption in the removal process (Michael et al., 2013). Such an example is ciprofloxacin that can sorb onto sludge by 80%, indicating that sorption is its main elimination process (Golet et al., 2003; Michael et al., 2013). Despite the relatively high removal efficiency in WWTPs, ciprofloxacin, is a substance that is very often identified in treated wastewater. For instance, the detection frequency for ciprofloxacin in the effluent of 90 wastewater treatment plants located in the EU 90%, respectively (Loos et al., 2013). Effluents from hospitals are also a significant source in the spread of fluoroquinolones in the aquatic environment. The concentrations of norfloxacin and ciprofloxacin in this medium reached a very high value, that is, 37000 ng/L and 26000 ng/L, respectively (Verlicchi et al., 2012). It can be also confirmed by Watkinson et al. (2009) who detected ciprofloxacin in all samples taken from hospital effluents. The fluoroquinolones, due to their hydrophilic properties, are mobile in the aquatic environment, which causes that their presence was confirmed in groundwater and even so in drinking water samples (Hanna et al., 2018; Reis et al., 2019). Spreading in the environment caused that ciprofloxacin was included in the second EU watch list (EU Decision, 2018/840 of June 5, 2018).

2.1.5. Sulfonamides and trimetoprim

Another group of antimicrobial drugs that is very often identified in the aquatic environment are sulfonamides and trimethoprim. The antibacterial activity of sulfonamides and trimethoprim are different, however, due to the fact that sulfonamides are very often used in fixed combination with trimethoprim, these substances will be discussed jointly. Among the sulfonamides, sulfamethoxazole is the most commonly detected substance in the environment (Loos et al., 2013; Hanna et al., 2018). Information on the removal efficiency of this compound in conventional WWTPs is very different and varies from 20% to over 90% (Göbel et al., 2007; Michael et al., 2013; Ternes and Joss, 2006). Such differences in the removal effectiveness of SMX may be due to the presence of its main human metabolite, i.e. N^4-acetylsulfamethoxazole (N^4-AcSMX). Under environmental conditions N^4-AcSMX molecule can be reconverted to the sulfamethoxazole molecule and it is also possible that WWTP microbial community may transform sulfamethoxazole back into N^4-AcSMX (Göbel et al., 2005, 2007). Therefore, it is very important that in the environmental samples monitor the occurrence both SMX and N^4-AcSMX. All substances from this class of APs were detected in surface and groundwater samples, and additionally all sulfonamides were detected in drinking water samples (Batt et al., 2007; Hanna et al., 2018). According to Loos et al. (2013), it can be concluded that sulfamethoxazole and trimethoprim are in the group of the most often detected xenobiotics in the European WWTPs effluents - the detection frequency for trimethoprim and sulfamethoxazole in the effluent of 90 WWTPs located in EU was 93% and 83%, respectively.2.1.6. Tetracyclines.

Tetracyclines, as well as other antimicrobials, have been detected in wastewater, surface water or even drinking water samples (Azanu et al., 2018; Hanna et al., 2018; Gbylik-Sikorska et al., 2015). Most authors indicate that these substances are relatively well removed in conventional WWTPs (up to over 90%, depending on the substance and the technology used), however, the observed removal efficiency is not a result of their biodegradation, but sorption onto activated sludge (Michael et al., 2013). This is because tetracyclines exhibit chelating properties and in the presence of metal ions as calcium, aluminum, iron or magnesium, they may form stable complexes that are characterized by a strong affinity for activated sludge or other suspended fractions (Ternes and Joss, 2006). These properties may also cause that concentration of tetracyclines in surface water does not exceed 40 ng/L, and they are not detectable in groundwater, because calcium, iron and magnesium ions are ubiquitous in the aquatic environment. The presence of these ions in surface (or ground) water will result in forming stable tetracycline-containing complexes showing greater affinity for soil/sediment than for the liquid phase.

The continuous presence of antibiotics in the aquatic environment may be related to their persistence to degradation (be it biodegradation, photodegradation, hydrolysis and other processes) or be due to their continuous consumption and input in large volumes. In the latter case, despite relatively good degradability the compounds can be frequently detected in the environment and thus be considered as pseudo persistent. For example, the detection frequency for trimethoprim, ciprofloxacin and sulfamethoxazole in the effluent of 90 wastewater treatment plants located in the EU was 93%, 90% and 83%, respectively (Loos et al., 2013). For this reason, these compounds could be suspected to be continuously present in the recipient waters.

2.2. Persistence and degradation of the antimicrobial pharmaceuticals

The persistence of antimicrobials in water is defined based on their half-life value. For example, according to REACH (i.e. European legislation on *Registration, Evaluation and Authorisation of Chemicals*), a chemical is persistent if its half-life in marine water is more than 60 days and 40 days in fresh or estuarine water. It is considered very persistent when the half-life in marine, estuarine or fresh water is higher than 60 days (Goldenman et al., 2017). The half-life values for the substances selected from the discussed classes of the APs are given in Table 3. The given half-life values refer to surface water. These values can be much higher (longer half-life) in the case of groundwater or soil/sediments because of the scarcity or lack of sunlight and aerobic conditions.

The degradation of antibiotics in the wastewater treatment plants or in the environment is governed by several processes, which often can be interrelated. The degradation may lead to at least partial mineralisation of a compound but in many cases the degradation reactions produce metabolites that can create significant environmental concern.

For example, the metabolite of amoxicillin, which is amoxicillin-S-oxide contains active β-lactam ring may lead to the development of

Table 3
Half-life of selected antimicrobials in surface water.

Compound	Surface water half-life	Source
Amoxicillin	< 1 day	Längin et al. (2009)
Azithromycin	< 5 h	Tong et al. (2011)
Tylosin	9.5–54 days	Sarmah et al. (2006)
Erythromycin	< 17 days	Sarmah et al. (2006)
Ciprofloxacin	< 46 h	Cardoza et al., 2005
Levofloxacin	6.3 days	Lam et al. (2004)
Ofloxacin	10.6 days	Andreozzi et al. (2003)
Norfloxacin	77 days	Burhenne et al. (1999)
Sulfamethoxazole	20.3 days	Lam et al. (2004)
Sulfamethazine	< 4.2	Carstens et al. (2013)
Trimethoprim	< 11.8 days	Giang et al. (2015)

Table 4
Toxicity values for selected antimicrobial agents concerning aquatic organisms.

Class/compound	Organism	Ecotoxicity indicator*, mg/L	Reference
Aminoglycosides			
Streptomycin	Planktonic communities of limnic bacteria	46 (EC_{50})	Brosche and Backhaus (2010)
	Daphnia magna (crustacean)	487 (LC_{50})	Wollenberger et al. (2000)
	Lemna gibba (duckweed)	> 1000 (EC_{25})	Brain et al. (2004)
Gentamycin	*Daphnia magna* (crustacean)	16.8 (EC_{50})	Straub et al. (2012)
	Poecila reticulata (fish)	> 0.08 (LC_{50})	Straub et al. (2012)
	Synechococcus leopoliensis (cyanobacteria)	0.069 (EC_{50})	Straub et al. (2012)
Amikacin	not available		
β-lactams			
Amoxicillin	*Vibrio fischeri* (luminescent bacteria)	1320 (IC_{50})	Park and Choi (2008)
	Oryzias latipes (fish)	> 1000 (LC_{50})	Park and Choi (2008)
	Raphidocelis subcapitata (green algae)	250 (NOEC)	Lützhøft et al. (1999)
Penicillin G	*Vibrio fischeri* (luminescent bacteria)	not obtainable	Havelkova et al. (2016)
	Daphnia magna (crustacean)	1496.9 (EC_{50})	Havelkova et al. (2016)
	Pseudokirchneriella subcapitata (green algae)	7114.3 (IC_{50})	Havelkova et al. (2016)
Cefuroxime	*Selenastrum capricornutum* (green algae)	> 91 (EC_{50})	Ribeiro et al. (2018)
	Activated sludge (respiration test)	> 100 (IC_{50})	Kümmerer et al. (2004)
Glycopeptides			
Vancomycin	*Daphnia magna* (crustacean)	687 (EC_{50})	Havelkova et al. (2016)
	Pseudokirchneriella subcapitata (green algae)	371 (EC_{50})	Havelkova et al. (2016)
	Vibrio fischeri (luminescent bacteria)	4.4 (EC_{20})	Havelkova et al. (2016)
Macrolides			
Azithromycin	*Daphnia magna* (crustacean)	120 (IC_{50})	Vestel et al. (2016)
	Pseudokirchneriella subcapitata (green algae)	0.5 (IC_{50})	Minguez et al. (2016)
	Skeletonema marinoi (diatom)	0.214 (IC_{50})	Minguez et al. (2016)
Clarithromycin	*Vibrio fischeri* (luminescent bacteria)	no effect	Isidori et al. (2005)
	Daphnia magna (crustacean)	25.72 (EC_{50})	Isidori et al. (2005)
	Pseudokirchneriella subcapitata (green algae)	0.002 (IC_{50})	Isidori et al. (2005)
Tylosin	*Selenastrum capricornutum* (green algae)	0.95 (EC_{50})	De Liguoro et al. (2003)
	Lemna gibba (duckweed)	0.3 (LOEC)	Brain et al. (2004)
	Pseudokirchneriella subcapitata (green algae)	3.8 (EC_{50})	Guo et al. (2016)
Erythromycin	*Vibrio fischeri* (luminescent bacteria)	no effect	Isidori et al. (2005)
	Daphnia magna (crustacean)	22.45 (EC_{50})	Isidori et al. (2005)
	Pseudokirchneriella subcapitata (green algae)	0.02 (IC_{50})	Isidori et al. (2005)
Fluoroquinolones			
Ciprofloxacin	*Danio rerio* (zebrafish)	1407 (MNLC) 1949 (LC_{10})	Shen et al. (2019)
	Marine biofilms (SWIFT periphyton test system)	0.16 (EC_{50}) 0.009 (NOEC)	Johansson et al. (2014)
	Chlamydomonas mexicana (green algae)	65 (IC_{50})	Xiong et al. (2017a)
Levofloxacin	*Pseudokirckneriella subcapitata* (green algae)	0.93 (EC_{10}) 4.5 (EC_{20}) > 120 (EC_{50})	González-Pleiter et al. (2013)
	Anabaena sp. (cyanobacteria)	1.1 (EC_{10}) 1.9 (EC_{20}) 4.8 (EC_{50})	González-Pleiter et al. (2013)
	Chlorella vulgaris (green algae)	58.6 (IC_{50})	Xiong et al. (2017b)
Norfloxacin	*Pseudokirchneriella subcapitata* (green algae)	10.9 (IC_{10}) 20.6 (IC_{20}) > 80 (IC_{50})	González-Pleiter et al. (2013)
	Anabaena sp. (cyanobacteria)	1.2 (EC_{10}) 2.1 (EC_{20}) 5.6 (EC_{50})	González-Pleiter et al. (2013)
	Chlorella vulgaris (green algae)	10.4 (IC_{50}) 4.02 (NOEC)	Eguchi et al. (2004)
Ofloxacin	*Pseudomonas putida* (bacteria)	0.11 (EC_{50})	Carbajo et al. (2015)
	Pimephales promelas (fish)	> 10 (NOEC)	Robinson et al. (2005)
	Ceriodaphnia dubia (crustacean)	1.05–7.82 (EC_{50})	Isidori et al. (2005)
Ciprofloxacin	*Danio rerio* (zebrafish)	1407 (MNLC) 1949 (LC_{10})	Shen et al. (2019)
	Daphnia magna (crustacean)	10 (NOEC)	Robinson et al. (2005)
	Lemna minor (duckweed)	0.203 (IC_{50})	Robinson et al. (2005)
Sulfonamides and trimethoprim			
Sulfamethoxazole	*Lemna gibba* (duckweed)	0.000010 (NOEC_7d)	Brain et al. (2004)
	Lemna minor (duckweed)	0.21 (IC_{50})	Białk-Bielińska et al. (2011)
	Vibrio fischeri (luminescent bacteria)	> 1.5 (EC_{50})	Van der Grinten et al. (2010)
	Pseudokirchneriella subcapitata (green algae)	> 9.0 (IC_{50})	Van der Grinten et al. (2010)
	Selenastrum capricornutum (green algae)	1.53 (IC_{50}) 0.614 (NOEC)	Eguchi et al. (2004)
	Danio rerio (zebrafish)	> 100 (LC_{50})	Ternes and Joss (2006)
	Microcystis aeruginosa (cyanobacteria)	0.55 (EC_{50})	Van der Grinten et al. (2010)
Sulfapirydyne	*Vibrio fischeri* (luminescent bacteria)	27.4 (EC_{50})	García-Galán et al. (2012)
	Scenedesmus vacuolatus (green algae)	5.3 (IC_{50})	Białk-Bielińska et al. (2011)

(*continued on next page*)

Table 4 (*continued*)

Class/compound	Organism	Ecotoxicity indicator*, mg/L	Reference
	Lemna minor (duckweed)	0.46 (IC_{50})	Białk-Bielińska et al. (2011)
Sulfamethazine	*Vibrio fischeri* (luminescent bacteria)	303 (EC_{50}; 5 min)	Kim et al. (2007)
	Daphnia magna (crustacean)	159 (EC_{50})	Kim et al. (2007)
	Oryzias latipes (fish)	> 100 (LC_{50})	Kim et al. (2007)
Trimethoprim	*Selenastrum capricornutum* (green algae)	80 (IC_{50}) 25.5 (NOEC)	Eguchi et al. (2004)
	Microcystis aeruginosa (cyanobacteria)	112 (EC_{50})	Välitalo et al. (2017)
	Pseudokirchneriella subcapitata (green algae)	84 (EC_{50})	Välitalo et al. (2017)
Tetracyclines			
Doxycycline	*Lemna gibba* (duckweed)	0.316 (IC_{50})	Brain et al. (2004)
Oxytetracycline	*Raphidocelis subcapitata* (green algae)	3.1 (IC_{50})	Zounková et al. (2011)
	Oryzias latipes (fish)	110 (LC_{50})	Park and Choi (2008)
	Daphnia magna (crustacean)	621 (EC_{50})	Park and Choi (2008)
Tetracycline	*Lemna gibba* (duckweed)	0.723 (IC_{50})	Brain et al. (2004)
	Daphnia magna (crustacean)	340 (NOEC)	Wollenberger et al. (2000)
	Vibrio fischeri (luminescent bacteria)	6.7 (EC_{50})	Havelkova et al. (2016)

*EC_{50}-Effective concentration of the pollutant that produces a response in 50% of the population; IC_{50}-inhibition concentration - concentration of the pollutant that produces 50% inhibition of process (growth, activity, etc.); LC_{50} – Lethal concentration observed in 50% of the population; NOEC-Non-observed effect concentration - highest concentration of antimicrobial agent that produces no effect in intoxicated organisms.

resistant bacteria and even cause other possible health hazards to human and wild or domestic animals (Elizalde-Velázquez et al., 2016). Also, for sulfamethoxazole, it was observed that its metabolites that have been modified at the *para* amino group retained the antibacterial activity of theparent compound or exhibited greater activity (Majewsky et al., 2014). The above examples indicate that even partially or completely transformed compounds (even if parent compounds are not detectable in the environment) can cause similar or even greater effects. Such effect is related to the pseudo-persistence of the discussed antimicrobials.

3. Ecotoxicity of antimicrobial compounds

The ecotoxicity of the discussed antibiotics is shown in Table 4. While fluoroquinolones, macrolides and sulfonamides showed the greatest toxicity to aquatic organisms; β-lactams with penicillin G showed the weakest toxic effect.

Freshwater organisms show different sensitivity to antimicrobials depending on the type, class and species. It can be easily observed that bacteria and cyanobacteria are the most sensitive to antibiotics, because this class of drugs is inherently antibacterial. The mode of action of antibiotics is based on specific interactions with bacterial cells. There are five mechanisms that discriminate the effect of antibiotics: inhibition of cell wall synthesis, inhibition of protein synthesis, change of cell membranes, inhibition of nucleic acid synthesis and antimetabolite activity. Considering the basic ecosystem services that the microbial communities provide - including wastewater treatment, maintenance of soil structure and biogeochemical cycle, etc. it is of particular importance to protect non-target microbial communities from unintended contamination by antibiotics (Kumar et al., 2019). There are only few reports on the influence of antibiotics on bacterial communities important in remediation processes. Kümmerer et al. (2004) showed that cefuroxime was not toxic to activated sludge population, as 50% respiration inhibition was observed at a concentration higher than 100 mg/L. Shan et al. (2018) described the adverse effect of sulfamethazine and tetracycline on dissimilatory NO_3 reduction. Direct effect of antibiotics on bacterial population might be negative effect on abundance and species richness. On the other hand, due to long term exposition antibiotic resistance might be developed (Grenni et al., 2018; Haller et al., 2002). The antibiotic resistance of non-target bacteria is discussed in detail in chapter 4.

The organisms that are very sensitive to different antibiotics are freshwater algae and duckweeds. Brain et al. (2004) reported that the concentration of sulfametoxazole that did not cause any adverse effect (NOEC) to *Lemna gibba* was 10 ng/L. High toxicity to algae was shown also for macrolides, fluoroquinolones and tetracyclines. Since green algae are eukaryotic organisms and the chloroplast belongs to the semi-autonomous organelle, the toxic effects of antibiotics on green algae are related to the inhibition and interference of chloroplast metabolism such as photosynthesis procedures and interrelated protein synthesis, which disturb the function of the photosynthetic apparatus and finally affect cell growth (Fu et al., 2017; Magdaleno et al., 2015). Algae play an important role in the whole aquatic ecosystem as primary producers. Deleterious effects of antibiotics on algae might disrupt organisms of higher trophic levels. Eguchi et al. (2004) stated that the mixture of sulfamethoxazole and trimethoprim (at 20:3 of a molar ratio) caused synergistic growth inhibition for green algae. The value of IC_{50} in this case was calculated to be 0.28 mg/L, and it was statistically significant lower than for these compounds alone. For single compounds, this value was equal to 1.53 mg/L and 80.3 mg/L for sulfamethoxazole and trimethoprim, respectively. It should therefore be emphasized that the effects induced by the mixture can be significantly greater than the effect of individual compounds. Antimicrobial residues in the aquatic environment are present generally as a mixture, so the final effect is actually the result of all compounds contained in the mixture, not a single drug. It can therefore be assumed that this effect will be much greater.

Environmental risk assessment procedures are based in general on estimation of no effect concentration (PNEC) from standard ecotoxicity tests and comparison of this value with predicted (PEC) or measured (MEC) environmental concentrations. The methodology of this assessment is based on 'worst-case scenario' and therefore safety factors in the range 50–1000 (depending on the type of assays) are used to predict no effect concentrations (EU, 2003; Hernando et al., 2006). Based on this assumption it must be concluded that, except for bacteria and cyanobacteria, the risk quotient for surface waters shows that there is actually no acute risk from antibiotic pharmaceuticals to non-target organisms. However, it is important to realize that concentrations of pharmaceuticals detected in surface waters are increasing in recent years. There are also so-called hot spots such as the points of discharge of hospital wastewater, sewage from municipal sewage treatment plants and, finally, wastewater from the production of medicines. As shown in Table 2 at these points, much higher concentrations of antibacterial pharmaceutical have been detected, which increases the risk to the environment. In addition, drugs in wastewater are present in the mixture. It is most often difficult to estimate which pharmaceutical ingredients are included in such a mixture. As it is known, various types of interactions may exist between the components of mixtures:

synergistic, antagonistic and additive. In addition, these interactions are dependent not only on the type of pharmaceuticals, but also on the type and composition of sewage. Prolonged exposure of organisms in the environment to such mixtures may result in significant changes in the composition and type of populations. The presence of pharmaceuticals in the environment is a serious threat whose effects are not easily predictable at the moment. It is necessary to conduct long-term ecotoxicological studies that allow better assess environmental risk.

4. Environmental aspects of antibiotic resistance and its implications

The main concern for the release of antimicrobials into the environment is related to the development of antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARB), which reduce the therapeutic potential against human and animal pathogens (Kumar et al., 2019). A number of reservoir and habitats may be sites for emergence and maintenance of resistant microorganisms. These include hospitals effluents, WWTPs, farms, aquaculture and habitats to which feces and urine from humans and animals are excreted (Karkman et al., 2019; Korzeniewska and Harnisz, 2018; Niestępski et al., 2019; Osińska et al., 2019; Zhou et al., 2018). However, urban WWTPs have been recognized as one of the most important means for propagation of antibiotic resistance from humans to the environment (be it water or soil). Moreover, the antibiotic resistance profiles in WWTPs were found to mirror the antibiotic resistance gradients observed in clinics (Pärnänen et al., 2019). Antibiotics and antibiotic resistance determinants have occurred naturally in the environment long before the humans have discovered and used antibiotics to treat diseases, but this turning point has been marked by ever increasing concentration or abundance of antimicrobial pharmaceuticals and antibiotic resistance determinants in all the compartments of the biosphere (Berkner et al., 2014). Understanding the mechanisms of resistance to antibiotics, as well as ways to transfer this information between cells and documenting the occurrence of ARGs in a cross-section of environmental compartments will take a step toward understanding the fate and transport phenomena associated with these emerging contaminants.

4.1. Mechanisms of antibiotic resistance

There are a number of ways in which antibiotics affect bacterial cells (briefly described in SI (Section S2 and Table S2). However, bacteria have created a number of defense mechanisms against antibiotics, for example:

- modification of antibiotic target and reduction of drug affinity to binding sites, e.g. to the ribosome - MLSB (macrolide-lincosamide-streptogramin B) resistant *S. aureus*, to penicillin binding protein (PBP) in the cell wall - *S. pneumoniae*, to enzymes - gyrase DNA and fluroquinolones (Malmir et al., 2018),
- biofilm formation reducing the susceptibility to antibiotic activity – the increased cell density in a biofilm enhances its ability to resist antibiotics (Ali et al., 2018),
- active efflux pumps – bacterial efflux pumps actively transport antibiotics out of the cell and are major contributors to the intrinsic resistance of both Gram-negative and Gram-positive bacteria to many of the drugs. Some efflux pumps have narrow substrate specificity, e.g. the tetracycline pumps, but some of them transport a wide range of structurally dissimilar substrates and are known as multidrug resistance (MDR) efflux pumps. Efflux pumps of *S. aureus* remove e.g. fluoroquinolones, macrolides, tetracyclines, clindamycin (Munita and Arias, 2016),
- acquisition of alternative metabolic pathways to those inhibited by the drug, e.g. bacterial mutants that can take the life-sustaining products (eg thymidine) present in the environment and which are not synthesized within the bacteria (e.g. sulfonamides) (Kumar et al., 2019).

4.2. Transmission of antibiotic resistance

Genes carrying genetic information of microbial resistance to antibiotics can be located on a bacterial chromosome or embedded in plasmid DNA. If they are associated with the bacterial chromosome they become characteristic of a given species, and thus it is impossible to transfer them through horizontal gene transfer. Their location on mobile elements of the bacterial genome such as: plasmids, transposons, integrons and gene cassettes determines their mobility and the possibility of transferring between different strains, sometimes far phylogenetic (von Wintersdorff et al., 2016). The commensals and the environment can be also an important reservoirs of ARGs on mobile genetic elements (MGEs) which can be found in human pathogens and which can have originated from those reservoirs. Many clinically relevant resistance genes are believed to have originated from non-pathogenic environmental bacteria. A well-known example is that of the $bla_{\mathrm{CTX-M}}$ genes, which have become the most prevalent cause of extended-spectrum β-lactamases (ESBLs) in *Enterobacteriaceae* worldwide and a major cause of clinical treatment problems. The potential origin of these genes was identified as the chromosomal DNA of various environmental *Kluyvera* species, from where they spread very successfully to different bacterial species (Lerminiaux and Cameron, 2019). As with the $bla_{\mathrm{CTX-M}}$ genes, the OXA-48-type carbapenem-hydrolyzing β-lactamase genes, which are increasingly reported in enterobacterial species worldwide, were also found to originate from the chromosomes of waterborne, environmental *Shewanella* species (Poirel et al., 2012).

For microbial species to maintain resistance to antibiotics, they must not only pass resistance genes to their progeny (mutation, vertical gene transfer) but also have the ability to transfer genes between species, known as horizontal gene transfer (HGT) (Touchon et al., 2017). There are three different ways in which HGT can occur (von Wintersdorff et al., 2016), but in each case genetic material is transferred from antibiotic-resistant bacteria to other bacterial cells, making them resistant to antibiotics as well:

- transformation - this is the uptake, integration, and functional expression of naked fragments of extracellular DNA. As an example, studies of fluoroquinolone resistance have demonstrated that genes *par*C, *par*E, and *gyr*A are readily transformed between *Streptococcus pyogenes* and *Streptococcus dysgalactiae* (von Wintersdorff et al., 2016). Moreover, streptococcal species have been shown to exchange conjugative transposons via transformation in addition to conjugation (Chancey et al., 2015).
- transduction - through specialized or generalized transduction, bacteriophages may transfer bacterial DNA from a previously infected donor cell to the recipient cell. During generalized transduction, bacterial DNA may be accidently loaded into the phage head. During specialized transduction, genomic DNA neighboring the prophage DNA is co-excised and loaded into a new phage. As an example, the mobilization or transfer of ARGs by bacteriophages has been documented for various bacterial species, e.g. the carriage of β-lactamase genes by bacteriophages in *Escherichia coli* (Billard-Pomares et al., 2014) and the transfer of antibiotic resistance plasmids in methicillin-resistant *Staphylococcus aureus* (MRSA) (Varga et al., 2012)
- conjugation–this is a process requiring cell to cell contact via cell surface pili or adhesins, through which DNA is transferred from the donor cell to the recipient cell. The conjugation of MGEs conferring AMR has been observed in many types of ecosystems, ranging from transfer between bacteria in insects, soil, and water environments to various food and healthcare associated pathogens. Transfer of plasmids and conjugative transposons, such as the Tn916 family, between unrelated bacteria over large taxonomic distances has been also noted, indicating that this mechanism contributes significantly

Table 5
Antibiotic resistance gene (ARGs) abundances in wastewater and environmental samples.

Antimicrobials	Genes	WWTPs' effluent (genes copy/mL)	River water (genes copy/mL)	Groundwater (genes copy/mL)	References
Beta-lactam antibacterials, penicillins	bla_{CTX}	6.0×10^1 - 1.0×10^6	1.2×10^1 - 1.6×10^2	*not available*	Pallares-Vega et al. (2019); Tuo et al. (2018); Wen et al. (2016) Laht et al. (2014)
	bla_{TEM}	1.4×10^2 – 1.7×10^4	1×10^3–1.9×10^6	*not available*	Guan et al. (2018); Korzeniewska and Harnisz (2018); Wang et al. (2018b)
	bla_{OXA}	1.0×10^3 – 1.5×10^7	*not available*	*not available*	Korzeniewska and Harnisz (2018); Laht et al. (2014)
	bla_{SHV}	1.7×10^1 – 1.8×10^8	*not available*	*not available*	Korzeniewska and Harnisz (2018); Laht et al. (2014)
Tetracyclines	*tet*A	1.1×10^5 – 1.1×10^7	1.3×10^3 – 1.0×10^7	*not available*	Harnisz et al. (2015b); Korzeniewska and Harnisz (2018); Su et al. (2018)
	*tet*B	1.8×10^1 – 3.0×10^7	2.1×10^1 – 1.0×10^7	*not available*	Harnisz et al. (2015a,b); Makowska et al. (2016)
	*tet*M	1.0×10^1 – 1.7×10^4	1.7×10^3 – 1.2×10^4	1.0×10^3	Koike et al. (2007); Pallares-Vega et al. (2019); Su et al. (2018)
	*tet*W	4.8×10^3 – 2.2×10^5	1.7×10^4 – 1.0×10^5	*not available*	Wen et al., 2016; Su et al. (2018)
	*tet*O	1.0×10^4 – 1.6×10^6	1.0×10^4 – 1.5×10^4	3.9×10^3	Harnisz et al. (2015b); Koike et al. (2007); Su et al. (2018)
	*tet*Q	2.1×10^3 – 3.4×10^4	1.0×10^4 – 3.7×10^4	1.9×10^3	Koike et al. (2007); Harnisz et al. (2015b); Su et al. (2018)
	*tet*X	1.0×10^5 – 4.9×10^5	1.0×10^4 – 5.7×10^5	*not available*	Harnisz et al. (2015b); Su et al. (2018)
Macrolides, lincosamides and streptogramins	*erm*B	1.9×10^2 – 1.5×10^6	1.9×10^4 – 8.9×10^5	*not available*	Di Cesare et al. (2016); Pallares-Vega et al., 2019; Su et al. (2018); Tuo et al. (2018)
	*erm*C	7.0×10^4 – 1.8×10^6	1.3×10^1–7.9×10^1	*not available*	Guan et al. (2018); Mao et al. (2015)
	*erm*F		3.2×10^2–2.1×10^7	1.6×10^4	Guan et al. (2018); Tien et al. (2017)
Quinolone antibacterials	*aac(6′)-Ib-cr*	1.6×10^2 – 1.7×10^4	7.9×10^2 – 6.3×10^5	*not available*	Korzeniewska and Harnisz (2018); Tuo et al. (2018)
	*qep*A	1.0×10^3 – 1.1×10^7	7×10^1 – 1.2×10^2	*not available*	Korzeniewska and Harnisz (2018); Su et al. (2018)
	*qnr*S	4.0×10^2 – 6.6×10^3	7×10^1 – 7.9×10^4	*not available*	Guan et al. (2018); Di Cesare et al. (2016); Pallares-Vega et al., 2019; Su et al. (2018)
Sulfonamides and trimethoprim	*sul*1	6.2×10^3 – 1.3×10^7	1.8×10^5 – 1.0×10^6	2.5×10^4	Korzeniewska and Harnisz (2018); Pallares-Vega et al., 2019; Su et al. (2018)
	sul2	5.4×10^2 – $1{,}1 \times 10^6$	1.7×10^4 – 1.1×10^5	*not available*	Di Cesare et al. (2016); Pallares-Vega et al., 2019; Su et al. (2018)
Other substances	*van*A	1.4×10^4 – 6.5×10^4	0–1.1×10^1	*not available*	Caucci et al. (2016); Tuo et al. (2018)
	*mec*A	0–1.5×10^0	0–1.9×10^1	*not available*	Jäger et al., 2018; Wang et al. (2018b)

to the dissemination of ARGs between different reservoirs via such broad host range MGEs (von Wintersdorff et al., 2016).

The mechanisms of resistance to antibiotics, MGEs and HGT are important in modulating the spread of AMR, especially if antibiotics are present in the environment and there is a strong selective pressure on the living microorganisms. Gene transfer is also more likely in environments such as the wastewater (or soil) where bacteria are in close proximity to each other and in relatively high density. In order to control the spread of resistance it is important to have an understanding of the molecular biology of the different mobile genetic elements and of the ecology of the environments in which spread of ARGs is likely. For instance, it is assumed that under the environmental conditions, the low temperatures can promote antibiotic resistance in microbes (Maal-Bared et al., 2013) and the horizontal gene transfer of mobile genetic elements associated with ARGs (Miller et al., 2014). An example of such

genetic mobile element can be a clinical class 1 integron-integrase gene (*intI1*), which is mentioned to be a good proxy for pollution because it is linked to genes conferring resistance to antibiotics and its abundance may change rapidly because host cells can have fast generation times and this mobile element can move between bacteria as a result of horizontal gene transfer (Gillings et al., 2014).

Table 5 presents information on the abundances of most common ARGs in the environment, in relation to antimicrobials against which this resistance is observed. Based on the information provided, it can be concluded that tetracycline resistance genes are the most common in the environment and they are identified not only in treated wastewater, but also in surface water and even in ground water samples. In addition to tetracycline-resistant genes, one of the sulfonamide resistance genes (*sul1*) is particularly widespread in the environment. It was also found in groundwater at the highest concentrations observed in this medium. Unfortunately, there is no information about the survival of ARGs during the process of producing drinking water from groundwater (or surface water), as well as its disinfection. It may pose a threat to humans and animals, especially in the context of potable water consumption with ARGs present in it. Additionally, occurrence of ARGs may be a problem when treated wastewater is reused for different purposes, like for instance crops irrigation. Therefore, it should be emphasized that antibiotic resistance threat can be successfully tackled only if the environmental issues, and not only the clinical ones, are addressed (Ferro et al., 2016).

5. Conclusions

The environmental occurrence of antimicrobial pharmaceuticals (along with their transformation products) and antibiotic resistant bacteria and antibiotic resistant genes (and other mobile genetic elements) has become a global phenomenon and a threat. The direct threat is primarily due to the potential effects of antimicrobials and their transformation products present in the treated wastewater, surface water and groundwater on living organisms, including humans. The occurrence of these compounds in such media may pose a problem when considering their use (direct or indirect re-use) for food purposes. Admittedly, the results of ecotoxicological studies suggest that, except for bacteria and cyanobacteria, risk quotient for surface waters shows that there is actually no acute risk from antibiotic pharmaceuticals to non-target organisms, however, it should be emphasized that knowledge about the potential long-term exposure of the antimicrobials towards living organisms is still negligible. Therefore, it is necessary to conduct long-term ecotoxicological studies that allow better assess environmental risk. A serious threat to the environment is the spread of antibiotic resistant bacteria and antibiotic resistant genes (and other mobile genetic elements). The main sources responsible for the prevalence of these factors in the aquatic environment are wastewater discharges (usually effluents from urban WWTPs) (Krzeminski et al., 2019; Rizzo et al., 2013; Pärnänen et al., 2019). This is because conventional WWTPs are not capable of complete inactivation of all these agents. Furthermore, conditions prevailing in WWTPs, such as the ubiquity of nutrients, enhance the chances of survival or even proliferation of antibiotic resistant bacteria.

In order to limit the spread of both antimicrobial pharmaceuticals and ABR and ARGs in the aquatic environment it is necessary to take steps to control this type of contaminants at the source. To this end additional standards of water and wastewater treatment quality (e.g. concentrations of selected antimicrobials in treated media, but also the abundance of selected ARGs or other mobile genetic elements) should be gradually imposed by the authorities. Such activities should be supported globally, but also at the local level, because very often the occurrence of the specific combination of contaminants is a local problem.

However, it should be emphasized that the phenomenon of environmental occurrence of antimicrobials and spreading drug resistance is multifaceted, and the environmental aspect is only one of them, but to counteract it effectively, it is necessary to undertake integrated activities based on cooperation of professionals and scientists from various fields of science or industry, such as environmental sciences, medicine, veterinary, pharmacology, chemical engineering and others.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2019.172813.

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