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Review article

Antibiotics bioremediation: Perspectives on its ecotoxicity and resistance

Mohit Kumar[a,1], Shweta Jaiswal[b,1], Kushneet Kaur Sodhi[a,1], Pallee Shree[a], Dileep Kumar Singh[a], Pawan Kumar Agrawal[c], Pratyoosh Shukla[b,*]

[a] Soil Microbial Ecology and Environmental Toxicology Laboratory, Department of Zoology, University of Delhi, Delhi 110007, India
[b] Enzyme Technology and Protein Bioinformatics Laboratory, Department of Microbiology, Maharshi Dayanand University, Rohtak 124001, Haryana, India
[c] National Agriculture Science Fund, Krishi Anusandhan Bhavan-I, Indian Agricultural Research Institute, Delhi 110012, India

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ABSTRACT

Antibiotic is one of the most significant discoveries and have brought a revolution in the field of medicine for human therapy. In addition to the medical uses, antibiotics have broad applications in agriculture and animal husbandry. In developing nations, antibiotics use have helped to increase the life expectancy by lowering the deaths due to bacterial infections, but the risks associated with antibiotics pollution is largely affecting people. Since antibiotics are released partially degraded and undegraded into environment creating antibiotic pollution, and its bioremediation is a challenging task. In the present review, we have discussed the primary antibiotic sources like hospitals, dairy, and agriculture causing antibiotic pollution and their innovative detection methods. The strong commitment towards the resistance prevention and participation, nations through strict policies and their implementations now come to fight against the antibiotic resistance under WHO. The review also deciphers the bacterial evolution based strategies to overcome the effects of antibiotics, so the antibiotic degradation and elimination from the environment and its health benefits. The present review focuses on the environmental sources of antibiotics, it's possible degradation mechanisms, health effects, and bacterial antibiotics resistance mechanisms.

1. Introduction

Antibiotics are natural, synthetic and semi-synthetic compounds which show antimicrobial activities (Catteau et al., 2018). Antibiotics are probably the most successful family of drugs to treat the microbial infections in humans and animals with specific action on the target. Alexander Fleming in 1928, accidentally discovered penicillin, since then many antibiotics have been synthesized for human, plants and animal health. Antibiotics are used as growth promoters in animal farming *i.e.*, cattle, hogs, poultry and to improve the feeding efficiency (Cowieson and Kluenter, 2018) although they are banned in EU in 2006, but are still in practice in India and China (Ronquillo and Hernandez, 2017) especially in agriculture and livestock industries. The accelerated use of all known antimicrobials for the benefit of human, animals, and agriculture conclude their regular and repeated release into the environment and natural ecosystem (Nielsen et al., 2018). Antibiotics not only affect the target population but also influence the non-target population with high toxicity impact (Grenni et al., 2018). The main failing of all antibiotics and other pharmaceutical industries lies in the development of antibiotic resistance in all organisms (Tacconelli et al., 2018). HGT (resistance) in the bacterial population represents serious health risks and concern to humans and animals (Kivits et al., 2018). The ARGs and ARB, curtails the curative potential of antibacterial compounds against human and animal pathogens. Hence, the potential of antibiotic residues in surface water can disturb the key bacterial cycles/mechanisms/processes, critical to aquatic balance or (soil fertility) agricultural balance and animal production (Ribeiro et al., 2018). WWTP effluents, leakage of sewage and agricultural waste are some of the secondary contributors as these compounds are not entirely metabolized and may escape degradation.

Abbreviations: EU, European Union; US, United States; WHO, World Health Organization; ARGs, antibiotic resistance genes; ARB, antibiotic resistant bacteria; WWTP, waste water treatment plants; STPs, sewage treatment plants; GAP, good agricultural practices; SDZ, sulfonamides; AMX, amoxicillin; NOR, norfloxacin; OFL, ofloxacin; ETM, erythromycin; MIC, minimum inhibitory concentration; MDRS, multi drug resistance strains; MRSA, methicillin resistant *Staphylococcus aureus*; PBP, pyrrolidinobutiophenone; HGT, horizontal gene transfer; MS, mass spectrometry; HPLC, high-performance liquid chromatography; SPE, solid phase extraction; UPLC, ultra-performance liquid chromatography; FLD, fluorescence detector; UV, ultra violet; ATC, anhydrotetracycline; EATC, 4-epianhydrotetracycline

* Corresponding author.
E-mail address: pratyoosh.shukla@gmail.com (P. Shukla).

[1] Mohit Kumar, Shweta Jaiswal, Kushneet Kaur Sodhi are the joint first authors and have equal contributions.

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Antibiotics have been reported in hospital wastewaters, WWTP effluents (Barancheshme and Munir, 2018), WWTP biosolids, soil, surface waters, groundwaters (Zhang et al., 2018), sediments, biota and drinking water (Williams and Kookana, 2018). Antibiotic pollution has posed a major global threat. The above issue insights concern towards the inherent capabilities of bacteria possessing the antibiotic resistance and for the assessment of the post-therapeutic effects on biological systems prior to the treatment with antibiotics (Kim et al., 2018). The unprecedented advantage of antibiotics in medical healthcare is undeniable (Berger et al., 2018); however, pharmaceutical residues are widespread and occasionally found in surface water with inherent bioactive properties, while water security is the matter of debate and arguments among policymakers. The trace amount of antibiotics in the aquatic ecosystem is a great challenge for water quality assessment due to their toxic impact on non-target organisms (Vasiliadou et al., 2018). The pioneering discovery of antibiotics has made a revolutionary storm in medical world saving lives by treating the microbial infections, but now due to extensive use and consumption, terrestrial and aquatic ecosystems are negatively affected (Leung et al., 2012). The remediation strategies for antibiotics has shown the possibilities of their removal *i.e.*, adsorption mechanisms, bioelectrochemical methods, hydrolysis, redox reactions, acidic, alkaline or ionic, metal-assisted, photolysis, phytolysis, microbial and enzymatic (Saitoh and Shibayama, 2016; Yan et al., 2018; Massé et al., 2014; Dangi et al., 2018). We suggest that the future work for the bioremediation will focused on enzymatic remediation and biological techniques should be preferred over chemical treatment to minimize the post treatment contamination moieties.

2. Sources of antibiotics in wastewater

Antibiotics and its metabolites are continually discharged into the natural environment. Furthermore, discharge of hospital waste, veterinaries, pharmaceutical plants (Obayiuwana et al., 2018), dairies, animal excreta, domestics, animal husbandry, municipal waste and poultry (Pruden et al., 2013) are also conferring the threat of antibiotic pollution (Fig. 3). Antibiotics application in agriculture enhances the livestock growth, bee-keeping, and fish farming (Hong et al., 2018) but also contaminates the environment *via* the excretion of unused antibiotic and metabolites from the feces of the poultry animals. Antibiotics, *i.e.*, monensin, promotes animal growth and feed efficiency for milk production in dairy farms reaches down to the natural resources. Hence antibiotic residue indirectly contaminates soil and water resource (Mutiyar and Mittal, 2014). Although as compared to animals, in plants, antibiotics consumption is very low. Antibiotics are frequently detected in waterways of agricultural land which points the presence of large-scale use of the same in the agricultural field (Piña et al., 2018). The pharmaceutical industries contribute significantly in total antibiotic concentration added to the influent of the sewage treatment plant, in addition to the domestic and industrial effluents (Harrabi et al., 2018). Some antibiotics are of low molecular weight (< 1000 D), thus, quickly dissolved in water bodies resulting in the persistence and recalcitrance of antibiotics (*i.e.*, beta-lactams, aminoglycosides, lincosamides, macrolides, nitrofurans, amphenicols, phosphonates, quinolones and fluoroquinolones, rifamycins, sulfonamides, and tetracyclines) and their isomers (Krzeminski et al., 2018). General properties of some of these antibiotics are depicted in Table 1. These compounds are partially removed by WWTPs, however, the STPs are considered significant contributors to the spread of antibiotics in the environment. Globally, WWTPs are not able to eliminate the micropollutants like antibiotics and therefore are continually discharged into the sediments and water bodies (Kim and Carlson, 2006; He et al., 2018). Antibiotics which are administered to livestock can also be dispersed in fields *via* manure and leaches soil and ground-water, while those used in crops and fish farming can accumulate in the environment, thus increasing the contaminant concentration (Ishikawa et al., 2018). Antibiotic added to the feed are excreted as the parent compounds or as metabolites and might contaminate soils when manure is applied to agricultural fields in accordance with GAP. They may also be transported to ditches, streams, and rivers *via* runoff and drain flow, to groundwater *via* leaching and might also enter into the food chain (Korada et al., 2018). Improper disposal of unused/expired drugs, which are directly discharged in the sewage network or deposited in landfills, waste effluents from manufacture or accidental spills during manufacturing or distribution can also be considered as significant points of contamination (Akici et al., 2018). These persistent compounds may exert selective pressure on microorganisms and result in the development of resistance (Kim et al., 2018).

3. Presence of antibiotics in biological system

Both narrow and broad-spectrum antibiotics have been detected globally in different environmental samples (Sarpong and Miller, 2015). Based on the consumption by living beings, antibiotics are discharged to nearby drains, followed by river and seas. Some examples, *i.e.*, Sulfamethoxazole and Trimethoprim are detected more frequently in sea water of Belgian harbors (Larsson, 2014), fluoroquinolone was detected in samples from Hailing island, ofloxacin in Laizhou Bay and tetracycline & sulfonamides in effluents of waste water treatment plants (Gao et al., 2012). With the development of intensive rearing in aquaculture industries, antibiotic drugs have become a necessity as a feed additive in aquaculture industries.

Antibiotics have been detected globally in developing countries. Fluoroquinolones, macrolides, sulfamethoxazole, sulfonamides, trimethoprim, lincomycin, and beta-lactams have been detected frequently in hospital effluents with the detection rate (up to 35,500 ng/l) (Meena et al., 2015).

In European countries, hospitals confer only 5–20% pharmaceuticals in municipal sewage water (Kümmerer, 2009). However, these antibiotics are detected in hospital effluents; hence we cannot deny the contamination of these antibiotics to the surface water sources and their consumption borne health issues. It may be possible that one kind of antibiotic's detection rate differs from other type/kind of antibiotic as in dairies, lincomycin detected more frequently while tylosine is occasionally (Sarpong and Miller, 2015). Sulfamethoxazole, trimethoprim, ciprofloxacin, and ofloxacin detection have been reported in municipal wastewater. Oxytetracycline, florfenicol, premix, sarafloxacin, erythromycin sulphonamides are widely used in aquaculture so detected in aqua samples. In China generally, 5 compounds, SDZ, AMX, NOR, OFL and ETM were found in the water samples with concentrations ranging from 65 to 7722 ng L^{-1}. All the five antibiotics were found in the fish pond with the concentration upto 315 ng L^{-1}.

Tetracyclines, oxytetracyclins, sulfamethazine, tylosin, penicillin G and lincomycin are widespread in veterinary and medicinal practice to treat the bacterial infections (García-Fernández et al., 2018). In dairies, antibiotic injections are widely used, and these antibiotics are administered in animals for prophylaxis of diseases, growth promotion and more commonly administered in milk replacer for calves and treatment during lactation. Chlortetracycline, sulfamethazine, and lincomycin were frequently detected in wastewater while tylosin and oxytetracycline were occasionally detected, so there is a need to for more research on dairies effluents for the detection of other metabolites and isoforms of antibiotics. Sarafloxacin has been used against poultry disease, which strongly binds to soil and hence there is a need for the detection of other isoforms in the soil as to check the level of toxicity of new contaminants (Lysnyansky et al., 2013). Antibiotics have a short half-life, but enough to give resistance to the microorganisms by continuous exposure, *i.e.*, virginiamycin, a food additive to livestock is used as a growth enhancer and is found in excreta of treated animals whose manure is used as fertilizer and due to its soil binding capacity (Tasho and Cho, 2016), it contaminates the water supply. Virginiamycin, also known to be biodegradable in soil but its exposure is enough to provide

Table 1
Commonly used antibiotics and their general characteristics.

Antibiotic class	Example	Application	Chemical formula	Type	Target	Mol. Wt. (g/mol)
Aminoglycosides	Streptomycin	Veterinary	$C_{21}H_{39}N_7O_{12}$	Bactericidal	Inhibit protein synthesis	581.574
	Amikacin	Vet.	$C_{22}H_{43}N_5O_{13}$			585.603
	Kanamycin A	Human	$C_{18}H_{36}N_4O_{11}$			484.499
	Neomycin	Vet.	$C_{23}H_{46}N_6O_{13}$			614.644
	Gentamycin	Vet.	$C_{21}H_{43}N_5O_7$			477.596
Beta-Lactams	Penicillin G	Ani.,hum.,vet.	$C_{16}H_{18}N_2O_4S$	Bactericidal	Inhibit cell wall synthesis	334.39
	Amoxicillin	Vet.	$C_{16}H_{19}N_3O_5S$			365.4
	Ampicillin	Vet.	$C_{16}H_{19}N_3O_4S$			349.41
	Cloxacillin	Vet.	$C_{19}H_{18}ClN_3O_5S$			435.88
	Cephalexin	Vet.	$C_{16}H_{17}N_3O_4S$			347.39
	Cephalotin	Human	$C_{16}H_{16}N_2O_6S_2$			396.44
	Cefazolin	Human	$C_{14}H_{14}N_8O_4S_3$			454.51
	Ceftiofur	Vet.	$C_{19}H_{17}N_5O_7S_3$			523.56
	Cefotaxin	Human	$C_{16}H_{17}N_5O_7S_2$			455.47
	Cefquinome	Vet.	$C_{23}H_{24}N_6O_5S_2$			528.6
Glycopeptides	Vancomycin	Vet	$C_{66}H_{75}Cl_2N_9O_{24}$	Bactericidal	Inhibit cell wall synthesis	1449.3
	Bleomycin	Human	$C_{55}H_{84}N_{17}O_{21}S_3$			1415.551
	Polymyxin B	Vet, human	$C_{56}H_{98}N_{16}O_{13}$			1203.499
	Polymyxin E	Vet, human	$C_{52}H_{98}N_{16}O_{13}$			1155.455
Lincosamides	Clindamycin	Human	$C_{18}H_{33}ClN_2O_5S$	Bacteriostatic	Inhibit protein synthesis	424.98
	Lincomycin	Vet.	$C_{18}H_{34}N_2O_6S$			406.538
Macrolides	Azithromycin	Human	$C_{38}H_{72}N_2O_{12}$	Bacteriostatic	Inhibit protein synthesis	748.996
	Erythromycin	Human,Vet.	$C_{37}H_{67}NO_{13}$			733.93
	Natamycin	Food add.	$C_{33}H_{47}NO_{13}$			665.725
	Roxythromycin	Human	C41H76N2O15			837.047
	Clarithromycin	Human	$C_{38}H_{69}NO_{13}$			747.953
	Tylosin	Vet.	$C_{46}H_{77}NO_{17}$			916.1
Nitrofurans	Furaltadone	Human and vet.	$C_{13}H_{16}N_4O_6$	Bactericidal	Inhibit nucleic acid synthesis	324.293
	Nitrofuranation		$C_8H_6N_4O_5$			238.16
	nitrofurazone		$C_6H_6N_4O_4$			198.14
Amphenicols	Chloramphenicol	Vet.	$C_{11}H_{12}Cl_2N_2O_5$	Bacteriostatic	Inhibit protein synthesis	323.132
	thiamphenicol	Vet.	$C_{12}H_{15}Cl_2NO_5S$			356.223
Phosphonates	Fosfomycin	Human	$C_3H_7O_4P$	Bacteriostatic	Inhibit cell wall synthesis	138.059
Polyether ionophores	Monensin	Vet.	$C_{36}H_{62}O_{11}$			670.871
Quinolones and fluoroquinolones	Ciprofloxacin	Human	$C_{17}H_{18}FN_3O_3$	Bactericidal	Inhibit DNA replication	331.346
	Oxolinic acid	Vet. Plants	$C_{13}H_{11}NO_5$			261.23
Rifamycin	Rifampicin	Human	$C_{43}H_{58}N_4O_{12}$	Bactericidal	Inhibit nucleic acid synthesis	822.94
	Rifapentine	Human	$C_{47}H_{64}N_4O_{12}$			877.031
Sulfonamides	Sulfachloropyridazine	Human,vet.	$C_{10}H_9ClN_4O_2S$	Bacteriostatic	Inhibit folic acid synthesis	284.718
	Sulphanilamide	Human				
	Sulfamethazine	vet.	$C_6H_8N_2O_2S$			172.2
	Sulfadimethoxine	vet.	$C_{12}H_{14}N_4O_2S$			278.33
	Sulfamethoxazole	vet.	$C_{12}H_{14}N_4O_4S$			310.33
	Sulfapyridine	Human	$C_{10}H_{11}N_3O_3S$			253.279
	sulfadiazine	vet.	$C_{11}H_{11}N_3O_2S$			249.29
			$C_{10}H_{10}N_4O_2S$			250.278
Tetracyclines	Chlortetracycline	vet.	$C_{22}H_{23}ClN_2O_8$	Bacteriostatic	Inhibit protein synthesis	478.882
	Doxycycline	vet.	$C_{22}H_{24}N_2O_8$			444.43
	Oxytetracycline	Human,vet.	$C_{22}H_{24}N_2O_9$			460.434
	tetracycline	Human,vet.	$C_{22}H_{24}N_2O_8$			444.435

resistance to the soil microbiota before it gets degraded (Radu et al., 2017). Their degradation rate also varies depending on the variety of antibiotics, *i.e.*, Cyclosporin A degradation by microorganism occurs at a very slow rate. Europian pharmacopoeia has fixed the amount of many antibiotics and related compounds in the pharmaceutical formulations and is strictly followed by western companies. But in India due to no legal action and norms for antibiotics prescription along with, lack of strictness, shortage of expertise and absence of regular monitoring, the problem of antibiotic resistance is rising at a fast pace, culminating towards the development of superbugs, *i.e.*, multidrug resistance. The concentration of antibiotics ranges from few nanograms to micrograms per litre or kilograms of soil. Antibiotics such as fluoroquinolones, macrolides, and tetracyclines are not degraded unlike penicillins and are found to be persistent in the environment (Grenni et al., 2018). The highest amount of antibiotic is found in hospital effluents wastewater effluents, and soil treated with manure especially in the winter season.

Natural microbial communities show bactericidal and bacteriostatic effects as detrimental consequences of antibiotic treatment. Antibiotics acting on these microbial communities lead to antibiotic resistance (Hu et al., 2018). The biodiversity of the microorganisms is used for the maintenance of the biological processes in water and soil as biogeochemical cycles. Few reports on the impact of antibiotics on biogeochemical cycles are well tabulated by researchers *i.e.*, Shan et al., 2018 described the altered dissimilatory NO_3 reduction in paddy along with the enhanced release of N_2O under the influence of sulfamethazine and tetracycline (applied separately and in conjunction) in soil slurry experimentation. ^{15}N tracer technique revealed the reduced potential of *nirZ* and *nirS* genes resulting in altered (Shan et al., 2018) nitrogen cycle. Antibiotic resistance patterns and the antibiotics prescription rates vary across geographical areas, the increase in antibiotics prescription is increased with the increase in resistance of pathogens against antibiotics (MacFadden et al., 2017). Antibiotic resistance is strongly correlated with the latitude coordinates, and the local temperature and the higher temperature leads to the proliferation of antibiotic resistance. In *Escherichia coli*, *Klebsiella pneumonia* and

Staphylococcus aureus, there is a 4.2, 2.2 and 3.2% increase in antibiotic resistance respectively with a 10 degree Celsius increase in temperature (Blair, 2018).

4. Antibiotics ecotoxicity and impact on bacteria

Antibiotics get mixed up with fresh water sources *via* rains and soil erosion (Mutiyar and Mittal, 2014). By mixing of sewage waste, incompletely degraded and least eliminated effluents of wastewater treatment plants, enter into the environment, antibiotics from veterinary and poultry come *via* aquaculture and manure applications, and by the disposal of unused antibiotics (Nödler et al., 2014). We can predict from the point of evolution that the microbes raised antibiotics for their protection which has resulted in their antagonistic effect on other microorganisms. Antibiotic resistance can spread globally through HGTs and gets selected and proliferated during the course of evolution (Chu et al., 2018).

Antibiotics contamination not only affect the targeted microbial population but it also severely affect the non-target populations, as shown in Fig. 2 (Leung et al., 2012). Fluoroquinolones frequently found in hospital waste are more toxic to prokaryotes than eukaryotes (Ao et al., 2018). Antibiotics not even act on target organisms but it also acts on non-target organisms (Kümmerer, 2009) including freshwater algae, fishes and zooplankton, as negative effects of monensin have been reported on species richness and abundance of zooplankton and phytoplankton biomass in an artificial pond (Hillis et al., 2007). Antibiotics have direct as well as indirect effects on bacterial population (Grenni et al., 2018). Indirect effects, antibiotics may acts as bactericidal or bacteriostatic but on the other hand due to their long term exposures, antibiotics results in the development of resistance even in the non target organisms (Haller et al., 2002).

The effluents antibiotics and their residues causes seawater contamination in Germany, Greece, Italy, Turkey, Belgium, China and USA, and the study has been supported by the detection of clarithromycin, erythromycin, roxithromycin and sulfamethoxazole in 153 seashore water samples from Baltic sea, Northern Madriatic Sea, Aegean Sea, Pacific Sea, San Francisco Bay, Mediterranean, and Dardanelles (Nödler et al., 2014). Recent reports also concluded that antibiotics are taken up by vegetables irrigated with contaminated water, *i.e.*, carrot, radish (Bassil et al., 2013), corn (Kang et al., 2013) and cabbage (Chowdhury et al., 2016). Internationally antibiotic consumption data is scarce because of variation in their prescription and administration. For instance, a particular antibiotic is widely used in a country, and the same is banned in other, *i.e.*, vancomycin is prescribed in USA and banned in Germany. A report estimated 1,000,000–2,000,000 ton antibiotic consumption *per annum* (Centers for Disease Control and Prevention (CDC), 2015). All the international data on antibiotic usage is only estimated and approximated, since many countries do not spectacle their monitoring data and *vice versa*, hence actual data remains unrevealed.

A particular antibiotic can act differently, based on their physical, chemical and biological properties (Yelin and Kishony, 2018). Antibiotic used in veterinary and poultry increase the reluctant mechanism in bacteria to survive under antibiotic stress resulting in the evolution of multidrug-resistant bacteria. These resistant strains of bacteria are reported in aquatic as well as soil environment (Esiobu et al., 2002). Fluoroquinolone detected in hospital effluents (up to 87,000 ng/l) showed high genotoxicity and human health risks with its long-term use (Brown et al., 2006). Sulfonamides and fluroquinolones are more persistent in environment followed by macrolides while aminoglycosides and β-lactams are least persistent. Tetracyclines can persist for a relatively long period in the absence of sunlight, at the expense of its mobility. The fluoroquinolones, norfloxacin and ciprofloxacin at low concentration (5000 ng/l and 25,000 ng/l respectively) have shown to exert genotoxic effects on genetically modified *Salmonella typhimurium* (Ao et al., 2018).

Studies on *Bifidobacterium*, *Clostridium*, *Escherichia coli*, *Enterococcus and Lactobacillus* showed that their structural composition and metabolic activities are severely affected by antibiotics as they play a crucial role in changing the ecology particularly the niche through the genetic exchanges taking place (Newton et al., 2013). Moreover, *Clostridium* showed reduced growth rate due to toxicity affects of penicillin, tylosin, ciprofloxacin and erythromycin, sulfamethoxazole and amoxicillin (Yasser and Adli, 2015). The *Vibrio fischeri* is found to be negatively compromises its luminescence efficiency under the conjunctive application of penicillin G, tetracycline and vancomycin (Havelkova et al., 2016). A recent study on the presence of unmetabolized antibiotics in manure in correlation with ARGs was done by McKinney et al., 2018. They observed the variation in six ARGs and one integron (intI1, blaCTX-M-1, erm(B), sul1, tet(A), tet(W) and tet(X)). The significant results were simultaneous increase in ARGs with manure treatment and with respect to soil depth and level, the abundance of ARGs are directly proportional.

5. Bacterial strategies for antibiotic resistance

Traditionally, fungal and bacterial species were the key sources of antibiotics (*i.e.*, penicillin & streptomycin) but due to the resistance acquired by the bacteria since last few decades, the synthesis of artificial antibiotics (chemically synthesized and modified natural antibiotics) is the demand of time (Lin et al., 2018a). Overuse, underuse, and misuse of the antibiotics is moulding and bringing new cases of microbial resistance especially among bacterial species. The rationale behind this scenario is long-term exposure with the low concentration of antibiotics (Wistrand-Yuen et al., 2018). Antibiotic resistance refers to an increase in the MIC of antibiotics towards the microbes. It is a mechanism through which the bacteria can survive the stress of antibiotics (Trinh et al., 2018). Microbes can execute antibiotic resistance *via* escaping the drug-target interaction, efflux of antibiotics from the cell (efflux pump TolC in *E. coli*), modification of antibiotics and their metabolites by enzymes (Kumar et al., 2017; Sharma et al., 2018) (*i.e.,* ADP-ribosyltransferases and glycosyl transferases). These antibiotic modifying enzymes assisted by co-substrate *i.e.*, ATP can transfer functional groups which covalently modify the antibiotics by acetylation, phosphorylation, adenylation, nucleotidylation, ribosylation, and glycosylation (Camotti Bastos et al., 2018). Above consequences can lead to modification of cell surface receptors, redox mechanisms, hydrolysis and many more culminating towards MDRS (Rajivgandhi et al., 2018). Different kind of resistant genes activated under the heavy antibiotic stress which ultimately becomes a part of normal bacterial machinery and hence produces the resistant enzymes even in the control conditions (Cruz-Loya et al., 2018). Although thousands of resistant enzymes against the classical and modern antibiotics have evolved, Table 3 summarizes some beta lactamases which are involved in immense resistance against different class of antibiotics. Bypass of antibiotics is another specific mechanism of bacterial resistance. PBP an alternative produced by MRSA, the bacteria produces a simple target (PBP) which is susceptible to antibiotics. This alternative target is important for the survival of bacteria which plays the role of a simple protein (Gao et al., 2012). However bacterial cell posses different molecular hierarchy (Fig. 1) (DNA, RNA or Protein), each antibiotic has its specific target for action (Mack et al., 2018).

High cell density and quorum sensing of microbial consortium form biofilm. Biofilm prevents the antibiotic penetration due to matrix acting as a barrier (Maurice et al., 2018). Positively charged aminoglycosides antibiotics (*i.e.*, gentamicin and streptomycin) are prevented from penetrating the negatively charged biofilm matrix (Radlinski and Conlon, 2018). The high density of bacteria in biofilm's consortium increases the chances of selection of resistant bacteria because of antibiotic pressure by enhancing the rate of HGT and increasing the frequency of mutation (Fan et al., 2018). In various experiments, antibiotic diffusion coefficients are measured in polysaccharide gels which differ around 36–76% as compared to their diffusion in water (Wang et al., 2018a).

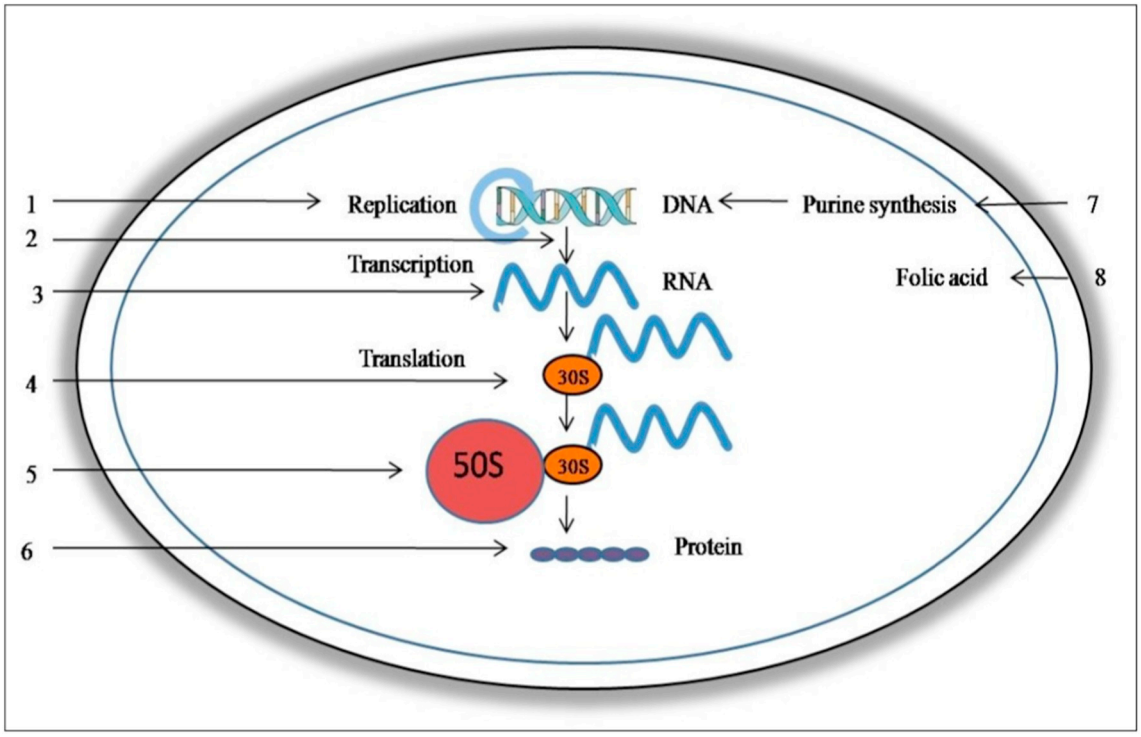

Fig. 1. Representation of target sites of antibiotic for a bacterial cell. Target (1), DNA replication, target (2), transcription, target (3), translation, target (4) & (5), ribosomal subunits, target (6), protein modifications, target (7) & (8), folic acid and Purine synthesis. Based on the targets, the antibiotic can be recognized as bactericidal or bacteriostatic and rather than gene and protein alterations; antibiotic also targets the precursors of cellular machinery molecules *i.e.*, folic acid and thymine.

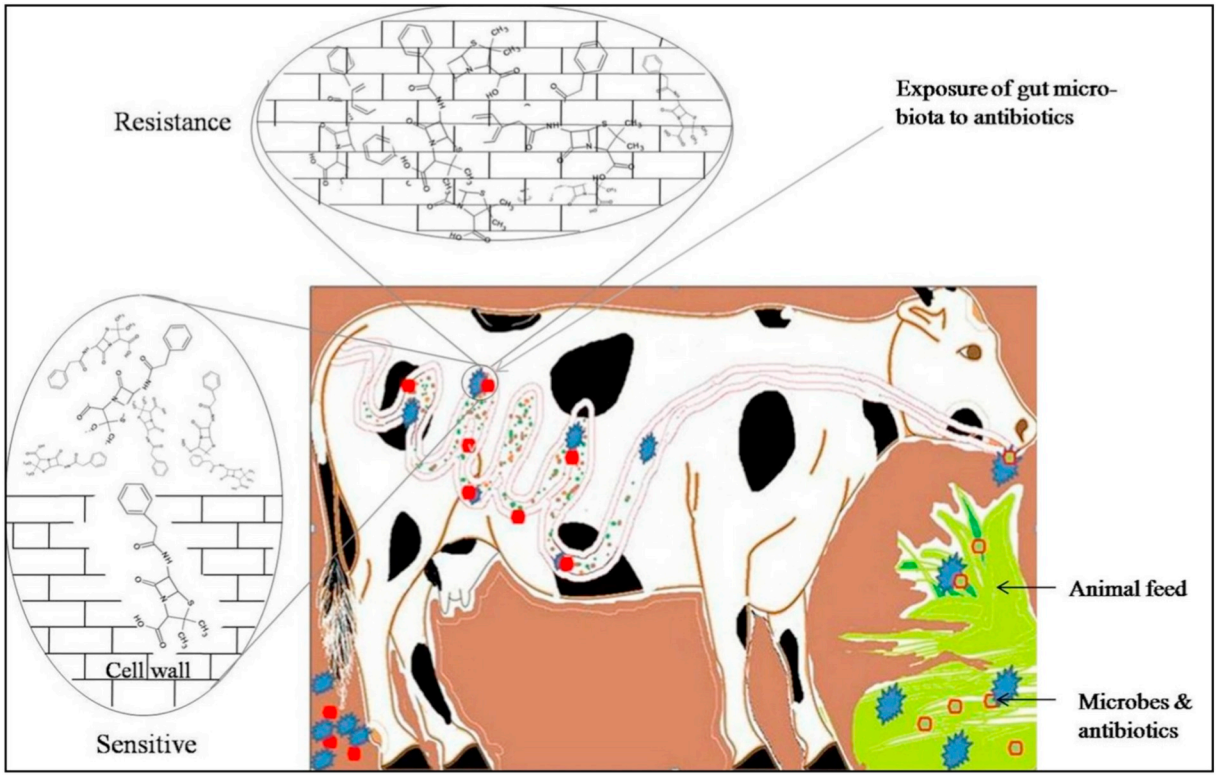

Fig. 2. Non-target bacterial diversity affected by antibiotics through unintentional feeding in dairy farms. The resistant bacteria survive due to mutations and adaptations in the antibiotic load surrounding the bacteria in the gut of animals. The contamination further spreads from the feces and urine into the environment and contributes to the natural environmental cycles.

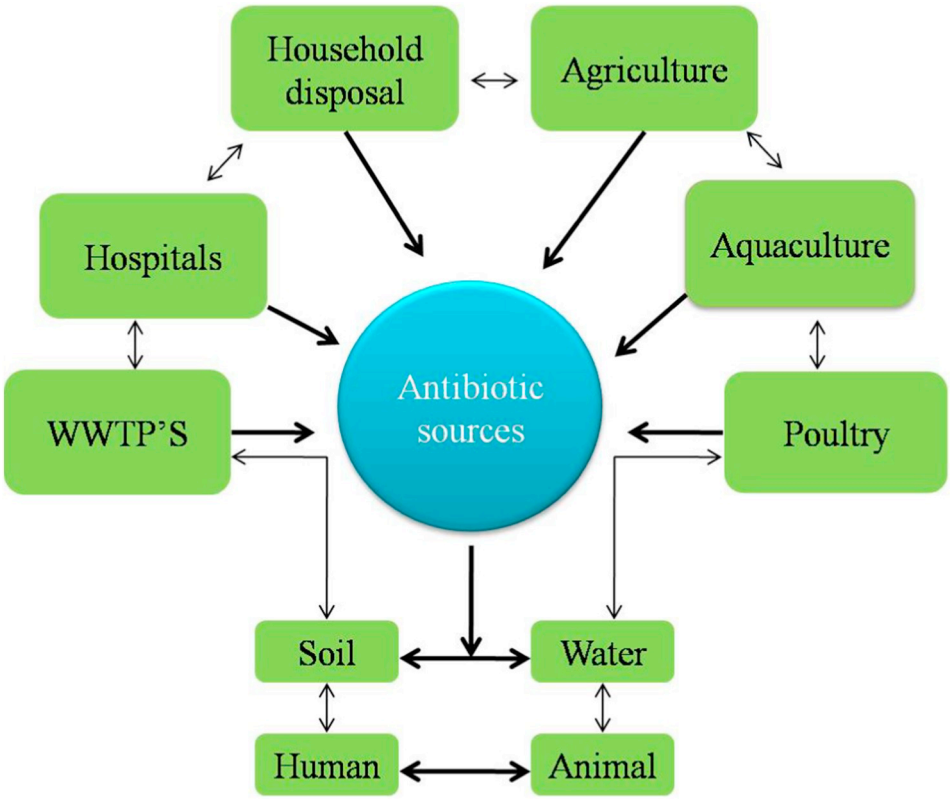

Fig. 3. Different kind of sources of antibiotic contamination to soil and water.

So there is a reduction by a factor of two to three in diffusion of antibiotics in biofilms that explains the resistance level of these aggregated bacteria to antibiotics (Ahmed et al., 2018). The exopolysaccharide and extracellular DNA can render a drug ineffective against bacteria due to poor diffusion as the structural composition of biofilms can act as a barrier to diffusion, preventing the antibiotic to reach the living cell (He et al., 2012). The diffusion rate varies between antibiotics that are positively charged, *i.e.*, aminoglycosides and the large molecules are less effective in diffusing across the extracellular matrix, but beta-lactams antibiotics and quinolones can diffuse easily (Zhang et al., 2012). In the outer regions, inactivation of drugs takes place, and the drugs are prevented from diffusing into deeper layers, which allow the sensitive bacteria to survive. The concentration of drugs and oxygen is highest at the particular spatial niche which is near the biofilm surface. A gradient of oxygen, cations are generated which affects the efficiency of antibiotics in deeper regions. Due to the scarcity of nutrients, there is a sort of metabolic response generated which helps to control the tolerance of antibiotics in bacterial cells in which the growth is ceased. The biofilm consortium is even not phenotypically homogeneous as subpopulations (*i.e.*, persister cells) show different susceptibility to antibiotics (Ayrapetyan et al., 2018).

Several studies have been conducted for determination of antibiotic in the Rio Grande (McKenney et al., 2018), major U.S. Rivers (Wu et al., 2018) and Wild Canada Geese (Rasmussen et al., 2017). The widespread and improper use of antibiotics in livestock, human and pets have resulted in the development of antibiotic-resistant bacteria. The antibiotic-resistant bacteria might develop from long-term environmental exposure to low concentration of antibiotics with limited data support (Oliveira et al., 2017). In sewage, receiving hospital and pharmaceutical plant waste is reported to have relatively more resistant bacteria against oxytetracycline in comparison to sewage receiving wastes from pharmaceutical plants only. Latter also shows resistant bacteria against multiple drugs including sulfamethoxazole (Szekeres et al., 2018). *Pseudomonas fluorescens*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Staphylococcus* sp. were found to be multi-resistant against some antibiotics (Hathroubi et al., 2017). Even from the natural water some antibiotic-resistant bacteria also detected. The continuous increment in antibiotic-resistant pathogenic bacterial strains leads to the severity of the health problem (García-Fernández et al., 2018).

Antibiotic fosfomycin known for the treatment of multi-drug resistant bacterial infection (Wagenlehner et al., 2011) is a potent bactericidal against *E.coli*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *Enterococcus faecalis*, and *Enterococcus faecium*, but some bacteria show decreased susceptibility against it, *i.e.*, *Klebsiella pneumonia* and *Enterobacter cloacae* (Kumbhakar et al., 2018). And this reduced susceptibility is due to mutations in GipT and UhpT transporters (Lucas et al., 2018), modification of antibiotic target MurA enzyme (Guo et al., 2017), and antibiotic modification by proteins (FosA, FosB or FosX) (Scortti et al., 2018). Fosfomycin has been used for many decades, so antibiotic resistance has developed in many strains of different bacteria, so more exploration of the molecular mechanism of resistance development is the need (Zhanel et al., 2018). Tetracycline is bacteriostatic and is active against gram negative and gram positive bacteria. Bacterial isolates of genera *Moraxella*, *Pseudomonas*, *Flavobacterium*, *Vibrio*, *Xanthomonas*, *Alcaligens*, *Micrococcus*, *Aeromonas*, and *Acinetobacter* were reported to have resistance against ampicillin (Olaimat et al., 2018).

6. Detection and analysis of antibiotics

Analytical methods for quantification of tetracyclines and sulfonamides in wastewater, soil, sludge, and manure has been developed with difficulty in tetracyclines extraction due to strong adsorption on sludge particles (Pamreddy et al., 2013). But many antibiotics have been extracted out from solid samples by ultrasonic assisted extraction method

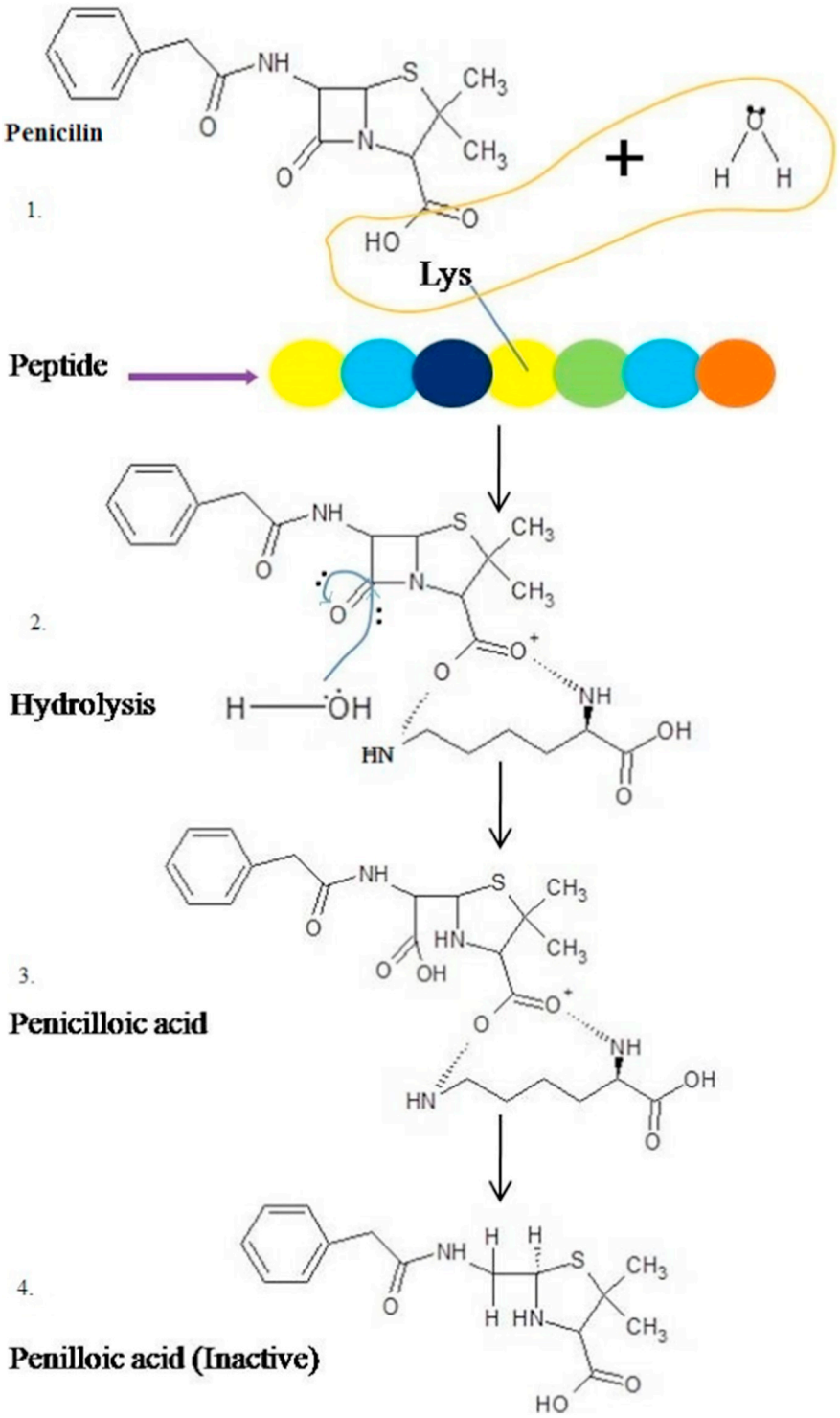

Fig. 4. The proposed degradation pathway of penicillin G in the presence of hypothetical microbial enzyme possessing the active amino acid lysine.

(Neves et al., 2018), microwave assisted extraction method, accelerated solvent extraction method (Abdel-Hameed et al., 2018) and their determination confirmed by liquid chromatography (Lehotay and Lightfield, 2018), MS or tandem MS (Sparbier et al., 2012). From a few hundred to several thousand ng/l antibiotics are detected in municipal wastewater (Li et al., 2018). Structural and chemical properties of antibiotics and their abiotic transformations help in the determination of fate and presence of antibiotics in the environment (Bouki et al., 2013; Yan et al., 2018). Studies showed that sulfamethoxazole, trimethoprim, and ofloxacin were detected in influents as well as effluents of wastewater treatment plants (Barancheshme and Munir, 2018). And this shows that WWTPs are not able to undo the antibiotics inclusion entirely hence there is a necessity to advance the quality and standard of the WWTP. HPLC is the well known and established chromatography technique in the field of liquid sample separation for contaminations, *i.e.*, extraction or detection of virginiamycin in soil samples (Wang et al., 2018b). The common detection methods for antibiotics are listed in Table 2. Tetracyclines produce fluorescence on reaction with magnesium ion and fluorescence is intensified by base addition, *i.e.*, sodium hydroxide and hence is the useful method of antibiotic detection.

Table 2
Detection methods of various antibiotics.

S. no.	Method	Antibiotic	Detection (Upto ng/L)	Country	Reference
1.	SPE-HPLC-MS/MS	Cefalexin	700	China	Gulkowska et al. (2008)
			283 & 994	Taiwan	Lin et al. (2008)
			250		
			1410	Australia	Watkinson et al. (2007)
				China	Minh et al. (2009)
		Roxithromycin	500	Australia	Watkinson et al. (2007)
		Ampicillin	7	Taiwan	Lin et al. (2008)
		Amoxicillin	1670	China	Minh et al. (2009)
			50	Australia	Watkinson et al. (2007)
			50	China	Bengtsson-Palme and Larsson (2016)
		Penicillin G	300	Australia	Watkinson et al. (2007)
		Cloxacillin	700	Australia	Watkinson et al. (2007)
		Cefotaxim	< 12	China	Gulkowska et al. (2008)
			7	Taiwan	Lin et al. (2008)
			34	China	Bengtsson-Palme and Larsson (2016)
		Cefaclor	1800	Australia	Watkinson et al. (2007)
			1800	China	Bengtsson-Palme and Larsson (2016)
		Cephradine	Upto 12	Taiwan	Lin et al. (2008)
		Sulfamethoxazole	200	Australia	Watkinson et al. (2007)
			964	Taiwan	Lin et al. (2008)
			278	China	Minh et al. (2009)
			472	USA	Spongberg and Witter (2008)
			226	Taiwan	Lin et al. (2008)
			400	Germany	Richard et al. (2014)
			3176	Croatia	Senta et al. (2008)
			964	China	Bengtsson-Palme and Larsson (2016)
		Sulfapyridine	124	Croatia	Senta et al. (2008)
			28	Spain	Díaz-Cruz et al. (2008)
		Sulfadiazine	34.3	Spain	Díaz-Cruz et al. (2008)
			6	Taiwan	Lin et al. (2008)
			10	Croatia	Senta et al. (2008)
		Sulfisoxazole	11.9	USA	Spongberg and Witter (2008)
			1.6	Spain	Díaz-Cruz et al. (2008)
		Sulfadimethoxine	1.9	USA	Spongberg and Witter (2008)
			12	Spain	Díaz-Cruz et al. (2008)
			2	Taiwan	Lin et al. (2008)
		Sulfamethizole	48.5	Spain	Díaz-Cruz et al. (2008)
		Sulfanilamide	26	Taiwan	Lin et al. (2008)
			219	Croatia	Senta et al. (2008)
		Norfloxacin	110	China	Gulkowska et al. (2008)
			14	Taiwan	Lin et al. (2008)
			1035	Croatia	Senta et al. (2008)
			54	Croatia	Senta et al. (2008)
			546	Australia	Watkinson et al. (2007)
			320	China	Bengtsson-Palme and Larsson (2016)
		Ciprofloxacin	42	Taiwan	Lin et al. (2008)
			427	Croatia	Senta et al. (2008)
			46	Croatia	Senta et al. (2008)
			31.5	Sweden	Zorita et al. (2009)
			742	China	Bengtsson-Palme and Larsson (2016)
		Enrofloxacin	50	Australia	Watkinson et al. (2007)
			50	China	Bengtsson-Palme and Larsson (2016)
		Tetracycline	210 & 62	China	Minh et al. (2009)
			620	China	Bengtsson-Palme and Larsson (2016)
		Oxytetracycline	100	China	Minh et al. (2009)
		Chlortetracycline	250	Australia	Watkinson et al. (2007)
		Erythromycin	850	China	Gulkowska et al. (2008)
			695	Taiwan	Lin et al. (2008)
			297	Croatia	Senta et al. (2008)
			811	Taiwan	Lin et al. (2009)
			630	China	Minh et al. (2009)
			2841	UK	Kasprzyk-Hordern et al. (2009)
			620	China	

(*continued on next page*)

Table 2 (*continued*)

S. no.	Method	Antibiotic	Detection (Upto ng/L)	Country	Reference
					Bengtsson-Palme and Larsson (2016)
		Tylosin	3400	Australia	Watkinson et al. (2007)
			3400	China	Bengtsson-Palme and Larsson (2016)
		Trimethoprime	1037	Croatia	Senta et al. (2008)
			415	Taiwan	Lin et al. (2009)
		Chloramphenicol	307	China	Minh et al. (2009)
		Clindamycin	51	Taiwan	Lin et al. (2008)
			700	China	Bengtsson-Palme and Larsson (2016)
		Nalidixic acid	178	Taiwan	Lin et al. (2008)
			200	Taiwan	Lin et al. (2009)
		Ofloxacin	137	China	Xu et al. (2007)
			123	Taiwan	Lin et al. (2008)
			10	Sweden	Zorita et al. (2009)
			1220	China	Minh et al. (2009)
			991	Taiwan	Lin et al. (2009)
			4820	China	Bengtsson-Palme and Larsson (2016)
2.	SPE-HPLC/MS	Sulfamethoxazole	2600	China	Chang et al. (2008)
			492	Korea	Choi et al. (2008)
		Sulfadiazine	960	China	Chang et al. (2008)
			98	China	Xiong et al. (2015)
		sulfadimethoxine	70	Korea	Choi et al. (2008)
		Sulfamethizole	10	China	Chang et al. (2008)
		sulfamerazine	42		Chang et al. (2008)
3.	SPE-HPLC-FLD	ciprofloxacin	309	Portugal	Seifrtová et al. (2008)
		Norfloxacin	35	Portugal	Seifrtová et al. (2008)
4.	SPE-HPLC-UV-FLD	Sulfamethoxazole	< 80	China	Peng et al. (2008)
5.	SPE-UPLC-MS/MS	Sulfamethoxazole	12	UK	Kasprzyk-Hordern et al. (2009)
		Sulfacetamide	2	USA	Spongberg and Witter (2008)
			10.7	Spain	Díaz-Cruz et al. (2008)
		Sulfapyridine	161	Japan	Chang et al. (2008)
		Sulfadiazine	3.8	Japan	Chang et al. (2008)
		sulfisoxazole	0.13	Japan	Chang et al. (2008)
		Sulfamethoxazole	28	Japan	Chang et al. (2008)
			2200 & 800	USA	Batt et al. (2008)
		Norfloxacin	85	China	Xiao et al. (2008)
			< 5.5	Sweden	Zorita et al. (2009)
		Ciprofloxacin	27	China	Xiao et al. (2008)
		Erythromycin	830	UK	Kasprzyk-Hordern et al. (2009)
		Trimethoprime	1004	UK	Kasprzyk-Hordern et al. (2009)
		Ofloxacin	503	China	Xiao et al. (2008)
6.	SPE-UPLC-MS	Sulfamethoxazole	23	UK	Kasprzyk-Hordern et al. (2009)
			98	China	Xiong et al. (2015)
		Norfloxacin	98	China	Xiong et al. (2015)
		Ciprofloxacin	98	China	Xiong et al. (2015)
		Enrofloxacin	98	China	Xiong et al. (2015)
		Oxytetracycline	98	China	Xiong et al. (2015)
		Chlortetracycline	98	China	Xiong et al. (2015)
		Trimethoprime	3052	UK	Kasprzyk-Hordern et al. (2009)

During dehydration, tetracycline fluorescence more and it can be used for sensitive detection of tetracycline and its epimers (Barancheshme and Munir, 2018).

7. Biodegradability of antibiotics

Biodegradation of antibiotics occurs by both biotic and abiotic processes. Biotic factor involves the use of microorganisms, and abiotic factor requires sorption, hydrolysis, photolysis, oxidation and reduction reactions (Massé et al., 2014). Microbial population aiding in removal and remediation are explored for treating terrestrial and aquatic contaminants. The bioremediation process can be elucidated as metabolic potential possessed by microorganisms (Dangi et al., 2018). Web of interconnected metabolic pathways utilize various environmental, *i.e.*, petroleum, oil spill, pesticide, plastic, heavy metals (Basu et al., 2018), *etc.* as substrate and release biodegradable byproducts (Noda-Garcia et al., 2018). In the case of antibiotics bioremediation, the microbial population attains ARGs (Zad et al., 2018). Recent studies showed the correlation between generation of resistance genes and antibiotic degradation potential. However, Wen et al. (2018) found no parallelism in degradation of doxycycline and production of ARGs in *Candida* sp. and *Escherichia* sp. Thus, these species would be the best

Table 3
Beta lactamase and producing bacteria with the active amino acids and comparison of their sequence similarity and identity.

S.no.	Beta lactamase	NCBI accession no.	Organism	Active amino acids	Similarity (%)	Identity (%)
1.	SHV	ABM89167.1	*Klebsiella pneumoniae*	101 TYR, 125 MET, 126 SER, 128 ASN, 162 GLU, 163 THR, 166 ASN, 232 GLU, 233 ALA, 234 GLY	Query sequence	Query sequence
2.	TEM-50	KDJ73937.1	*Klebsiella pneumoniae* CHS 50	49 LEU, 192 LEU, 193 THR, 199 LEU, 202 ARG, 203 GLU, 206 ILE, 228 PHE, 246 ALA, 252 LYS, 253 PRO	79.0	64.3
3.	TEM-68	CAB92324.1	*Klebsiella pneumoniae*	68 SER, 71 LYS, 103 TYR, 105 PRO, 125 ILE, 126 THR, 127 MET, 128 SER, 130 ASN, 168 ASN, 213 LYS, 214 VAL, 215 ALA, 216 GLY	78.7	63.2
4.	TEM-80	AAM15527.1	*Enterobacter cloacae*	217 PRO, 218 LEU, 219 LEU, 220 ARG, 231 ASP, 232 LYS, 233 SER, 235 ALA, 236 SER, 241 ARG, 243 ILE, 268 MET	79.0	63.2
5.	OXA-2	AUR45171.1	*Pseudomonas aeruginosa*	49 GLU, 50 ARG, 51 GLN, 52 ALA, 91 GLU, 92 PHE, 94 ILE, 109 GLN, 110 ASP, 111 GLN, 112 ASP, 114 ARG, 115 SER, 118 ARG, 119 ASN, 179 TYR, 180 ARG, 191 ARG, 192 LEU, 194 LYS, 195 ASP, 204 ASN, 208 ARG, 225 GLU, 226 TRP, 227 PRO, 228 THR, 229 GLY, 230 SER	31.7	21.8
6.	OXA-29	CAC35728.1	*Fluoribacter gormanii*	48 GLU, 49 SER, 80 GLU, 81 LEU, 82 TYR, 83 LEU, 855 VAL, 86 TRP, 97 ARG. 98 ASP, 99 SER, 101 VAL, 102 TRP, 105 GLU, 133 ASP, 138 ASN, 142 HIS, 145 LEU, 146 SER, 147 SER, 197 THR, 198 GLU, 199 ASN, 200 GLY, 201 ARG, 202 GLN, 203 LEU, 212 SER, 241 HIS, 243 THR, 246 SER, 247 PHE	26.7	15.8
7.	OXA-45	WP_032490761.1	*Pseudomonas aeruginosa*	53 MET, 54 SER, 87 TYR, 89 PHE, 90 GLU, 102 ASP, 103 SER, 105 VAL, 149 LEU, 200 THR, 201 GLY, 202 THR, 203 GLY, 204 SER, 212 LYS, 213 ALA, 214 PRO, 240 LYS, 241 GLY, 242 GLU, 243 GLN, 244 PRO, 245 ALA, 247 PRO	35.4	23.7
8.	CTX-M	AWH12054.1	*Acinetobacter* sp.	53 MET, 54 SER, 87 TYR, 89 PHE, 90 GLN, 102 ASP, 103 SER, 105 VAL, 149 LEU, 200 THR, 201 GLY, 202 THR, 203 GLY 204, 212 LYS, 213 ALA, 214 PRO, 240 LYS, 241 GLY, 242 GLN, 244 PRO, 245 ALA, 247 PRO	52.9	36.4
9.	PER	ADI16146.1	*Acinetobacter baumannii*	54 GLN, 55 SER, 58 LYS, 88 LEU, 91 THR, 92 TRP, 119 SER, 121 SER, 155 GLU, 158 MET, 159 HIS, 162 ASP, 165 GLN, 166 TYR, 224 THR, 225 GLY, 226 THR, 227 SER, 228 GLY, 230 LYS, 231 ALA, 233 LYS, 235 ALA	52.5	32.4
10.	TLA-3	BAQ22139.1	*Serratia marcescens*	75 GLN, 76 SER, 113 TRP, 140 SER, 142 ASN, 176 GLU, 179 MET, 180 HIS, 182 ALA, 183 TRP, 186 GLN, 247 SER, 248 SER, 249 ASP	40.9	22.6
11.	VEB	ANQ47251.1	*Acinetobacter baumannii*	1 MET, 2 GLN, 112 GLN, 113 TYR, 115, ASN, 116 TRP, 117 ALG, 184 ALG, 184 ALG, 185 ALG, 187 ASN, 205 PHE, 207 ALG	43.3	22.7
12.	VEB-1	AEW28548.1	*Klebsiella pneumoniae*	25 THR, 28 LEU, 47 ILE, 49 ASN, 54 ASP, 55 THR, 56 LEU, 259 LEU, 265 ILE, 292 THR, 295 TYR	29.8	17.8
13.	CME-1	CAL64954.1	*Citrobacter freundii*	70 GLU, 107 THR, 137 ASN, 171 GLU, 174 MET, 175 HIS, 242 THR, 243 SER, 244 GLY	41.2	23.5
14.	SFO-1	AFO69259.1	*Klebsiella pneumoniae*	56 LEU, 58 ASP, 60 ALG, 236 TRP, 258 PRO, 267 HIS, 262 ALG, 264 LEU, 291 VAL, 292 THR, 293 GLU, 294 GLY	43.1	25.2
15.	FEC-1	BAC53608.1	*Escherichia coli*	73 SER, 107 ASN, 108 TYR, 133 SER, 135 ASN, 173 ASN, 238 THR, 239 GLY	54.5	35.9
16.	BES-1	AEZ35972.1	*Serratia marcescens*	42 ARG, 63 ARG, 64 PHE, 65 ALA, 167 LEU, 169 SER, 170 ALA, 171 GLU, 172 PRO, 173 GLN, 174 ASP, 176 ARG, 177 ASP, 178 THR, 238 TYR, 263 GLN	56.2	37.4
17.	PEN A	AAA25927.1	*Burkholderia cepacia*	150 ALA, 151 VAL, 152 ALA, 154 LEU, 166 TYR, 188 LEU, 191 GLY, 194 GLU	54.5	37.2
18.	IBC-1	AAP22974.1	*Escherichia coli*	63 CYS, 64 SER, 67 LYS, 98 LYS, 99 TRP, 125 SER, 127 ASN, 161 GLU, 162 PRO, 165 GLY, 166 ASP, 232 THR, 233 CYS, 234 ALA	24.2	15.0
19.	IBC-2	AAK18183.1	*Pseudomonas aeruginosa*	38 GLN, 58 GLN, 59 ARG, 60 PHE, 61 ALA, 159 ARG, 164 MET, 166 ASP, 167 ASN, 168 THR, 169 PRO, 170 GLY, 171 ASP, 172 LEU, 173 ARG, 174 ASP, 175 THR, 233 CYS, 235 ASN, 237 GLY, 239 ASN, 257 THR, 258 THR, 260 PRO	53.4	33.6
20.	GES	AVK93083.1	*Pseudomonas aeruginosa*	58 CYS, 59 SER, 62 LYS, 93 GLU, 94 TRP, 120 SER, 122 ASN, 156 GLU, 157 PRO, 159 MET, 160 GLY, 161 ASP, 225 THR, 226 GLY, 227 THR, 228 CYS, 229 ALA	53.7	33.2
21.	GES-1	AVK17353.1	*Pseudomonas aeruginosa*	38 GLN, 58 GLN, 59 ARG, 60 PHE, 61 ALA, 159 ARG, 164 MET, 166 MET, 167 ASN, 168 THR, 169 PRO, 170 GLY, 171 ASP, 172 LEU, 173 ARG, 174 ASP, 175 THR, 233 CYS, 235 ASN, 237 GLY, 239 ASN, 257 THR, 258 THR, 260 PRO	53.7	33.6
22.	GES-2	AAM08182.1	*Pseudomonas aeruginosa*	38 GLN, 58 GLN, 59 ARG, 60 PHE, 61 ALA, 159 ARG, 164 MET, 166 ASP, 167 ASN, 168 THR, 169 PRO, 170 GLY, 171 ASP, 172 LEU, 173 ARG, 174 ARG, 175 THR, 233 CYS, 235 ASN, 237 GLY, 239 ASN, 257 THR, 258 THR, 260 PRO	54.0	33.9
23.	ROB-2	WP_015431537.1	*Bibersteinia trehalosi*	86 SER, 89 LYS, 118 SER, 119 TYR, 146 ASN, 180 GLU, 181 PRO, 182 ASP, 184 ASN, 185 GLN, 251 ALA, 252 GLY, 253 LYS	52.4	35.1
24.	OXY-2	WP_049127974.1	*Klebsiella oxytoca*	73 SER, 75 LYS, 107 TRP, 131 TYR, 132 SER, 134 ASN, 172 ASN, 218 THR, 222 SER, 237 THR, 238 GLY, 239 ALA, 240 GLY, 241 ASP, 245 THR, 246 ASN	55.9	36.7

#The common beta lactamases produced by different bacteria were checked for the molecular similarity between them by EMBOSS Needle (an online sequence similarity checking tool). The protein SHV was used here as a query sequence, and rest of all sequences were checked with it. The sequence similarities and their identities showed that all the resistant proteins have an average of > 50% similarities, which suggest some evolutionary relationship among their ARGs. The Serine, Glutamine, Glutamate, Tyrosine, Arginine, Leucine, Valine, Alanine, Methionine, Lysine, Cysteine are the commonly found amino acids in all the bacterial strains, and they may be supposed to play a significant role in the development of bacterial resistance. This may provide the evolutionary traces of pass on routes of ARGs.

eco-friendly option for engineering antibiotics degrading bacteria. Closed bottle test showed that Penicillin G is more degraded than ciprofloxacin, meropenem, sulfamethoxazole and cefotian dihydrochloride (Al-Ahmed et al., 1999; Lin et al., 2018b). In aqueous solution, in presence of the sunlight, fluoroquinolone carboxylic acid is known to be degradable. Elimination of ciprofloxacin occurred by adsorption phenomenon on sediments, and low biodegradation of many antibiotics is seen in soil samples because of the adsorption phenomenon in soil (Zhang et al., 2018). Approximately 50–70% administered antibiotic molecule in excreta, is found in both recalcitrant and degraded form but still shows activity (Ahn et al., 2018). Monensin is resistant to direct photolysis due to its absorbance spectra (Bohn et al., 2013). Tetracyclines, quinolones, sulphonamides, tylosin, nitrofuran antibiotics are light sensitive. Photolysis of tylosin, nitrofuran, and decaying of oxolinic acid is seen under light conditions. Fluoroquinolones are susceptible to degradation by ultraviolet light but insensitive to hydrolysis (Okaikue-Woodi et al., 2018). Efficient degradation of sulfamethoxazole and oxytetracycline by ozonation had been reported (Sirés and Brillas, 2012; Benner et al., 2008). Oxygen is present everywhere in the atmosphere, so oxidation is the most common and vital pathway of antibiotic degradation and on the other hand photolysis (deterioration of the compound by gaining light energy) is also an important mechanism of antibiotic degradation (Ge et al., 2018). Bioelectrochemical system, which includes the knowledge of microbes, ARBs, ARGs and redox reactions, can be used to design such an innovation which can reduce the antibiotic contamination (Yan et al., 2018). UV sunlight can convert antibiotic compound to other different known and unknown forms, so there is a need to study more about the product formed by the photolysis of known antibiotics and their effects on microbial fauna & human biochemical reaction intermediates (Zhang et al., 2016). Tetracycline is a significantly smaller antibiotic than cephalexin, and so tetracycline degradation by sunlight is faster than cephalexin and is proved by their zone of inhibition (Azimi and Nezamzadeh-Ejhieh, 2015). Degradation of antibiotics leads to the release of toxic products in the environment and is proved by studies on ATC and EATC. Methanol is mainly used in tetracycline detection, a universal solvent of tetracyclines and can accelerate the degradation of tetracycline molecules. Enzymatic degradation and bioremediation of antibiotics may be a potential biological technique to minimize the chemical load in the water or soil matrices *i.e.*, Cytochrome P450 enzymes (Bhattacharya and Yadav, 2018). Penicillin degrades in the presence of enzyme beta-lactamase or penicillinase, acidic or alkaline condition and even in the presence of weak nucleophiles, *i.e.*, water and metal ions (Popovich et al., 2018). Fig. 4 showing the proposed degradation pathway for penicillin G degradation till the last biologically inactive metabolite, Penilloic acid, through the hydrolysis reaction. Ampicillin degradation is seen in the presence of alkaline conditions. Cephalosporin and penicillin degradation is seen in the presence of metal ions *i.e.*, mercury, copper (Bischoff et al., 2018), zinc, cadmium, and cobalt (Saitoh and Shibayama, 2016). These metal ions help in opening the β-lactam ring and catalyze the rate of inactivation by forming intermediate complexes with penicillin and cephalosporin. The penicillin degradation by enzymatic strategies can be an excellent eco-friendly technology, which may impart their non-toxic effects on the target and non-target organisms.

8. Global policy execution

Survival of the fittest makes bacteria to become the antibiotic resistant among the same population. Antibiotic resistance cause 25,000 deaths in EU and 23,000 in USA (CDC, 2015). While in developing countries *i.e.*, in India, 58,000 neonatal deaths were reported due to antimicrobial resistance. This may be one of the reasons for increased antibiotic resistance in the developing countries like India (Laxminarayan et al., 2013). The rate of antibiotic resistance in Denmark is very low signifies strict policy and their implementations within the country (Center for Disease Dynamics, Economics & Policy (CDDEP), 2015).

In South Africa, the standard unit *per capita* is very high while the GDP *per capita* is very low clearly indicating the situation of antibiotic resistance consequences, its management, government policies, and their implementation (Gelband et al., 2015). South Africa initiated to come with the government and private sector professionals for the prevention of resistance problem through national policies and their strict implementation. In present, the highest consumption of antibiotics in livestock has been reported in China ($>$ 15,000 tons) while France and Canada (approximately 2 tons) shown the least consumption (Center for Disease Dynamics, Economics & Policy (CDDEP), 2015).

The Center for Disease Dynamics, Economics & Policy report, 2015 suggested minimization of antibiotic use and overuse by reducing the incentives on antibiotics and related items by education based awareness among public, professionals and policy makers along with a strong political commitment for international antibiotic policies. US made a national action plan to prevent the antibiotic resistance bacteria through stewardship (House, 2015) while EU already started work in the same direction (European Commission, 2011). In Jaipur declaration, Southeast Asian countries under WHO, also showed commitment towards antibiotic resistance stewardship (WHO, 2015).

9. Conclusion and future perspectives

Antibiotic contamination is a major global threat and has increased the risk of antibiotic resistance in the microorganisms. Although the European Union has banned many antibiotics, they are still in use and creating a future global challenge for health issues. WWTP are not able to completely eliminate the antibiotic residues from the water matrices; hence, more investigations on WWTP's capacities and capabilities are the calls of present conditions worldwide. Microorganism mainly bacteria and fungi which are most affected as ARB, MDRS, and ARGs, is a matter of concern in the health sector. Antibiotics have a short life span, but still, their hydrophobicity and lipophilic nature lead to their persistence in the environment. Measures should be adopted for the controlled use of antibiotics, and no antibiotic should be sold without being prescribed along with the safe removal of the discarded antibiotics along with the excreta. It is obvious that the complete removal of residual antibiotics is impractical but though, the observations lie at the core of mechanisms associated with their uptake and abolition. This may explore the antibiotic bioremediation strategies in the current scenario. Bioremediation technology is the best suitable and non-replaceable technique for cleaning of our water ecosystem. Finally, more in-depth studies are needed for better technology development for the clean environment and safer future for our next generations.

Conflict of interest statement

None of the authors have any conflict of interest.

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References

Abdel-Hameed, E.S.S., Salman, M.S., Fadl, M.A., Elkhateeb, A., El-Awady, M.A., 2018. Chemical composition of hydrodistillation and solvent free microwave extraction of essential oils from *Mentha piperita* L. growing in Taif, Kingdom of Saudi Arabia, and their anticancer and antimicrobial activity. Orient. J. Chem. 34 (1), 222–233.

Ahmed, M.N., Porse, A., Sommer, M.O.A., Hoiby, N., Ciofu, O., 2018. Evolution of antibiotic resistance in biofilm and planktonic P. aeruginosa populations exposed to sub-inhibitory levels of ciprofloxacin. Antimicrob. Agents Chemother. 62 (8), e00320–18. https://doi.org/10.1128/AAC.00320-18.

Ahn, Y., Jung, J.Y., Veach, B.T., Khare, S., Gokulan, K., Piñeiro, S.A., Cerniglia, C.E., 2018. In vitro test systems to determine tetracycline residue binding to human feces. Regul. Toxicol. Pharmacol. 99, 105–115.

Al-Ahmad, A., Daschner, F.D., Kümmerer, K., 1999. Biodegradability of cefotiam, ciprofloxacin, meropenem, penicillin G, and sulfamethoxazole and inhibition of waste water bacteria. Arch. Environ. Con. Tox. 37, 158–163.

Akici, A., Aydin, V., Kiroglu, A., 2018. Assessment of the association between drug disposal practices and drug use and storage behaviors. Saudi Pharm. J. 26 (1), 7–13.

Ao, X., Liu, W., Sun, W., Cai, M., Ye, Z., Yang, C., ... Li, C., 2018. Medium pressure UV-activated peroxymonosulfate for ciprofloxacin degradation: kinetics, mechanism, and genotoxicity. Chem. Eng. J. 345, 87–97.

Ayrapetyan, M., Williams, T., Oliver, J.D., 2018. Relationship between the viable but nonculturable state and antibiotic persister cells. J. Bacteriol. 200 (20), e00249-18.

Azimi, S., Nezamzadeh-Ejhieh, A., 2015. Enhanced activity of clinoptilolite-supported hybridized PbS–CdS semiconductors for the photocatalytic degradation of a mixture of tetracycline and cephalexin aqueous solution. J. Mol. Catal. A Chem. 408, 152–160.

Barancheshme, F., Munir, M., 2018. Strategies to combat antibiotic resistance in the wastewater treatment plants. Front. Microbiol. 8, 2603.

Bassil, R.J., Bashour, I.I., Sleiman, F.T., Abou-Jawdeh, Y.A., 2013. Antibiotic uptake by plants from manure-amended soils. J. Environ. Sci. Health B 48 (7), 570–574.

Basu, S., Rabara, R.C., Negi, S., Shukla, P., 2018. Engineering PGPMOs through gene editing and systems biology: a solution for phytoremediation? Trends Biotechnol. 36 (5), 499–510.

Batt, A.L., Kostich, M.S., Lazorchak, J.M., 2008. Analysis of ecologically relevant pharmaceuticals in wastewater and surface water using selective solid-phase extraction and UPLC–MS/MS. Anal. Chem. 80 (13), 5021–5030.

Bengtsson-Palme, J., Larsson, D.J., 2016. Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation. Environ. Int. 86, 140–149.

Benner, J., Salhi, E., Ternes, T., von Gunten, U., 2008. Ozonation of reverse osmosis concentrate: kinetics and efficiency of beta blocker oxidation. Water Res. 42 (12), 3003–3012.

Berger, F.K., Mellmann, A., Färber, J., von Müller, L., Gärtner, B., 2018. Advantages and disadvantages of rifampicin use in orthopedic patients to avoid Clostridium difficile infections. J. Orthop. Ther. 10, 2575–8241 JORT-170. DOI.

Bhattacharya, S., Yadav, J., 2018. Microbial P450 enzymes in bioremediation and drug discovery: emerging potentials and challenges. Curr. Protein Pept. Sci. 19 (1), 75–86.

Bischoff, S., Walter, T., Gerigk, M., Ebert, M., Vogelmann, R., 2018. Empiric antibiotic therapy in urinary tract infection in patients with risk factors for antibiotic resistance in a German emergency department. BMC Infect. Dis. 18 (1), 56.

Blair, J.M., 2018. A climate for antibiotic resistance. Nat. Clim. Chang. 1.

Bohn, P., Bak, S.A., Björklund, E., Krogh, K.A., Hansen, M., 2013. Abiotic degradation of antibiotic ionophores. Environ. Pollut. 182, 177–183.

Bouki, C., Venieri, D., Diamadopoulos, E., 2013. Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review. Ecotoxicol. Environ. Saf. 91, 1–9.

Brown, K.D., Kulis, J., Thomson, B., Chapman, T.H., Mawhinney, D.B., 2006. Occurrence of antibiotics in hospital, residential, and dairy effluent, municipal wastewater, and the Rio Grande in New Mexico. Sci. Total Environ. 366 (2-3), 772–783.

Camotti Bastos, M., Rheinheimer dos Santos, D., Aubertheau, É., de Castro Lima, J.A.M., Le Guet, T., Caner, L., ... Labanowski, J., 2018. Antibiotics and microbial resistance in Brazilian soils under manure application. Land Degrad. Dev. 29 (8), 2472–2484.

Catteau, L., Zhu, L., Van Bambeke, F., Quetin-Leclercq, J., 2018. Natural and hemi-synthetic pentacyclic triterpenes as antimicrobials and resistance modifying agents against *Staphylococcus aureus*: a review. Phytochem. Rev. 1–35.

Center for Disease Dynamics, Economics & Policy (CDDEP), 2015. State of the World's Antibiotics, 2015. CDDEP, Washington, DC.

Chang, H., Hu, J., Asami, M., Kunikane, S., 2008. Simultaneous analysis of 16 sulfonamide and trimethoprim antibiotics in environmental waters by liquid chromatography–electrospray tandem mass spectrometry. J. Chromatogr. A 1190 (1–2), 390–393.

Choi, K., Kim, Y., Park, J., Park, C.K., Kim, M., Kim, H.S., Kim, P., 2008. Seasonal variations of several pharmaceutical residues in surface water and sewage treatment plants of Han River, Korea. Sci. Total Environ. 405 (1–3), 120–128.

Chowdhury, F., Langenkämper, G., Grote, M., 2016. Studies on uptake and distribution of antibiotics in red cabbage. J. Verbr. Lebensm. 11 (1), 61–69.

Chu, H.Y., Sprouffske, K., Wagner, A., 2018. Assessing the benefits of horizontal gene transfer by laboratory evolution and genome sequencing. BMC Evol. Biol. 18 (1), 54.

Cowieson, A.J., Kluenter, A.M., 2018. Contribution of exogenous enzymes to potentiate the removal of antibiotic growth promoters in poultry production. Anim. Feed Sci. Technol. https://doi.org/10.1016/j.anifeedsci.2018.04.026. In press.

Cruz-Loya, M., Kang, T.M., Lozano, N.A., Watanabe, R., Tekin, E., Damoiseaux, R., ... Yeh, P.J., 2018. Stressor interaction networks suggest antibiotic resistance co-opted from stress responses to temperature. ISME J. 1.

Dangi, A.K., Sharma, B., Hill, R.T., Shukla, P., 2018. Bioremediation through microbes: systems biology and metabolic engineering approach. Crit. Rev. Biotechnol. 1–20.

Díaz-Cruz, M.S., García-Galán, M.J., Barceló, D., 2008. Highly sensitive simultaneous determination of sulfonamide antibiotics and one metabolite in environmental waters by liquid chromatography–quadrupole linear ion trap–mass spectrometry. J. Chromatogr. A 1193 (1–2), 50–59.

Esiobu, N., Armenta, L., Ike, J., 2002. Antibiotic resistance in soil and water environments. Int. J. Environ. Health Res. 12 (2), 133–144.

European Commission, 2011. Action Plan against Antimicrobial Resistance. (Brussels).

Fan, Y., Xiao, Y., Momeni, B., Liu, Y.Y., 2018. Horizontal gene transfer can help maintain the equilibrium of microbial communities. J. Theor. Biol. 454 (7), 53–59.

Gao, P., Munir, M., Xagoraraki, I., 2012. Correlation of tetracycline and sulfonamide antibiotics with corresponding resistance genes and resistant bacteria in a conventional municipal wastewater treatment plant. Sci. Total Environ. 421, 173–183.

García-Fernández, A., Dionisi, A.M., Arena, S., Iglesias-Torrens, Y., Carattoli, A., Luzzi, I., 2018. Human Campylobacteriosis in Italy: emergence of multi-drug resistance to ciprofloxacin, tetracycline, and erythromycin. Front. Microbiol. 9.

Ge, L., Halsall, C., Chen, C.E., Zhang, P., Dong, Q., Yao, Z., 2018. Exploring the aquatic photodegradation of two ionisable fluoroquinolone antibiotics-gatifloxacin and balofloxacin: degradation kinetics, photobyproducts and risk to the aquatic environment. Sci. Total Environ. 633, 1192–1197.

Gelband, H., Molly Miller, P., Pant, S., Gandra, S., Levinson, J., Barter, D., ... Laxminarayan, R., 2015. The state of the world's antibiotics 2015. In: Wound Healing Southern Africa. 8(2). pp. 30–34.

Grenni, P., Ancona, V., Caracciolo, A.B., 2018. Ecological effects of antibiotics on natural ecosystems: a review. Microchem. J. 136, 25–39.

Gulkowska, A., Leung, H.W., So, M.K., Taniyasu, S., Yamashita, N., Yeung, L.W., ... Lam, P.K., 2008. Removal of antibiotics from wastewater by sewage treatment facilities in Hong Kong and Shenzhen, China. Water Res. 42 (1–2), 395–403.

Guo, Y., Tomich, A.D., McElheny, C.L., Cooper, V.S., Tait-Kamradt, A., Wang, M., ... Doi, Y., 2017. High-level fosfomycin resistance in vancomycin-resistant enterococcus faecium. Emerg. Infect. Dis. 23 (11), 1902.

Haller, M.Y., Müller, S.R., McArdell, C.S., Alder, A.C., Suter, M.J.F., 2002. Quantification of veterinary antibiotics (sulfonamides and trimethoprim) in animal manure by liquid chromatography–mass spectrometry. J. Chromatogr. A 952 (1-2), 111–120.

Harrabi, M., Della Giustina, S.V., Aloulou, F., Rodriguez-Mozaz, S., Barceló, D., Elleuch, B., 2018. Analysis of multiclass antibiotic residues in urban wastewater in Tunisia. Environ. Nanotechnol. Monit. Manag. 10, 163–170.

Hathroubi, S., Mekni, M.A., Domenico, P., Nguyen, D., Jacques, M., 2017. Biofilms: microbial shelters against antibiotics. Microb. Drug Resist. 23 (2), 147–156.

Havelkova, B., Beklova, M., Kovacova, V., Hlavkova, D., Pikula, J., 2016. Ecotoxicity of selected antibiotics for organisms of aquatic and terrestrial ecosystems. Neuroendocrinol. Lett. 37, 38–44.

He, X., Wang, Z., Nie, X., Yang, Y., Pan, D., Leung, A.O., ... Chen, K., 2012. Residues of fluoroquinolones in marine aquaculture environment of the Pearl River Delta, South China. Environ. Geochem. Health 34 (3), 323–335.

He, Y., Nurul, S., Schmitt, H., Sutton, N.B., Murk, T.A., Blokland, M.H., ... Langenhoff, A.A., 2018. Evaluation of attenuation of pharmaceuticals, toxic potency, and antibiotic resistance genes in constructed wetlands treating wastewater effluents. Sci. Total Environ. 631, 1572–1581.

Hillis, D.G., Lissemore, L., Sibley, P.K., Solomon, K.R., 2007. Effects of monensin on zooplankton communities in aquatic microcosms. Environ. Sci. Technol. 41 (18), 6620–6626.

Hong, B., Lin, Q., Yu, S., Chen, Y., Chen, Y., Chiang, P., 2018. Urbanization gradient of selected pharmaceuticals in surface water at a watershed scale. Sci. Total Environ. 634, 448–458.

House, W., 2015. National action plan for combating antibiotic-resistant bacteria. Washington, DC, 62.

Hu, J., Zhang, N., Li, L., Ma, Y., Zhao, C., Wu, Q., ... Wang, X., 2018. The synergistic bactericidal effect of vancomycin on UTMD treated biofilm involves damage to bacterial cells and enhancement of metabolic activities. Sci. Rep. 8 (1), 192.

Ishikawa, N.K., Touno, E., Higashiyama, Y., Sasamoto, M., Soma, M., Yoshida, N., ... Umita, T., 2018. Determination of tylosin excretion from sheep to assess tylosin spread to agricultural fields by manure application. Sci. Total Environ. 633, 399–404.

Kang, D.H., Gupta, S., Rosen, C., Fritz, V., Singh, A., Chander, Y., ... Rohwer, C., 2013. Antibiotic uptake by vegetable crops from manure-applied soils. J. Agric. Food Chem. 61 (42), 9992–10001.

Kasprzyk-Hordern, B., Dinsdale, R.M., Guwy, A.J., 2009. The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. Water Res. 43 (2), 363–380.

Kim, S.C., Carlson, K., 2006. Occurrence of ionophore antibiotics in water and sediments of a mixed-landscape watershed. Water Res. 40 (13), 2549–2560.

Kim, B., Pang, H.B., Kang, J., Park, J.H., Ruoslahti, E., Sailor, M.J., 2018. Immunogene therapy with fusogenic nanoparticles modulates macrophage response to *Staphylococcus aureus*. Nat. Commun. 9 (1), 1969.

Kivits, T., Broers, H.P., Beeltje, H., van Vliet, M., Griffioen, J., 2018. Presence and fate of veterinary antibiotics in age-dated groundwater in areas with intensive livestock farming. Environ. Pollut. 241, 988–998.

Korada, S.K., Yarla, N.S., Putta, S., Hanumakonda, A.S., Lakkappa, D.B., Bishayee, A., ... Lu, D.Y., 2018. A critical appraisal of different food safety and quality management tools to accomplish food safety. In: Food Safety and Preservation, pp. 1–12.

Krzeminski, P., Tomei, M.C., Karaolia, P., Langenhoff, A., Almeida, C.M.R., Felis, E., ... Rizzo, L., 2018. Performance of secondary wastewater treatment methods for the removal of contaminants of emerging concern implicated in crop uptake and antibiotic resistance spread: a review. Sci. Total Environ. 648, 1052–1081.

Kumar, V., Baweja, M., Liu, H., Shukla, P., 2017. Microbial enzyme engineering:

applications and perspectives. In: Recent Advances in Applied Microbiology. Springer, Singapore, pp. 259–273.
Kumbhakar, S.K., Chauhan, S.S., Chandraker, S.K., 2018. A study on mutagen induced development of antibiotic resistance in some pathogenic bacteria. Int. J. Life Sci. 6 (1), 248–252.
Kümmerer, K., 2009. Antibiotics in the aquatic environment–a review–part I. Chemosphere 75 (4), 417–434.
Larsson, D.J., 2014. Antibiotics in the environment. Ups. J. Med. Sci. 119 (2), 108–112.
Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A.K., Wertheim, H.F., Sumpradit, N., ... Greko, C., 2013. Antibiotic resistance—the need for global solutions. Lancet Infect. Dis. 13 (12), 1057–1098.
Lehotay, S.J., Lightfield, A.R., 2018. Simultaneous analysis of aminoglycosides with many other classes of drug residues in bovine tissues by ultrahigh-performance liquid chromatography–tandem mass spectrometry using an ion-pairing reagent added to final extracts. Anal. Bioanal. Chem. 410 (3), 1095–1109.
Leung, H.W., Minh, T.B., Murphy, M.B., Lam, J.C., So, M.K., Martin, M., ... Richardson, B.J., 2012. Distribution, fate and risk assessment of antibiotics in sewage treatment plants in Hong Kong, South China. Environ. Int. 42, 1–9.
Li, L., Guo, C., Fan, S., Lv, J., Zhang, Y., Xu, Y., Xu, J., 2018. Dynamic transport of antibiotics and antibiotic resistance genes under different treatment processes in a typical pharmaceutical wastewater treatment plant. Environ. Sci. Pollut. Res. 1–8.
Lin, A.Y.C., Yu, T.H., Lin, C.F., 2008. Pharmaceutical contamination in residential, industrial, and agricultural waste streams: risk to aqueous environments in Taiwan. Chemosphere 74 (1), 131–141.
Lin, A.Y.C., Yu, T.H., Lateef, S.K., 2009. Removal of pharmaceuticals in secondary wastewater treatment processes in Taiwan. J. Hazard. Mater. 167 (1-3), 1163–1169.
Lin, J., Zhou, D., Steitz, T.A., Polikanov, Y.S., Gagnon, M.G., 2018a. Ribosome-targeting antibiotics: modes of action, mechanisms of resistance, and implications for drug design. Annu. Rev. Biochem. 0.
Lin, Y.C., Hsiao, K.W., Lin, A.Y.C., 2018b. Photolytic degradation of ciprofloxacin in solid and aqueous environments: kinetics, phototransformation pathways, and byproducts. Environ. Sci. Pollut. Res. 25 (3), 2303–2312.
Lucas, A.E., Ito, R., Mustapha, M.M., McElheny, C.L., Mettus, R.T., Bowler, S.L., ... Doi, Y., 2018. Frequency and mechanisms of spontaneous fosfomycin nonsusceptibility observed upon disk diffusion testing of *Escherichia coli*. J. Clin. Microbiol. 56 (1) (e01368-17).
Lysnyansky, I., Gerchman, I., Mikula, I., Gobbo, F., Catania, S., Levisohn, S., 2013. Molecular characterization of Enrofloxacin-acquired-resistance in mycoplasma synoviae field isolates. Antimicrob. Agents Chemother 57 (7), 3072–3077.
MacFadden, D., McGough, S., Fisman, D., Santillana, M., Brownstein, J., 2017. Antibiotic Resistance Increases with Local Temperature.
Mack, S.G., Turner, R.L., Dwyer, D.J., 2018. Achieving a predictive understanding of antimicrobial stress physiology through systems biology. Trends Microbiol. 26 (4), 296–312.
Massé, D.I., Saady, N.M.C., Gilbert, Y., 2014. Potential of biological processes to eliminate antibiotics in livestock manure: an overview. Animals 4 (2), 146–163.
Maurice, N.M., Bedi, B., Sadikot, R.T., 2018. *Pseudomonas aeruginosa* biofilms: host response and clinical implications in lung infections. Am. J. Respir. Cell Mol. Biol. 58 (4), 428–439.
McKenney, P.T., Yan, J., Vaubourgeix, J., Becattini, S., Lampen, N., Motzer, A., ... Pamer, E.G., 2018. Bile Acid Induced Morphotype Switch Mediates Intestinal Colonization in Vancomycin Resistant *Enterococcus*.
McKinney, C.W., Dungan, R.S., Moore, A., Leytem, A.B., 2018. Occurrence and abundance of antibiotic resistance genes in agricultural soil receiving dairy manure. FEMS Microb. Ecol. 94 (3), fiy010.
Meena, V.D., Dotaniya, M.L., Saha, J.K., Patra, A.K., 2015. Antibiotics and antibiotic resistant bacteria in wastewater: impact on environment, soil microbial activity and human health. Afr. J. Microbiol. Res. 9 (14), 965–978.
Minh, T.B., Leung, H.W., Loi, I.H., Chan, W.H., So, M.K., Mao, J.Q., ... Lee, J.H., 2009. Antibiotics in the Hong Kong metropolitan area: ubiquitous distribution and fate in Victoria Harbour. Mar. Pollut. Bull. 58 (7), 1052–1062.
Mutiyar, P.K., Mittal, A.K., 2014. Risk assessment of antibiotic residues in different water matrices in India: key issues and challenges. Environ. Sci. Pollut. Res. 21 (12), 7723–7736.
Neves, M.A., Silva, G.S., Brito, N.M., Araújo, K., Marques, E.P., Silva, L.K., 2018. Aqueous ultrasound-assisted extraction for the determination of fluoroquinolones in mangrove sediment by high-performance liquid chromatography and fluorescence detector. J. Braz. Chem. Soc. 29 (1), 24–32.
Newton, D.F., Macfarlane, S., Macfarlane, G.T., 2013. Effects of antibiotics on bacterial species composition and metabolic activities in chemostats containing defined populations of human gut microorganisms. Antimicrob. Agents Chemother. 57 (5), 2016–2025.
Nielsen, K.M., Gjøen, T., Asare, N.Y.O., Lunestad, B.T., Ytrehus, B., Yazdankhah, S.P., ... Tronsmo, A., 2018. Antimicrobial resistance in wildlife potential for dissemination. In: Opinion of the Panel on Microbial Ecology of the Norwegian Scientific Committee for Food and Environment. VKM Report.
Noda-Garcia, L., Liebermeister, W., Tawfik, D.S., 2018. Metabolite–enzyme coevolution: from single enzymes to metabolic pathways and networks. Annu. Rev. Biochem. 87, 187–216.
Nödler, K., Voutsa, D., Licha, T., 2014. Polar organic micropollutants in the coastal environment of different marine systems. Mar. Pollut. Bull. 85 (1), 50–59.
Obayiuwana, A., Ogunjobi, A., Yang, M., Ibekwe, M., 2018. Characterization of bacterial communities and their antibiotic resistance profiles in wastewaters obtained from pharmaceutical facilities in Lagos and Ogun states, Nigeria. Int. J. Environ. Res. Public Health 15 (7), 1365.
Okaikue-Woodi, F.E., Kelch, S.E., Schmidt, M.P., Martinez, C.E., Youngman, R.E., Aristilde, L., 2018. Structures and mechanisms in clay nanopore trapping of structurally-different fluoroquinolone antimicrobials. J. Colloid Interface Sci. 513, 367–378.
Olaimat, A.N., Al-Holy, M.A., Shahbaz, H.M., Al-Nabulsi, A.A., Abu Ghoush, M.H., Osaili, T.M., ... Holley, R.A., 2018. Emergence of antibiotic resistance in listeria monocytogenes isolated from food products: a comprehensive review. Compr. Rev. Food Sci. Food Saf. 17 (5), 1277–1292.
Oliveira, T.S., Al Aukidy, M., Verlicchi, P., 2017. Occurrence of common pollutants and pharmaceuticals in hospital effluents. In: Hospital Wastewaters. Springer, Cham, pp. 17–32.
Pamreddy, A., Hidalgo, M., Havel, J., Salvadó, V., 2013. Determination of antibiotics (tetracyclines and sulfonamides) in biosolids by pressurized liquid extraction and liquid chromatography–tandem mass spectrometry. J. Chromatogr. A 1298, 68–75.
Peng, X., Tan, J., Tang, C., Yu, Y., Wang, Z., 2008. Multiresidue determination of fluoroquinolone, sulfonamide, trimethoprim, and chloramphenicol antibiotics in urban waters in China. Environ. Toxicol. Chem. 27 (1), 73–79.
Piña, B., Bayona, J.M., Christou, A., Fatta-Kassinos, D., Guillon, E., Lambropoulou, D., ... Sayen, S., 2018. On the contribution of reclaimed wastewater irrigation to the potential exposure of humans to antibiotics, antibiotic resistant bacteria and antibiotic resistance genes–NEREUS COST Action ES1403 position paper. J. Environ. Chem. Eng. https://doi.org/10.1016/j.jece.2018.01.011.
Popovich, J., Stephens, M., Celaya, H., Suwarno, S., Barclay, S., Yee, E., ... Haydel, S.E., 2018. Building and breaking the cell wall in four acts: a kinesthetic and tactile role-playing exercise for teaching Beta-lactam antibiotic mechanism of action and resistance. J. Microbiol. Biol. Educ. 19 (1).
Pruden, A., Larsson, D.J., Amézquita, A., Collignon, P., Brandt, K.K., Graham, D.W., ... Topp, E., 2013. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Environ. Health Perspect. 121 (8), 878.
Radlinski, L., Conlon, B.P., 2018. Antibiotic efficacy in the complex infection environment. Curr. Opin. Microbiol. 42, 19–24.
Radu, E., Woegerbauer, M., Oismüller, M., Kreuzinger, N., 2017. Impact of Antibiotics of Anthropogenic Origin on Bacterial Soil Communities in Agricultural Ecosystems. (Review).
Rajivgandhi, G., Vijayan, R., Maruthupandy, M., Vaseeharan, B., Manoharan, N., 2018. Antibiofilm effect of Nocardiopsis sp. GRG 1 (KT235640) compound against biofilm forming Gram negative bacteria on UTIs. Microb. Pathog. 118, 190–198.
Rasmussen, C., Allender, M.C., Phillips, C.A., Byrd, J., Lloyd, T., Maddox, C., 2017. Multidrug resistance patterns of enteric bacteria in two populations of free-ranging eastern box turtles (terrapene carolina carolina). J. Zoo Wildl. Med. 48 (3), 708–715.
Ribeiro, A.R., Sures, B., Schmidt, T.C., 2018. Cephalosporin antibiotics in the aquatic environment: a critical review of occurrence, fate, ecotoxicity and removal technologies. Environ. Pollut. 241, 1153–1166.
Richard, J., Boergers, A., vom Eyser, C., Bester, K., Tuerk, J., 2014. Toxicity of the micropollutants bisphenol A, ciprofloxacin, metoprolol and sulfamethoxazole in water samples before and after the oxidative treatment. Int. J. Hyg. Environ. Health 217 (4–5), 506–514.
Ronquillo, M.G., Hernandez, J.C.A., 2017. Antibiotic and synthetic growth promoters in animal diets: review of impact and analytical methods. Food Control 72, 255–267.
Saitoh, T., Shibayama, T., 2016. Removal and degradation of β-lactam antibiotics in water using didodecyldimethylammonium bromide-modified montmorillonite organoclay. J. Hazard. Mater. 317, 677–685.
Sarpong, E.M., Miller, G.E., 2015. Narrow-and broad-spectrum antibiotic use among US children. Health Serv. Res. 50 (3), 830–846.
Scortti, M., Han, L., Alvarez, S., Leclercq, A., Moura, A., Lecuit, M., Vazquez-Boland, J., 2018. Epistatic control of intrinsic resistance by virulence genes in *Listeria*. PLoS Genet. 14 (9), e1007525.
Seifrtová, M., Pena, A., Lino, C.M., Solich, P., 2008. Determination of fluoroquinolone antibiotics in hospital and municipal wastewaters in Coimbra by liquid chromatography with a monolithic column and fluorescence detection. Anal. Bioanal. Chem. 391 (3), 799–805.
Senta, I., Terzić, S., Ahel, M., 2008. Simultaneous determination of sulfonamides, fluoroquinolones, macrolides and trimethoprim in wastewater and river water by LC-tandem-MS. Chromatographia 68 (9–10), 747.
Shan, J., Yang, P., Rahman, M.M., Shang, X., Yan, X., 2018. Tetracycline and sulfamethazine alter dissimilatory nitrate reduction processes and increase N_2O release in rice fields. Environ. Pollut. 242, 788–796.
Sharma, B., Dangi, A.K., Shukla, P., 2018. Contemporary enzyme based technologies for bioremediation: a review. J. Environ. Manag. 210, 10–22.
Sirés, I., Brillas, E., 2012. Remediation of water pollution caused by pharmaceutical residues based on electrochemical separation and degradation technologies: a review. Environ. Int. 40, 212–229.
Sparbier, K., Schubert, S., Weller, U., Boogen, C., Kostrzewa, M., 2012. Matrix-assisted laser desorption ionization–time of flight mass spectrometry-based functional assay for rapid detection of resistance against β-lactam antibiotics. J. Clin. Microbiol. 50 (3), 927–937.
Spongberg, A.L., Witter, J.D., 2008. Pharmaceutical compounds in the wastewater process stream in Northwest Ohio. Sci. Total Environ. 397 (1–3), 148–157.
Szekeres, E., Chiriac, C.M., Baricz, A., Szőke-Nagy, T., Lung, I., Soran, M.L., ... Coman, C., 2018. Investigating antibiotics, antibiotic resistance genes, and microbial contaminants in groundwater in relation to the proximity of urban areas. Environ. Pollut. 236, 734–744.
Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D.L., ... Ouellette, M., 2018. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect. Dis. 18 (3), 318–327.
Tasho, R.P., Cho, J.Y., 2016. Veterinary antibiotics in animal waste, its distribution in soil

and uptake by plants: a review. Sci. Total Environ. 563, 366–376.
Trinh, T.D., Zasowski, E.J., Claeys, K.C., Casapao, A.M., Compton, M., Lagnf, A., ... Rybak, M.J., 2018. Role of vancomycin minimum inhibitory concentrations by modified population analysis profile method and clinical outcomes in high inoculum methicillin-resistant *Staphylococcus aureus* infections. Infect. Dis. Ther. 7 (1), 161–169.
Vasiliadou, I.A., Molina, R., Martinez, F., Melero, J.A., Stathopoulou, P.M., Tsiamis, G., 2018. Toxicity assessment of pharmaceutical compounds on mixed culture from activated sludge using respirometric technique: the role of microbial community structure. Sci. Total Environ. 630, 809–819.
Wagenlehner, F.M., Hoyme, U., Kaase, M., Fünfstück, R., Naber, K.G., Schmiemann, G., 2011. Uncomplicated urinary tract infections. Dtsch. Arztebl. Int. 108 (24), 415.
Wang, L., Li, Y., Wang, L., Zhu, M., Zhu, X., Qian, C., Li, W., 2018a. Responses of biofilm microorganisms from moving bed biofilm reactor to antibiotics exposure: protective role of extracellular polymeric substances. Bioresour. Technol. 254, 268–277.
Wang, X., Wang, M., Zhang, K., Hou, T., Zhang, L., Fei, C., ... Hang, T., 2018b. Determination of virginiamycin M1 residue in tissues of swine and chicken by ultra-performance liquid chromatography tandem mass spectrometry. Food Chem. 250, 127–133.
Watkinson, A.J., Murby, E.J., Costanzo, S.D., 2007. Removal of antibiotics in conventional and advanced wastewater treatment: implications for environmental discharge and wastewater recycling. Water Res. 41 (18), 4164–4176.
Wen, X., Wang, Y., Zou, Y., Ma, B., Wu, Y., 2018. No evidential correlation between veterinary antibiotic degradation ability and resistance genes in microorganisms during the biodegradation of doxycycline. Ecotoxicol. Environ. Saf. 147, 759–766.
Williams, M., Kookana, R.S., 2018. Fate and behavior of environmental contaminants arising from health-care provision. Health Care Environ. Contam. 11, 21.
Wistrand-Yuen, E., Knopp, M., Hjort, K., Koskiniemi, S., Berg, O.G., Andersson, D.I., 2018. Evolution of high-level resistance during low-level antibiotic exposure. Nat. Commun. 9 (1), 1599.
World Health Organization (WHO), 2015. Antimicrobial Resistance: Draft Global Action Plan on Antimicrobial Resistance. (Geneva).
Wu, D., Ma, R., Wei, H., Yang, K., Xie, B., 2018. Simulated discharge of treated landfill leachates reveals a fueled development of antibiotic resistance in receiving tidal river. Environ. Int. 114, 143–151.
Xiao, Y., Chang, H., Jia, A., Hu, J., 2008. Trace analysis of quinolone and fluoroquinolone antibiotics from wastewaters by liquid chromatography–electrospray tandem mass spectrometry. J. Chromatogr. A 1214 (1–2), 100–108.
Xiong, W., Sun, Y., Zhang, T., Ding, X., Li, Y., Wang, M., Zeng, Z., 2015. Antibiotics, antibiotic resistance genes, and bacterial community composition in fresh water aquaculture environment in China. Microb. Ecol. 70 (2), 425–432.
Xu, W.H., Zhang, G., Zou, S.C., Li, X.D., Liu, Y.C., 2007. Determination of selected antibiotics in the Victoria Harbour and the Pearl River, South China using high-performance liquid chromatography-electrospray ionization tandem mass spectrometry. Environ. Pollut. 145 (3), 672–679.
Yan, W., Xiao, Y., Yan, W., Ding, R., Wang, S., Zhao, F., 2018. The effect of bioelectrochemical systems on antibiotics removal and antibiotic resistance genes: a review. Chem. Eng. J 358, 1421–1437.
Yasser, E.N., Adli, A., 2015. Toxicity of single and mixtures of antibiotics to cyanobacteria. J. Environ. Anal. Toxicol. 5 (3), 1.
Yelin, I., Kishony, R., 2018. Antibiotic Resistance. Cell 172 (5), 1136.
Zad, T.J., Astuti, M.P., Padhye, L.P., 2018. Fate of environmental pollutants. Water Environ. Res. 90 (10), 1104–1170.
Zhanel, G.G., Zhanel, M.A., Karlowsky, J.A., 2018. Intravenous fosfomycin: An assessment of its potential for use in the treatment of systemic infections in canada. Can. J. Infect. Dis. Med. Microbiol. 2018, 8912039.
Zhang, R., Zhang, G., Zheng, Q., Tang, J., Chen, Y., Xu, W., ... Chen, X., 2012. Occurrence and risks of antibiotics in the Laizhou Bay, China: impacts of river discharge. Ecotoxicol. Environ. Saf. 80, 208–215.
Zhang, R., Yang, Y., Huang, C.H., Zhao, L., Sun, P., 2016. Kinetics and modeling of sulfonamide antibiotic degradation in wastewater and human urine by UV/H_2O_2 and UV/PDS. Water Res. 103, 283–292.
Zhang, H., Jia, Y., Khanal, S.K., Lu, H., Fang, H., Zhao, Q., 2018. Understanding the role of extracellular polymeric substances (EPS) on ciprofloxacin (CIP) adsorption in aerobic sludge, anaerobic sludge and sulfate-reducing bacteria (SRB) sludge systems. Environ. Sci. Technol. 52 (11), 6476–6486.
Zorita, S., Mårtensson, L., Mathiasson, L., 2009. Occurrence and removal of pharmaceuticals in a municipal sewage treatment system in the south of Sweden. Sci. Total Environ. 407 (8), 2760–2770.