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Special Series

Does Environmental Exposure to Pharmaceutical and Personal Care Product Residues Result in the Selection of Antimicrobial-Resistant Microorganisms, and is this Important in Terms of Human Health Outcomes?

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Abstract: The environment plays a critical role in the development, dissemination, and transmission of antimicrobial resistance (AMR). Pharmaceuticals and personal care products (PPCPs) enter the environment through direct application to the environment and through anthropogenic pollution. Although there is a growing body of evidence defining minimal selective concentrations (MSCs) of antibiotics and the role antibiotics play in horizontal gene transfer (HGT), there is limited evidence on the role of non-antibiotic PPCPs. Existing data show associations with the development of resistance or effects on bacterial growth rather than calculating selective endpoints. Research has focused on laboratory-based systems rather than in situ experiments, although PPCP concentrations found throughout wastewater, natural water, and soil environments are often within the range of laboratory-derived MSCs and at concentrations shown to promote HGT. Increased selection and HGT of AMR by PPCPs will result in an increase in total AMR abundance in the environment, increasing the risk of exposure and potential transmission of environmental AMR to humans. There is some evidence to suggest that humans can acquire resistance from environmental settings, with water environments being the most frequently studied. However, because this is currently limited, we recommend that more evidence be gathered to understand the risk the environment plays in regard to human health. In addition, we recommend that future research efforts focus on MSC-based experiments for non-antibiotic PPCPS, particularly in situ, and investigate the effect of PPCP mixtures on AMR. *Environ Toxicol Chem* 2024;43:623–636. © 2022 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

Keywords: Antimicrobials; personal care products; pharmaceuticals; soil ecotoxicology; water quality

INTRODUCTION

Antimicrobial resistance (AMR) is a global health crisis, with estimates suggesting that 1.27 million deaths globally in 2019 were attributable to antibacterial resistance (Antimicrobial Resistance Collaborators, 2022). Predictions have suggested that this could rise to 10 million deaths annually by 2050 if no steps are taken to address the issue (O'Neill, 2014). Many studies regard the environment as a source of AMR, clinically relevant or otherwise (Pärnänen et al., 2016; Perry & Wright, 2013); and increasing evidence supports the view that the environment plays an important role in the development, dissemination, and transmission of AMR (Singer et al., 2016).

Many sources and dissemination routes of pharmaceuticals and personal care products (PPCPs) into the environment exist (Figure 1). Pharmaceuticals and personal care products, such as prescription and non-prescription drugs, illicit drugs, cosmetics, disinfectants, detergents, and food preservatives, enter the environment through anthropogenic pollution sources (e.g., biocides released from laundry detergent [Dey et al.,

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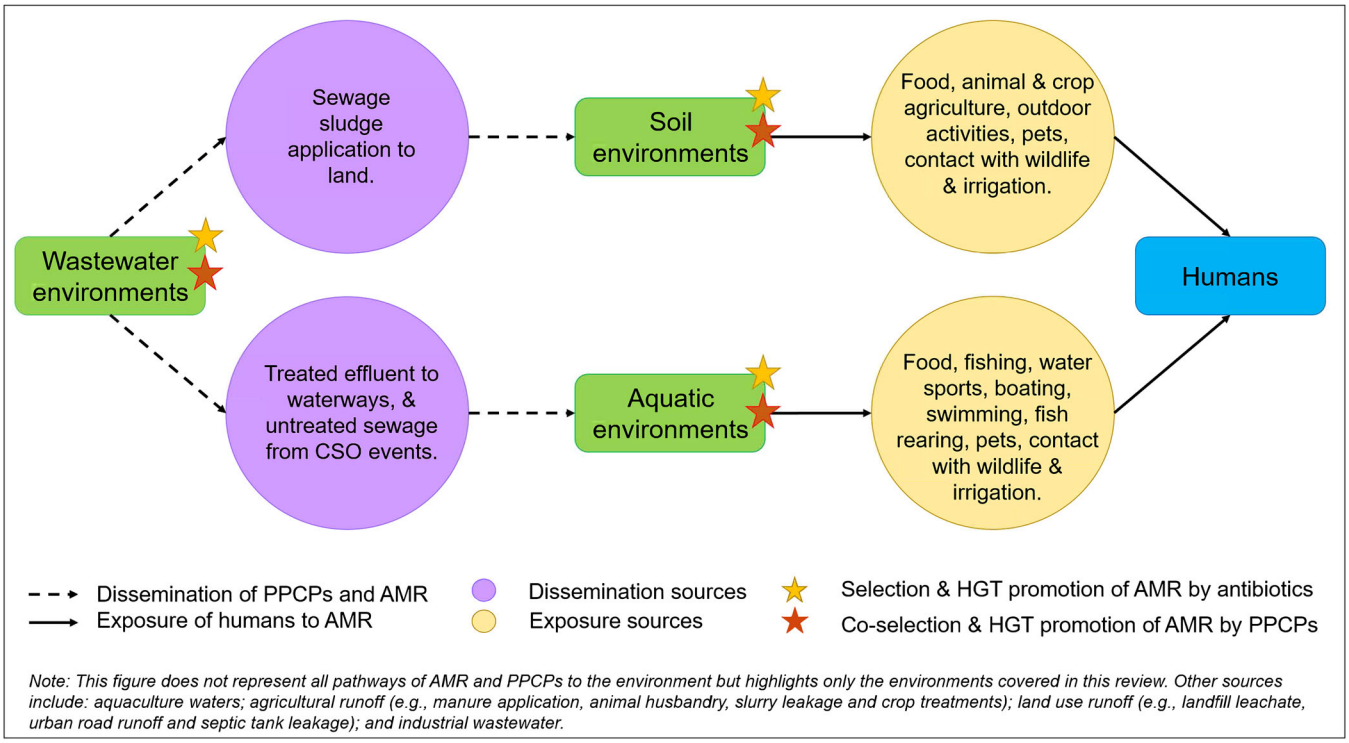

FIGURE 1: Systems map showing pharmaceutical and personal care product (PPCP) and antimicrobial resistance (AMR) dissemination routes through the environment covered in the present review, from wastewater environments to the natural environment. Environments where selection (by antibiotics) and co-selection (by non-antibiotic PPCPs) may occur are indicated. Exposure sources and routes of AMR to humans that may result in a human health outcome are also shown. The figure does not represent all anthropogenic sources of AMR or PPCPs into the natural environment but provides a summary of those discussed in the present review. CSO = combined sewage overflow; HGT = horizontal gene transfer.

2019] or pharmaceuticals released from drug manufacturing effluent [Kümmerer, 2009]). Inappropriate disposal practices, such as discarding licit and illicit drugs into household waste, can also contribute (Dey et al., 2019).

In the environment, PPCPs potentially increase AMR levels through selection or co-selection. Selection occurs when a chemical exerts direct selective pressure on a resistance gene or mutation that confers resistance against that chemical. Co-selection occurs when a non-antimicrobial chemical exerts an indirect selection pressure on an antibiotic resistance gene (ARG). This occurs via co-location of genes conferring resistance to different compounds on a plasmid or other genetic element (co-resistance; Baker-Austin et al., 2006) or when a single resistance mechanism provides resistance to multiple compounds (cross-resistance; e.g., efflux pumps; Chapman, 2003).

In 2012, the top 20 questions concerning the hazards, exposure assessment, and environmental and health risks of PPCPs in the natural environment were derived by a set of prominent experts in the field at a technical workshop hosted by the Society of Environmental Toxicology and Chemistry's Pharmaceutical Advisory Group (Boxall et al., 2012). The question posed in the title of the present review—"Does environmental exposure to PPCP residues result in the selection of antimicrobial resistant microorganisms, and is this important in terms of human health outcomes?"—was ranked third most important out of the final 20 key questions decided by workshop participants. On the tenth anniversary of the Boxall et al. publication, we hope to address this question by reviewing whether PPCP residues in the environment select or co-select for AMR and discuss the relevant importance to human health outcomes.

LABORATORY-BASED STUDIES INVESTIGATING SELECTION AND CO-SELECTION OF AMR

Selection

A number of laboratory studies have investigated whether subinhibitory (environmentally relevant) concentrations of antibiotics select for AMR. The lowest-observable-effect concentration (LOEC) that selection occurs at is often called the minimal selective concentration (MSC), and these terms are often used interchangeably. The MS/LOECs can inform discharge limits of antibiotics and can be used in risk assessments to understand the hazard posed by measured environmental concentrations (MECs). The highest concentration tested directly below the MSC/LOEC is termed the no-observable-effect concentration, on which assessment factors can be applied to calculate a predicted-no-effect concentration (PNEC; or PNEC for resistance [$PNEC_R$] in the case of AMR). By dividing MECs by PNEC values, a risk quotient can be calculated, where risk quotients >1 indicate high-risk environments (European Medicines Agency, 2006; Murray et al., 2021). Risk of selection is likely greater than single-chemical risk quotient values when we consider the total mixed chemical load in the environment.

The main experimental methods used to derive MSCs have been single-species competition assays. For single-species competition assays, selection coefficients (changes in the ratio of resistant to susceptible bacteria over time) were calculated to estimate MSCs (Gullberg et al., 2011, 2014; Kraupner et al., 2020; Liu et al., 2011; Vos et al., 2020). Competition assays have also been used to show that mixed communities require higher antibiotic concentrations to cause selection (Klümper et al., 2019).

Other studies have used complex, environmental communities that resemble natural environments to define MSCs. These often involve liquid microcosm experiments or biofilms inoculated with sewage bacterial communities that are evolved in the presence of antibiotics. Increases in resistance can be measured phenotypically (e.g., agar plating) or genotypically, with changes in gene prevalence quantitated with quantitative polymerase chain reaction (qPCR) or metagenomic sequencing. The three key approaches taken are as follows. 1) Microcosm evolution experiments using qPCR to measure ARGs (Kraupner et al., 2018; Murray et al., 2018, 2020; Stanton et al., 2020), sequencing to measure ARGs (Murray et al., 2018; Stanton et al., 2020), and/or plating to measure phenotypic resistance (Kraupner et al., 2020; Stanton et al., 2020). 2) A validated growth rate assay using growth rate as a proxy for selection (the Selection Endpoints in Communities of Bacteria assay; Murray et al., 2020). 3) Biofilms used in flow-through experiments exposing wastewater to antibiotics using qPCR to measure ARGs (Lundström et al., 2016), sequencing to measure ARGs (Kraupner et al., 2018, 2020; Lundström et al., 2016), and plating to measure phenotypic resistance (Lundström et al., 2016).

A table of available MSCs/LOECs has been collated by Murray et al. (2021), detailing test antibiotics, methods, analyses, and the MSCs/LOECs/PNECs found. We have provided a condensed version of this (Table 1), with updated experimentally derived MSC and LOEC values that were published after Murray et al. (2021). In addition to experimentally derived endpoints, $PNEC_R$s have been modelled for 111 antimicrobials and 11 antibiotic combinations. These $PNEC_R$s were based on minimum inhibitory concentration (MIC) values from the EUCAST database (European Committee on Antimicrobial Susceptibility Testing, 2022). The lowest 1% of observed MICs was identified and a 10-fold assessment factor applied. Values of $PNEC_R$ ranged from 0.008 (itraconazole) to 64 μg/L (nitrofurantoin; Bengtsson-Palme & Larsson, 2016).

Evidence suggests that antibiotic transformation products (Fatta-Kassinos et al., 2011) and enantiomeric antibiotics (Elder et al., 2020) could also select for AMR. In addition, sub-MSC concentrations have been shown to increase persistence of ARGs within bacteria communities (Kraupner et al., 2020; Larsson & Flach, 2021; Stanton et al., 2020). The lowest concentration at which this occurs is termed the minimal increased persistence concentration (Stanton et al., 2020).

The laboratory work investigating antimicrobials selecting for AMR has largely focused solely on antibiotics selecting for antibiotic resistance. However, Khan et al. (2017) determined multiple MSCs for the disinfectants chlorine and monochloramine using single-species competition assays. In addition, a recent review compared laboratory methodologies used to define MSCs for antibiotics and discussed the strengths and weaknesses of these in relation to their use in defining antifungal MSCs for antifungal resistance (Stevenson et al., 2022).

Co-selection

Many compounds can potentially co-select for resistance, including PPCPs and non-PPCPs, such as metals. Non-antibiotic PPCPs potentially co-select for AMR, although research remains limited. Research often focuses on co-selection by disinfectants, insect repellents, and preservatives in personal care products (PCPs). Benzalkonium chloride (BAC) is a quaternary ammonium compound (QAC) and disinfectant found in cosmetics, household cleaners, and washing detergents (Buffet-Bataillon et al., 2012). The QAC-resistance gene *qacEΔ1* forms part of the backbone of the genetic element Class 1 integron that carries numerous AMR gene cassettes. Thus, exposure to QACs may maintain or select for Class 1 integrons (harboring ARGs), resulting in co-selection of AMR by co-resistance (Moura et al., 2009; Partridge et al., 2009).

Several studies have investigated the co-selective potential of BAC. *Listeria monocytogenes* evolved higher ciprofloxacin MICs when experimentally exposed to BAC, with environmental strains having higher basal QAC MICs than those isolated from food (Guérin et al., 2021). Studies on Gram-positive species found that BAC exposure can decrease antibiotic susceptibility (Kampf, 2019) and increase antibiotic MICs (Nordholt et al., 2021). The relevance of this to contaminated environments is questionable, given the use of single-strain experiments and inhibitory concentrations. However, increases in AMR and antibiotic tolerance have been observed in experiments using river sediment communities exposed to subinhibitory concentrations of BAC (Kim et al., 2018; Oh et al., 2013). Another study exposed *Pseudomonas aeruginosa* to increasing concentrations of BAC and found that ciprofloxacin MICs increased by 256-fold. However, a study using untreated sewage as inoculum found that BAC exposure did not enrich antimicrobial, metal, or biocide resistance genes (Murray et al., 2019).

Triclosan is a disinfectant found in PCPs, though it has now been banned in soap products in many countries (Sinicropi et al., 2022). One study evolving *Stenotrophomonas maltophilia* in the presence of triclosan found reduced susceptibility to tetracycline, chloramphenicol, and ciprofloxacin, mediated through overexpression of the multidrug efflux pump *SmeDEF* (Sanchez et al., 2005). Another study using a complex community in an anaerobic digester showed that high triclosan concentrations increased tolerance to ciprofloxacin (Carey & McNamara, 2016). Subinhibitory concentrations of triclosan also decrease susceptibility of *Escherichia coli* to ciprofloxacin, penicillin, kanamycin, and gentamicin, although penicillin tolerance reverted to wild-type levels after 20 generations with no triclosan exposure (Li et al., 2019). *Salmonella enterica* serovar Typhimurium strains exposed to increasing triclosan concentrations showed decreased susceptibility to chloramphenicol, tetracycline, and ampicillin, with overexpression of the *AcrAB* efflux pump, suggesting further co-selective

TABLE 1: Summary table of laboratory-derived minimal selective concentration/lowest-observable-effect concentration values

Antibiotic	Methodology	MSC/LOEC (μg/L)	Reference
Amikacin	Single-species evolution experiment	400	Sanz-García et al. (2021)
Azithromycin	qPCR of ARGs from sewage microcosm	750	Stanton et al. (2020)
	OD using SELECT assay with sewage	1000	Murray et al. (2020)
Cefapime	Isogenic competition experiment	4.74–13.61	H. Wang et al. (2022)
Cefotaxime	qPCR of ARGs from sewage microcosm	4	Murray et al. (2018)
	qPCR of ARGs from sewage microcosm	15.63	Murray et al. (2020)
	qPCR of ARGs from sewage microcosm	125	Murray et al. (2020)
Ceftazidime	Single-species evolution experiment	400	Sanz-García et al. (2021)
Ciprofloxacin	Isogenic competition experiment	0.1	Gullberg et al. (2011)
	OD using SELECT assay with sewage	0.98	Murray et al. (2020)
	qPCR of ARGs from biofilm microcosm	1	Kraupner et al. (2018)
	qPCR of ARGs from sewage microcosm	10.77	Stanton et al. (2020)
	Isogenic competition experiment	0.004	Vos et al. (2020)
	qPCR of ARGs from sewage microcosm	15.625	Stanton et al. (2020)
	Isogenic competition in mallard gut	21	Atterby et al. (2021)
	Single-species evolution experiment	5	Sanz-García et al. (2021)
	Competition experiment in a biofilm	0.96	Tang et al. (2022)
Chloramphenicol	OD using SELECT assay with sewage	250	Murray et al. (2020)
	qPCR of ARGs from sewage microcosm	500	Murray et al. (2020)
Clarithromycin	qPCR of ARGs from sewage microcosm	750	Stanton et al. (2020)
	OD using SELECT assay with sewage	5000	Murray et al. (2020)
Erythromycin	qPCR of ARGs from sewage microcosm	514.1	Stanton et al. (2020)
	qPCR of ARGs from sewage microcosm	750	Stanton et al. (2020)
	Isogenic competition experiment	3000	Gullberg et al. (2014)
	OD using SELECT assay with sewage	25 000	Murray et al. (2020)
Fosfomycin	Isogenic competition in planktonic system	400	Hjort et al. (2022)
	Isogenic competition in biofilm system	1200	Hjort et al. (2022)
Gentamicin	OD using SELECT assay with sewage	250	Murray et al. (2020)
	qPCR of ARGs from sewage microcosm	250	Murray et al. (2020)
Imipenem	Single-species evolution experiment	250	Sanz-García et al. (2021)
Kanamycin	Isogenic competition experiment	470	Gullberg et al. (2014)
Levofloxacin	Single-species evolution experiment	80	Sanz-García et al. (2021)
Nitrofurantoin	Isogenic competition in planktonic system	400	Hjort et al. (2022)
Polymyxin B	Single-species evolution experiment	2000	Sanz-García et al. (2021)
Rifampicin	Isogenic competition in planktonic system	1100	Hjort et al. (2022)
	Isogenic competition in biofilm system	1500	Hjort et al. (2022)
Streptomycin	Isogenic competition experiment	1	Gullberg et al. (2011)
	Isogenic competition in planktonic system	300–3100	Hjort et al. (2022)
	Isogenic competition in biofilm system	2200–5900	Hjort et al. (2022)
Tetracycline	qPCR of ARGs from biofilm microcosm	1	Lundström et al. (2016)
	Single-species evolution experiment	1500	Sanz-García et al. (2021)
	Isogenic competition experiment	15	Gullberg et al. (2011)
	Isogenic competition experiment	45	Gullberg et al. (2014)
Trimethoprim	OD using SELECT assay with sewage	31.25	Murray et al. (2020)
	Isogenic competition experiment	33	Gullberg et al. (2014)
	qPCR of ARGs from sewage microcosm	62.5	Murray et al. (2020)
	Isogenic competition experiment	100	Kraupner et al. (2020)
	Escherichia coli microcosm	100	Kraupner et al. (2020)
	qPCR of ARGs from biofilm microcosm	100	Kraupner et al. (2020)
	Isogenic competition in planktonic system	17	Hjort et al. (2022)
	Isogenic competition in biofilm system	23	Hjort et al. (2022)

Adapted from Murray et al. (2021).
ARG = antibiotic resistance gene; LOEC = lowest observable effect concentration; MSC = minimal selective concentration; qPCR = quantitative polymerase chain reaction; OD = optical density; SELECT = Selection Endpoints in Communities of Bacteria.

potential (Karatzas et al., 2007). However, collateral sensitivity (whereby acquisition of resistance to one compound results in increased susceptibility to another compound) arising from triclosan (Curiao et al., 2016) and triclocarban (Carey & McNamara, 2016) exposure in *S. enterica* has also been documented. Beyond BAC and triclosan, chlorhexidine exposure has also been associated with increasing AMR (Kampf, 2019).

Zinc is used in numerous cosmetic products as an antioxidant, antiaging, antimicrobial, and anti-inflammatory agent (Abendrot & Kalinowska-Lis, 2018). In a single-species competition experiment, zinc increased the MSC of ciprofloxacin by fivefold, suggesting that zinc and ciprofloxacin behave antagonistically (Vos et al., 2020).

Though studies directly investigating selection for resistance by other PPCPs have not been performed, research indicates

they are warranted. For example, the anticonvulsant carbamazepine has been shown to increase ARGs in the *Folsomia candida* gut (Y.-F. Wang et al., 2020). Further, of 835 human-targeted non-antimicrobial pharmaceuticals, 24% inhibited growth of at least one bacterial species in vitro (Maier et al., 2018). Any reduction in growth could indicate a potential selective pressure (Greenfield et al., 2018; Gullberg et al., 2011, 2014; Murray et al., 2020). In addition, the insect repellents picaridin and *N*,*N*-diethyl-meta-toluamide have shown antimicrobial properties against bacteria, yeast, and fungal species (Kalaycı et al., 2014). 2-Ethyl-hexyl-4-trimethoxycinnamate, an ultraviolet filter in sunscreens, caused reduced nitrification in a river sediment community (Xu et al., 2020), again suggestive of selective pressure. Parabens are used as preservatives in PCPs, and resistance in bacteria is often mediated through similar mechanisms to antibiotic resistance (Bolujoko et al., 2021). To date, a single study has found little evidence to support co-selection of AMR by parabens when testing *Enterobacter gergoviae* (Davin-Regli et al., 2006). Finally, linalool is an aromatic plant metabolite found in 60%–90% of cosmetic products and is used in detergents (Aprotosoaie et al., 2014). A study exposing *S. enterica* serovar Senftenberg to linalool determined that resistance to five antibiotics increased and amikacin resistance decreased postexposure in comparison to non-exposed strains (Kalily et al., 2017).

LABORATORY-BASED STUDIES INVESTIGATING HORIZONTAL GENE TRANSFER

Pharmaceuticals and personal care products can increase the mobility of ARGs by enhancing horizontal gene transfer (HGT). Elevated HGT rates increase the absolute abundance and potential microbial host range of ARGs. Through the ability to transfer to diverse hosts (Klümper et al., 2015), mobile traits encoded on plasmids increase their potential to persist and be selected and transported to novel environments (Hülter et al., 2017; Séveno et al., 2002). Further, HGT can result in ARGs transferring to pathogens. The three main HGT mechanisms, conjugation, transformation, and transduction (Gogarten et al., 2002; Zhaxybayeva & Doolittle, 2011) need to be considered to evaluate the effects of PPCPs.

Conjugation, the direct exchange of DNA between bacteria, is thought to be the most efficient HGT mechanism (Guglielmini et al., 2011; Halary et al., 2010). Effects of PPCPs on conjugation have been widely studied, evidencing that environmentally relevant concentrations of antibiotics regularly increase plasmid transfer rates within bacterial communities (Jutkina et al., 2016, 2018; Shun-Mei et al., 2018). In addition, this has been described for a number of non-antibiotic pharmaceuticals like carbamazepine, ibuprofen, naproxen, diclofenac, gemfibrozil, and propranolol (Y. Wang et al., 2018, 2021). The mechanism responsible for PPCPs elevating plasmid transfer rates is their ability to trigger the bacterial SOS stress response, increasing reactive oxygen species and cell membrane permeability (Y. Wang et al., 2021). Triggering the SOS response can induce conjugation of AMR-encoding transposons from bacterial chromosomes (Seier-Petersen et al., 2014). Non-antibiotic pharmaceuticals have also been shown to trigger the bacterial stress response (Lagadinou et al., 2020), suggesting potential effects on transfer rates of AMR-encoding plasmids. Evidence also exists of metal cations (regularly used in PPCPs) altering plasmid transfer rates in soil communities in short-term (Klümper et al., 2017) and long-term (Song et al., 2020) exposures. Particularly strong effects were proven for metal nanoparticles of copper (Zhang et al., 2019) and silver (Lu, Wang, Jin, et al., 2020), which are used in antibacterial coatings in plasters, for example.

Transformation refers to bacterial uptake of free extracellular environmental DNA (eDNA). A small proportion of bacteria can absorb and integrate eDNA (i.e., competent cells). Competence occurs constitutionally or is induced by environmental factors (Hanahan, 1983; Nielsen & van Elsas, 2001). Pharmaceuticals and personal care products can induce bacterial competence or increase availability of free eDNA, promoting spread of AMR by transformation (Winter et al., 2021), as evidenced at environmentally relevant concentrations of antibiotics (Charpentier et al., 2012; Prudhomme et al., 2006), non-antibiotic pharmaceuticals (Y. Wang et al., 2020), and triclosan (Lu, Wang, Zhang, et al., 2020).

Finally, transduction, the indirect transfer of DNA by bacteriophages, relies on mistakes in viral packaging or prophage excision, during which genes from the current host are integrated into phage DNA (Watson et al., 2018). During infection, phage DNA is integrated into the host chromosome, including mispackaged former host's genes. Pharmaceuticals and personal care products affecting transduction through inducing prophages at environmentally relevant concentrations include antibiotics (Allen et al., 2011; Maiques et al., 2006) and nonantibiotic pharmaceuticals (Sutcliffe et al., 2021). These compounds are known to be able to cause oxidative stress inside the prophage hosting bacteria (Y. Wang et al., 2021), a common trigger for up-regulation of prophage excision from the chromosome (Liu et al., 2015). This leads to higher phage abundance and hence a higher transduction likelihood.

While these laboratory studies have demonstrated that PPCPs at environmental concentrations can influence HGT, their relative environmental contribution needs further investigation.

FIELD-BASED STUDIES SHOWING EVIDENCE FOR EFFECTS OF PPCPs ON AMR

Wastewater

Sewage treatment is necessary for sanitation (Hunt, 2006). Large-scale convergence of wastewater creates niches distinct from those in nature, resulting in significant ecological impacts at confluence points of wastewater and natural waters. Wastewater is a complex physiochemical and biological matrix (Newton et al., 2015) posing significant potential for selection of AMR by PPCPs. Healthcare-associated wastewater from hospitals or care homes contains elevated levels of PPCPs and

AMR because antibiotic/disinfectant use and carriage of AMR are more frequent in these populations (Hocquet et al., 2016). Hospital wastewater has significantly higher antibiotic residues than domestic wastewater (Aydin et al., 2019; Carraro et al., 2018; Paulus et al., 2019; Perry et al., 2021), with some concentrations far exceeding MSCs (Yao et al., 2021). For example, measured ciprofloxacin concentrations of 9900 μg/L (Perry et al., 2021) are much higher than reported MSCs (5–10.77 μg/L; Bengtsson-Palme & Larsson, 2016; Kraupner et al., 2018; Stanton et al., 2020). However, concentrations vary across antibiotics, hospitals, and seasons. In the Pharmaceuticals in the Environment database (UmweltBundesamt, 2021), the median ciprofloxacin concentration from hospital wastewater (7.5 μg/L) was lower than that seen by Perry et al. (2021) yet remained within the MSC range.

Effluents from industry and pharmaceutical production are known to contain highly concentrated mixtures of PPCPs, far in excess of discharges from healthcare or domestic wastewater (Bengtsson-Palme & Larsson, 2016; Larsson, 2014). Domestic wastewater contains not only large volumes of unmetabolized antibiotics from widespread use and excretion from large populations but also incorrectly disposed of and unused PPCPs. Antibiotic concentrations of domestic wastewater are generally lower than those in healthcare wastewater in direct point-prevalence surveys. However, several studies normalizing total antibiotic loads in wastewater-treatment plant (WWTP) influent have shown that households can contribute more than point sources such as healthcare (Aydin et al., 2019; Santos et al., 2013; Verlicchi et al., 2012). While higher total loads do not necessarily result in antibiotic concentrations reaching MSCs after dilution, they may represent the accumulation of antibiotics in sewer sediments via sorption to biofilms (Jarnheimer et al., 2004). This is expected to attenuate temporal flux of antibiotics, maintain supply to WWTPs, and potentially result in sewer hotspots with locally high antibiotic concentrations reaching MSCs.

These findings highlight the importance of domestic effluents as sources of PPCPs entering WWTPs. In addition, parabens are often used as preservatives in PCPs, and paraben-resistant bacteria have been isolated from sewage-treatment plants in India (Selvaraj et al., 2013). However, based on the limited research conducted to date, parabens have not yet been definitively linked to co-selection of AMR (Davin-Regli et al., 2006).

Studies have found that HGT of AMR occurs in WWTPs, with antibiotics, polycyclic aromatic hydrocarbons, and WWTP processes promoting stress responses and phage proliferation (Woegerbauer et al., 2020). Bacteriophages carrying ARGs have been isolated from urban wastewater, which, when cloned into susceptible *E. coli*, rendered them resistant (Colomer-Lluch et al., 2014). Conjugative plasmids have also been demonstrated to facilitate persistence of ARGs (Che et al., 2019). Finally, Hutinel et al. (2021) found that although PPCPs (including antibiotics, biocides, and non-antibiotic pharmaceuticals) in municipal wastewater were unable to promote HGT, PPCPs from hospital wastewater increased the proportion of *E. coli* recipients of HGT (Hutinel et al., 2021).

Modern sanitation infrastructure is a closed system, which reduces human exposure to PPCPs and AMR. However, many low- and middle-income countries lack WWTP infrastructure; thus, populations may be exposed to untreated wastewater from open drainage trenches or contamination of tap water (Tong et al., 2020). High-income countries with modern sewage systems minimize these risks but are reliant on effective treatment of waste. Failure to adequately reduce PPCP loads puts receiving environments at risk.

Natural water environments

Natural water environments encompass marine and freshwater environments (including rivers, streams, lakes, coastal water bodies, and estuaries). Often, aquatic environments are exposed to and act as receivers of anthropogenic pollution, including treated and untreated domestic, hospital, and industrial wastewater; agricultural and other land-use runoff (e.g., landfill leachate, urban road runoff, and septic tank leakage); and aquaculture waters. This exposure facilitates the release of PPCPs into water bodies, allowing AMR to proliferate (Amos et al., 2015; Cabello et al., 2016; Williams et al., 2016). The development and spread of AMR in the environment is a result of the exposure of microbial communities to multiple stressors (e.g., mixed selective agents; Berendonk et al., 2015; McArthur & Tuckfield, 2000) and changing environmental conditions (e.g., nutrient concentrations and pH; Khan et al., 2017).

Measured environmental concentrations of PPCPs throughout natural water bodies vary substantially, depending on pollution inputs, sample type, and season. A common entry point of PPCPs into water bodies is from WWTP effluent. Pharmaceuticals are often not fully metabolized and, like some PCPs, may not be eradicated during wastewater treatment. Pharmaceuticals and personal care products and their degradation products are found in complex mixtures in WWTPs (Backhaus & Faust, 2012; Brandt et al., 2015; Marx et al., 2015). For example, 56 unique pharmaceuticals were investigated in the effluent of 50 WWTPs, with hydrochlorothiazide detected in every sample; metoprolol, atenolol, and carbamazepine detected in 90% of samples; and antibiotics on average detected 56% of the time (Kostich et al., 2014). In a study examining sites up- and downstream of WWTP outflows, Amos et al. (2018) found higher levels of Class 1 integrons downstream and showed that QACs co-select for the mobilization of Class 1 integrons and *blaCTX-M* from environmental isolates. Similarly, Middleton and Salierno (2013) showed that triclosan-resistant isolates from surface water near WWTP outfalls were significantly more resistant to chloramphenicol and nitrofurantoin.

Untreated sewage can be discharged from combined sewage overflows (CSOs), contaminating the receiving environment. The impact of CSOs on AMR selection is understudied but has recently become a topic of public (BBC News, 2021), policy (Department for Environment, Food & Rural Affairs, 2021; Singer et al., 2021), and scientific (Eramo et al., 2017; Honda et al., 2020) interest. Socioeconomic factors can amplify wastewater contamination of water bodies. For example, some low- and middle-income countries lack wastewater-treatment and sanitation processes and directly dispose of fecal waste onto land or into water bodies (Segura et al., 2015). This can occur in

high-income countries, although concentrations are likely lower because of more effective wastewater treatment, improved antimicrobial stewardship, and policies that reduce pollution (e.g., European Union Water Framework Directive; Bougnom & Piddock, 2017; Nadimpalli et al., 2018; Vikesland et al., 2019). Data from rivers across 104 countries found that the highest concentrations of active pharmaceutical ingredients (APIs) in rivers (e.g., caffeine, metformin, paracetamol, sulfamethoxazole) were detected in lower-middle-income countries (categorized by using gross national income index; Wilkinson et al., 2022). Regions with less regulated access to medicines had greater variability and range of API concentrations (Wilkinson et al., 2022).

Release of PPCPs into water bodies from drug manufacturing effluent is also of concern. Often, antibiotic concentrations in pharmaceutical effluents far exceed MSCs (e.g., ciprofloxacin MECs 28 000–31 000 μg/L [Larsson et al., 2007] exceeding the MSC of 10.77 μg/L [Stanton et al., 2020]), posing a high risk for selection. This is also likely exacerbated by socioeconomic factors (e.g., in low- and middle-income countries; Segura et al., 2015). However, instances of concentrations reaching MSCs have been reported even after wastewater treatment in high-income countries (Babić et al., 2006; Phillips et al., 2010).

Another route by which PPCPs enter water bodies is through agricultural runoff. Pharmaceuticals are used in livestock rearing, as prophylactics, therapeutics, or growth promoters (Landers et al., 2012). This results in the transfer of PPCPs and AMR through livestock defecation and addition of fecal waste to farmland, inevitably ending up in water bodies (Lee et al., 2019). Pharmaceuticals and personal care products are also used in aquaculture and are administered in feed or directly released into water. Of the antibiotics ingested by fish, approximately 80% enter water and sediment via excretion (Cabello et al., 2013), resulting in fish farms being one of the most contaminated types of water body (Guruge et al., 2019).

There is a lack of data showing the effects of PPCP concentrations on selection for AMR in natural water bodies (Ebele et al., 2017; Fu et al., 2019; Luo et al., 2014). In the absence of realistic experiments, many studies infer risk of selection by calculating metrics such as risk quotients (as described above *Selection*). For example, risk quotients derived from MECs for 98 PPCPs in water environments in India showed that 81% and 38% of antibiotics detected in surface and groundwater, respectively, were at concentrations high enough to pose a risk of AMR selection (Sengar & Vijayanandan, 2022). That study is at the extreme end of the scale, and concentrations of singular PPCPs in natural water bodies are often not high enough to select for resistance alone. However, it is likely that the net effect of a mixture of antimicrobial compounds will exert a greater effect than each compound would exert individually (e.g., through additive or synergistic effects; Marx et al., 2015; Mitosch & Bollenbach, 2014).

Soil environments

Soil represents one of the evolutionary origins of AMR (Cytryn, 2013; Forsberg et al., 2012; Nesme & Simonet, 2015), and soil-associated ARGs have been suggested as the primary reservoir for clinical ARGs (Kim & Cha, 2021). Therefore, the contribution of PPCPs to the mobilization, maintenance, and dissemination of AMR in soil needs elucidation.

Manure, municipal waste, and treated wastewater irrigation are regularly input into soil environments during agricultural processes and have been identified as critical sources of AMR in soil (Cytryn, 2013). Biosolids and manure are valued resources of nutrients for crop growth and are commonly used as agricultural fertilizers (Case & Jensen, 2019; Subirats et al., 2021). Reuse of treated wastewater for agricultural irrigation is increasing in arid and semiarid regions of the world as a result of dwindling freshwater resources, expanding agricultural sectors, and the influence of climate change (Ungureanu et al., 2020). Such resources contain PPCPs, which may enter agricultural soils and elevate AMR levels. The bioavailability of PPCPs in the soil is dependent on their sorption and soil parameters (e.g., pH; Wegst-Uhrich et al., 2014). Soil antibiotic concentrations are strongly linked to land-use patterns, with agricultural land being the main source of antibiotics entering the soil (Zhao et al., 2020).

Antibiotic concentrations in soils amended with long-term manure application were significantly elevated in comparison to non-treated soils. Concentrations ranged from 81.50 to 178.99 μg/kg and from 60.59 to 202.37 μg/kg for tetracyclines and sulfonamides, respectively (Rahman et al., 2018). In addition, application of pig manure increased ARG levels for up to a year (Scott et al., 2018). A macrolide resistance gene, *ermB* persisted at high levels for a decade after manure application (Scott et al., 2018). Further, a 10 000-fold increase of four tetracycline ARGs was observed for manure amended soil in comparison to a control (Leclercq et al., 2016). Manure has been shown to increase the HGT of sulfadiazine resistance, with the application of manure and sulfadiazine increasing Class 1 integrons in soil (Heuer & Smalla, 2007).

Also, PPCPs can be found in soils amended with biosolids. Gottschall et al. (2012) monitored over 80 PPCPs in soil after application of dewatered biosolids. Dissipation of many PPCPs in biosolid-amended soils occurred within the first few months after application; however, PPCPs such as miconazole, triclocarban, and carbamazepine were still detectable over 1-year post–biosolid application at concentrations of 127, 22, and 30 μg/kg, respectively (Gottschall et al., 2012).

Irrigation using reclaimed water has been shown to promote the maintenance of antibiotics in soils (Gao et al., 2015). Soils irrigated with treated wastewater generally have concentrations of antibiotics <10 μg/kg (Biel-Maeso et al., 2018; Christou et al., 2017). In turn, those irrigated with untreated wastewater can contain concentrations ranging from not detectable to 2160 μg/kg, with median values of 52.8 and 0.15 μg/kg and not detectable for quinolone, sulfonamide, and macrolide antibiotics, respectively (Gao et al., 2015). Regarding the effect of PPCPs in reclaimed wastewater on AMR in soils, a study comparing agricultural soils irrigated with freshwater and treated wastewater found similar levels of AMR (Negreanu et al., 2012). However, long-term untreated wastewater irrigation had a significant impact on ARG levels in agricultural soils (Dalkmann et al., 2012).

The presence of antibiotics in the soil, even at sub-MIC concentrations, can select for antibiotic-resistant bacteria and enhance the transfer of ARGs and mobile genetic elements (Cycoń et al., 2019). Although no MSCs have been defined in situ in soil environments, Han et al. (2022) investigated the direct application of erythromycin fermentation residues (a by-product of the production of erythromycin) to soil, which is often used as organic fertilizer. Resulting concentrations of erythromycin in soil ranged from 0.83 to 76 μg/kg, and a significant increase in macrolide–lincosamide–streptogramin ARGs was observed gradually during the 3-year experiment (Han et al., 2022). Similarly, Brown et al. (2022) tested long-term (10 years) contamination of soil at high concentrations of three macrolides (10 mg/kg) and at concentrations similar to those detected in biosolids or manure (0.1 mg/kg). No effect was observed at 0.1 mg/kg, yet at 10 mg/kg, 21 clinically relevant ARGs and 20 mobile genetic elements increased (Brown et al., 2022). While this suggests that concentrations in manure and biosolids are not high enough to select for resistance, laboratory studies (described above) have shown that MSCs/LOECs vary significantly based on antibiotic type (Murray et al., 2021; Stanton et al., 2020), with macrolides having some of the highest MSC values (Murray et al., 2020; Stanton et al., 2020). Antibiotics with lower MSC values (such as ciprofloxacin [Kraupner et al., 2018; Murray et al., 2020; Stanton et al., 2020]) may be more potent, potentially resulting in increased levels of ARGs and mobile genetic elements, although MSCs for these antibiotics have yet to be derived in soils. These laboratory-derived MSCs are calculated from liquid experiments and are therefore represented in different units (i.e., micrograms per liter as opposed to micrograms per kilogram), making soil comparisons to these laboratory endpoints difficult. Further, the distinct properties of soil and changing behavior of PPCPs within soil (i.e., compound- and environment-dependent sorption and/or degradation; Chen & Akhtar, 2022) can also make laboratory endpoint comparisons complicated.

IMPORTANCE TO HUMAN HEALTH

Increased levels of AMR driven by selection and HGT may result in increased exposure events when humans interact with the above environments, whether through recreational (e.g., swimming in designated bathing waters, swimming in natural waters that are not monitored for bathing water quality), occupational (e.g., WWTP worker), or essential (e.g., drinking water) activities.

A recent publication systematically compiled evidence on transmission of AMR from the environment to humans and found only 40 articles globally (Stanton et al., 2022). Papers investigated the risk of exposure to AMR in natural environments by calculating the burden of AMR in a particular volume of environmental matrix. Exposure risks were subsequently calculated based on the volume of matrices humans are exposed to (Stanton et al., 2022). For example, the number of third-generation cephalosporin-resistant *E. coli* in coastal water was determined, and ingestion estimates of different water users were used to calculate exposure events during a bathing session (Leonard et al., 2015). Further, AMR exposure based on consumption of surface water–irrigated lettuce has been studied (O'Flaherty et al., 2019). Finally, estimated daily intake of ARGs via inhalation of airborne fine particles, ingestion of drinking water, and accidental ingestion of agricultural soil has been calculated (Xie et al., 2018).

Direct transmission of AMR from the environment to humans has also been investigated (Stanton et al., 2022). For example, surfers are four times more likely (following ingestion of coastal water) to be colonized by *CTX-M*-producing *E. coli* than non-surfers (Leonard et al., 2018). Further, 32% of reclaimed water irrigation workers were colonized by resistant *Staphylococci* compared to 4% of control office workers (Goldstein et al., 2017). While the exposure to AMR is occurring during an occupational activity, the source of the AMR is still environmental (reclaimed water).

Finally, Stanton et al. (2022) reported studies where AMR was transmitted from the environment following an accident and resulted in a human health outcome. For example, a near-drowning event in a river resulted in a carbapenemase-producing *Enterobacter asburiae* infection (Laurens et al., 2018).

Stanton et al. (2022) highlighted that transmission of AMR from the environment to humans is an underresearched topic area, with only 40 studies globally. However, within those 40 studies, water environments were studied most frequently ($n = 40$ water environments, although, on occasion, the same study investigated more than one water exposure source). In contrast, only one study investigated the potential exposure to AMR from soil that could result in an adverse human health outcome (described above; Stanton et al., 2022).

Since the systematic map from Stanton et al. (2022), further work has been published investigating human health risks of exposure to environmental sources of AMR, with water environments continuing to be the focus of research on exposure risk. For example, Rodríguez-Molina et al. (2021) found that WWTP workers, residents who lived within 300 m of WWTPs, and residents who lived >300 m from a WWTP (as a control) carried 11%, 29%, and 7% extended-spectrum beta-lactamase Enterobacterales, respectively. This suggests that proximity and exposure to wastewater increase the risk of being colonized by antibiotic-resistant bacteria. In addition, Devi and Chattopadhya (2022) investigated colonization by extended-spectrum beta-lactamase *E. coli* of farmers who washed buffalo in earth ponds (37.5% rate of colonization) in comparison to age-matched household members who worked with the buffalo but did not wash them (20.7%), suggesting that transmission could occur from animal to human via a water source.

If AMR in natural environments increases as a result of selection, co-selection, or HGT by PPCPs, there will be an elevated risk to humans in contact with these environments, which could potentially result in a human health outcome. As demonstrated in the present review, selection, co-selection, and HGT can occur at environmentally relevant concentrations of PPCPs in water environments; and transmission of AMR can occur from water environments, resulting in a human health

outcome. However, there is a significant lack of research on selection, co-selection, and promotion of HGT in soil environments and on transmission of AMR from soil to humans.

PRIORITY RESEARCH QUESTIONS

Below is a list of questions deemed a priority for tackling the development of AMR as a result of selection from PPCPs in the environment:

1. What are the MECs of PPCPs in various natural environments?
2. What are the MSCs of non-antibiotic PPCPs?
3. What are the in situ MSCs of PPCPs in the environment, and do these align with laboratory-derived MSCs?
4. What are the effects of PPCP mixtures on selection and HGT in the environment?
5. Does transmission from various underresearched natural environments result in a human health outcome?

CONCLUSIONS

As evidenced throughout the present review, PPCPs are present in both wastewater and natural environments. There is a growing body of empirical evidence suggesting that environmental concentrations of antibiotics are often high enough to select for resistance and cause HGT, but until relatively recently there had been limited laboratory studies with mixed microbial community context. While there are limited data defining MSCs/LOECs for non-antibiotic PPCPs, a growing body of research suggests that these do affect both microbial growth and MICs. There is also evidence to suggest that non-antibiotic PPCPs affect HGT (e.g., by enhancing plasmid transfer rates). There is limited evidence of the effects of PPCP mixtures on selection and co-selection, even in laboratory studies, which could potentially exert a greater effect than the constituent compounds individually (Brown et al., 2022; Stanton, 2020; Vos et al., 2020).

Our understanding of the fate and effects of PPCPs in natural environments is incomplete (Ebele et al., 2017; Fu et al., 2019; Luo et al., 2014) and is exacerbated by the difficulty in performing in situ experiments because of an inability to control external factors such as exposure to a complex mix of selecting and co-selecting compounds, exposure to other pollutants, weather events, and other biotic and abiotic factors (Chow et al., 2015). Extensive research exists detailing correlative concentrations of PPCPs and ARGs in natural environments, but knowledge gaps remain regarding selection, co-selection, and acquisition of AMR in these environments (Niegowska et al., 2021). Often, studies report the co-occurrence of PPCPs and AMR, using statistical associations, predictive modeling (Singer et al., 2019), or network analyses to infer selection. In the absence of in situ evidence of transmission and selection and any standardized guidelines on the environmental risk assessment for selection of AMR (Ågerstrand et al., 2015; Murray et al., 2021), many studies have taken to calculating PNECs, MSCs and risk quotients, to give an AMR risk context to their findings.

If AMR does increase as a result of selection, co-selection, and HGT by PPCPs in the environment, as suggested by laboratory data, elevated PPCP concentrations in the environment will put people who interact with the environment at increased risk of both exposure to and transmission of AMR. There is a growing, yet still limited, body of evidence to suggest that transmission from the environment can occur, particularly from water environments. Addressing the priority research questions described in the present review will increase collective understanding of the effects of PPCPs on the selection of AMR in the environment. Complementary to this, reducing PPCP load, and therefore selection pressure, will reduce human exposure and transmission risk to AMR.

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REFERENCES

Abendrot, M., & Kalinowska-Lis, U. (2018). Zinc-containing compounds for personal care applications. *International Journal of Cosmetic Science*, *40*(4), 319–327. https://doi.org/10.1111/ics.12463

Ågerstrand, M., Berg, C., Björlenius, B., Breitholtz, M., Brunström, B., Fick, J., Gunnarsson, L., Larsson, D. G. J., Sumpter, J. P., Tysklind, M., & Rudén, C. (2015). Improving environmental risk assessment of human pharmaceuticals. *Environmental Science & Technology*, *49*(9), 5336–5345. https://doi.org/10.1021/acs.est.5b00302

Allen, H. K., Looft, T., Bayles, D. O., Humphrey, S., Levine, U. Y., Alt, D., & Stanton, T. B. (2011). Antibiotics in feed induce prophages in swine fecal microbiomes. *mBio*, *2*(6). https://doi.org/10.1128/mBio.00260-11

Amos, G. C. A., Gozzard, E., Carter, C. E., Mead, A., Bowes, M. J., Hawkey, P. M., Zhang, L., Singer, A. C., Gaze, W. H., & Wellington, E. M. H. (2015). Validated predictive modelling of the environmental resistome. *ISME Journal*, *9*(6), 1467–1476. https://doi.org/10.1038/ismej.2014.237

Amos, G. C. A., Ploumakis, S., Zhang, L., Hawkey, P. M., Gaze, W. H., & Wellington, E. M. H. (2018). The widespread dissemination of integrons throughout bacterial communities in a riverine system. *ISME Journal*, *12*(3), 681–691. https://doi.org/10.1038/s41396-017-0030-8

Antimicrobial Resistance Collaborators. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet*, *399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0

Aprotosoaie, A. C., Hăncianu, M., Costache, I.-I., & Miron, A. (2014). Linalool: A review on a key odorant molecule with valuable biological properties. *Flavour and Fragrance Journal*, *29*(4), 193–219. https://doi.org/10.1002/ffj.3197

Atterby, C., Nykvist, M., Lustig, U., Andersson, D. I., Järhult, J. D., & Sandegren, L. (2021). Selection of resistant bacteria in mallards exposed to subinhibitory concentrations of ciprofloxacin in their water environment. *Antimicrobial Agents and Chemotherapy*, *65*(3), e1858-20. https://doi.org/10.1128/AAC.01858-20

Aydin, S., Aydin, M. E., Ulvi, A., & Kilic, H. (2019). Antibiotics in hospital effluents: Occurrence, contribution to urban wastewater, removal in a wastewater treatment plant, and environmental risk assessment. *Environmental Science and Pollution Research International*, *26*(1), 544–558. https://doi.org/10.1007/s11356-018-3563-0

Babić, S., Mutavdžić, D., Ašperger, D., Horvat, A. J. M., & Kaštelan-Macan, M. (2006). Determination of veterinary pharmaceuticals in production

wastewater by HPTLC-videodensitometry. *Chromatographia*, *65*(1–2), 105–110. https://doi.org/10.1365/s10337-006-0109-2

Backhaus, T., & Faust, M. (2012). Predictive environmental risk assessment of chemical mixtures: A conceptual framework. *Environmental Science & Technology*, *46*(5), 2564–2573. https://doi.org/10.1021/es2034125

Baker-Austin, C., Wright, M. S., Stepanauskas, R., & McArthur, J. V. (2006). Co-selection of antibiotic and metal resistance. *Trends in Microbiology*, *14*(4), 176–182. https://doi.org/10.1016/j.tim.2006.02.006

BBC News. (2021). *Water companies illegally dumping sewage in England and Wales rivers*. https://www.bbc.co.uk/news/uk-56721660

Bengtsson-Palme, J., & Larsson, D. G. J. (2016). Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International*, *86*, 140–149. https://doi.org/10.1016/j.envint.2015.10.015

Berendonk, T. U., Manaia, C. M., 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, J. L. (2015). Tackling antibiotic resistance: The environmental framework. *Nature Reviews Microbiology*, *13*(5), 310–317. https://doi.org/10.1038/nrmicro3439

Biel-Maeso, M., Corada-Fernández, C., & Lara-Martín, P. A. (2018). Monitoring the occurrence of pharmaceuticals in soils irrigated with reclaimed wastewater. *Environmental Pollution*, *235*, 312–321. https://doi.org/10.1016/j.envpol.2017.12.085

Bolujoko, N. B., Unuabonah, E. I., Alfred, M. O., Ogunlaja, A., Ogunlaja, O. O., Omorogie, M. O., & Olukanni, O. D. (2021). Toxicity and removal of parabens from water: A critical review. *Science of the Total Environment*, *792*, Article 148092. https://doi.org/10.1016/j.scitotenv.2021.148092

Bougnom, B. P., & Piddock, L. J. V. (2017). Wastewater for urban agriculture: A significant factor in dissemination of antibiotic resistance. *Environmental Science & Technology*, *51*, 5863–5864. https://doi.org/10.1021/acs.est.7b01852

Boxall, A. B., Rudd, M. A., Brooks, B. W., Caldwell, D. J., Choi, K., Hickmann, S., Innes, E., Ostapyk, K., Staveley, J. P., Verslycke, T., Ankley, G. T., Beazley, K. F., Belanger, S. E., Berninger, J. P., Carriquiriborde, P., Coors, A., Deleo, P. C., Dyer, S. D., Ericson, J. F., … Van Der Kraak, G. (2012). Pharmaceuticals and personal care products in the environment: What are the big questions? *Environmental Health Perspectives*, *120*(9), 1221–1229. https://doi.org/10.1289/ehp.1104477

Brandt, K. K., Amézquita, A., Backhaus, T., Boxall, A., Coors, A., Heberer, T., Lawrence, J. R., Lazorchak, J., Schönfeld, J., Snape, J. R., Zhu, Y.-G., & Topp, E. (2015). Ecotoxicological assessment of antibiotics: A call for improved consideration of microorganisms. *Environment International*, *85*, 189–205. https://doi.org/10.1016/j.envint.2015.09.013

Brown, L. P., Murray, R., Scott, A., Tien, Y.-C., Lau, C. H.-F., Tai, V., & Topp, E. (2022). Responses of the soil bacterial community, resistome, and mobilome to a decade of annual exposure to macrolide antibiotics. *Applied and Environmental Microbiology*, *88*, Article e0031622. https://doi.org/10.1128/aem.00316-22

Buffet-Bataillon, S., Tattevin, P., Bonnaure-Mallet, M., & Jolivet-Gougeon, A. (2012). Emergence of resistance to antibacterial agents: The role of quaternary ammonium compounds—A critical review. *International Journal of Antimicrobial Agents*, *39*(5), 381–389. https://doi.org/10.1016/j.ijantimicag.2012.01.011

Cabello, F. C., Godfrey, H. P., Buschmann, A. H., & Dölz, H. J. (2016). Aquaculture as yet another environmental gateway to the development and globalisation of antimicrobial resistance. *Lancet Infectious Diseases*, *16*(7), e127–e133. https://doi.org/10.1016/S1473-3099(16)00100-6

Cabello, F. C., Godfrey, H. P., Tomova, A., Ivanova, L., Dölz, H., Millanao, A., & Buschmann, A. H. (2013). Antimicrobial use in aquaculture re-examined: Its relevance to antimicrobial resistance and to animal and human health. *Environmental Microbiology*, *15*(7), 1917–1942. https://doi.org/10.1111/1462-2920.12134

Carey, D. E., & McNamara, P. J. (2016). Altered antibiotic tolerance in anaerobic digesters acclimated to triclosan or triclocarban. *Chemosphere*, *163*, 22–26. https://doi.org/10.1016/j.chemosphere.2016.07.097

Carraro, E., Bonetta, S., & Bonetta, S. (2018). Hospital wastewater: Existing regulations and current trends in management. *Hospital Wastewaters*, *60*, 1–16. https://doi.org/10.1007/698_2017_10

Case, S. D. C., & Jensen, L. S. (2019). Nitrogen and phosphorus release from organic wastes and suitability as bio-based fertilizers in a circular economy. *Environmental Technology*, *40*(6), 701–715. https://doi.org/10.1080/09593330.2017.1404136

Chapman, J. S. (2003). Disinfectant resistance mechanisms, cross-resistance, and co-resistance. *International Biodeterioration & Biodegradation*, *51*(4), 271–276. https://doi.org/10.1016/S0964-8305(03)00044-1

Charpentier, X., Polard, P., & Claverys, J.-P. (2012). Induction of competence for genetic transformation by antibiotics: Convergent evolution of stress responses in distant bacterial species lacking SOS. *Current Opinion in Microbiology*, *15*(5), 570–576. https://doi.org/10.1016/j.mib.2012.08.001

Che, Y., Xia, Y., Liu, L., Li, A.-D., Yang, Y., & Zhang, T. (2019). Mobile antibiotic resistome in wastewater treatment plants revealed by nanopore metagenomic sequencing. *Microbiome*, *7*(1), Article 44. https://doi.org/10.1186/s40168-019-0663-0

Chen, H., & Akhtar, L. (2022). Chapter 3—Fate and transport of pharmaceuticals and personal care products in soils and groundwater. In B. Gao (Ed.), *Emerging contaminants in soil and groundwater systems* (pp. 49–82). Elsevier. https://doi.org/10.1016/B978-0-12-824088-5.00004-5

Chow, L., Waldron, L., & Gillings, M. R. (2015). Potential impacts of aquatic pollutants: Sub-clinical antibiotic concentrations induce genome changes and promote antibiotic resistance. *Frontiers in Microbiology*, *6*, Article 803. https://doi.org/10.3389/fmicb.2015.00803

Christou, A., Karaolia, P., Hapeshi, E., Michael, C., & Fatta-Kassinos, D. (2017). Long-term wastewater irrigation of vegetables in real agricultural systems: Concentration of pharmaceuticals in soil, uptake and bioaccumulation in tomato fruits and human health risk assessment. *Water Research*, *109*, 24–34. https://doi.org/10.1016/j.watres.2016.11.033

Colomer-Lluch, M., Calero-Cáceres, W., Jebri, S., Hmaied, F., Muniesa, M., & Jofre, J. (2014). Antibiotic resistance genes in bacterial and bacteriophage fractions of Tunisian and Spanish wastewaters as markers to compare the antibiotic resistance patterns in each population. *Environment International*, *73*, 167–175. https://doi.org/10.1016/j.envint.2014.07.003

Curiao, T., Marchi, E., Grandgirard, D., León-Sampedro, R., Viti, C., Leib, S. L., Baquero, F., Oggioni, M. R., Martinez, J. L., & Coque, T. M. (2016). Multiple adaptive routes of *Salmonella enterica* Typhimurium to biocide and antibiotic exposure. *BMC Genomics*, *17*, Article 491. https://doi.org/10.1186/s12864-016-2778-z

Cycoń, M., Mrozik, A., & Piotrowska-Seget, A. (2019). Antibiotics in the soil environment—Degradation and their impact on microbial activity and diversity. *Frontiers in Microbiology*, *10*, Article 338. https://doi.org/10.3389/fmicb.2019.00338

Cytryn, E. (2013). The soil resistome: The anthropogenic, the native, and the unknown. *Soil Biology and Biochemistry*, *63*, 18–23. https://doi.org/10.1016/j.soilbio.2013.03.017

Dalkmann, P., Broszat, M., Siebe, C., Willaschek, E., Sakinc, T., Huebner, J., Amelung, W., Grohmann, E., & Siemens, J. (2012). Accumulation of pharmaceuticals, *Enterococcus*, and resistance genes in soils irrigated with wastewater for zero to 100 years in central Mexico. *PLOS ONE*, *7*(9), Article e45397. https://doi.org/10.1371/journal.pone.0045397

Davin-Regli, A., Chollet, R., Bredin, J., Chevalier, J., Lepine, F., & Pagès, J. M. (2006). *Enterobacter gergoviae* and the prevalence of efflux in parabens resistance. *Journal of Antimicrobial Chemotherapy*, *57*(4), 757–760. https://doi.org/10.1093/jac/dkl023

Department for Environment, Food & Rural Affairs. (2021, November 18). *Water companies could face legal action after investigation launched into sewage treatment works* [Press release]. https://www.gov.uk/government/news/water-companies-could-face-legal-action-after-investigation-launched-into-sewage-treatment-works

Devi, L. S., & Chattopadhya, D. (2022). Possible acquisition of ESBL-mediated antimicrobial resistance by farmers from aquatic reservoir used for bathing and cleaning of water buffalos (*Bubalus bubalis*) with intestinal carriage of ESBL producing *Escherichia coli*. *Journal of Pure Applied Microbiology*, *16*(2), 1084–1095. https://doi.org/10.22207/JPAM.16.2.33

Dey, S., Bano, F., & Malik, A. (2019). Pharmaceuticals and personal care product (PPCP) contamination—A global discharge inventory. In M. N. V. Prasad, M. Vithanage, & A. Kapley (Eds.), *Pharmaceuticals and personal care products: Waste management and treatment technology* (pp. 1–26). Elsevier. https://doi.org/10.1016/B978-0-12-816189-0.00001-9

Ebele, A. J., Abou-Elwafa Abdallah, M., & Harrad, S. (2017). Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. *Emerging Contaminants*, *3*(1), 1–16. https://doi.org/10.1016/j.emcon.2016.12.004

Elder, F. C. T., Feil, E. J., Snape, J., Gaze, W. H., & Kasprzyk-Hordern, B. (2020). The role of stereochemistry of antibiotic agents in the development of antibiotic resistance in the environment. *Environment International*, *139*, Article 105681. https://doi.org/10.1016/j.envint.2020.105681

Eramo, A., Delos Reyes, H., & Fahrenfeld, N. L. (2017). Partitioning of antibiotic resistance genes and fecal indicators varies intra and inter-storm during combined sewer overflows. *Frontiers in Microbiology*, *8*, Article 2024. https://doi.org/10.3389/fmicb.2017.02024

European Committee on Antimicrobial Susceptibility Testing. (2022, January). *Breakpoint tables for interpretation of MICs and zone diameters* (Version 12.0). https://www.eucast.org/clinical_breakpoints

European Medicines Agency. (2006). *Guideline on the environmental* https://www.eucast.org/clinical_breakpointsrisk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). Committee for Medicinal Products for Human Use.

Fatta-Kassinos, D., Vasquez, M. I., & Kümmerer, K. (2011). Transformation products of pharmaceuticals in surface waters and wastewater formed during photolysis and advanced oxidation processes—Degradation, elucidation of byproducts and assessment of their biological potency. *Chemosphere*, *85*(5), 693–709. https://doi.org/10.1016/j.chemosphere.2011.06.082

Forsberg, K. J., Reyes, A., Wang, B., Selleck, E. M., Sommer, M. O. A., & Dantas, G. (2012). The shared antibiotic resistome of soil bacteria and human pathogens. *Science*, *337*(6098), 1107–1111. https://doi.org/10.1126/science.1220761

Fu, Q., Malchi, T., Carter, L. J., Li, H., Gan, J., & Chefetz, B. (2019). Pharmaceutical and personal care products: From wastewater treatment into agro-food systems. *Environmental Science & Technology*, *53*(24), 14083–14090. https://doi.org/10.1021/acs.est.9b06206

Gao, L., Shi, Y., Li, W., Liu, J., & Cai, Y. (2015). Occurrence and distribution of antibiotics in urban soil in Beijing and Shanghai, China. *Environmental Science and Pollution Research International*, *22*(15), 11360–11371. https://doi.org/10.1007/s11356-015-4230-3

Gogarten, J. P., Doolittle, W. F., & Lawrence, J. G. (2002). Prokaryotic evolution in light of gene transfer. *Molecular Biology and Evolution*, *19*(12), 2226–2238. https://doi.org/10.1093/oxfordjournals.molbev.a004046

Goldstein, R. R., Kleinfelter, L., He, X., Micallef, S. A., George, A., Gibbs, S. G., & Sapkota, A. R. (2017). Higher prevalence of coagulase-negative staphylococci carriage among reclaimed water spray irrigators. *Science of the Total Environment*, *595*, 35–40. https://doi.org/10.1016/j.scitotenv.2017.03.174

Gottschall, N., Topp, E., Metcalfe, C., Edwards, M., Payne, M., Kleywegt, S., Russell, P., & Lapen, D. R. (2012). Pharmaceutical and personal care products in groundwater, subsurface drainage, soil, and wheat grain, following a high single application of municipal biosolids to a field. *Chemosphere*, *87*(2), 194–203. https://doi.org/10.1016/j.chemosphere.2011.12.018

Greenfield, B. K., Shaked, S., Marrs, C. F., Nelson, P., Raxter, I., Xi, C., McKone, T. E., & Jolliet, O. (2018). Modeling the emergence of antibiotic resistance in the environment: An analytical solution for the minimum selection concentration. *Antimicrobial Agents and Chemotherapy*, *62*(3), Article e01686-17. https://doi.org/10.1128/AAC.01686-17

Guérin, A., Bridier, A., Le Grandois, P., Sévellec, Y., Palma, F., Félix, B., Roussel, S., Soumet, C., & Listadapt Study Group. (2021). Exposure to quaternary ammonium compounds selects resistance to ciprofloxacin in *Listeria monocytogenes*. *Pathogens 10*(2), Article 220. https://doi.org/10.3390/pathogens10020220

Guglielmini, J., Quintais, L., Garcillán-Barcia, M. P., de la Cruz, F., & Rocha, E. P. C. (2011). The repertoire of ICE in prokaryotes underscores the unity, diversity, and ubiquity of conjugation. *PLOS Genetics*, *7*(8), Article e1002222. https://doi.org/10.1371/journal.pgen.1002222

Gullberg, E., Albrecht, L. M., Karlsson, C., Sandegren, L., & Andersson, D. I. (2014). Selection of a multidrug resistance plasmid by sublethal levels of antibiotics and heavy metals. *mBio*, *5*(5), Article e01918–14. https://doi.org/10.1128/mBio.01918-14

Gullberg, E., Cao, S., Berg, O. G., Ilbäck, C., Sandegren, L., Hughes, D., & Andersson, D. I. (2011). Selection of resistant bacteria at very low antibiotic concentrations. *PLOS Pathogens*, *7*(7), Article e1002158. https://doi.org/10.1371/journal.ppat.1002158

Guruge, K. S., Goswami, P., Tanoue, R., Nomiyama, K., Wijesekara, R. G. S., & Dharmaratne, T. S. (2019). First nationwide investigation and environmental risk assessment of 72 pharmaceuticals and personal care products from Sri Lankan surface waterways. *Science of the Total Environment*, *690*, 683–695. https://doi.org/10.1016/j.scitotenv.2019.07.042

Halary, S., Leigh, J. W., Cheaib, B., Lopez, P., & Bapteste, E. (2010). Network analyses structure genetic diversity in independent genetic worlds. *Proceedings of the National Academy of Sciences of the United States of America 107*, 127–132. https://doi.org/10.1073/pnas.0908978107

Han, Z., Feng, H., Luan, X., Shen, Y., Ren, L., Deng, L., Larsson, D. G. J., Gillings, M., Zhang, Y., & Yang, M. (2022). Three-year consecutive field application of erythromycin fermentation residue following hydrothermal treatment: Cumulative effect on soil antibiotic resistance genes. *Engineering*, *15*, 78–88. https://doi.org/10.1016/j.eng.2022.05.011

Hanahan, D. (1983). Studies on transformation of *Escherichia coli* with plasmids. *Journal of Molecular Biology*, *166*(4), 557–580. https://doi.org/10.1016/S0022-2836(83)80284-8

Heuer, H., & Smalla, K. (2007). Manure and sulfadiazine synergistically increased bacterial antibiotic resistance in soil over at least two months. *Environmental Microbiology*, *9*(3), 657–666. https://doi.org/10.1111/j.1462-2920.2006.01185.x

Hjort, K., Fermér, E., Tang, P., & Andersson, D. I. (2022). Antibiotic minimal selective concentrations and fitness costs during biofilm and planktonic growth. *mBio*, *13*(3), Article e0144722. https://doi.org/10.1128/mbio.01447-22

Hocquet, D., Muller, A., & Bertrand, X. (2016). What happens in hospitals does not stay in hospitals: Antibiotic-resistant bacteria in hospital wastewater systems. *Journal of Hospital Infection*, *93*(4), 395–402. https://doi.org/10.1016/j.jhin.2016.01.010

Honda, R., Tachi, C., Yasuda, K., Hirata, T., Noguchi, M., Hara-Yamamura, H., Yamamoto-Ikemoto, R., & Watanabe, T. (2020). Estimated discharge of antibiotic-resistant bacteria from combined sewer overflows of urban sewage system. *NPJ Clean Water*, *3*(1), Article 15. https://doi.org/10.1038/s41545-020-0059-5

Hülter, N., Ilhan, J., Wein, T., Kadibalban, A. S., Hammerschmidt, K., & Dagan, T. (2017). An evolutionary perspective on plasmid lifestyle modes. *Current Opinion in Microbiology*, *38*, 74–80. https://doi.org/10.1016/j.mib.2017.05.001

Hunt, C. (2006). *Sanitation and human development*. Human Development Report Office.

Hutinel, M., Fick, J., Larsson, D. G. J., & Flach, C.-F. (2021). Investigating the effects of municipal and hospital wastewaters on horizontal gene transfer. *Environmental Pollution*, *276*, Article 116733. https://doi.org/10.1016/j.envpol.2021.116733

Jarnheimer, P., Ottoson, J., Lindberg, R., Strenström, T., Johansson, M., Tysklind, M., Winner, M., & Oslen, B. (2004). Fluoroquinolone antibiotics in a hospital sewage line: Occurrence, distribution and impact on bacterial resistance. *Scandinavian Journal of Infectious Diseases*, *36*(10), 752–757. https://doi.org/10.1080/00365540410021027a

Jutkina, J., Marathe, N. P., Flach, C. F., & Larsson, D. G. J. (2018). Antibiotics and common antibacterial biocides stimulate horizontal transfer of resistance at low concentrations. *Science of the Total Environment*, *616–617*, 172–178. https://doi.org/10.1016/j.scitotenv.2017.10.312

Jutkina, J., Rutgersson, C., Flach, C.-F., & Joakim Larsson, D. G. (2016). An assay for determining minimal concentrations of antibiotics that drive horizontal transfer of resistance. *Science of the Total Environment*, *548–549*, 131–138. https://doi.org/10.1016/j.scitotenv.2016.01.044

Kalaycı, S., Demirci, S., & Sahin, F. (2014). Determination of antimicrobial properties of picaridin and DEET against a broad range of microorganisms. *World Journal of Microbiology & Biotechnology*, *30*(2), 407–411. https://doi.org/10.1007/s11274-013-1456-4

Kalily, E., Hollander, A., Korin, B., Cymerman, I., & Yaron, S. (2017). Adaptation of *Salmonella enterica* serovar Senftenberg to linalool and its association with antibiotic resistance and environmental persistence. *Applied and Environmental Microbiology*, *83*(10), Article e03398-16. https://doi.org/10.1128/AEM.03398-16

Kampf, G. (2019). Antibiotic resistance can be enhanced in Gram-positive species by some biocidal agents used for disinfection. *Antibiotics*, *8*(1), Article 13. https://doi.org/10.3390/antibiotics8010013

Karatzas, K. A. G., Webber, M. A., Jorgensen, F., Woodward, M. J., Piddock, L. J. V., & Humphrey, T. J. (2007). Prolonged treatment of *Salmonella enterica* serovar Typhimurium with commercial disinfectants selects for multiple antibiotic resistance, increased efflux and reduced invasiveness. *Journal of Antimicrobial Chemotherapy*, *60*(5), 947–955. https://doi.org/10.1093/jac/dkm314

Khan, S., Beattie, T. K., & Knapp, C. W. (2017). The use of minimum selectable concentrations (MSCs) for determining the selection of antimicrobial resistant bacteria. *Ecotoxicology*, *26*(2), 283–292. https://doi.org/10.1007/s10646-017-1762-y

Kim, D.-W., & Cha, C.-J. (2021). Antibiotic resistome from the One-Health perspective: Understanding and controlling antimicrobial resistance transmission. *Experimental & Molecular Medicine*, *53*(3), 301–309. https://doi.org/10.1038/s12276-021-00569-z

Kim, M., Weigand, M. R., Oh, S., Hatt, J. K., Krishnan, R., Tezel, U., Pavlostathis, S. G., & Konstantinidis, K. T. (2018). Widely used benzalkonium chloride disinfectants can promote antibiotic resistance. *Applied and Environmental Microbiology*, *84*(17), Article e01201-18. https://doi.org/10.1128/AEM.01201-18

Klümper, U., Dechesne, A., Riber, L., Brandt, K. K., Gülay, A., Sørensen, S. J., & Smets, B. F. (2017). Metal stressors consistently modulate bacterial conjugal plasmid uptake potential in a phylogenetically conserved manner. *ISME Journal*, *11*(1), 152–165. https://doi.org/10.1038/ismej.2016.98

Klümper, U., Recker, M., Zhang, L., Yin, X., Zhang, T., Buckling, A., & Gaze, W. H. (2019). Selection for antimicrobial resistance is reduced when embedded in a natural microbial community. *ISME Journal*, *13*(12), 2927–2937. https://doi.org/10.1038/s41396-019-0483-z

Klümper, U., Riber, L., Dechesne, A., Sannazzarro, A., Hansen, L. H., Sørensen, S. J., & Smets, B. F. (2015). Broad host range plasmids can invade an unexpectedly diverse fraction of a soil bacterial community. *ISME Journal*, *9*(4), 934–945. https://doi.org/10.1038/ismej.2014.191

Kostich, M. S., Batt, A. L., & Lazorchak, J. M. (2014). Concentrations of prioritized pharmaceuticals in effluents from 50 large wastewater treatment plants in the US and implications for risk estimation. *Environmental Pollution*, *184*, 354–359. https://doi.org/10.1016/j.envpol.2013.09.013

Kraupner, N., Ebmeyer, S., Bengtsson-Palme, J., Fick, J., Kristiansson, E., Flach, C.-F., & Larsson, D. G. J. (2018). Selective concentration for ciprofloxacin resistance in *Escherichia coli* grown in complex aquatic bacterial biofilms. *Environment International*, *116*, 255–268. https://doi.org/10.1016/j.envint.2018.04.029

Kraupner, N., Ebmeyer, S., Hutinel, M., Fick, J., Flach, C.-F., & Larsson, D. G. J. (2020). Selective concentrations for trimethoprim resistance in aquatic environments. *Environment International*, *144*, Article 106083. https://doi.org/10.1016/j.envint.2020.106083

Kümmerer, K. (2009). Antibiotics in the aquatic environment—A review—Part I. *Chemosphere*, *75*(4), 417–434. https://doi.org/10.1016/j.chemosphere.2008.11.086

Lagadinou, M., Onisor, M. O., Rigas, A., Musetescu, D.-V., Gkentzi, D., Assimakopoulos, S. F., Panos, G., & Marangos, M. (2020). Antimicrobial properties on non-antibiotic drugs in the era of increased bacterial resistance. *Antibiotics*, *9*(3), Article 107. https://doi.org/10.3390/antibiotics9030107

Landers, T. F., Cohen, B., Wittum, T. E., & Larson, E. L. (2012). A review of antibiotic use in food animals: Perspective, policy, and potential. *Public Health Reports*, *127*, 4–22. https://doi.org/10.1177/003335491212700103

Larsson, D. G. J. (2014). Pollution from drug manufacturing: Review and perspectives. *Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences*, *369*(1656). https://doi.org/10.1098/rstb.2013.0571

Larsson, D. G. J., de Pedro, C., & Paxeus, N. (2007). Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *Journal of Hazardous Materials*, *148*(3), 751–755. https://doi.org/10.1016/j.jhazmat.2007.07.008

Larsson, D. G. J., & Flach, C.-F. (2021). Antibiotic resistance in the environment. *Nature Reviews Microbiology*, *20*, 257–269. https://doi.org/10.1038/s41579-021-00649-x

Laurens, C., Jean-Pierre, H., Licznar-Fajardo, P., Hantova, S., Godreuil, S., Martinez, O., & Jumas-Bilak, E. (2018). Transmission of IMI-2 carbapenemase-producing Enterobacteriaceae from river water to human. *Journal of Global Antimicrobial Resistance*, *15*, 88–92. https://doi.org/10.1016/j.jgar.2018.06.022

Leclercq, S. O., Wang, C., Sui, Z., Wu, H., Zhu, B., Deng, Y., & Feng, J. (2016). A multiplayer game: Species of *Clostridium*, *Acinetobacter*, and *Pseudomonas* are responsible for the persistence of antibiotic resistance genes in manure-treated soils. *Environmental Microbiology*, *18*(10), 3494–3508. https://doi.org/10.1111/1462-2920.13337

Lee, W.-I., Park, Y., Park, J., Shrivastava, S., Son, Y.-M., Choi, H.-J., Lee, J., Jeon, B., Lee, H., & Lee, N.-E. (2019). A smartphone fluorescence imaging-based mobile biosensing system integrated with a passive fluidic control cartridge for minimal user intervention and high accuracy. *Lab on a Chip*, *19*(8), 1502–1511. https://doi.org/10.1039/c8lc01344f

Leonard, A. F. C., Zhang, L., Balfour, A. J., Garside, R., & Gaze, W. H. (2015). Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters. *Environment International*, *82*, 92–100. https://doi.org/10.1016/j.envint.2015.02.013

Leonard, A. F. C., Zhang, L., Balfour, A. J., Garside, R., Hawkey, P. M., Murray, A. K., Ukoumunne, O. C., & Gaze, W. H. (2018). Exposure to and colonisation by antibiotic-resistant *E. coli* in UK coastal water users: Environmental surveillance, exposure assessment, and epidemiological study (Beach Bum Survey). *Environment International*, *114*, 326–333. https://doi.org/10.1016/j.envint.2017.11.003

Li, M., He, Y., Sun, J., Li, J., Bai, J., & Zhang, C. (2019). Chronic exposure to an environmentally relevant triclosan concentration induces persistent triclosan resistance but reversible antibiotic tolerance in *Escherichia coli*. *Environmental Science & Technology*, *53*(6), 3277–3286. https://doi.org/10.1021/acs.est.8b06763

Liu, A., Fong, A., Becket, E., Yuan, J., Tamae, C., Medrano, L., Maiz, M., Wahba, C., Lee, C., Lee, K., Tran, K. P., Yang, H., Hoffman, R. M., Salih, A., & Miller, J. H. (2011). Selective advantage of resistant strains at trace levels of antibiotics: A simple and ultrasensitive color test for detection of antibiotics and genotoxic agents. *Antimicrobial Agents and Chemotherapy*, *55*(3), 1204–1210. https://doi.org/10.1128/AAC.01182-10

Liu, X., Li, Y., Guo, Y., Zeng, Z., Li, B., Wood, T. K., Cai, X., & Wang, X. (2015). Physiological function of Rac prophage during biofilm formation and regulation of Rac excision in *Escherichia coli* K-12. *Scientific Reports*, *6*, Article 16074. https://doi.org/10.1038/srep16074

Lu, J., Wang, Y., Jin, M., Yuan, Z., Bond, P., & Guo, J. (2020). Both silver ions and silver nanoparticles facilitate the horizontal transfer of plasmid-mediated antibiotic resistance genes. *Water Research*, *169*, Article 115229. https://doi.org/10.1016/j.watres.2019.115229

Lu, J., Wang, Y., Zhang, S., Bond, P., Yuan, Z., & Guo, J. (2020). Triclosan at environmental concentrations can enhance the spread of extracellular antibiotic resistance genes through transformation. *Science of the Total Environment*, *713*, Article 136621. https://doi.org/10.1016/j.scitotenv.2020.136621

Lundström, S. V., Östman, M., Bengtsson-Palme, J., Rutgersson, C., Thoudal, M., Sircar, T., Blanck, H., Eriksson, K. M., Tysklind, M., Flach, C.-F., & Larsson, D. G. J. (2016). Minimal selective concentrations of tetracycline in complex aquatic bacterial biofilms. *Science of the Total Environment*, *553*, 587–595. https://doi.org/10.1016/j.scitotenv.2016.02.103

Luo, Y., Guo, W., Ngo, H. H., Nghiem, L. D., Hai, F. I., Zhang, J., Liang, S., & Wang, X. C. (2014). A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. *Science of the Total Environment*, *473–474*, 619–641. https://doi.org/10.1016/j.scitotenv.2013.12.065

Maier, L., Pruteanu, M., Kuhn, M., Zeller, G., Telzerow, A., Anderson, E. E., Brochado, A. R., Fernandez, K. C., Dose, H., Mori, H., Patil, K. R., Bork, P., & Typas, A. (2018). Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*, *555*(7698), 623–628. https://doi.org/10.1038/nature25979

Maiques, E., Ubeda, C., Campoy, S., Salvador, N., Lasa, I., Novick, R. P., Barbé, J., & Penadés, J. R. (2006). Beta-lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in *Staphylococcus aureus*. *Journal of Bacteriology*, *188*(7), 2726–2729. https://doi.org/10.1128/JB.188.7.2726-2729.2006

Marx, C., Mühlbauer, V., Krebs, P., & Kuehn, V. (2015). Environmental risk assessment of antibiotics including synergistic and antagonistic combination effects. *Science of the Total Environment*, *524–525*, 269–279. https://doi.org/10.1016/j.scitotenv.2015.04.051

McArthur, J. V., & Tuckfield, R. C. (2000). Spatial patterns in antibiotic resistance among stream bacteria: Effects of industrial pollution. *Applied and Environmental Microbiology*, *66*(9), 3722–3726. https://doi.org/10.1128/AEM.66.9.3722-3726.2000

Middleton, J. H., & Salierno, J. D. (2013). Antibiotic resistance in triclosan tolerant fecal coliforms isolated from surface waters near wastewater treatment plant outflows (Morris County, NJ, USA). *Ecotoxicology and Environmental Safety*, *88*, 79–88. https://doi.org/10.1016/j.ecoenv.2012.10.025

Mitosch, K., & Bollenbach, T. (2014). Bacterial responses to antibiotics and their combinations. *Environmental Microbiology Reports*, *6*(6), 545–557. https://doi.org/10.1111/1758-2229.12190

Moura, A., Soares, M., Pereira, C., Leitão, N., Henriques, I., & Correia, A. (2009). INTEGRALL: A database and search engine for integrons, integrases and gene cassettes. *Bioinformatics*, *25*(8), 1096–1098. https://doi.org/10.1093/bioinformatics/btp105

Murray, A. K., Stanton, I., Gaze, W. H., & Snape, J. (2021). Dawning of a new ERA: Environmental risk assessment of antibiotics and their potential to select for antimicrobial resistance. *Water Research*, *200*, Article 117233. https://doi.org/10.1016/j.watres.2021.117233

Murray, A. K., Stanton, I. C., Wright, J., Zhang, L., Snape, J., & Gaze, W. H. (2020). The "SELection End points in Communities of bacTeria" (SELECT) method: A novel experimental assay to facilitate risk assessment of selection for antimicrobial resistance in the environment. *Environmental Health Perspectives*, *128*(10), Article 107007. https://doi.org/10.1289/EHP6635

Murray, A. K., Zhang, L., Snape, J., & Gaze, W. H. (2019). Comparing the selective and co-selective effects of different antimicrobials in bacterial communities. *International Journal of Antimicrobial Agents*, *53*(6), 767–773. https://doi.org/10.1016/j.ijantimicag.2019.03.001

Murray, A. K., Zhang, L., Yin, X., Zhang, T., Buckling, A., Snape, J., & Gaze, W. H. (2018). Novel insights into selection for antibiotic resistance in complex microbial communities. *mBio*, *9*(4). https://doi.org/10.1128/mBio.00969-18

Nadimpalli, M., Delarocque-Astagneau, E., Love, D. C., Price, L. B., Huynh, B.-T., Collard, J.-M., Lay, K. S., Borand, L., Ndir, A., Walsh, T. R., & Guillemot, D., Bacterial Infections and Antibiotic-Resistant Diseases among Young Children in Low-Income Countries (BIRDY) Study Group. (2018). Combating global antibiotic resistance: Emerging one health concerns in lower- and middle-income countries. *Clinical Infectious Diseases*, *66*(6), 963–969. https://doi.org/10.1093/cid/cix879

Negreanu, Y., Pasternak, Z., Jurkevitch, E., & Cytryn, E. (2012). Impact of treated wastewater irrigation on antibiotic resistance in agricultural soils. *Environmental Science & Technology*, *46*(9), 4800–4808. https://doi.org/10.1021/es204665b

Nesme, J., & Simonet, P. (2015). The soil resistome: A critical review on antibiotic resistance origins, ecology and dissemination potential in telluric bacteria. *Environmental Microbiology*, *17*(4), 913–930. https://doi.org/10.1111/1462-2920.12631

Newton, R. J., McLellan, S. L., Dila, D. K., Vineis, J. H., Morrison, H. G., Eren, A. M., & Sogin, M. L. (2015). Sewage reflects the microbiomes of human populations. *mBio*, *6*(2), Article e02574. https://doi.org/10.1128/mBio.02574-14

Niegowska, M., Sanseverino, I., Navarro, A., & Lettieri, T. (2021). Knowledge gaps in the assessment of antimicrobial resistance in surface waters. *FEMS Microbiology Ecology*, *97*(11), Article fiab140. https://doi.org/10.1093/femsec/fiab140

Nielsen, K. M., & van Elsas, J. D. (2001). Stimulatory effects of compounds present in the rhizosphere on natural transformation of *Acinetobacter* sp. BD413 in soil. *Soil Biology and Biochemistry*, *33*(3), 345–357. https://doi.org/10.1016/S0038-0717(00)00147-4

Nordholt, N., Kanaris, O., Schmidt, S. B. I., & Schreiber, F. (2021). Persistence against benzalkonium chloride promotes rapid evolution of tolerance during periodic disinfection. *Nature Communications*, *12*(1), Article 6792. https://doi.org/10.1038/s41467-021-27019-8

O'Flaherty, E., Solimini, A. G., Pantanella, F., De Giusti, M., & Cummins, E. (2019). Human exposure to antibiotic resistant-*Escherichia coli* through irrigated lettuce. *Environment International*, *122*, 270–280. https://doi.org/10.1016/j.envint.2018.11.022

Oh, S., Tandukar, M., Pavlostathis, S. G., Chain, P. S. G., & Konstantinidis, K. T. (2013). Microbial community adaptation to quaternary ammonium biocides as revealed by metagenomics. *Environmental Microbiology*, *15*(10), 2850–2864. https://doi.org/10.1111/1462-2920.12154

O'Neill, J. (2014). *Antimicrobial resistance: Tackling a crisis for the health and weather of nations*. Review on Antimicrobial Resistance. https://amr-review.org/Publications.html

Pärnänen, K., Karkman, A., Tamminen, M., Lyra, C., Hultman, J., Paulin, L., & Virta, M. (2016). Evaluating the mobility potential of antibiotic resistance genes in environmental resistomes without metagenomics. *Scientific Reports*, *6*, Article 35790. https://doi.org/10.1038/srep35790

Partridge, S. R., Tsafnat, G., Coiera, E., & Iredell, J. R. (2009). Gene cassettes and cassette arrays in mobile resistance integrons. *FEMS Microbiology Reviews*, *33*(4), 757–784. https://doi.org/10.1111/j.1574-6976.2009.00175.x

Paulus, G. K., Hornstra, L. M., Alygizakis, N., Slobodnik, J., Thomaidis, N., & Medema, G. (2019). The impact of on-site hospital wastewater treatment on the downstream communal wastewater system in terms of antibiotics and antibiotic resistance genes. *International Journal of Hygiene and Environmental Health*, *222*(4), 635–644. https://doi.org/10.1016/j.ijheh.2019.01.004

Perry, J. A., & Wright, G. D. (2013). The antibiotic resistance "mobilome": Searching for the link between environment and clinic. *Frontiers in Microbiology*, *4*, Article 138. https://doi.org/10.3389/fmicb.2013.00138

Perry, M. R., Lepper, H. C., McNally, L., Wee, B. A., Munk, P., Warr, A., Moore, B., Kalima, P., Philip, C., de Roda Husman, A. M., Aarestrup, F. M., Woolhouse, M. E. J., & van Bunnik, B. A. D. (2021). Secrets of the hospital underbelly: Patterns of abundance of antimicrobial resistance genes in hospital wastewater vary by specific antimicrobial and bacterial family. *Frontiers in Microbiology*, *12*, Article 703560. https://doi.org/10.3389/fmicb.2021.703560

Phillips, P. J., Smith, S. G., Kolpin, D. W., Zaugg, S. D., Buxton, H. T., Furlong, E. T., Esposito, K., & Stinson, B. (2010). Pharmaceutical formulation facilities as sources of opioids and other pharmaceuticals to wastewater treatment plant effluents. *Environmental Science & Technology*, *44*(13), 4910–4916. https://doi.org/10.1021/es100356f

Prudhomme, M., Attaiech, L., Sanchez, G., Martin, B., & Claverys, J.-P. (2006). Antibiotic stress induces genetic transformability in the human pathogen *Streptococcus pneumoniae*. *Science*, *313*(5783), 89–92. https://doi.org/10.1126/science.1127912

Rahman, M. M., Shan, J., Yang, P., Shang, X., Xia, Y., & Yan, X. (2018). Effects of long-term pig manure application on antibiotics, abundance of antibiotic resistance genes (ARGs), anammox and denitrification rates in paddy soils. *Environmental Pollution*, *240*, 368–377. https://doi.org/10.1016/j.envpol.2018.04.135

Rodríguez-Molina, D., Berglund, F., Blaak, H., Flach, C., Kemper, M., Marutescu, L., Gradisteanu, G. P., Popa, M., Spießberger, B., Weinmann, T., Wengenroth, L., Chifiriuc, M. C., Larsson, D. G. J., Nowak, D., Radon, K., de Roda Husman, A. M., Wieser, A., & Schmitt, H. (2021). Carriage of ESBL-producing Enterobacterales in wastewater treatment plant workers and surrounding residents—The AWARE study. *European Journal of Clinical Microbiology & Infectious Diseases*, *13*, 1–16. https://doi.org/10.1007/s10096-021-04387-z

Sanchez, P., Moreno, E., & Martinez, J. L. (2005). The biocide triclosan selects *Stenotrophomonas maltophilia* mutants that overproduce the SmeDEF multidrug efflux pump. *Antimicrobial Agents and Chemotherapy*, *49*(2), 781–782. https://doi.org/10.1128/AAC.49.2.781-782.2005

Santos, L. H. M. L. M., Gros, M., Rodriguez-Mozaz, S., Delerue-Matos, C., Pena, A., Barceló, D., & Montenegro, M. C. B. S. M. (2013). Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals. *Science of the Total Environment*, *461–462*, 302–316. https://doi.org/10.1016/j.scitotenv.2013.04.077

Sanz-García, F., Hernando-Amado, S., & Martínez, J. L. (2021). Evolution under low antibiotic concentrations: A risk for the selection of *Pseudomonas aeruginosa* multidrug-resistant mutants in nature. *Environmental Microbiology*, *24*(3), 1279–1293. https://doi.org/10.1111/1462-2920.15806

Scott, A., Tien, Y.-C., Drury, C. F., Reynolds, W. D., & Topp, E. (2018). Enrichment of antibiotic resistance genes in soil receiving composts derived from swine manure, yard wastes, or food wastes, and evidence for multiyear persistence of swine *Clostridium* spp. *Canadian Journal of Microbiology*, *64*(3), 201–208. https://doi.org/10.1139/cjm-2017-0642

Segura, P. A., Takada, H., Correa, J. A., El Saadi, K., Koike, T., Onwona-Agyeman, S., Ofosu-Anim, J., Sabi, E. B., Wasonga, O. V., Mghalu, J. M., dos Santos Junior, A. M., Newman, B., Weerts, S., & Yargeau, V. (2015). Global occurrence of anti-infectives in contaminated surface waters: Impact of income inequality between countries. *Environment International*, *80*, 89–97. https://doi.org/10.1016/j.envint.2015.04.001

Seier-Petersen, M. A., Jasni, A., Aarestrup, F. M., Vigre, H., Mullany, P., Roberts, A. P., & Agersø, Y. (2014). Effect of subinhibitory concentrations of four commonly used biocides on the conjugative transfer of Tn916 in *Bacillus subtilis*. *Journal of Antimicrobial Chemotherapy*, *69*(2), 343–348. https://doi.org/10.1093/jac/dkt370

Selvaraj, K. K., Sivakumar, S., Sampath, S., Shanmugam, G., Sundaresan, U., & Ramaswamy, B.R. (2013). Paraben resistance in bacteria from sewage treatment plant effluents in India. *Water Science and Technology*, *68*(9), 2067–2073. https://doi.org/10.2166/wst.2013.447

Sengar, A., & Vijayanandan, A. (2022). Human health and ecological risk assessment of 98 pharmaceuticals and personal care products (PPCPs) detected in Indian surface and wastewaters. *Science of the Total Environment*, *807*(Part 1), Article 150677. https://doi.org/10.1016/j.scitotenv.2021.150677

Séveno, N. A., Kallifidas, D., Smalla, K., van Elsas, J. D., Collard, J.-M., Karagouni, A. D., & Wellington, E. M. H. (2002). Occurrence and reservoirs of antibiotic resistance genes in the environment. *Reviews and Research in Medical Microbiology*, *13*(1), 15–27.

Shun-Mei, E., Zeng, J., Yuan, H., Lu, Y., Cai, R., & Chen, C. (2018). Subinhibitory concentrations of fluoroquinolones increase conjugation frequency. *Microbial Pathogenesis*, *114*, 57–62. https://doi.org/10.1016/j.micpath.2017.11.036

Singer, A., Shaw, H., Rhodes, V., & Hart, A. (2016). Review of antimicrobial resistance in the environment and its relevance to environmental regulators. *Frontiers in Microbiology*, *7*, Article 1728. https://doi.org/10.3389/fmicb.2016.01728

Singer, A. C., Stanton, H. J., Tipper, I. C., & Read, D. S. (2021). *Evidence review on the entry and spread of antimicrobial resistance (AMR) in the rural water environment in Wales* (Report 55). ERAMMP.

Singer, A. C., Xu, Q., & Keller, V. D. J. (2019). Translating antibiotic prescribing into antibiotic resistance in the environment: A hazard characterisation case study. *PLOS ONE*, *14*(9), Article e0221568. https://doi.org/10.1371/journal.pone.0221568

Sinicropi, M. S., Iacopetta, D., Ceramella, J., Catalano, A., Mariconda, A., Pellegrino, M., Saturnino, C., Longo, P., & Aquaro, S. (2022). Triclosan: A small molecule with controversial roles. *Antibiotics*, *11*(6), Article 735. https://doi.org/10.3390/antibiotics11060735

Song, J., Klümper, U., Riber, L., Dechesne, A., Smets, B. F., Sørensen, S. J., & Brandt, K. K. (2020). A converging subset of soil bacterial taxa is permissive to the IncP-1 plasmid pKJK5 across a range of soil copper contamination. *FEMS Microbiology Ecology*, *96*(11), Article fiaa200. https://doi.org/10.1093/femsec/fiaa200

Stanton, I. (2020). *Selection for antibiotic resistance in complex microbial communities* [Unpublished doctoral dissertation]. https://ore.exeter.ac.uk/repository/handle/10871/40299

Stanton, I. C., Bethel, A., Leonard, A. F. C., Gaze, W. H., & Garside, R. (2022). Existing evidence on antibiotic resistance exposure and transmission to humans from the environment: A systematic map. *Environmental Evidence*, *11*(1), Article 8. https://doi.org/10.1186/s13750-022-00262-2

Stanton, I. C., Murray, A. K., Zhang, L., Snape, J., & Gaze, W. H. (2020). Evolution of antibiotic resistance at low antibiotic concentrations including selection below the minimal selective concentration. *Communications Biology*, *3*(1), Article 467. https://doi.org/10.1038/s42003-020-01176-w

Stevenson, E. M., Gaze, W. H., Gow, N. A. R., Hart, A., Schmidt, W., Usher, J., Warris, A., Wilkinson, H., & Murray, A. K. (2022). Antifungal exposure and resistance development: Defining minimal selective antifungal concentrations and testing methodologies. *Frontiers in Fungal Biology*, *3*, Article 918717. https://doi.org/10.3389/ffunb.2022.918717

Subirats, J., Murray, R., Yin, X., Zhang, T., & Topp, E. (2021). Impact of chicken litter pre-application treatment on the abundance, field persistence, and transfer of antibiotic resistant bacteria and antibiotic resistance genes to vegetables. *Science of the Total Environment*, *801*, Article 149718. https://doi.org/10.1016/j.scitotenv.2021.149718

Sutcliffe, S. G., Shamash, M., Hynes, A. P., & Maurice, C. F. (2021). Common oral medications lead to prophage induction in bacterial isolates from the human gut. *Viruses*, *13*(3), Article 455. https://doi.org/10.3390/v13030455

Tang, P., Eriksson, O., Sjögren, J., Fatsis-Kavalopoulos, N., Kreuger, J., & Andersson, D. I. (2022). A microfluidic chip for studies of the dynamics of antibiotic resistance selection in bacterial biofilms. *Frontiers in Cellular and Infection Microbiology*, *12*, Article 896149. https://doi.org/10.3389/fcimb.2022.896149

Tong, L., Qin, L., Guan, C., Wilson, M. E., Li, X., Cheng, D., Ma, J., Liu, H., & Gong, F. (2020). Antibiotic resistance gene profiling in response to antibiotic usage and environmental factors in the surface water and groundwater of Honghu Lake, China. *Environmental Science and Pollution Research International*, *27*(25), 31995–32005. https://doi.org/10.1007/s11356-020-09487-5

Umweltbundesamt. (2021). *Pharmaceuticals in the environment* [Database]. https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0

Ungureanu, N., Vlăduț, V., & Voicu, G. (2020). Water scarcity and wastewater reuse in crop irrigation. *Sustainability*, *12*(21), Article 9055. https://doi.org/10.3390/su12219055

Verlicchi, P., Al Aukidy, M., Galletti, A., Petrovic, M., & Barceló, D. (2012). Hospital effluent: Investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment. *Science of the Total Environment*, *430*, 109–118. https://doi.org/10.1016/j.scitotenv.2012.04.055

Vikesland, P., Garner, E., Gupta, S., Kang, S., Maile-Moskowitz, A., & Zhu, N. (2019). Differential drivers of antimicrobial resistance across the world. *Accounts of Chemical Research*, *52*(4), 916–924. https://doi.org/10.1021/acs.accounts.8b00643

Vos, M., Sibleyras, L., Lo, L. K., Hesse, E., Gaze, W., & Klümper, U. (2020). Zinc can counteract selection for ciprofloxacin resistance. *FEMS Microbiology Letters*, *367*(3), Article fnaa038. https://doi.org/10.1093/femsle/fnaa038

Wang, H., Feng, Y., & Lu, H. (2022). Low-level cefepime exposure induces high-level resistance in environmental bacteria: Molecular mechanism and evolutionary dynamics. *Environmental Science & Technology*. Advance online publication. https://doi.org/10.1021/acs.est.2c00793

Wang, Y., Lu, J., Engelstädter, J., Zhang, S., Ding, P., Mao, L., Yuan, Z., Bond, P. L., & Guo, J. (2020). Non-antibiotic pharmaceuticals enhance the transmission of exogenous antibiotic resistance genes through bacterial transformation. *ISME Journal*, *14*(8), 2179–2196. https://doi.org/10.1038/s41396-020-0679-2

Wang, Y., Lu, J., Mao, L., Li, J., Yuan, Z., Bond, P. L., & Guo, J. (2018). Antiepileptic drug carbamazepine promotes horizontal transfer of plasmid-borne multi-antibiotic resistance genes within and across bacterial genera. *ISME Journal*, *13*(2), 509–522. https://doi.org/10.1038/s41396-018-0275-x

Wang, Y., Lu, J., Zhang, S., Li, J., Mao, L., Yuan, Z., Bond, P. L., & Guo, J. (2021). Non-antibiotic pharmaceuticals promote the transmission of multidrug resistance plasmids through intra- and intergenera conjugation. *ISME Journal*, *15*(9), 2493–2508. https://doi.org/10.1038/s41396-021-00945-7

Wang, Y.-F., Qiao, M., Zhu, D., & Zhu, Y.-G. (2020). Antibiotic resistance in the collembolan gut microbiome accelerated by the nonantibiotic drug carbamazepine. *Environmental Science & Technology*, *54*(17), 10754–10762. https://doi.org/10.1021/acs.est.0c03075

Watson, B. N. J., Staals, R. H. J., & Fineran, P. C. (2018). CRISPR-Cas-mediated phage resistance enhances horizontal gene transfer by transduction. *mBio*, *9*(1). https://doi.org/10.1128/mBio.02406-17

Wegst-Uhrich, S. R., Navarro, D. A., Zimmerman, L., & Aga, D. S. (2014). Assessing antibiotic sorption in soil: A literature review and new case studies on sulfonamides and macrolides. *Chemistry Central Journal*, *8*(1), Article 5. https://doi.org/10.1186/1752-153X-8-5

Wilkinson, J. L., Boxall, A. B. A., Kolpin, D. W., Leung, K. M. Y., Lai, R. W. S., Galbán-Malagón, C., Adell, A. D., Mondon, J., Metian, M., Marchant, R. A., Bouzas-Monroy, A., Cuni-Sanchez, A., Coors, A., Carriquiriborde, P., Rojo, M., Gordon, C., Cara, M., Moermond, M., Luarte, T., & Teta, C. (2022). Pharmaceutical pollution of the world's rivers. *Proceedings of the National Academy of Sciences of the United States of America*, *119*(8), Article e2113947119. https://doi.org/10.1073/pnas.2113947119

Williams, M. R., Stedtfeld, R. D., Guo, X., & Hashsham, S. A. (2016). Antimicrobial resistance in the environment. *Water Environment Research*, *88*(10), 1951–1967. https://doi.org/10.2175/106143016X14696400495974

Winter, M., Buckling, A., Harms, K., Johnsen, P. J., & Vos, M. (2021). Antimicrobial resistance acquisition via natural transformation: Context is everything. *Current Opinion in Microbiology*, *64*, 133–138. https://doi.org/10.1016/j.mib.2021.09.009

Woegerbauer, M., Bellanger, X., & Merlin, C. (2020). Cell-Free DNA: An underestimated source of antibiotic resistance gene dissemination at the interface between human activities and downstream environments in the context of wastewater reuse. *Frontiers in Microbiology*, *11*, Article 671. https://doi.org/10.3389/fmicb.2020.00671

Xie, J., Jin, L., Luo, X., Zhao, Z., & Li, X. (2018). Seasonal disparities in airborne bacteria and associated antibiotic resistance genes in $PM_{2.5}$ between urban and rural sites. *Environmental Science & Technologies Letters*, *5*, 74–79. https://doi.org/10.1021/acs.estlett.7b00561

Xu, H., Lu, G., & Xue, C. (2020). Effects of sulfamethoxazole and 2-ethylhexyl-4-methoxycinnamate on the dissimilatory nitrate reduction processes and N_2O release in sediments in the Yarlung Zangbo River. *International Journal of Environmental Research and Public Health*, *17*(6), Article 1822. https://doi.org/10.3390/ijerph17061822

Yao, S., Ye, J., Yang, Q., Hu, Y., Zhang, T., Jiang, L., Munezero, S., Lin, K., & Cui, C. (2021). Occurrence and removal of antibiotics, antibiotic resistance genes, and bacterial communities in hospital wastewater. *Environmental Science and Pollution Research International*, *28*(40), 57321–57333. https://doi.org/10.1007/s11356-021-14735-3

Zhang, S., Wang, Y., Song, H., Lu, J., Yuan, Z., & Guo, J. (2019). Copper nanoparticles and copper ions promote horizontal transfer of plasmid-mediated multi-antibiotic resistance genes across bacterial genera. *Environment International*, *129*, 478–487. https://doi.org/10.1016/j.envint.2019.05.054

Zhao, F., Chen, L., Yen, H., Li, G., Sun, L., & Yang, L. (2020). An innovative modeling approach of linking land use patterns with soil antibiotic contamination in peri-urban areas. *Environment International*, *134*, Article 105327. https://doi.org/10.1016/j.envint.2019.105327

Zhaxybayeva, O., & Doolittle, W. F. (2011). Lateral gene transfer. *Current Biology*, *21*(7), R242–R246. https://doi.org/10.1016/j.cub.2011.01.045

