Influence of Abiotic Factors in the Emergence of Antibiotic Resistance

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1 Introduction

The number of bacterial species living in all biospheres may exceed one million, and majority of them are harmless or beneficial to humans. A larger number of species are opportunistic pathogens, which only in certain conditions cause human diseases; and several more are just a part of the normal human flora, not linked to diseases. With the aim of treating infectious diseases and limiting microbial proliferation, antimicrobial agents are being developed. Many organisms produce their own antimicrobials for self-defense that protect them from other microbes concurrently existing in the same milieu. For the treatment of different infectious diseases, many of these innate antimicrobial agents are characterized, studied, and modified extensively to enhance the activity (Munita and Arias 2016; Aslam et al. 2018). Some of the antimicrobial agents are very specific to pathogens or have broad-spectrum activity affecting a wide range of microbes.

The discovery and use of antimicrobial agents have brought a big transformation in the infection management, but simultaneously generated resistance as an adaptive response in microbes (Cleveland et al. 2012; Alexander et al. 2013; Vale-Silva and Sanglard 2015; Alareqi et al. 2016; Lima et al. 2016; Brinkac et al. 2017). This mechanism is often due to acquired resistance from the same or other bacterial species, whereas in some, innate resistance plays a considerable role in antimicrobial resistance (AMR).

AMR dates centuries back, as footprint of tetracycline has been described from the skeletons of Sudanese Nubia (350–500 AD) (Bassett et al. 1980). Several antimicrobial resistance genes (ARGs) have been testified from microbiota of an eleventh-century mummy (Santiago-Rodriguez et al. 2015), millions of years-old

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S. Thomas (ed.), *Antimicrobial Resistance*,
https://doi.org/10.1007/978-981-15-3658-8_4

caves, and ancient permafrost sediment (D'Costa et al. 2011; Bhullar et al. 2012). AMR is considered as one of the most important public health concerns of the twenty-first century by the World Health Organization (WHO) and has been a cause of huge economic burden globally (Munita and Arias 2016; Aslam et al. 2018). AMR bacteria infect about two million people, causing 23,000 deaths each year in the United States (Li and Webster 2018). In Europe, the fatal number is approximately 25,000 due to antibiotic resistance (Brinkac et al. 2017). Misuse or uncontrolled use of antibiotics in clinical settings is linked to rise in AMR in microbes.

AMR is common in the microbial community and has evolved with different defense and adaptive mechanisms with time (Martinez 2009; Davies and Davies 2010; Leisner et al. 2016). Several species of bacteria have remarkable genomic plasticity that helps them to survive and compete in response to antimicrobial molecules produced by the other microbes. Due to genomic plasticity, bacteria are flexible enough to use several different genetic mechanisms like mutation, horizontal gene transfer (HGT) to adopt or survive the action of antimicrobials (Fletcher 2015), and/or a wide range of adverse environmental factors. The presence of more than one ARG coupled with other factors leads to multidrug resistance (MDR).

Recently, many studies have reported the role of the environment as an important reservoir and in transmission of resistance (Martínez 2008; Wright 2010; Ashbolt et al. 2013; Bondarczuk et al. 2016; Hiltunen et al. 2017; Bengtsson-Palme et al. 2018). An increase in the level of antimicrobial-resistant bacteria (ARB) carrying ARGs, especially in water and wastewater, has been reported in several studies (Rizzo et al. 2013; Devarajan et al. 2015; Sharma et al. 2016; Li et al. 2017). The increasing concentration of ARB in different environmental niches like soil and industrial and farming wastewater is a potential threat to the ecosystems (Devarajan et al. 2015), which eventually enters the human food chain through different vectors.

Some of the ARGs found in pathogens are thought to have originated from bacteria mostly present in the external environment that exist as a result of conjugation, where genetic materials are transferred from cell to cell or acquiring genetic material from the virus by transduction (Martínez 2012; Wellington et al. 2013). After the gene-acquiring process, a microbe can transform itself by incorporating exogenous DNA from the environment into its own genome. Mobile genetic elements (MGEs) that often contain ARGs can spread very effectively between unrelated species. All these events are initiated to a certain extent due to selective forces exerted by antibiotics both in clinical and natural environmental sources like infection site, soil, water, and manure used in agriculture, which in turn results in maintenance and spread of antibiotic resistance (Huang et al. 2012; Ashbolt et al. 2013; Berendonk et al. 2015; He et al. 2016). Many findings suggest chemicals other than antibiotics also act as selective factors in stimulating AMR, which include heavy metals (Baker-Austin et al. 2006; Seiler and Berendonk 2012), pesticides (Rangasamy et al. 2018; Ramakrishnan et al. 2019), nano-materials (Qiu et al. 2012; Ding et al. 2016), disinfectants (Guo et al. 2015; Zhang et al. 2017), cosmetics (Orús et al. 2015), and disinfection derivatives (Lv et al. 2015; Li et al. 2016). Heavy metals are naturally present in the environment, and studies have proved that anthropogenic activities accelerate the release and deposition of metals in various

environments (Seiler and Berendonk 2012; Rodríguez Martín et al. 2015; Wang et al. 2015; Zhang et al. 2015; Zhang et al. 2018).

The decrease in the antibiotic use directly prevents the spread and maintenance of antibiotic resistance in clinical and in environmental settings (Salyers and Amábile-Cuevas 1997). The other factors like deposition of heavy metals from manure, anthropogenic chemicals, and micro−/nanoplastic molecules should be taken into consideration and managed accordingly. This chapter reviews different environmental factors that support in the increase of AMR.

2 Environmental Factors

It is well documented that antibiotic resistance is a serious health concern (Pruden et al. 2006; Peak et al. 2007; Munir et al. 2011), and an increase in the spread of the ARGs is directly responsible for the emergence of resistant bacteria. The upsurge and dissemination of the ARGs are directly associated with the constant antibiotic pressure. AMR bacteria are stimulated and signaled to transfer ARGs to other bacteria with the help of MGEs (Allen et al. 2010; Rizzo et al. 2013). With advancement of time, researchers have detected considerable rise in the level of ARGs even in the absence of antibiotic pressure (Alonso et al. 2001; Ji et al. 2012). Studies have also been conducted to identify other chemicals responsible for selecting or supporting AMR in several bacterial populations. In many of these studies, it was established that substances other than antibiotics, such as heavy metals, pesticides, detergents, microplastics, and cosmetics, could also support the spread of ARGs (Alonso et al. 2001; Baker-Austin et al. 2006; Ji et al. 2012). Several studies have successfully established the relationships between heavy metals and ARG abundance in diverse environmental compartments like soil (Zhao et al. 2019), different types of animal manure, and water (Zhao et al. 2018; Sui et al. 2019). Different factors and anthropogenic activities that drive antimicrobial resistance are discussed below.

2.1 Heavy Metals

In the environment, heavy metals are naturally present in abundance or deposited by various human activities. Some of these heavy metals are required in trace amounts for several cellular functions. Metals are divided into four groups based on our health requirements (Kochare and Tamir 2015): (1) Essential metals, also known as the micronutrients, are required for cellular functions; and they are the components for DNA and RNA polymerase, e.g., copper (Cu), zinc (Zn), cobalt (Co), chromium (Cr), manganese (Mn), and iron (Fe). (2) Nonessential metals, e.g., barium (Ba), aluminum (Al), and lithium (Li); (3) less toxic metals, e.g., tin (Sn) and aluminum (Al); and (4) highly toxic metals, e.g., mercury (Hg), cadmium (Cd), and arsenic (As), are considered as cellular toxins as they can form harmful complexes. Heavy

Table 1 Similar resistance mechanisms exhibited by microbes in response to metals or antibiotics

Resistance Mechanism	Antibiotics	Metals	References
Reduction of membrane permeability	Cip, Tet, β-lactams	Cu, Zn, Mn, Co	Ruiz et al. (2003); Knapp et al. (2017)
Inactivation of the antibiotic molecule	β-lactams, Chlor	As, Hg	Wright (2005)
Rapid efflux of the antibiotic	Chlor, Tet, β-lactams	Cu, Co, Zn, Ni	Nies (2003); Ma et al. (2019)
Mutation of cellular targets	Cip, β-lactams, trim	Hg, Zn, Cu	Levy (2002); Baker-Austin et al. (2006)

metals from the environment interact with microorganisms and induce the development of resistance.

The mechanisms underlying microbial resistance to antimicrobials are for self-defense or expressed in response to other antibiotics/chemicals which are broadly classified under four different categories (Krulwich et al. 2005; Baker-Austin et al. 2006): (1) reduction of membrane permeability, (2) inactivation of the antibiotic molecules, (3) rapid efflux of the antibiotic, and/or (4) mutation of cellular targets. Microbes adopt almost similar resistance mechanisms for heavy metals as well as antimicrobials (Table 1). It is well known that different MGEs such as plasmids or transposons help the bacteria to get converted to AMR phenotype. One widely reported mechanism is integron, which is actively associated with gene transfer in the presence of metal ions. The stress exerted by heterogeneous metal ions leads to the selection of resistant bacteria. Heavy metals have long-term selection pressure on ARGs compared to antibiotics because of their nonbiodegradable nature (Stepanauskas et al. 2005). Recent studies have shown that an increase of ARGs is related to the presence of Cu and Ni in soil samples (Hu et al. 2016, 2017). Oxides of Cu, Zn, and Cd at higher concentrations have shown to increase the rate of horizontal gene transfer (HGT) but decrease conjugational transfer (Martinez et al. 2006; Suzuki et al. 2012). Few other studies have shown the increase of conjugational transfer and HGT even at sublethal concentrations, but with a different mechanism (Jutkina et al. 2018; Zhang et al. 2018).

Several reports emphasize the importance of co-occurrence of AMR and resistance to metals in the same bacteria. When a metabolic pathway is activated as a defense mechanism in response to two different antimicrobials, it is termed as a cross-reaction (Baker-Austin et al. 2006; Zhu et al. 2013; Poole 2017; Ding et al. 2019) (Fig. 1). An example of a cross-reaction is an efflux pump, in which several MDR efflux pumps help microbes sustain exposure to both antibiotics and heavy metals. In the co-resistance category, the ARGs and metal resistance genes (MRGs) are positioned on the same genetic element like integrons, plasmids, or transposons (Fig. 2). Co-resistance has been reported in *Salmonella enterica* serotype abortus equi that showed resistance to ampicillin, arsenic, chromium, cadmium, and mercury positioned in a plasmid (Ghosh et al. 2000). Removal of this plasmid makes the strain susceptible to ampicillin and all the metals (Ghosh et al. 2000).

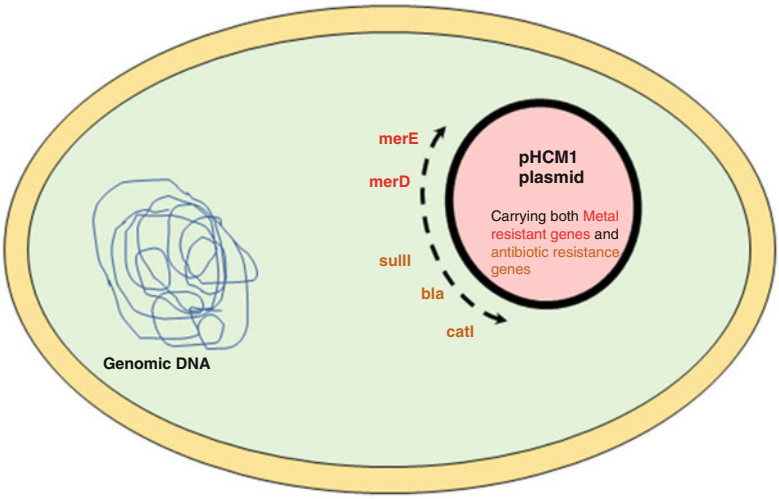

Fig. 1 Co-selection of metal and antibiotic by (i) co-resistance: when resistance-conferring genes to both antibiotics and metals are located in the same genetic element. Due to this physical linkage, when one is expressed, it co-selects the other. pHCM1 plasmid is one such example where mercury resistance is linked to other antibiotic resistance genes

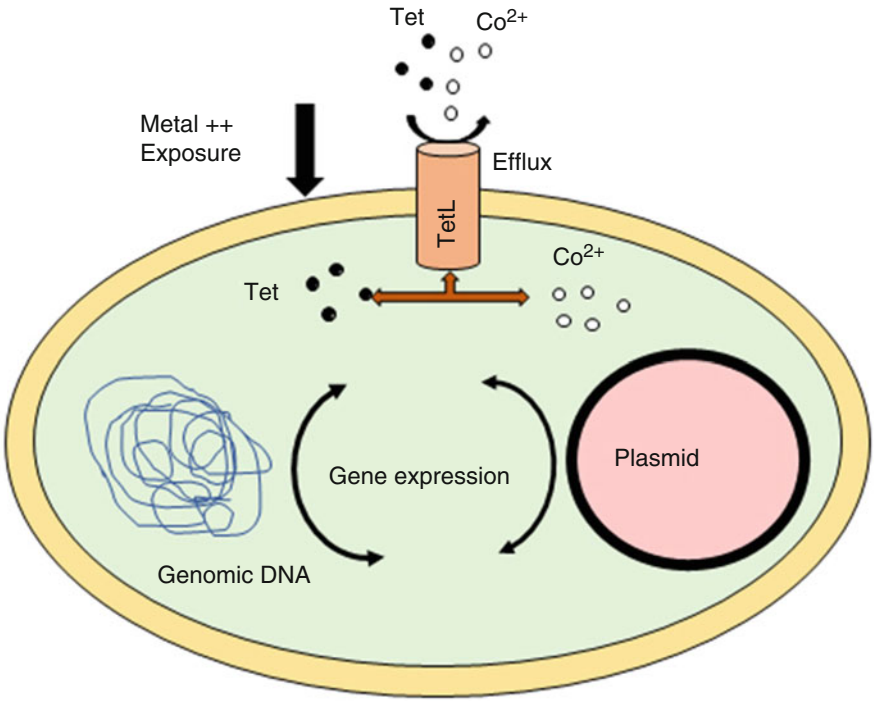

Fig. 2 Co-selection of metal and antibiotic by (ii) cross-regulation: when the same pathway is activated as a defense mechanism in response to metals or antibiotics, for example, TetA(L) efflux pump which pumps out tetracycline and heavy metal cobalt conferring cross-resistance to both metals (cobalt) and antibiotics (tetracycline)

Heavy metals are present in all the environmental niches. Metal atoms form cations by losing electrons making them more bioavailable and express antimicrobial activity. This process is greatly influenced by several environmental conditions modified by pH, oxygen level, or concentration of organic matter. Generally, microbial toxicity of heavy metals is due to their chemical affinity for thiol groups and macro-biomolecules and also depends on the solubility of the metal compounds under physiological conditions (Lemire et al. 2013). In response to the exposure of different toxic metals, bacterial self-defense has developed a certain resistance mechanism to avoid cellular toxicity. This mechanism has been divided into four groups. (1) First is complex formation or sequestration of toxic metals (Silver and Phung 1996). By selectively binding to macromolecules as a biochemical response, the concentration of the free toxic ions in the cytoplasm is reduced. The addition of either metals or antibiotics to planktonic cells can stimulate the production of extracellular polymeric substances (EPSs), which leads to cell adhesion and ultimately the formation of a biofilm as a survival mechanism (Teitzel and Parsek 2003). Bacterial cells within biofilm can withstand a higher concentration of antimicrobial agents. The EPS matrix and the polysaccharides contained in biofilm bind toxic metals (Teitzel and Parsek 2003). As a result, tolerance of bacteria to heavy metals and antibiotics is enhanced. (2) The second mechanism is by detoxification through reduction of intracellular ions (Nies 2003). An example is mercury reductase, encoded by the *merA* gene. The MerA protein reduces Hg^{2+} ions to less toxic Hg (Schiering et al. 1991). (3) Third is excretion of toxic ions by efflux systems (Nies and Silver 1995). In this, the cation/proton antiporter Czc has been identified in *Alcaligenes eutrophus* that mediates resistance to the metal ions Cd^{2+}, Zn^{2+}, and Co^{2+} by removal of metals though the inner and outer membranes from the cytoplasm (Silver and Phung 1996). Genes responsible for efflux mechanism to metal resistance also confer resistance to antibiotics. (4) Fourth is change in morphology and/or pigment production. To overcome environmental change due to toxic metal contamination, a bacterial cell can undergo morphological changes and even secretes pigments. On exposure to toxic lead, *Pseudomonas aeruginosa* show pyoverdine and pyochelin pigment production (Naik et al. 2013).

In the environment, there is a continuous inflow of heavy metals due to anthropogenic, industrial, agricultural, or other human activities. Use of heavy metals such as Cd, Hg, Cu, and Zn in feeds, organic and inorganic fertilizers, and aquaculture substances has immensely contributed to metal contamination. Along with heavy metals, antibiotics are also used in different forms to increase agricultural or farm produce. Many studies have proved genetic exchange of resistance genes between environmental antibiotic-resistant bacteria and human pathogens sustained by the heavy metals in various environmental niches.

2.2 Pesticides

Pesticides are widely used to increase agricultural products. Improper application and storage of pesticides often contaminate plant tissues and environments that remain for a very long time. Pesticide contamination may cause changes at all levels of biological organization directly or indirectly. Terrestrial and aquatic ecosystems are polluted with pesticides due to leach-out from the agricultural fields. The presence of pesticides in these environments can induce resistance or persistence, even to degradation by the microbes. The pesticide-resistant microbes can use biofilm formation, efflux pumps, enzymes, membrane transport systems, and genetic makeup with plasmid- and chromosome-encoded catabolic genes for degradation. These pesticide degraders may also develop antimicrobial resistance as an extra functional trait (Ramakrishnan et al. 2019). Similar to heavy metal resistance genes, pesticide resistance genes are also transferred as gene clusters along with the genes crucial for antibiotic resistance. The consumption of pesticide-contaminated food products and the use of antibiotics by humans and in livestock animals have helped the development of antibiotic- and pesticide-resistant bacterial communities. Pesticide-antibiotic cross-resistance and the subsequent expansion of MDR bacteria are detailed in several reviews (Rangasamy et al. 2018; Ramakrishnan et al. 2019).

In a study, it was shown that the presence of monocrotophos insecticides in the agricultural soil led to the development of multidrug resistance among bacteria (Rangasamy et al. 2017). In the agricultural soil, *Bacillus* isolates were resistant against monocrotophos as well as antibiotics such as chloramphenicol, ampicillin, cefotaxime, streptomycin, and tetracycline. Involvement of plasmid in drug as well as insecticide resistance was confirmed through plasmid curing of resistant bacterial strains (Rangasamy et al. 2017). Several other studies also have proved that the MDR has been increased in phyto- and human pathogenic bacteria due to the presence of pesticides (Kurenbach et al. 2015; Patyka et al. 2016).

2.3 Anthropogenic Substances

Different anthropogenic activities lead to accumulation of substances in the environment that causes a potential rise and spread of resistant bacteria. The mode of action involved in the selection of resistant bacteria employs one or more of the mechanisms discussed before, i.e., "co-selection." Polyaromatic hydrocarbons (PAHs) enter into the environment primarily through activities like coal pyrolysis, liquid fossil fuels, and biomass combustion (Bosch et al. 2015). Some PAHs are considered hazardous to humans with carcinogenic, mutagenic, and genotoxic effects. When exposed to PAH, metabolic activation of bacterial molecules with cytochrome P450 leads to the formation of highly reactive electrophilic species binding with DNA (Binková and Srám 2004). PAH was also responsible for causing a major shift in the composition of the soil microbial community (Yang et al. 2014; Gorovtsov et al. 2018). *Proteobacteria* are prevalent in a PAH-contaminated soil along with the PAH-degrading *Streptomyces* group. This same genus of bacteria is

reported to carry ARGs (D'costa et al. 2006). Few findings indicate decreased HGT rate in the presence of PAH due to the formation of covalent bonding to the plasmids (Kang et al. 2015; Chen et al. 2017). Even when the HGT is interrupted in certain cases, the copy number of ARG can still increase with the growth of PAH-degrading bacteria (Gorovtsov et al. 2018).

2.4 Microplastics

Microplastics of $\geq$5.0 mm in size exist as contaminants in the environment and possess a very long half-life up to centuries (Kazmiruk et al. 2018). They are decisively made for a specific purpose (primary microplastics) or formed through natural degradation of plastics (secondary microplastics) (Rummel et al. 2017; Imran et al. 2019). Millions of tons of particles are discharged into the marine environment as industrial by-products, degraded plastic wastes, municipal wastes, fishing nets, etc. (Cole et al. 2011; Law and Thompson 2014; Keswani et al. 2016; Arias-Andres et al. 2018). Plastics causing marine pollution are mostly polyethylene (PE), polystyrene (PS), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polyurethane (PUR), and polypropylene (PP) (Hidalgo-Ruz et al. 2012; Fok et al. 2017; Revel et al. 2018). Due to their very small size, microplastics are accumulated by oysters and crabs (Watts et al. 2016), get ingested by fishes, and eventually spread in the aquatic ecosystem (Nelms et al. 2018; Revel et al. 2018). Microplastics are considered as one of the most difficult pollutants to control with a long-lasting reactive surface. They can adhere to or adsorb organic matter and chemical substances like antibiotics, pesticides, heavy metals, and other xenobiotics (Hirai et al. 2011). These microplastics support colonization by different microbial species (Zettler et al. 2013; Oberbeckmann et al. 2016; Kettner et al. 2017), and these communities are collectively termed as "the plastisphere" (Keswani et al. 2016). They are also capable of changing the structure and composition of other microbial communities present in the surrounding environment (Reisser et al. 2013; Harrison et al. 2014; Oberbeckmann et al. 2014; Bryant et al. 2016).

It has been well documented that microplastics can adsorb antibiotics (sulfadiazine, ciprofloxacin, amoxicillin, trimethoprim, and tetracycline) on their surfaces and its low density often helps them get dispersed into the food chains and humans and animals (Li et al. 2018). Microplastics can vary in their physicochemical properties like specific surface area, crystallinity, and pore size distribution, which determine the adsorption capacity of each type (Li et al. 2018). It has been reported that tetracycline-containing microplastics in the soil can stimulate bacterial phage-mediated ARG dispersion (Sun et al. 2018). Increased proportion of HGT is reported among phylogenetically diverse bacteria on the microplastic surface compared to the free-living aquatic bacterial population (Arias-Andres et al. 2018). This microsurface acts as a perfect platform for selection of AMR in the presence of metal ions, antibiotics, and other pollutants.

2.5 Biocides

Biocides are used to control microbial growth; and these agents are used most commonly in antiseptics, disinfectants, and preservatives. Biocides functionally differ from antibiotics. Unlike antibiotics, which are very precise in action, biocides are formulated to act on multiple cellular targets and hence mostly used in higher concentrations compared to antibiotics. Biocides mostly disturb the bacterial membrane and react with the cell protein molecule or genetic material. Biocidal agents like alcohol target the bacterial membrane, whereas aldehydes and anionic surfactants affect the cell wall. In the case of hydrogen peroxide, acridine dyes, and chlorine compounds, it is the nucleic acid that gets affected (Davin-Regli and Pagès 2012).

The activity of biocides depends on the duration of contact time, pH, and temperature, the presence of organic matter or other interfering or enhancing materials/compounds, and the target microorganism. The most common adaptation mechanism expressed by microbes in response to biocide exposure is the activation of efflux pump, but some studies have observed an adaptive mechanism due to changes in protein synthesis only when biocide is present in low concentrations (Mutoh et al. 1999). Resistance to formaldehyde among members of *Enterobacteriaceae* is plasmid mediated and in *P. aeruginosa* is due to chromosomal elements. Both these resistant forms are quite stable to even grow at a concentration much higher than the lethal dose (Meyer and Cookson 2010). Biocides in certain isolates can upregulate efflux pumps by activating different biochemical pathways, which is reversed in the absence of biocides. Hence, the defense mechanisms expressed by the microbes to biocides raise the concern of simultaneous development of antimicrobial resistance as a co-selection mechanism as both the antibacterial molecules at certain extent use the similar resistance mechanisms (Pal et al. 2017; Jutkina et al. 2018; Wales and Davies 2015) (Table 2). One of the most commonly used biocides, triclosan, has received great attention in relation to the rise of resistant bugs. Triclosan is most commonly and widely used in disinfectants, preservatives, toothpastes, baby toys, and many other daily products (Westfall et al. 2019). It is bacteriostatic at lower concentrations, but is bactericidal at higher concentrations and causes cell death by affecting the plasma membrane. Just like antibiotics but unlike other biocides, triclosan at low concentrations acts on a specific cellular target. The most studied and mapped target site for triclosan is enoyl-acyl carrier protein reductase (FabI), an essential enzyme in bacterial fatty acid synthesis. Researchers have shown that mutations in FabI and its overexpression decrease bacterial susceptibility to triclosan (Heath et al. 1999; Slater-Radosti et al. 2001). Along with defective fatty acid synthesis, accumulation of the alarmone guanosine tetraphosphate (ppGpp) gives rise to persistent bacterial cells which show high resistance to antibiotics (Westfall et al. 2019). Another aspect that raises concern in biocide use is that some antibiotics share same target site FabI-like triclosan. The selective pressure created by its use may co-regulate resistance to both biocides and antibiotics (Ciusa et al. 2012).

Table 2 Reduced antibiotic sensitivity on exposure to low-level biocide

Species	Biocide	Reduced Sensitivity to Antibiotics	References
E. coli	Benzalkonium chloride, triclosan	Cefotaxime, ampicillin, tetracycline, ciprofloxacin, trimethoprim, vancomycin, gentamicin	Soumet et al. (2012)
Campylobacter jejuni, *Campylobacter coli*	Didecyldimethyl ammonium chloride and benzalkonium chloride	Ampicillin, tetracycline, gentamicin, streptomycin, erythromycin, and enrofloxacin	Donaghy et al. (2019)
Pseudomonas aeruginosa	Benzalkonium chloride	Ciprofloxacin, gentamycin, amikacin, imipenem, polymyxin B	Mc Cay et al. (2010)
Salmonella typhimurium	Benzalkonium chloride, aldehydes, quaternary ammonium compounds	Chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamicin, tetracycline, nalidixic acid, kanamycin	Donaghy et al. (2019); Braoudaki and Hilton (2004)
Enterobacter spp.	Chlorhexidine digluconate	Cefotaxime, ceftazidime, imipenem, sulfamethoxazole	Gadea et al. (2017)
Salmonella spp.	Triclosan	Piperacillin, ceftiofur, amikacin, Gentamicin, kanamycin, nalidixic acid, cefoxitin	Condell et al. (2012)

2.6 Cosmetic Products

The development of AMR microorganisms is due to the selective pressure from preservatives, which are added in the cosmetic formulations mainly to inhibit the growth of microorganisms. Cosmetic products could also be a risk for the emergence and spread of AMR bacteria. Tolerance to formaldehyde donors such as diazolidinyl urea, imidazolidinyl urea, quaternium-15, sodium hydroxymethylglycinate, and DMDM hydantoin by *Enterobacter gergoviae*, *Pseudomonas putida*, and *Burkholderia cepacia* isolated from cosmetics products has shown cross-resistance to antibiotics (Orús et al. 2015). Reduced susceptibility to formaldehyde donors was detected in isolates along with increasing resistance to β-lactams, quinolones, rifampicin, and tetracycline. The outer membrane protein modifications and efflux mechanism activities were found to be responsible for the resistance traits (Orús et al. 2015). Chlorhexidine/chlorhexidine gluconate (CHG) has been used in disinfectants, oral care, and cosmetics. In vitro exposure of *Staphylococcus aureus* to sublethal concentrations of chlorhexidine showed cross-resistance to amikacin, cefepime, and tetracycline (Wu et al. 2016). Also, studies on *Klebsiella pneumoniae* had shown that bacterial exposure to CHG induced cross-resistance to colistin, which is used in the treatment of MDR pathogens (Wand et al. 2016).

3 Transmission of Antibiotic Resistance from the Environment to Humans

The environment is continuously exposed to different substances favoring the emergence and spread of antimicrobial-resistant bacteria. Microbes work as a reservoir for ARGs in the environment as well as the human body. Depending on the environmental conditions and other stress factors, different bacterial species remain viable and act as potential carriers. Genetic elements of the dead bacterial cells also act as probable sources of HGTs. Many human activities exert a high level of AMR transmission (Fletcher 2015). Several abiotic stress conditions directly support the emergence of AMR mechanism, which will be sustained through several genetic mechanisms including HGTs. The human microbiota is under constant pressure with several stimulating factors of AMR. Microplastics harboring AMR bacteria and/or substances that initiate different resistant mechanisms in microbes also reach the food chain.

4 Mitigation Policies

With the rise of the AMR issue globally, many strategies have been proposed based on several research to clearly understand the mechanism of AMR selection and transmission. One of the risk mitigation strategies commonly and widely focused is on minimizing the uptake of antibiotics and reducing the spread of AMR from the key environmental reservoirs like sewage, wastewater, manure, farms, and antibiotic manufacture waste. The most common mitigation method is restricting the use and release of antibiotics into the environment. The principle behind this is decreasing the antibiotic load, thereby lowering the selection pressure for ARGs which eventually controls the risk of AMR (Bengtsson-Palme and Larsson 2016). With the rise in risk of AMR globally, the number of research on the same aspect is numerous. A large number of data are also available which could be translated to administer a mitigation process (Vikesland et al. 2017).

There are uses of similar antibacterial approaches in treating human and/or animal infections, and the rise of a resistant form of bacteria can spread from one to another and eventually to the environment. Each plays an important role in the global spread of AMR. With the aim of bridging the multidisciplinary knowledge gap between humans, animals, and the environment to deal with AMR risk, a very comprehensive and multisectoral approach is "One Health," where humans, animals, and the environment are considered as one. Under this initiative, the WHO, Food and Agriculture Organization (FAO) of the United Nations, World Organisation for Animal Health (OIE), Centers for Disease Control and Prevention (CDC), United States Department of Agriculture (USDA), National Oceanic and Atmospheric Administration (NOAA), and US National Environmental Health Association (NEHA) all work together in minimizing the risk of rise and spread of AMR. But it is to be remembered that there are also other selection pressures simultaneously

present in the environment responsible for ARG and AMR pool, proper understanding of which is also required.

5 Conclusion

The rise of antibiotic-resistant bacteria has been a major global issue for years which is facing challenges for control due to several processes and factors. Most importantly, the microbial community acts as a reservoir, and their rapid adaptive mechanisms to withstand environmental challenges are very high. As a result, long-lasting solutions for the AMR control will be a challenging issue. The resistant phenotypes will continue to occur until the establishment of a new metabolic pathway that restricts AMR acquirement and dissemination. Limiting the use of fertilizers and pesticides and controlling the effluents may reduce the ARGs in the microbial community. Replacing AMR-promoting substances in different products that causes less stress to the microbial community may limit the rise of AMR. Understanding the role of ecological factors in AMR transfer could help us devise strategies to control this fundamental evolutionary process. The most important aspect is human awareness. For this, results generated from various environmental studies should be compiled for the proper implementation of control measures.

References

Alareqi LMQ, Mahdy MAK, Lau YL, Fong MY, Abdul-Ghani R, Mahmud R (2016) Molecular markers associated with resistance to commonly used antimalarial drugs among *Plasmodium falciparum* isolates from a malaria-endemic area in Taiz governorate-Yemen during the transmission season. Acta Trop 162:174–179. https://doi.org/10.1016/j.actatropica.2016.06.016

Alexander BD, Johnson MD, Pfeiffer CD, Jiménez-Ortigosa C, Catania J, Booker R, Castanheira M, Messer SA, Perlin DS, Pfaller MA (2013) Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis 56(12):1724–1732. https://doi.org/10.1093/cid/cit136

Allen HK, Donato J, Wang HH, Cloud-Hansen KA, Davies J, Handelsman J (2010) Call of the wild: antibiotic resistance genes in natural environments. Nat Rev Microbiol 8(4):251–259. https://doi.org/10.1038/nrmicro2312

Alonso A, Sánchez P, Martínez JL (2001) Environmental selection of antibiotic resistance genes. Environ Microbiol 3(1):1–9. https://doi.org/10.1046/j.1462-2920.2001.00161

Arias-Andres M, Klümper U, Rojas-Jimenez K, Grossart HP (2018) Microplastic pollution increases gene exchange in aquatic ecosystems. Environ Pollut 237:253–261. https://doi.org/10.1016/j.envpol.2018.02.058

Ashbolt NJ, Amézquita A, Backhaus T, Borriello P, Brandt KK, Collignon P, Coors A, Finley R, Gaze WH, Heberer T, Lawrence JR, Joakim Larsson DG, McEwen SA, Ryan JJ, Schönfeld J, Silley P, Snape JR, Van den Eede C, Topp E (2013) Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. Environ Health Perspect 121(9):993–1001. https://doi.org/10.1289/ehp.1206316

Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF, Baloch Z (2018) Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist 11:1645–1658. https://doi.org/10.2147/IDR.S173867

Baker-Austin C, Wright MS, Stepanauskas R, McArthur JV (2006) Co-selection of antibiotic and metal resistance. Trends Microbiol 14(4):176–182. https://doi.org/10.1016/j.tim.2006.02.006

Bassett EJ, Keith MS, Armelagos GJ, Martin DL, Villanueva AR (1980) Tetracycline-labeled human bone from ancient Sudanese Nubia (A.D. 350). Science 209(4464):1532–1534. https://doi.org/10.1126/science.7001623

Bengtsson-Palme J, Kristiansson E, Larsson DGJ (2018) Environmental factors influencing the development and spread of antibiotic resistance. FEMS Microbiol Rev 42(1). https://doi.org/10.1093/femsre/fux053

Bengtsson-Palme J, Larsson DG (2016) Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation. Environ Int 86:140–149. https://doi.org/10.1016/j.envint.2015.10.015

Berendonk TU, Manaia CM, Merlin C, Fatta-Kassinos D, Cytryn E, Walsh F, Bürgmann H, Sørum H, Norström M, Pons M-N, Kreuzinger N, Huovinen P, Stefani S, Schwartz T, Kisand V, Baquero F, Martinez JL (2015) Tackling antibiotic resistance: the environmental framework. Nat Rev Microbiol 13(5):310–317. https://doi.org/10.1038/nrmicro3439

Bhullar K, Waglechner N, Pawlowski A, Koteva K, Banks ED, Johnston MD, Barton HA, Wright GD (2012) Antibiotic resistance is prevalent in an isolated cave microbiome. PLoS One 7(4):e34953. https://doi.org/10.1371/journal.pone.0034953

Binková B, Srám RJ (2004) The genotoxic effect of carcinogenic PAHs, their artificial and environmental mixtures (EOM) on human diploid lung fibroblasts. Mutat Res 547 (1-2):109–121. https://doi.org/10.1016/j.mrfmmm.2003.12.006

Bondarczuk K, Markowicz A, Piotrowska-Seget Z (2016) The urgent need for risk assessment on the antibiotic resistance spread via sewage sludge land application. Environ Int 87:49–55. https://doi.org/10.1016/j.envint.2015.11.011

Bosch C, Andersson A, Kruså M, Bandh C, Hovorková I, Klánová J, Knowles TD, Pancost RD, Evershed RP, Gustafsson Ö (2015) Source apportionment of polycyclic aromatic hydrocarbons in central European soils with compound-specific triple isotopes (δ(13)C, Δ(14)C, and δ(2)H). Environ Sci Technol 49(13):7657–7665. https://doi.org/10.1021/acs.est.5b01190

Braoudaki M, Hilton AC (2004) Adaptive resistance to biocides in salmonella enterica and *Escherichia coli* O157 and cross-resistance to antimicrobial agents. J Clin Microbiol 42 (1):73–78. https://doi.org/10.1128/JCM.42.1.73-78.2004

Brinkac L, Voorhies A, Gomez A, Nelson KE (2017) The threat of antimicrobial resistance on the human microbiome. Microb Ecol 74(4):1001–1008. https://doi.org/10.1007/s00248-017-0985-z

Bryant JA, Clemente TM, Viviani DA, Fong AA, Thomas KA, Kemp P, Karl DM, White AE, DeLong EF (2016) Diversity and activity of communities inhabiting plastic debris in the North Pacific gyre. mSystems 1(3):e00024–e00016. https://doi.org/10.1128/mSystems.00024-16

Chen B, He R, Yuan K, Chen E, Lin L, Chen X, Sha S, Zhong J, Lin L, Yang L, Yang Y, Wang X, Zou S, Luan T (2017) Polycyclic aromatic hydrocarbons (PAHs) enriching antibiotic resistance genes (ARGs) in the soils. Environ Pollut 220(Pt B):1005–1013. https://doi.org/10.1016/j.envpol.2016.11.047

Ciusa ML, Furi L, Knight D, Decorosi F, Fondi M, Raggi C, Coelho JR, Aragones L, Moce L, Visa P, Freitas AT, Baldassarri L, Fani R, Viti C, Orefici G, Martinez JL, Morrissey I, Oggioni MR (2012) A novel resistance mechanism to triclosan that suggests horizontal gene transfer and demonstrates a potential selective pressure for reduced biocide susceptibility in clinical strains of *Staphylococcus aureus*. Int J Antimicrob Agents 40(3):210–220. https://doi.org/10.1016/j.ijantimicag.2012.04.021

Cleveland AA, Farley MM, Harrison LH, Stein B, Hollick R, Lockhart SR, Magill SS, Derado G, Park BJ, Chiller TM (2012) Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008-2011. Clin Infect Dis 55(10):1352–1361. https://doi.org/10.1093/cid/cis697

Cole M, Lindeque P, Halsband C, Galloway TS (2011) Microplastics as contaminants in the marine environment: a review. Mar Pollut Bull 62(12):2588–2597. https://doi.org/10.1016/j.marpolbul.2011.09.025

Condell O, Iversen C, Cooney S, Power KA, Walsh C, Burgess C, Fanning S (2012) Efficacy of biocides used in the modern food industry to control salmonella enterica, and links between biocide tolerance and resistance to clinically relevant antimicrobial compounds. Appl Environ Microbiol 78(9):3087–3097. https://doi.org/10.1128/AEM.07534-11

Davies J, Davies D (2010) Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 74(3):417–433. https://doi.org/10.1128/MMBR.00016-10

Davin-Regli A, Pagès JM (2012) Cross-resistance between biocides and antimicrobials: an emerging question. Rev Sci Tech 31(1):89–104. Review. PMID: 22849270

D'Costa VM, King CE, Kalan L, Morar M, Sung WW, Schwarz C, Froese D, Zazula G, Calmels F, Debruyne R, Golding GB, Poinar HN, Wright GD (2011) Antibiotic resistance is ancient. Nature 477(7365):457–461. https://doi.org/10.1038/nature10388

D'Costa VM, McGrann KM, Hughes DW, Wright GD (2006) Sampling the antibiotic resistome. Science 311(5759):374–377. https://doi.org/10.1126/science.1120800

Devarajan N, Laffite A, Graham ND, Meijer M, Prabakar K, Mubedi JI, Elongo V, Mpiana PT, Ibelings BW, Wildi W, Poté J (2015) Accumulation of clinically relevant antibiotic-resistance genes, bacterial load, and metals in freshwater lake sediments in Central Europe. Environ Sci Technol 49(11):6528–6537. https://doi.org/10.1021/acs.est.5b01031

Ding C, Pan J, Jin M, Yang D, Shen Z, Wang J, Zhang B, Liu W, Fu J, Guo X, Wang D, Chen Z, Yin J, Qiu Z, Li J (2016) Enhanced uptake of antibiotic resistance genes in the presence of nanoalumina. Nanotoxicology 10(8):1051–1060. https://doi.org/10.3109/17435390.2016.1161856

Ding J, An XL, Lassen SB, Wang HT, Zhu D, Ke X (2019) Heavy metal-induced co-selection of antibiotic resistance genes in the gut microbiota of collembolans. Sci Total Environ 683:210–215. https://doi.org/10.1016/j.scitotenv.2019.05.302

Donaghy JA, Jagadeesan B, Goodburn K, Grunwald L, Jensen ON, Jespers AD, Kanagachandran K, Lafforgue H, Seefelder W, Quentin MC (2019) Relationship of sanitizers, disinfectants, and cleaning agents with antimicrobial resistance. J Food Prot 82(5):889–902. https://doi.org/10.4315/0362-028X.JFP-18-373

Fletcher S (2015) Understanding the contribution of environmental factors in the spread of antimicrobial resistance. Environ Health Prev Med 20(4):243–252. https://doi.org/10.1007/s12199-015-0468-0

Fok L, Cheung PK, Tang G, Li WC (2017) Size distribution of stranded small plastic debris on the coast of Guangdong, South China. Environ Pollut 220(PtA):407–412. https://doi.org/10.1016/j.envpol.2016.09.079

Gadea R, Glibota N, Pérez Pulido R, Gálvez A, Ortega E (2017) Adaptation to biocides cetrimide and chlorhexidine in bacteria from organic foods: association with tolerance to other antimicrobials and physical stresses. J Agric Food Chem 65(8):1758–1770. https://doi.org/10.1021/acs.jafc.6b04650

Ghosh A, Singh A, Ramteke PW, Singh VP (2000) Characterization of large plasmids encoding resistance to toxic heavy metals in Salmonella abortus equi. Biochem Biophys Res Commun 272(1):6–11. https://doi.org/10.1006/bbrc.2000.2727

Gorovtsov AV, Sazykin IS, Sazykina MA (2018) The influence of heavy metals, polyaromatic hydrocarbons, and polychlorinated biphenyls pollution on the development of antibiotic resistance in soils. Environ Sci Pollut Res Int 25(10):9283–9292. https://doi.org/10.1007/s11356-018-1465-9

Guo MT, Yuan QB, Yang J (2015) Distinguishing effects of ultraviolet exposure and chlorination on the horizontal transfer of antibiotic resistance genes in municipal wastewater. Environ Sci Technol 49(9):5771–5778. https://doi.org/10.1021/acs.est.5b00644

Harrison JP, Schratzberger M, Sapp M, Osborn AM (2014) Rapid bacterial colonization of low-density polyethylene microplastics in coastal sediment microcosms. BMC Microbiol 14:232. https://doi.org/10.1186/s12866-014-0232-4

He LY, Ying GG, Liu YS, Su HC, Chen J, Liu SS, Zhao JL (2016) Discharge of swine wastes risks water quality and food safety: antibiotics and antibiotic resistance genes from swine sources to the receiving environments. Environ Int 92-93:210–219. https://doi.org/10.1016/j.envint.2016.03.023

Heath RJ, Rubin JR, Holland DR, Zhang E, Snow ME, Rock CO (1999) Mechanism of triclosan inhibition of bacterial fatty acid synthesis. J Biol Chem 274(16):11110–11114. https://doi.org/10.1074/jbc.274.16.11110

Hidalgo-Ruz V, Gutow L, Thompson RC, Thiel M (2012) Microplastics in the marine environment: a review of the methods used for identification and quantification. Environ Sci Technol 46 (6):3060–3075. https://doi.org/10.1021/es2031505

Hiltunen T, Virta M, Laine AL (2017) Antibiotic resistance in the wild: an eco-evolutionary perspective. Philos Trans R Soc Lond Ser B Biol Sci 372(1712). https://doi.org/10.1098/rstb.2016.0039

Hirai H, Takada H, Ogata Y, Yamashita R, Mizukawa K, Saha M, Kwan C, Moore C, Gray H, Laursen D, Zettler ER, Farrington JW, Reddy CM, Peacock EE, Ward MW (2011) Organic micropollutants in marine plastics debris from the open ocean and remote and urban beaches. Mar Pollut Bull 62(8):1683–1692. https://doi.org/10.1016/j.marpolbul.2011.06.004

Hu HW, Wang JT, Li J, Li JJ, Ma YB, Chen D, He JZ (2016) Field-based evidence for copper contamination induced changes of antibiotic resistance in agricultural soils. Environ Microbiol 18(11):3896–3909. https://doi.org/10.1111/1462-2920.13370

Hu HW, Wang JT, Li J, Shi XZ, Ma YB, Chen D, He JZ (2017) Long-term nickel contamination increases the occurrence of antibiotic resistance genes in agricultural soils. Environ Sci Technol 51(2):790–800. https://doi.org/10.1021/acs.est.6b03383

Huang J-J, Hu H-Y, Lu S-Q, Li Y, Tang F, Lu Y, Wei B (2012) Monitoring and evaluation of antibiotic-resistant bacteria at a municipal wastewater treatment plant in China. Environ Int 42:31–36. https://doi.org/10.1016/j.envint.2011.03.001

Imran M, Das KR, Naik MM (2019) Co-selection of multi-antibiotic resistance in bacterial pathogens in metal and microplastic contaminated environments: An emerging health threat. Chemosphere 215:846–857. https://doi.org/10.1016/j.chemosphere.2018.10.114

Ji X, Shen Q, Liu F, Ma J, Xu G, Wang Y, Wu M (2012) Antibiotic resistance gene abundances associated with antibiotics and heavy metals in animal manures and agricultural soils adjacent to feedlots in Shanghai; China. J Hazard Mater 235–236:178–185. https://doi.org/10.1016/j.jhazmat.2012.07.040

Jutkina J, Marathe NP, Flach CF, Larsson DGJ (2018) Antibiotics and common antibacterial biocides stimulate horizontal transfer of resistance at low concentrations. Sci Total Environ 616-617:172–178. https://doi.org/10.1016/j.scitotenv.2017.10.312

Kang F, Hu X, Liu J, Gao Y (2015) Noncovalent binding of polycyclic aromatic hydrocarbons with genetic bases reducing the in vitro lateral transfer of antibiotic resistant genes. Environ Sci Technol 49(17):10340–10348. https://doi.org/10.1021/acs.est.5b02293

Kazmiruk TN, Kazmiruk VD, Bendell LI (2018) Abundance and distribution of microplastics within surface sediments of a key shellfish growing region of Canada. PLoS One 13(5): e0196005. https://doi.org/10.1371/journal.pone.0196005

Keswani A, Oliver DM, Gutierrez T, Quilliam RS (2016) Microbial hitchhikers on marine plastic debris: human exposure risks at bathing waters and beach environments. Mar Environ Res 118:10–19. https://doi.org/10.1016/j.marenvres.2016.04.006

Kettner MT, Rojas-Jimenez K, Oberbeckmann S, Labrenz M, Grossart HP (2017) Microplastics alter composition of fungal communities in aquatic ecosystems. Environ Microbiol 19 (11):4447–4459. https://doi.org/10.1111/1462-2920.13891

Knapp CW, Callan AC, Aitken B, Shearn R, Koenders A, Hinwood A (2017) Relationship between antibiotic resistance genes and metals in residential soil samples from Western Australia. Environ Sci Pollut Res Int 24(3):2484–2494. https://doi.org/10.1007/s11356-016-7997-y

Kochare T, Tamir B (2015) Assessment of dairy feeds for heavy metals. Am Sci Res J Eng Technol Sci 11:20–31

Krulwich TA, Lewinson O, Padan E, Bibi E (2005) Do physiological roles foster persistence of drug/multidrug-efflux transporters? A case study. Nat Rev Microbiol 3(7):566–572. https://doi.org/10.1038/nrmicro1181

Kurenbach B, Marjoshi D, Amabile-Cuevas CF, Ferguson GC, Godsoe W, Gibson P, Heinemann JA (2015) Sublethal exposure to commercial formulations of the herbicides dicamba, 2,4-dichlorophenoxyacetic acid, and glyphosate cause changes in antibiotic susceptibility in *Escherichia coli* and *Salmonella enterica* serovar Typhimurium. MBio 6(2):e00009–e00015. https://doi.org/10.1128/mBio.00009-15

Law KL, Thompson RC (2014) Microplastics in the seas. Science 345(6193):144–145. https://doi.org/10.1126/science.1254065

Leisner JJ, Jørgensen NO, Middelboe M (2016) Predation and selection for antibiotic resistance in natural environments. Evol Appl 9(3):427–434. https://doi.org/10.1111/eva.12353

Lemire JA, Harrison JJ, Turner RJ (2013) Antimicrobial activity of metals: mechanisms, molecular targets and applications. Nat Rev Microbiol 11(6):371–384. https://doi.org/10.1038/nrmicro3028

Levy SB (2002) Active efflux, a common mechanism for biocide and antibiotic resistance. J Appl Microbiol 92(Suppl):65S–71S. https://doi.org/10.1046/j.1365-2672.92.5s1.4.x

Li B, Webster TJ (2018) Bacteria antibiotic resistance: new challenges and opportunities for implant-associated orthopedic infections. J Orthop Res 36(1):22–32. https://doi.org/10.1002/jor.23656

Li D, Zeng S, He M, Gu AZ (2016) Water disinfection byproducts induce antibiotic resistance-role of environmental pollutants in resistance phenomena. Environ Sci Technol 50(6):3193–3201. https://doi.org/10.1021/acs.est.5b00644

Li H, Duan M, Gu J, Zhang Y, Qian X, Ma J, Zhang R, Wang X (2017) Effects of bamboo charcoal on antibiotic resistance genes during chicken manure composting. Ecotoxicol Environ Saf 140:1–6. https://doi.org/10.1016/j.ecoenv.2017.01.007

Li J, Zhang K, Zhang H (2018) Adsorption of antibiotics on microplastics. Environ Pollut 237:460–467. https://doi.org/10.1016/j.envpol.2018.02.050

Lima YA, Cardoso LP, Reis MN, Stefani MM (2016) Incident and long-term HIV-1 infection among pregnant women in Brazil: transmitted drug resistance and mother-to-child transmission. J Med Virol 88(11):1936–1943. https://doi.org/10.1002/jmv.24540

Lv L, Yu X, Xu Q, Ye C (2015) Induction of bacterial antibiotic resistance by mutagenic halogenated nitrogenous disinfection byproducts. Environ Pollut 205:291–298. https://doi.org/10.1016/j.envpol.2015.06.026

Ma X, Guo N, Ren S, Wang S, Wang Y (2019) Response of antibiotic resistance to the co-existence of chloramphenicol and copper during bio-electrochemical treatment of antibiotic-containing wastewater. Environ Int 126:127–133. https://doi.org/10.1016/j.envint.2019.02.002

Martínez JL (2008) Antibiotics and antibiotic resistance genes in natural environments. Science 321(5887):365–367. https://doi.org/10.1126/science.1159483

Martinez JL (2009) The role of natural environments in the evolution of resistance traits in pathogenic bacteria. Proc Biol Sci 276(1667):2521–2530. https://doi.org/10.1098/rspb.2009.0320

Martínez JL (2012) Bottlenecks in the transferability of antibiotic resistance from natural ecosystems to human bacterial pathogens. Front Microbiol 2:265. https://doi.org/10.3389/fmicb.2011.00265

Martinez RJ, Wang Y, Raimondo MA, Coombs JM, Barkay T, Sobecky PA (2006) Horizontal gene transfer of PIB-type ATPases among bacteria isolated from radionuclide- and metal-contaminated subsurface soils. Appl Environ Microbiol 72(5):3111–3118. https://doi.org/10.1128/AEM.72.5.3111-3118.2006

Mc Cay PH, Ocampo-Sosa AA, Fleming GT (2010) Effect of subinhibitory concentrations of benzalkonium chloride on the competitiveness of *Pseudomonas aeruginosa* grown in continuous culture. Microbiology 156(Pt 1):30–38. https://doi.org/10.1099/mic0.029751-0

Meyer B, Cookson B (2010) Does microbial resistance or adaptation to biocides create a hazard in infection prevention and control? J Hosp Infect 76(3):200–205. https://doi.org/10.1016/j.jhin.2010.05.020

Munir M, Wong K, Xagoraraki I (2011) Release of antibiotic resistant bacteria and genes in the effluent and biosolids of five wastewater utilities in Michigan. Water Res 45(2):681–693. https://doi.org/10.1016/j.watres.2010.08.033

Munita JM, Arias CA (2016) Mechanisms of antibiotic resistance. Microbiol Spectr 4(2). https://doi.org/10.1128/microbiolspec.VMBF-0016-2015

Mutoh N, Nakagawa CW, Yamada K (1999) The role of catalase in hydrogen peroxideresistance in fission yeast Schizosaccharomyces pombe. Can J Microbiol 45(2):125–129. https://doi.org/10.1139/w98-216

Naik M, Dubey S, Khanolkar D, D'Costa B (2013) P-type ATPase and MdrL efflux pump-mediated lead and multi-drug resistance in estuarine bacterial isolates. Curr Sci 105(10):1366–1372. www.jstor.org/stable/24098901

Nelms SE, Galloway TS, Godley BJ, Jarvis DS, Lindeque PK (2018) Investigating microplastic trophic transfer in marine top predators. Environ Pollut 238:999–1007. https://doi.org/10.1016/j.envpol.2018.02.016

Nies DH (2003) Efflux-mediated heavy metal resistance in prokaryotes. FEMS Microbiol Rev 27 (2-3):313–339. https://doi.org/10.1016/S0168-6445(03)00048-2

Nies DH, Silver S (1995) Ion efflux systems involved in bacterial metal resistances. J Ind Microbiol 14(2):186–199. https://doi.org/10.1007/BF01569902

Oberbeckmann S, Loeder MG, Gerdts G, Osborn AM (2014) Spatial and seasonal variation in diversity and structure of microbial biofilms on marine plastics in northern European waters. FEMS Microbiol Ecol 90(2):478–492. https://doi.org/10.1111/1574-6941.12409

Oberbeckmann S, Mark Osborn A, Duhaime MB, Carter DA (2016) Microbes on a bottle: substrate, season and geography influence community composition of microbes colonizing marine plastic debris. PLoS ONE 11(8):e0159289. https://doi.org/10.1371/journal.pone.0159289

Orús P, Gomez-Perez L, Leranoz S, Berlanga M (2015) Increasing antibiotic resistance in preservative-tolerant bacterial strains isolated from cosmetic products. Int Microbiol 18 (1):51–59. https://doi.org/10.2436/20.1501.01.234

Pal C, Asiani K, Arya S, Rensing C, Stekel DJ, Larsson DGJ, Hobman JL (2017) Metal resistance and its association with antibiotic resistance. Adv Microb Physiol 70:261–313. https://doi.org/10.1016/bs.ampbs.2017.02.001

Patyka V, Buletsa N, Pasichnyk L, Zhitkevich N, Kalinichenko A, Gnatiuk T, Butsenko L (2016) Specifics of pesticides effects on the phytopathogenic bacteria. Ecol Chem Eng 23(2):311–331. https://doi.org/10.1515/eces-2016-0022

Peak N, Knapp CW, Yang RK, Hanfelt MM, Smith MS, Aga DS, Graham DW (2007) Abundance of six tetracycline resistance genes in wastewater lagoons at cattle feedlots with different antibiotic use strategies. Environ Microbiol 9(1):143–151. https://doi.org/10.1111/j.1462-2920.2006.01123.x

Poole K (2017) At the nexus of antibiotics and metals: the impact of cu and Zn on antibiotic activity and resistance. Trends Microbiol 25(10):820–832. https://doi.org/10.1016/j.tim.2017.04.010

Pruden A, Pei R, Storteboom H, Carlson KH (2006) Antibiotic resistance genes as emerging contaminants: studies in northern Colorado. Environ Sci Technol 40(23):7445–7450. https://doi.org/10.1021/es060413l

Qiu Z, Yu Y, Chen Z, Jin M, Yang D, Zhao Z, Wang J, Shen Z, Wang X, Qian D, Huang A, Zhang B, Li J-W (2012) Nanoalumina promotes the horizontal transfer of multiresistance genes mediated by plasmids across genera. Proc Natl Acad Sci 109(13):4944–4949. https://doi.org/10.1073/pnas.1107254109

Ramakrishnan B, Venkateswarlu K, Sethunathan N, Megharaj M (2019) Local applications but global implications: can pesticides drive microorganisms to develop antimicrobial resistance? Sci Total Environ 654:177–189. https://doi.org/10.1016/j.scitotenv.2018.11.041

Rangasamy K, Athiappan M, Devarajan N, Parray JA (2017) Emergence of multi drug resistance among soil bacteria exposing to insecticides. Microb Pathog 105:153–165. https://doi.org/10.1016/j.micpath.2017.02.011

Rangasamy K, Athiappan M, Devarajan N, Samykannu G, Parray JA, Aruljothi KN, Shameem N, Alqarawi AA, Hashem A, Abd Allah EF (2018) Pesticide degrading natural multidrug resistance bacterial flora. Microb Pathog 114:304–310. https://doi.org/10.1016/j.micpath.2017.12.013

Reisser J, Shaw J, Wilcox C, Hardesty BD, Proietti M, Thums M, Pattiaratchi C (2013) Marine plastic pollution in waters around Australia: characteristics, concentrations, and pathways. PLoS One 8(11):e80466. https://doi.org/10.1371/journal.pone.0080466

Revel M, Châtel A, Mouneyrac C (2018) Micro(nano)plastics: a threat to human health? Curr Opin Environ Sci Health 1:17–23. https://doi.org/10.1016/j.coesh.2017.10.003

Rizzo L, Manaia C, Merlin C, Schwartz T, Dagot C, Ploy MC, Michael I, Fatta-Kassinos D (2013) Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. Sci Total Environ 447:345–360. https://doi.org/10.1016/j.scitotenv.2013.01.032

Rodríguez Martín JA, De Arana C, Ramos-Miras JJ, Gil C, Boluda R (2015) Impact of 70 years urban growth associated with heavy metal pollution. Environ Pollut 196:156–163. https://doi.org/10.1016/j.envpol.2014.10.014

Ruiz N, Montero T, Hernandez-Borrell J, Viñas M (2003) The role of Serratia marcescens porins in antibiotic resistance. Microb Drug Resist 9(3):257–264. https://doi.org/10.1089/107662903322286463

Rummel CD, Jahnke A, Gorokhova E, Kühnel D, Schmitt-Jansen M (2017) The impacts of biofilm formation on the fate and potential effects of microplastic in the aquatic environment. Environ Sci Technol Lett 4(7):258–267. https://doi.org/10.1021/acs.estlett.7b00164

Salyers AA, Amábile-Cuevas CF (1997) Why are antibiotic resistance genes so resistant to elimination? Antimicrob Agents Chemother 41(11):2321–2325

Santiago-Rodriguez TM, Fornaciari G, Luciani S, Dowd SE, Toranzos GA, Marota I, Cano RJ (2015) Gut microbiome of an 11th century A.D. pre-Columbian Andean mummy. PLoS One 10(9):e0138135. https://doi.org/10.1371/journal.pone.0138135

Schiering N, Kabsch W, Moore MJ, Distefano MD, Walsh CT, Pai EF (1991) Structure of the detoxification catalyst mercuric ion reductase from Bacillus sp. strain RC607. Nature 352(6331):168–172. https://doi.org/10.1038/352168a0

Seiler C, Berendonk TU (2012) Heavy metal driven co-selection of antibiotic resistance in soil and water bodies impacted by agriculture and aquaculture. Front Microbiol 3:399. https://doi.org/10.3389/fmicb.2012.00399

Sharma VK, Johnson N, Cizmas L, McDonald TJ, Kim H (2016) A review of the influence of treatment strategies on antibiotic resistant bacteria and antibiotic resistance genes. Chemosphere 150:702–714. https://doi.org/10.1016/j.chemosphere.2015.12.084

Silver S, Phung LT (1996) Bacterial heavy metal resistance: new surprises. Annu Rev Microbiol 50:753–789. https://doi.org/10.1146/annurev.micro.50.1.753

Slater-Radosti C, Van Aller G, Greenwood R, Nicholas R, Keller PM, DeWolf WE Jr, Fan F, Payne DJ, Jaworski DD (2001) Biochemical and genetic characterization of theaction of triclosan on *Staphylococcus aureus*. J Antimicrob Chemother 48(1):1–6. https://doi.org/10.1093/jac/48.1.1

Soumet C, Sheath E, Legrandois P, Maris P (2012) Resistance to phenicol compounds following adaptation to quaternary ammonium compounds in *Escherichia coli*. Vet Microbiol 158(1–2):147–152. https://doi.org/10.1016/j.vetmic.2012.01.030

Stepanauskas R, Glenn TC, Jagoe CH, Tuckfield RC, Lindell AH, McArthur JV (2005) Elevated microbial tolerance to metals and antibiotics in metal-contaminated industrial environments. Environ Sci Technol 39(10):3671–3678. https://doi.org/10.1021/es048468f

Sui Q, Zhang J, Chen M, Wang R, Wang Y, Wei Y (2019) Fate of microbial pollutants and evolution of antibiotic resistance in three types of soil amended with swine slurry. Environ Pollut 245:353–362. https://doi.org/10.1016/j.envpol.2018.11.003

Sun M, Ye M, Jiao W, Feng Y, Yu P, Liu M, Jiao J, He X, Liu K, Zhao Y, Wu J, Jiang X, Hu F (2018) Changes in tetracycline partitioning and bacteria/phage-comediated ARGs in microplastic-contaminated greenhouse soil facilitated by sophorolipid. J Hazard Mater 345:131–139. https://doi.org/10.1016/j.jhazmat.2017.11.036

Suzuki S, Kimura M, Agusa T, Rahman HM (2012) Vanadium accelerates horizontal transfer of tet (M) gene from marine Photobacterium to *Escherichia coli*. FEMS Microbiol Lett 336(1):52–56. https://doi.org/10.1111/j.1574-6968.2012.02653.x

Teitzel GM, Parsek MR (2003) Heavy metal resistance of biofilm and planktonic *Pseudomonas aeruginosa*. Appl Environ Microbiol 69(4):2313–2320. https://doi.org/10.1128/AEM.69.4.2313-2320.2003

Vale-Silva LA, Sanglard D (2015) Tipping the balance both ways: drug resistance and virulence in *Candida glabrata*. FEMS Yeast Res 15(4):fov025. https://doi.org/10.1093/femsyr/fov025

Vikesland PJ, Pruden A, Alvarez PJJ, Aga D, Bürgmann H, Li XD, Manaia CM, Nambi I, Wigginton K, Zhang T, Zhu YG (2017) Toward a comprehensive strategy to mitigate dissemination of environmental sources of antibiotic resistance. Environ Sci Technol 51 (22):13061–13069. https://doi.org/10.1021/acs.est.7b03623

Wales AD, Davies RH (2015) Co-selection of resistance to antibiotics, biocides and heavy metals, and its relevance to foodborne pathogens. Antibiotics (Basel) 4(4):567–604. https://doi.org/10.3390/antibiotics4040567

Wand ME, Bock LJ, Bonney LC, Sutton JM (2016) Mechanisms of increased resistance to chlorhexidine and cross-resistance to colistin following exposure of *Klebsiella pneumoniae* clinical isolates to chlorhexidine. Antimicrob Agents Chemother 61(1):e01162–e01116. https://doi.org/10.1128/AAC.01162-16

Wang R, Zhou X, Shi H (2015) Triple functional DNA-protein conjugates: signal probes for Pb(2+) using evanescent wave-induced emission. Biosens Bioelectron 74:78–84. https://doi.org/10.1016/j.bios.2015.06.003

Watts AJ, Urbina MA, Goodhead R, Moger J, Lewis C, Galloway TS (2016) Effect of microplastic on the gills of the shore crab *Carcinus maenas*. Environ Sci Technol 50(10):5364–5369. https://doi.org/10.1021/acs.est.6b01187

Wellington EM, Boxall AB, Cross P, Feil EJ, Gaze WH, Hawkey PM, Johnson-Rollings AS, Jones DL, Lee NM, Otten W, Thomas CM, Williams AP (2013) The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. Lancet Infect Dis 13 (2):155–165. https://doi.org/10.1016/S1473-3099(12)70317-1

Westfall C, Flores-Mireles AL, Robinson JI, Lynch AJL, Hultgren S, Henderson JP, Levin PA (2019) The widely used antimicrobial triclosan induces high levels of antibiotic tolerance in vitro and reduces antibiotic efficacy up to 100-fold in vivo. Antimicrob Agents Chemother 63(5):e02312–e02318. https://doi.org/10.1128/AAC.02312-18

Wright GD (2005) Bacterial resistance to antibiotics: enzymatic degradation and modification. Adv Drug Deliv Rev 57(10):1451–1470. https://doi.org/10.1016/j.addr.2005.04.002

Wright GD (2010) Antibiotic resistance in the environment: a link to the clinic? Curr Opin Microbiol 13(5):589–594. https://doi.org/10.1016/j.mib.2010.08.005

Wu D, Lu R, Chen Y, Qiu J, Deng C, Tan Q (2016) Study of cross-resistance mediated by antibiotics, chlorhexidine and Rhizoma coptidis in *Staphylococcus aureus*. J Glob Antimicrob Resist 7:61–66. https://doi.org/10.1016/j.jgar.2016.07.011

Yang S, Wen X, Zhao L, Shi Y, Jin H (2014) Crude oil treatment leads to shift of bacterial communities in soils from the deep active layer and upper permafrost along the China-Russia crude oil pipeline route. PLoS One 9(5):e96552. https://doi.org/10.1371/journal.pone.0096552

Zettler ER, Mincer TJ, Amaral-Zettler LA (2013) Life in the "plastisphere":microbial communities on plastic marine debris. Environ Sci Technol 47(13):7137–7146. https://doi.org/10.1021/es401288x

Zhang LP, Xing YP, Liu C, Zhou XH, Shi HC (2015) Label-free colorimetricdetection of Cu2þ, on the basis of Fenton reaction-assisted signal amplificationwith unmodified gold nanoparticles as indicator. Sens Actuators B Chem 215:561–567. https://doi.org/10.1016/j.snb.2015.03.062

Zhang Y, Gu AZ, He M, Li D, Chen J (2017) Subinhibitory concentrations of disinfectants promote the horizontal transfer of multidrug resistance genes within and across Genera. Environ Sci Technol 51(1):570–580. https://doi.org/10.1021/acs.est.6b03132

Zhang Y, Gu AZ, Cen T, Li X, He M, Li D, Chen J (2018) Sub-inhibitory concentrations of heavy metals facilitate the horizontal transfer of plasmid-mediated antibiotic resistance genes in water environment. Environ Pollut 237:74–82. https://doi.org/10.1016/j.envpol.2018.01.032

Zhao Y, Cocerva T, Cox S, Tardif S, Su JQ, Zhu YG, Brandt KK (2019) Evidence for co-selection of antibiotic resistance genes and mobile genetic elements in metal polluted urban soils. Sci Total Environ 656:512–520. https://doi.org/10.1016/j.scitotenv.2018.11.372

Zhao Y, Su JQ, An XL, Huang FY, Rensing C, Brandt KK, Zhu YG (2018) Feed additives shift gut microbiota and enrich antibiotic resistance in swine gut. Sci Total Environ 621:1224–1232. https://doi.org/10.1016/j.scitotenv.2017.10.106

Zhu YG, Johnson TA, Su JQ, Qiao M, Guo GX, Stedtfeld RD, Hashsham SA, Tiedje JM (2013) Diverse and abundant antibiotic resistance genes in Chinese swine farms. Proc Natl Acad Sci U S A 110(9):3435–3440. https://doi.org/10.1073/pnas.1222743110