

Antibiotic Resistance in Soil



Fang Wang and James M. Tiedje

Contents

1	Introduction	269
2	ARG Distribution in Soil	269
2.1	Natural ARGs in Soil	269
2.2	ARGs in Soil with Human Activity	270
3	Anthropogenic Sources of ARGs in Soil	271
3.1	ARGs from Manure	271
3.2	ARGs from Wastewater	274
3.3	ARGs from Sludge	274
3.4	ARGs from the Atmosphere	275
4	The Persistence of ARGs in Soil	276
5	The Transmission of ARGs in Soil to Groundwater and Underground Water	276
6	The Transmission of ARGs from Soil to Plant	277
7	Effect of Anthropogenic Activities and Natural Factors on Transmission of ARGs	278
7.1	Agricultural Regulation	278
7.2	Soil Properties	279
7.3	Environment Pollutants	279
8	Direct Relationships to Human Health	281
9	Technology for Reducing the Introduction of ARGs into Soil	281
9.1	Aerobic Compost	282
9.2	Anaerobic Digestion	282
9.3	Disinfection	285
10	Conclusions	285
	References	286

F. Wang (✉)

Key Laboratory of Soil Environment and Pollution Remediation, Institute of Soil Science,
Chinese Academy of Sciences, Nanjing, China

University of Chinese Academy of Sciences, Beijing, China

e-mail: fangwang321@issas.ac.cn; wangfang@issas.ac.cn

J. M. Tiedje

Department of Plant, Soil and Microbial Sciences, Center for Microbial Ecology, Michigan
State University, East Lansing, MI, USA

Célia M. Manaia, Erica Donner, Ivone Vaz-Moreira, and Peiyong Hong (eds.),

267

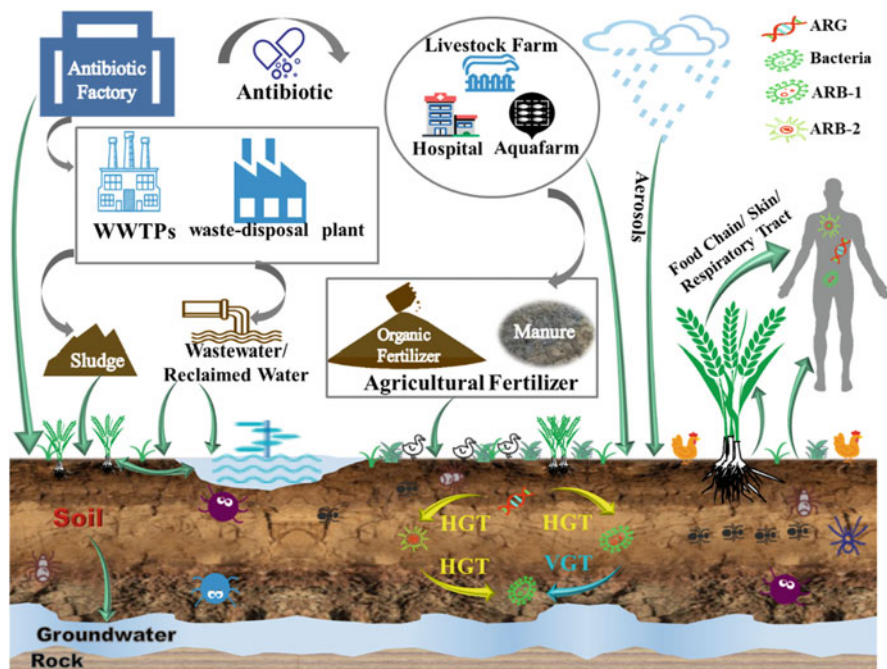
Antibiotic Resistance in the Environment: A Worldwide Overview,

Hdb Env Chem (2020) 91: 267–294, DOI 10.1007/698_2020_562,

© Springer Nature Switzerland AG 2020, Published online: 2 July 2020

Abstract Exposure to antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) from natural and agricultural ecosystems such as soil can significantly affect the dissemination of resistance determinants to the human microbiome. Soil contains a diverse natural resistome and also serves as an important environmental reservoir for ARB and ARGs derived from water sources, aerosols, and sewage sludge. Soil microbiomes have been impacted worldwide by the use and overuse of antibiotics for anthropogenic activities (clinical use and livestock production) and agricultural practices (manure application and irrigation with wastewater). The dynamics and persistence of ARB and ARGs in soil are affected by soil management and environmental factors. Both abiotic and biotic factors (pH, temperature, organic matter, nutrient availability, and syntrophic, competing or antagonistic organisms) can act as driving forces for ARG fate, evolution, and horizontal gene transfer processes. Meanwhile, ARGs in soil may also be transferred to other environments, such as groundwater and the phytosphere. To tackle the potential threat of ARGs, treatment measures (aerobic composting, anaerobic digestion, and disinfection) have been evaluated to reduce the selective pressure and import of ARGs into soil. Furthermore, the “One Health” approach was put forward to manage the development and dissemination of ARGs in a cross-disciplinary manner, to more holistically reduce human risk to the lowest level.

Graphical Abstract



Keywords Antibiotics, Antibiotic resistance gene, One Health, Persistence, Resistome, Soil, Transmission

1 Introduction

Nowadays, millions of tons of antibiotics are produced each year, and veterinary antibiotics are largely used to promote the growth of animals globally [1, 2]. World-wide overuse and abuse of antibiotics in human health and livestock production over the last few decades have greatly contributed to the propagation of antibiotic resistance [3].

Antibiotics and antibiotic resistance genes (ARGs) coexist naturally in the environment. The former are universal and multifarious, while the latter can be mobile and transferable [4]. ARGs may not only be transferred via environmental media, they may also be transmitted between parents and offspring or among different species of bacteria by vertical and horizontal gene transfer (HGT), respectively. Bacteria without ARGs may acquire antibiotic resistance by taking up naked DNA released into the environment after the death of microbes carrying ARGs, as extracellular DNA can exist for a long time under the protection of soil minerals and organic colloids [5].

ARGs have been widely identified in diverse environments, including livestock production systems, wastewater and sludge, atmosphere, and soil [6–9]. Soil undoubtedly contains the most diverse and richest DNA sequences and microorganisms [10], which significantly affect the emergence and propagation of antibiotic resistance, mainly facilitated through mobile genetic elements (MGEs) and selected mutations of existing genes exerted by antibiotics and even heavy metals [11]. The prevalence of resistance determinants is highly related to antibiotic-resistant bacteria (ARB) and ARGs in various environments [12, 13]. Widespread antibiotic resistance is identified as the top of the six emerging environmental issues and global challenges humans face in this century [14].

Antibiotic resistance has been described as the quintessential “One Health” issue [15], which requires an interdisciplinary vision, coordinated study and action across three main domains: human health, animal health, and the environment. Soil is a crucial component in the One Health approach since it not only harbors a diverse natural resistome but also receives ARB and ARGs from both human waste and livestock manures which can be further transferred to humans and animals through multiple pathways, including the production and use of vegetable and animal products, the water cycle, and aerosols [1].

2 ARG Distribution in Soil

2.1 *Natural ARGs in Soil*

In the early twentieth century, it is confirmed that ARGs disseminated long before the antibiotic era was proposed and claimed in many studies [16, 17]. For instance, there is a high diversity of ARGs conferring resistance to β -lactams, tetracyclines,

and glycopeptides, in the DNA from Late Pleistocene organisms in Arctic soil that has been frozen for 30,000 years [17]. A variety of novel β -lactamase genes and chloramphenicol resistance genes were found in frozen Alaskan soils that were largely unaffected by human activities, and the bifunctional β -lactamase gene was also first discovered in this environment [18]. Bacterial strains isolated from sediments below the land surface at the US Department of Energy's Hanford Site in Washington state were far away from sources of anthropogenic antibiotics, but still showed a relatively high frequency of resistance [16]. Microbes obtained from the Lechuguilla Cave in New Mexico, which had been isolated for 4 million years, also showed high resistance to antibiotics in nature, with some strains even tolerating up to 14 different commercially available antibiotics [19]. *Firmicutes*, *Arthrobacter*, *Bacteroidetes*, γ -*proteobacteria*, and α -*proteobacteria* from nine sites of Eastern Siberia permafrost sediments buried and frozen 15,000–3,000,000 years ago showed resistance to aminoglycoside, tetracycline and chloramphenicol antibiotics [20].

Thirteen subtypes of ARGs and MGEs were identified in soil, animal waste, and deposits that were unaffected by human use of antibiotics in Tibet, China, where *bacA*, *mexB*, *mexF*, and *mexW* were dominant over other subtypes. Eight major ARG categories consisting of 73 ARGs and MGEs (integrons, transposons, plasmids, and gene cassettes) were detected at the Gondwana Research Station and the new Jang Boggo Research Station in Antarctica, less affected by humans [21]. These studies confirm that ARGs existed in soil long before antibiotics were in widespread use by humans.

2.2 ARGs in Soil with Human Activity

Although there is plenty of evidence that some ARGs occur naturally, new ARB from humans and animals can potentially enter the soil environment and become important environmental contaminants [22]. Notably, a specific subset of clinically relevant ARGs is becoming enriched in the environment [23]. Therefore, the spread of ARGs in diverse environments is mainly due to increasing selection pressure from continuous anthropogenic usage of antibiotics [24].

Intensive animal husbandry has greatly increased the use of antibiotics and stimulated the development and spread of ARGs in agroecosystems [25]. Livestock production practices using antibiotics and the subsequent application of organic fertilizers to land can induce ARG expression in bacteria and/or mutation to produce new ARGs [26]. All major classes of antibiotics except vancomycin were found in manure-amended farm soils from three Chinese provinces (Beijing, Zhejiang, Fujian) after the use of in-feed and therapeutic antibiotics in swine production [25]. Compared with antibiotic-free manure or soil controls, the top 63 ARGs of 149 unique resistance genes, detected in these large-scale swine farm samples via high-capacity quantitative PCR arrays, are enriched up to 28,000-fold [25]. In addition, leachate from sewage and landfills increases the abundance and diversity of ARGs and bacteria in the soil [27]. One study found that as the composting time in

landfill increased, the abundance of target genes *sulI* and *tetO* in solid waste decreased, whereas the abundance of target genes in leachate increased [27]. Therefore, antibiotic residues and ARGs in landfills represent a potential risk to the environment.

In general, the external input has a profound effect on ARG pollution. Moreover, the soil bacteria commonly vary in different locations, and they respond to the environment differently; this is closely related to effects of human activities in those different regions [13]. Table 1 lists the types and abundance of ARB and ARGs in soils from different countries and regions.

3 Anthropogenic Sources of ARGs in Soil

3.1 ARGs from Manure

3.1.1 Manure Production and Antibiotic Use in Animal Production

Livestock feedlots from industrial farms (concentrated animal feeding operations, CAFOs) are the major source of animal manure worldwide, especially in developed countries [37]. In the USA, nearly 500 million pounds of animal feces are produced per year, with industrial farms generating approximately 300 million pounds, 90% of which is periodically disposed of by application as organic fertilizer for agriculture [38]. In China, over 80% of the manures produced in industrial farms are used on agricultural fields [39]. Household farms serve as another crucial source of manure. About 23% and 50% of the manures from integrated livestock farms and individual household farms, respectively, were first composted before field application in China [39]. The proportion of the manure from industrial farms is likely to increase as livestock husbandry transits to more integrated systems, giving rise to greater utilization of antibiotics in livestock production for disease prevention and animal growth enhancement because the administration of antibiotic usage lags behind [40]. Commensal microbiota and pathogenic microorganisms can exchange genes and spread in high-density farms during sub-therapeutic administration of antimicrobials. It is urgent to eliminate and reduce the use of nontherapeutic and sub-therapeutic administration of antimicrobials in poultry production [41]. Information on antibiotic utilization is important for evaluating their effects on the environment. Therefore, it is necessary to carry out market surveys to estimate the production of antibiotics and their utilization in animal and human medicines.

3.1.2 Effect of Manure Application on Soil Resistome

The overuse of antibiotics in livestock increases the risk of transmission of ARGs and MGEs from manures to soil environments [42, 43]. Highly diverse ARGs conferring resistance to tetracyclines, β -lactams, aminoglycosides, macrolides,

Table 1 Distribution of ARGs and ARB in soils and sediments

Country/ region	Agrotype	External source import	Type of ARGs or ARB	Absolute abundance (copies/g)	References
Distribution of ARGs and ARB in soils unaffected by human					
30,000- year-old Beringian	Permafrost sediments	Nature	Genes encoding resistance to β -lactam, tetracy- cline, and glycopep- tide antibiotics	–	[17]
Alaskan	Unpolluted soil	Nature	β -lactam-resistant bacteria	–	[18]
South Car- olina and Washington	Sediments	Nature	Resistance to nalidixic acid, mupirocin, or ampicillin	–	[16]
New Mexico	Soil	Nature	Resistance for macrolide antibiotics	–	[19]
Antarctica	Soil	Terra Nova Bay	73 ARGs and MGEs	–	[21]
Arctic permafrost	Sediments	Subsoil	Aminoglycoside-, chloramphenicol-, and tetracycline- resistant bacteria	–	[20]
Distribution of ARGs and ARB in soils affected by human					
China	Ryland (peanut) and paddy (rice) fields	Manure	<i>folP</i> , <i>sul1</i> , <i>sul2</i> , <i>sul3</i> , <i>ermB</i> , <i>mexF</i> , <i>oprJ</i> , <i>tetPA</i> , <i>acrA_5</i> , etc.	–	[9]
America	Farm soil	Cattle farms	<i>bla_{CMY-2}</i> , <i>tetB</i> , <i>tetC</i> , <i>tetO</i> , <i>tetW</i> , and β -macrolide resis- tance genes	–	[28]
America	Channel soil	Agricultural activity and sewage treat- ment plant discharge lake	<i>sul1</i> , <i>sul2</i> , <i>tetO</i> , <i>tetW</i>	–	[29]
China	Farm soil	Pig breeding farm	FCA, fluoroquino- lone, quinolone, florfenicol, chloram- phenicol, and amphenicol resis- tance genes	–	[25]
Denmark	Farm soil	Pig breeding farm	<i>tetA</i> , <i>tetB</i> , <i>tetC</i> , and other tetracycline resistance genes		[30]
Canada	Farm soil	Cow breed- ing farm	<i>ermA</i> , <i>ermB</i> , <i>ermF</i> , <i>qnrB</i> , <i>sul2</i> , <i>tetT</i>	10^4 – 10^5	[31]

(continued)

Table 1 (continued)

Country/ region	Agrotype	External source import	Type of ARGs or ARB	Absolute abundance (copies/g)	References
Israel	Farmland soil	Wastewater irrigation	<i>qnrA</i> , <i>tetO</i> , <i>sul1</i> , <i>sul2</i> , <i>ermB</i> , <i>ermF</i>	–	[32]
Poland	Farmland soil	Manure and plant compost	<i>tetO</i> , <i>tetB</i> , <i>tetD</i> , <i>tetT</i> , <i>tetW</i> , <i>ermC</i> , <i>ermV</i> , <i>strA</i> , <i>strB</i> , etc.	1.3×10^5 – 4.1×10^5	[33]
Switzerland	Organic soil	Pig manure	<i>tetC</i> , <i>tetH</i> , <i>tetQ</i> , <i>tetW</i> , <i>tetT</i> , etc.	4.63×10^5 – 3.74×10^6	[34]
Beijing and Tianjin, China	Farmland soil	Wastewater irrigated soil	<i>tetA</i> , <i>tetB</i> , <i>tetC</i> , <i>tetD</i> , <i>tetM</i> , <i>tetO</i> , <i>sul1</i> , <i>sul2</i> , <i>sul3</i> , etc.	1.9×10^3 – 5.6×10^7	[35]
Finland	Dairy farms and swine farms	Fresh manure from inside the animal shelter	Genes encoding resistance to aminoglycosides, disinfectants, MLSB, tetracyclines, sulfon- amide, trimethoprim, and vancomycin	–	[36]

chloramphenicol, sulfonamides, and multiple drugs exist in manures and manure composts [44]. The highest relative abundance of ARGs (relative to 16S rRNA gene) measured in manures ranged from 10^{-3} to 10^{-1} and 10^{-2} to 10^{-1} in Chinese and Finnish farms, respectively [2]. The transmission of ARGs from manure into soil might also be facilitated when ARGs co-occur with MGEs [45]. Many ARGs in manures are carried on plasmids or integrons [46, 47], implying a high risk of transmission from the manure into the soil ecosystem.

Utilization of manures or manure composts may increase the types and abundance of ARGs in soil via import of manure-borne ARGs and antibiotic residues [25]. After application of manure or compost, the relative abundance of some ARGs may decrease directly in soil, whereas the relative abundance of others may initially be enhanced followed by gradual attenuation [36]. This initial period of increasing relative abundance enhances the risk of transmission of manure-borne ARGs to microorganisms in soil niches, especially in the case of repeated and long-term applications of manures and composts into agricultural soil [2]. Manure-introduced bacteria hosting ARGs might be outcompeted by native soil microorganisms and gradually disappear from the soil microbiome [48]. Nevertheless, some manure-borne ARGs may still persist in the soil via gene transfer to indigenous microorganisms [43], and these ARGs may be further enriched due to the growth enhancement effects of introduced nutrients from the fertilizer [49, 50]. Therefore, applications of manure or compost may affect soil ARGs and MGEs by direct transfer of manure-borne ARGs and selection by manure-introduced antibiotics [2]. It is thus essential to distinguish manure-introduced ARGs and MGEs from the intrinsic soil resistome and indigenous soil ARGs and MGEs enhanced by manure or compost applications,

as well as to identify the ARG hosts selected by antibiotic residues and other co-selection pressures.

3.2 ARGs from Wastewater

It was estimated that global production of wastewater reached 135 and 275 km³ in the domestic and manufacturing sectors in 2010, respectively [51]. Approximately 167 km³ of global manufacturing wastewater comes from Russia, China, the USA, India, Indonesia, Brazil, and Japan [52]. According to the AQUASTAT data, only 60% of municipal wastewater is treated effectively [52].

In the past 20 years, the concentration of antibiotics has increased in untreated wastewater, which is rich in nutrients and bacteria [53]. The wastewater treatment system is thus considered to be a high-risk environment for the selection and transfer of microbial genetic material and is also one of the most important sources of ARGs in other water environments. Studies in irrigated soil in the Pearl River Delta Region in Southern China have suggested that wastewater irrigation can significantly increase the concentration of tetracycline and sulfamethazine and the relative abundance of ARGs associated with those drugs [54]. Compared with nonirrigated soil, the absolute abundance of ARGs other than *tetQ*, the *aadA*, *intI1*, *qacE+qacEΔ1*, and *IncP-1* plasmids (linked to multi-antibiotic resistance) increased by two orders of magnitude in soils irrigated with untreated wastewater for 100 years in Mexican soil [55]. In 12 urban park soils with reclaimed irrigation water in Victoria, Australia, a total of 40 unique ARGs were identified, with β-lactam resistance genes being most prevalent by high-throughput qPCR and terminal restriction fragment length polymorphism techniques. Compared with domestic wastewater-irrigated soils, there are higher concentrations of antibiotics and abundance of ARGs in soils irrigated by fishpond water, indicating that different types of wastewater exert different impacts on ARGs in the soil [54]. Generally, the increase of ARGs may be attributed to the accumulation rather than the in situ enrichment of ARGs in soil, and short-term wastewater irrigation cannot attenuate the accumulation of ARGs [55].

3.3 ARGs from Sludge

In the European Union, a total of 10 million tons (dry matter) of sewage sludge was produced in 2010 [56, 57], with 76% from Germany, the UK, Italy, France, and others. In the USA, over 8 million tons of solids is produced annually and 55% is applied to arable land [57]. In China, 6.25 million tons of dry solids were produced in 2013, with an average annual increase of 13% [58].

Antibiotics and ARGs might be absorbed to and enriched in sludge during sewage treatment. The abundance of ARGs significantly increased by an average of 947-fold in activated sludge compared to influent samples, which might be due to the increase in the total number of bacteria [59]. Various optimization measures have

been tried to reduce the abundance of ARGs in treated sludge/biosolids, such as the addition of natural zeolite to the sludge [60] and bio-drying [61]. Regardless of the disposal method of sludge, the process of treatment, or the use of recycled products, ARGs and ARB can be easily transferred into the soil. Bacteria can share genetic information through HGT with MGEs allowing ARGs to transfer from microorganisms in the sludge to indigenous microbes in the soil [62]. Furthermore, it indicates that sludge serves as a hot spot for the enrichment of ARGs and MGEs among bacteria, and its application may increase the HGT activities of ARGs in soil regardless of the difference in bacterial populations between sludge and soil [60].

Land application of sewage sludge is the key management approach of sludge disposal and an important channel for ARG spread to farmland [63], leading to the dissemination of ARGs into the soil [64]. Compared with ARGs in unamended soil, there was a short-term increase within 20 days in the number of ARGs in amended soils, but there was no significant difference in the relative abundance of ARGs [65]. The sludge can be mixed with straw or bark to produce organic fertilizer through microbial fermentation. The changing composition of the bacterial community is responsible for the reduction of ARGs upon composting, mainly because the high temperature produced by composting is conducive to the suppression or reduction of resistant bacteria and hence their resistance genes [66]. This was found to be driven by several key effects: (1) most of the pathogenic microorganisms were killed when temperatures exceeded 50°C for at least 5 days during composting; (2) high temperatures affect microbial enzyme activity, changing the rate of enzymatic reactions and ultimately affecting cell synthesis; and (3) the extracellular DNA in the sludge contains some ARGs whose rate of hydrolysis and biodegradation increases with increasing temperature.

3.4 ARGs from the Atmosphere

ARGs in soil can also be exchanged and transmitted through air [67]. Especially in heavily polluted air, the increased concentration of airborne particles is conducive to microbial transport as it provides more adhesion sites [6]. Studies have indicated that farms produce a large number of microorganisms, such as ARB, pathogenic bacteria, and opportunistic pathogens, which are easily aerosolized during animal production activities and fecal disposal, hence becoming a potential repository and carrier of ARGs [68].

ARGs can enter soil through either dry deposition or wet deposition. Dry deposition is caused by turbulent diffusion, gravity sedimentation, molecular diffusion, etc. and can transport aerosol particles carrying ARGs to the surface of the earth, where molecular forces enable them to adhere to soils [69]. Wet deposition refers to the process in which aerosol particles, participating in the formation of cloud droplets, are removed from the atmosphere by rainfall and snowfall. Cloud removal makes the aerosol particles with ARGs themselves become part of the cloud droplets as a result of condensation nuclei, and subcloud removal refers to the formation of a droplet of rain, snow, ice, etc., which can adsorb and contain aerosol

particles with ARGs [70]. The ARGs in air may disseminate across different regions, as the pollutants can be transported and settled to soil in remote areas [13]. Therefore, the ARGs coming from the air also increase in the soil [71]. In return, a series of soil pollutants and microbes may also be aerosolized and further exacerbate ARG spread via air.

4 The Persistence of ARGs in Soil

Although there are a number of reports focused on transmission of ARGs from soil to plants, and the effects of anthropogenic activities and environmental factors on transmission of ARGs, the persistence of ARGs in soil is still unclear. The potential factors that influence the dynamics and persistence of ARGs in soil are thus attracting more attention.

In a field study, the relative abundance of *sul1*, *sul2*, and *ermF* increased rapidly in soil after slurry application and dissipation rate of *ermF* in slurry-treated soils was higher than *sul1* and *sul2* in dry-stack-amended soils [72]. The relative abundance of ARGs increased rapidly at day 1 after application of manure, followed by a decrease to the background levels by day 60, whereas a slight increase of the relative abundance of ARGs, followed by a decrease to the background levels by day 32 after application of compost [73]. The half-lives of *ermB*, *sul1*, *tetA*, *tetW*, and *tetX* in soil range from 13 days to 81 days after the application of different ratios of the biosolids from a wastewater treatment plant [74]. Half-lives of ARGs (0.40–3.87 d) and specific genes (*ermF*, 1.42–3.51 d; *tetG*, 0.43–2.86 d; *tetX*, 1.35–8.79 d) differed in the treated soils according to the addition of different sludge composts [75]. However, long-term application of manure compost in a red soil did not greatly increase the relative abundance of ARGs and MGEs in dryland soil or paddy soil, compared to the soil without any fertilization over 26 years [9]. Therefore, the persistence of ARGs varies considerably depending on fertilizer treatments and a series of factors, such as cropping systems, soil oxygen status, the introduction of nutrients, and other factors related to microbial community structure. Therefore, the removal rates of ARGs in soil are highly related to several factors: transport of extracellular DNA containing ARGs and cells carrying ARGs [76], binding of ARGs to soil or organic matter [77], decay of extracellular ARGs [78], and death of host bacteria [79].

5 The Transmission of ARGs in Soil to Groundwater and Underground Water

There is an increasing concern that the resistant bacteria generated in farm activities may migrate into soil and groundwater with the land application of manure. Antibiotic resistance contaminants in soil (especially large animal facilities) may be carried

by runoff and erosion to secondary reception systems (surface water and groundwater) or leach directly to groundwater [80]. Several ARGs directly impacted by animal agriculture were characterized in natural groundwater [81]. Furthermore, seven tetracycline resistance genes (*tetM*, *tetO*, *tetQ*, *tetW*, *tetC*, *tetH*, and *tetZ*) in lagoons and groundwater adjacent to swine production facilities were monitored and source tracked from 2000 through 2003 [82]. Results showed that gene sequences in the impacted groundwater are highly identical to those in the lagoon. Additionally, novel sequence clusters and unique indigenous resistance gene pools were also found in the groundwater. Thus, swine manure seriously affected the ARGs in groundwater, as well as part of the indigenous gene pool [82].

6 The Transmission of ARGs from Soil to Plant

The enhanced water fluxes and nutrient input in the rhizosphere can stimulate bacterial metabolic activities and the transfer of conjugative plasmids in their inhabitants [83]. These conditions establish “hot spots” for microorganism gene transfer activity in the phytosphere, including both the rhizosphere and the phyllosphere [50]. ARGs in manure-amended soil can be potentially transferred to vegetables, including those that are eaten raw or with minimal processing [31]. It has been shown that organic lettuce may be apt to carry more diverse ARGs. For example, one recent study reported up to eightfold higher absolute abundance of 134 ARGs in organic lettuce than conventionally produced lettuce [84]. Furthermore, long-term exposure of plants to antibiotics and ARGs in soil has increased the risk that ARGs carried by pathogens can enter the food chain via contaminated crops, indicating that consumption of raw leafy vegetables may potentially increase direct human exposure to ARGs [85, 86].

More and more studies show that endophytic bacteria (root endophytes, leaf endophytes, and phyllosphere microorganisms) can acquire antibiotic resistance from manure-amended soil, and sulfonamide and tetracycline resistance genes, such as *sul1*, *sul2*, *tetC*, and *tetG*, have been detected in harvested vegetable samples [87]. Yang et al. [88] showed that nine subclasses of ARGs were shared among soil, roots, and shoots of lettuce and that ARGs were mainly located in endophytes within the lettuce [88]. These endophytic bacteria are the main carriers and disseminators of drug-resistant genomes and mobile genetic elements, and they can acquire drug resistance through various ways [89]. Such bacteria may be directly transmitted through the chain of soil vegetables from animal feces and act as an important driver of the change of multi-antibiotic-resistant bacteria in vegetables [90]. Therefore, microorganisms and secretions (sugars, organic acids, and amino acids) in the rhizosphere may affect the migration and attenuation of ARGs in soil [91, 92].

Additionally, the potentially transferable gene pool in the phytosphere was found to be highly mobile and directly correlated with host fitness. The conditions in these hot spots fluctuate temporally as they are heterogeneous and dynamic environments [50]. Therefore, it is difficult to evaluate the extent to which these factors affect HGT processes of ARGs under different conditions [93].

7 Effect of Anthropogenic Activities and Natural Factors on Transmission of ARGs

The development of bacterial resistance to antibiotics poses a major threat to human health [94]. The application of antibiotics in human medicines and livestock production and the use of manures and municipal wastes in agriculture are regarded as pivotal selective pressures on the dissemination of ARGs [25, 95]. In addition, resistance of bacteria to antibiotics co-occurs with other environmental factors, such as lack of nutrition, extreme temperature stress, and oxidative conditions [94, 96]. The current state of knowledge on the dissemination of ARGs induced by anthropological activities and natural factors can be described as follows.

7.1 Agricultural Regulation

7.1.1 Soil Management

Common soil management practices like cropping systems, irrigation, and fertilization are known to influence both the introduced and intrinsic soil resistome. Manure is rich in available carbon for bacterial growth and may also carry co-selectants such as antibiotics and metals [25]. Additionally, all these fertilizers also contain organic and inorganic contaminants, which have been related to a series of negative environmental impacts on the dissemination of antibiotic resistance [97]. Irrigation with treated wastewater may increase ARG levels in soil bacteria, potentially adding to the global dissemination of clinically relevant antibiotic resistance. It is also evident that ARG and ARB risks could be impacted differently under different cropping systems, e.g., dryland vs. paddy soils. Wang et al. [9] showed that the relative abundance of *tetPA*, *oprJ*, *mexF*, and *acrA_5* increased, whereas other genes decreased in paddy soil compared to the dryland soil, indicating that the overall pattern of ARGs in the soil varies according to cropping system and may have been driven by the differences between aerobic and anaerobic conditions [9]. Therefore, the origin, dynamics, and propagation of ARGs in soils are closely related to different agricultural practices and the physicochemical properties of soils. It is important to understand comprehensively the dynamics of intrinsic and introduced ARGs in soil and therefore develop strategies for risk mitigation.

7.1.2 Biochar Amendment

Biochar, a soil amendment produced via pyrolysis/carbonization of plant- and animal-based biomass, is widely used in agriculture to increase the soil water holding capacity and improve soil fertility [98]. π - π interactions play an important role between the aromatic rings on antibiotics and biochar [99, 100], probably driving selection or co-selection of ARGs among soil microorganisms.

Biochar amendment may significantly decrease the abundance of ARGs in non-planted soil [101]. The underlying mechanisms could be attributed to two factors: (1) the mobility of antibiotics and heavy metals being decreased through adsorption and (2) the bacterial community structure being influenced by the addition of biochar, with corresponding effects on the resistome [102, 103]. In another study, mushroom and rice straw biochar were both produced at 500°C for 4 h under oxygen-limited conditions using a muffle furnace. Whereas the application of mushroom biochar effectively removed ARGs and pathogenic bacteria, this is not the case with the rice straw biochar [104]. Therefore, further systematic and integrated study is needed to unveil the relationship between biochar physicochemical properties and their influence on the persistence and/or propagation of ARGs in soil.

7.2 Soil Properties

Soil physical, chemical, and biological parameters have been identified as environmental stresses that induce or maintain antibiotic resistance evolution and transmission [77]. Pearson correlation analysis indicated that there is a correlation between the abundance of ARGs and antibiotics or soil properties (pH and soil organic matter). The concentrations of tetracyclines and abundance of ARGs decreased with increasing soil depth [54, 105]. Relative studies showed that the abundance of ARGs in soil was increased after the long-term application of sewage sludge [11], whereas another study found inconsistent levels of ARGs in different sites of amended soil [106].

Soil microbial phylogenetic structure is commonly regarded as the dominant biotic determinant of ARG compositions [107], as soil microbes are not only the producers of many antibiotic compounds [4] but also hosts to various ARGs. Many studies have shown that soil physicochemical properties, plant species, and climate, as well as chemical substances, can significantly influence the diversity, structure, and function of microbial communities in soil [108, 109]. Moreover, it has been demonstrated that microbial community structures revealed great differences among the paddy soil samples, which were consistent with differences in pH values [110]. In addition, the total *tet* gene copies were highly related to soil organic matter near swine feedlots [111]. All the results verified that soil type and physicochemical properties exert an impact on the microbial community, which was correlated with the fate of ARGs.

7.3 Environment Pollutants

7.3.1 Heavy Metals

It is a common practice to add certain heavy metals into animal feeds to promote growth and control disease, and these metals are subsequently accumulated by soils

after the application of manure and sewage sludge [112, 113]. There is a link between the use of Zn in feed additives and the occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) in animal production [114]. Positive correlations exist between some ARGs and heavy metals in manures and manure-amended soils [115]. The positive correlation between ARGs and heavy metals is conducive to the survival of bacteria in a polluted environment, which promotes the spread of ARGs in soil to some extent [116].

It is vital to recognize that metals can co-select antibiotic resistance and drive strong selection of bacterial assemblages in various environments [117]. The types, abundance, and mobility potential of ARGs were significantly influenced by long-term heavy metal contamination and result in the unpredicted risk of the ARG dissemination in environments contaminated with heavy metals. Furthermore, the co-selection for antibiotic resistance induced by heavy metals has been highlighted, particularly when the same gene confers resistance to multiple types of metals and antibiotics and when diverse genes encoding metal and antibiotic resistance coexist on the same MGE.

7.3.2 Nanomaterials

Recently, it was estimated that the global market requirement for metal oxide nanoparticles will increase from 270,041 tons in 2012 to 1,663,168 tons by 2020 [118]. Although nanoparticles exist in various environments, such as wastewater effluent and sludge, knowledge about their influence on ARB and ARGs is lacking. The application of nanoalumina significantly promoted the HGT of multidrug resistance genes encoded by the plasmids of RP4, RK2, and pCF10 [119]. It is also reported that AgNP exposure reduced the occurrence of ARGs in collembolan gut microbiota [120]. The conjugative transfer of the RP4 plasmid from *E. coli* to *Salmonella* spp. treated with nanoalumina was enhanced 200-fold, indicating that the environmental and health risks from nanomaterials could include promoting sensitive bacteria to obtain antibiotic resistance [119].

7.3.3 Microplastics

Microplastics in aquatic environments may adsorb antibiotics on their surfaces, resulting in their long-range dissemination and entry into the food chain [121]. Sophorolipid can stimulate ARG dispersion mediated by bacteria/phage in soil co-contaminated with microplastic and tetracycline [122]. Compared to free-living bacteria, the transfer rate of plasmid DNA in phylogenetically diverse bacteria was increased, and this was associated with microplastics [123]. These reports indicate that microplastics could be the hot spot for HGT between phylogenetically distinct pathogens in the environment.

8 Direct Relationships to Human Health

Most clinically relevant ARGs may originate from environmental bacteria [124]. ARGs carried by soil bacteria that are also found in human clinical pathogens [125] and novel ones conferring high-level resistance against sulfonamides, aminoglycosides, and a broad range of β -lactams have been discovered [126]. Functional metagenomic analysis of soil-inhabiting bacteria revealed a high nucleotide identity (>99%) when comparing the multidrug-resistant resistome of soil bacteria with those in clinical human pathogens, inferring possible HGT among bacteria from these different environments [127]. It was also revealed that the contiguous nature of the *intI1* with the ARGs carried by the soil bacteria and clinical pathogens facilitated the HGT process [127]. The *intI1*, belonging to class 1 integrons, is closely related to the integration of multiple ARGs at the same genetic site. In natural and anthropogenically influenced environments, integrons have been acknowledged to be the prevalent carriers of multiple ARGs [46]. A substantially increased abundance of *intI1* was reported when manure was applied to archived soils, inferring the transfers of multiple resistances from soil environments to clinical activities. This resistance could be intensified by the applications of excessive antibiotic-contaminated manures to land.

To date, several limitations for confirming ARG transfer from environmental microbiomes to human pathogens have been identified although credible evidence of this process is yet to be well or fully documented [128, 129]. In any case many ARG hosts exist on the surfaces of leafy vegetables (arugula, cilantro) grown in manure-amended soil that are eaten raw [93, 130]. This represents a direct food chain link between the environment and humans. After incubation of lettuce or cilantro leaves, the total DNA of the bacterial community was obtained from the enrichment, and multiple resistance plasmids were found in *E. coli* isolates, indicating that bacteria colonizing leafy vegetables are the original source of transposons and integrons [130, 131]. As multiple ARGs in the bacterial genomes are being found in the plasmids, it is obvious that antibiotic resistance pathogens or “superbugs” may propagate on a global scale. This is supported by the occurrence of plasmid-carrying *mcr-1* resistant to colistin (polymyxin E) in various pathogens worldwide [132]. Colistin has been revived as a last resort drug to tackle the threat of multidrug-resistant bacterial outbreaks [133]. The plasmid-carrying *mcr-1* was first reported in animal and human sources in Shanghai, China. Nowadays, *mcr-1* has been identified in samples from various sources including human pathogens, swine, poultry, pork, and environmental sources worldwide [132]. The consumption of pork has also been reported to significantly promote the spread of the ARGs in Dutch travelers [134].

9 Technology for Reducing the Introduction of ARGs into Soil

Much effort is being spent to mitigate the threat of antibiotic resistance, namely, developing new or alternative antibiotics and reducing antibiotic usage [135, 136]. An alternative and complementary stewardship initiative consists of

monitoring and removing ARGs as environmental pollutants [29]. Various treatment processes, such as aerobic composting, anaerobic digestion, and disinfection, have been applied and tested for their efficacy in removing ARGs and antibiotics (Table 2). The intention is to reduce the selection pressure and introduction of ARGs into soil through manure and compost application and wastewater irrigation.

9.1 Aerobic Compost

Aerobic composting is widely used to treat organic wastes and manure. The effects of aerobic composting on the variation of ARGs are based on different processing technologies. For example, continuous thermophilic composting can significantly reduce ARGs and integrons in animal manure [140]. Superabsorbent polymers are also considered suitable amendments for reducing ARGs in swine aerobic compost [143]. Conversely, several types of ARGs cannot be effectively removed by aerobic composting, with compost products, thus remaining an important reservoir of ARGs [49]. Temperature was viewed as an important factor to influence the fate of ARGs in aerobic digested sludge where the shift in temperature would largely change the bacterial community [137]. The ARGs and MGEs from sewage sludge were significantly reduced by hyperthermophilic composting (temperatures up to 90°C), as were other indicators during the composting process (mushroom biochar, rhamnolipid, Tween 80 and other surfactants, etc.) [144, 145]. Additionally, the temperatures under elevated thermophilic composting up to 70–80°C without exogenous heating and additives (zeolite, superphosphate, or zeolite and ferrous sulfate) on the removal rate of ARGs during chicken manure composting were investigated. The removal of ARGs in manure was 86.5%, 68.6%, and 72.2% in zeolite, superphosphate, and zeolite and ferrous sulfate, respectively, which is higher than the control [146].

9.2 Anaerobic Digestion

Anaerobic digestion of manure from livestock and poultry can produce methane, while the digested residue can be applied as organic fertilizer [147]. Additionally, there is some evidence that anaerobic digestion can reduce populations of ARB in manure and biosolids, as well as genes coding for resistance to antibiotics, and may thus be an effective approach for recycling agricultural waste and removing ARGs [148]. Several treatment strategies including pretreatment, thermophilic digestion, two-stage digestion, additives, and solid-state digestion were employed to compare the removal of ARGs by anaerobic digestion [149]. Operating parameters played crucial roles in the reduction efficiency of ARGs. For example, longer solids retention time showed a higher level of ARG removal rate in anaerobic digestion of residual sludge [66]. Therefore, it is necessary to critically evaluate existing

Table 2 Technologies tested to reduce the introduction of ARGs into soil

Targeting antibiotics	Gene	Jang et al. [137]	Burch et al. [79]	Ghosh et al. [138]	Zhang et al. [139]	Qian et al. [140]		Zhang et al. [141]	Zhang et al. [142]		
		Aerobic (55°C) - ^a , + ^b - ^a , b	Aerobic (25°C) - ^a	Anaerobic (35°C) + ^b	Anaerobic (35°C)	Aerobic (<45°C)	Aerobic (55°C)	Ultraviolet disinfection (80 mJ cm ⁻²)	Thermophilic anaerobic	Mesophilic anaerobic	
Tetracycline	<i>tetA</i>							- ^b	+ ^a	+ ^a	
	<i>tetB</i>										
	<i>tetC</i>					+ ^b					
	<i>tetD</i>	- ^a , b									
	<i>tetE</i>	- ^a , b									
	<i>tetG</i>	- ^a , b			+ ^a , - ^b		- ^b				
	<i>tetH</i>	- ^a , b									
	<i>tetJ</i>										
	<i>tetL</i>										
	<i>tetM</i>	- ^a , b			+ ^a , b		- ^b				
	<i>tetO</i>										
	<i>tetQ</i>	- ^a , b					+ ^b				
	<i>tetS</i>										
	<i>tetT</i>										
	<i>tetW</i>										
	<i>tetX</i>	- ^a , b - ^a , b - ^a , b	- ^a	+ ^b	+ ^a , b		- ^b				
	<i>tetZ</i>	- ^a , b - ^a , b									
<i>tetBP</i>											
Sulfonamide	<i>sulI</i>	- ^a , b	- ^a	+ ^a , - ^b		±			- ^b	+ ^a	
	<i>sul2</i>	- ^a , b		+ ^a , b		±			- ^b		
	<i>sulA</i>										
	<i>dfrA1</i>										
	<i>dfrA7</i>										

(continued)

Table 2 (continued)

	Jang et al. [137]	Burch et al. [79]	Ghosh et al. [138]	Zhang et al. [139]	Qian et al. [140]	Zhang et al. [141]	Zhang et al. [142]
Targeting antibiotics	Aerobic (55°C)	Aerobic (25°C)	Anaerobic (35°C)	Anaerobic (35°C)	Aerobic (<45°C)	Aerobic (55°C)	Thermophilic anaerobic
Quinolone						Ultraviolet disinfection (80 mJ cm ⁻²)	Mesophilic anaerobic
	<i>gyrA</i>						— ^a
	<i>parC</i>						
	<i>qnrA</i>						
	<i>qnrC</i>						
	<i>qnrD</i>	— ^a , + ^b					
	<i>qnrS</i>	— ^a , b					
	<i>Aac(6')-ib-cr</i>	— ^a , b			— ^b		
Macrolide							
	<i>ermB</i>	— ^a , + ^b		+ ^a , b	— ^b		+ ^b
	<i>ermC</i>	— ^a , b					
	<i>ermF</i>						
	<i>ermQ</i>						
β-Lactam							
	<i>bla_{TEM}</i>	— ^a , b		+ ^a , b	— ^b		— ^b
	<i>bla_{CTX}</i>	— ^a , b					
	<i>bla_{CMV}</i>						
	<i>bla_{SHV}</i>	— ^a , b					
MDR							
	<i>oqxA</i>	— ^a , b					
	<i>floR</i>	— ^a , b					
MGEs							
	<i>Int11</i>	— ^a , b	— ^b	+ ^a , b	+ ^b		— ^a
	<i>Int12</i>				— ^b		

+, increase; —, decrease; ±, non-change; ND not detected

^aAbsolute abundance^bRelative abundance

anaerobic treatment processes for their potential in mitigating ARGs and their propagation in the environment.

9.3 *Disinfection*

Various techniques are used in wastewater treatment, such as UV, chlorine, and ozone disinfection. To induce bacterial damage, these techniques employ different mechanisms. Comparative studies of disinfection methods on ARG removal are widely reported in the literature [141, 150]. Disinfection process of ARB cells is significantly related to the disinfectants' relative activities and consumption by important cell constituents, including amino acids, saccharides, lipids, and nucleic acids [151]. The frequency of the transfers of ARGs was determined under different rates of UV or chlorine, indicating that UV disinfection and chlorination display different influences on conjugative transfer and that the dose of both UV and chlorine would be important factor in removing ARGs [152]. Additionally, when the ozone dose was 2 mg/L, the abundance of ARGs had higher removal efficiency, but there was no significant correlation between the concentration of ozone and ARG removal efficiency. Although inactivation of ARB via destroying bacterial DNA or the cellular structure could occur during disinfection processes, ARGs may still exist in the cell debris, constituting a potential downstream threat to human health.

10 **Conclusions**

Although the relevance of ARB and ARGs as environmental contaminants is widely recognized, there is currently limited evidence to assess the related human health risks quantitatively and objectively. Therefore, it is difficult to define threshold values for the maximum admissible levels of ARB and ARGs in treated wastewater and in sludge and manure used in agriculture. Increasing water scarcity and soil degradation will drive increased need for water reuse, and beneficial reuse of municipal sludge and manures, likely increasing inputs of ARGs and ARB into soil. Thus far, several primary strategies have been proposed to mitigate the propagation of antibiotic resistance, namely, the restriction of antibiotic use in clinical activities and veterinary applications, and to promote new drug design.

Given the urgency of the problem, secondary or follow-on strategies are also needed to help preserve the effectiveness of existing antibiotics. These include establishment of a global systematic and publicly available surveillance network, including regular, consecutive measurement of antibiotic application and the diversity of antibiotic resistance from agriculture and clinical activities. Continuous surveillance of antibiotic resistance is conducive to disease diagnosis, effective antimicrobial stewardship, and policy setting, thus the overriding importance of undertaking surveillance across the One Health framework. Governments should

pay more attention to ARG pollution with investment in both basic and applied research to provide a strong scientific basis for formulating effective mitigation practices and a standardized assessment system to document risk reduction of soil and water contaminated by antibiotics and ARGs. This will provide reference data for prevention, reduction, and removal of these important environmental pollutants.

References

1. Tiedje JM, Wang F, Manaia C, Virta M, Sheng H, Ma L, Zhang T, Topp E (2019) Antibiotic resistance genes in the human impacted environment: a One Health perspective. *Pedosphere* 29:273–282. [https://doi.org/10.1016/S1002-0160\(18\)60062-1](https://doi.org/10.1016/S1002-0160(18)60062-1)
2. Xie WY, Shen Q, Zhao FJ (2018) Antibiotics and antibiotic resistance from animal manures to soil: a review. *Eur J Soil Sci* 69:181–195
3. Nesme J, Simonet P (2015) The soil resistome: a critical review on antibiotic resistance origins, ecology and dissemination potential in telluric bacteria. *Environ Microbiol* 17:913–930
4. Allen HK, Donato J, Wang HH, Cloud-Hansen KA, Davies J, Handelsman J (2010) Call of the wild: antibiotic resistance genes in natural environments. *Nat Rev Microbiol* 8:251
5. Dolejska M, Papagiannitsis CC (2018) Plasmid-mediated resistance is going wild. *Plasmid* 99:99–111
6. Hu J, Zhao F, Zhang XX, Li K, Li C, Ye L, Li M (2018) Metagenomic profiling of ARGs in airborne particulate matters during a severe smog event. *Sci Total Environ* 615:1332–1340
7. Pärnänen KMM et al (2019) Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. *Sci Adv* 5:eaa9124
8. Thompson JM, Gundogdu A, Stratton HM, Katouli M (2013) Antibiotic resistant *Staphylococcus aureus* in hospital wastewaters and sewage treatment plants with special reference to methicillin-resistant *Staphylococcus aureus* (MRSA). *J Appl Microbiol* 114:44–54
9. Wang F, Xu M, Stedtfeld RD, Sheng H, Fan J, Liu M, Chai B, Soares de Carvalho T, Li H, Li Z, Hashsham SA, Tiedje JM (2018) Long-term effect of different fertilization and cropping systems on the soil antibiotic resistome. *Environ Sci Technol* 52:13037–13046
10. Rodriguez RL, Gunturu S, Tiedje JM, Cole JR, Konstantinidis KT (2018) Nonpareil 3: fast estimation of metagenomic coverage and sequence diversity. *mSystems* 3:3
11. Chen B, Yuan K, Chen X, Yang Y, Zhang T, Wang Y, Luan T, Zou S, Li X (2016) Metagenomic analysis revealing antibiotic resistance genes (ARGs) and their genetic compartments in the Tibetan environment. *Environ Sci Technol* 50:6670–6679
12. Leonard AFC, Zhang L, Balfour A, Garside R, Gaze WH (2015) Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters. *Environ Int* 82:92–100
13. Zhu YG, Zhao Y, Zhu D, Gillings M, Penuelas J, Ok YS, Capon A, Banwart S (2019) Soil biota, antimicrobial resistance and planetary health. *Environ Int* 131:105059
14. UNEP (2017) Antimicrobial resistance from environmental pollution among biggest emerging health threats, says UN Environment. <https://www.unenvironment.org/news-and-stories/press-release/antimicrobial-resistance-environmental-pollution-among-biggest>
15. Robinson DA, Sutcliffe JA, Tewodros W, Manoharan A, Bessen DE (2006) Evolution and global dissemination of macrolide-resistant group a Streptococci. *Antimicrob Agents Chemother* 50:2903–2911
16. Brown MG, Balkwill DL (2009) Antibiotic resistance in bacteria isolated from the deep terrestrial subsurface. *Microb Ecol* 57:484–493
17. D'Costa VM, King CE, Kalan L, Morar M, Sung WWL, Schwarz C, Froese D, Zazula G, Calmels F, Debruyne R, Golding GB, Poinar HN, Wright GD (2011) Antibiotic resistance is ancient. *Nature* 477:457

18. Allen HK, Moe LA, Rodbumrer J, Gaarder A, Handelsman J (2009) Functional metagenomics reveals diverse beta-lactamases in a remote Alaskan soil. *ISME J* 3:243–251
19. Bhullar K, Waglechner N, Pawlowski A, Koteva K, Banks ED, Johnston MD, Barton HA, Wright GD (2012) Antibiotic resistance is prevalent in an isolated cave microbiome. *Plos One* 7(4):e34953
20. Mindlin SZ, Soina VS, Prova MA, Gorlenko ZM (2008) Isolation of antibiotic resistance bacterial strains from East Siberia permafrost sediments. *Genetika* 44:36–44
21. Wang F, Stedtfeld R, Kim O-S, Chai B, Yang L, Stedtfeld T, Hong SG, Kim D, Lim HS, Hashsham S, Tiedje J, Sul WJ (2016) Influence of soil characteristics and proximity to antarctic research stations on abundance of antibiotic resistance genes in soils. *Environ Sci Technol* 50(23):12621–12629
22. Kevin JF, Alejandro R, Bin W, Elizabeth MS, Morten OAS, Gautam D (2012) The shared antibiotic resistome of soil bacteria and human pathogens. *Science* 337:4
23. Peterson E, Kaur P (2018) Antibiotic resistance mechanisms in bacteria: relationships between resistance determinants of antibiotic producers, environmental bacteria, and clinical pathogens. *Front Microbiol* 9:2928
24. Bengtsson-Palme J, Kristiansson E, Larsson DGJ (2018) Environmental factors influencing the development and spread of antibiotic resistance. *FEMS Microbiol Rev* 42(1):fux053
25. Zhu YG, Johnson TA, Su JQ, Qiao M, Guo GX, Stedtfeld RD, Hashsham SA, Tiedje JM (2013) Diverse and abundant antibiotic resistance genes in Chinese swine farms. *Proc Natl Acad Sci U S A* 110:3435–3440
26. Li L-G, Yin X, Zhang T (2018) Tracking antibiotic resistance gene pollution from different sources using machine-learning classification. *Microbiome* 6:93–93
27. Song L, Li L, Yang S, Lan J, He H, McElmurry SP, Zhao Y (2016) Sulfamethoxazole, tetracycline and oxytetracycline and related antibiotic resistance genes in a large-scale landfill, China. *Sci Total Environ* 551-552:9–15
28. Heuer H, Schmitt H, Smalla K (2011) Antibiotic resistance gene spread due to manure application on agricultural fields. *Curr Opin Microbiol* 14:236–243
29. Pruden A, Pei R, Storteboom H, Carlson KH (2006) Antibiotic resistance genes as emerging contaminants: studies in Northern Colorado. *Environ Sci Technol* 40:7445–7450
30. Sengelov G, Agero Y, Halling-Sorensen B, Baloda SB, Andersen JS, Jensen LB (2003) Bacterial antibiotic resistance levels in Danish farmland as a result of treatment with pig manure slurry. *Environ Int* 28:587–595
31. Marti R, Scott A, Tien Y-C, Murray R, Sabourin L, Zhang Y, Topp E (2013) Impact of manure fertilization on the abundance of antibiotic-resistant bacteria and frequency of detection of antibiotic resistance genes in soil and on vegetables at harvest. *Appl Environ Microbiol* 79:5701–5709
32. Negreanu Y, Pasternak Z, Jurkevitch E, Cytryn E (2012) Impact of treated wastewater irrigation on antibiotic resistance in agricultural soils. *Environ Sci Technol* 46:4800–4808
33. Popowska M, Rzczycka M, Miernik A, Krawczyk-Balska A, Walsh F, Duffy B (2012) Influence of soil use on prevalence of tetracycline, streptomycin, and erythromycin resistance and associated resistance genes. *Antimicrob Agents Chemother* 56:1434–1443
34. Schmitt H, Stoob K, Hamscher G, Smit E, Seinen W (2006) Tetracyclines and tetracycline resistance in agricultural soils: Microcosm and field studies. *Microb Ecol* 51:267–276
35. Pei RT, Kim SC, Carlson KH, Pruden A (2006) Effect of River Landscape on the sediment concentrations of antibiotics and corresponding antibiotic resistance genes (ARG). *Water Res* 40:2427–2435
36. Muurinen J, Stedtfeld R, Karkman A, Parnanen K, Tiedje J, Virta M (2017) Influence of manure application on the environmental resistome under Finnish agricultural practice with restricted antibiotic use. *Environ Sci Technol* 51:5989–5999
37. Witte W (1998) Medical consequences of antibiotic use in agriculture. *Science* 279:996–997
38. Moses A, Tomaselli P (2017) Industrial animal agriculture in the United States: concentrated animal feeding operations (CAFOs). In: Steier G, Patel KK (eds) *International farm animal, wildlife and food safety law*. Springer, Cham, pp 185–214

39. Yang F, Li R, Cui Y, Duan Y (2010) Utilization and develop strategy of organic fertilizer resources in China. *Soil Fert Sci China* 4:77–82
40. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, Teillant A, Laxminarayan R (2015) Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci* 112:5649–5654
41. Kumar D, Pornsukarom S, Thakur S (2019) Antibiotic usage in poultry production and antimicrobial-resistant Salmonella in poultry. In: Venkitanarayanan K, Thakur S, Ricke SC (eds) *Food safety in poultry meat production*. Springer, Cham, pp 47–66
42. Chen C, Pankow CA, Oh M, Heath LS, Zhang L, Du P, Xia K, Pruden A (2019) Effect of antibiotic use and composting on antibiotic resistance gene abundance and resistome risks of soils receiving manure-derived amendments. *Environ Int* 128:233–243
43. You Y, Silbergeld EK (2014) Learning from agriculture: understanding low-dose antimicrobials as drivers of resistome expansion. *Front Microbiol* 5:284
44. Xie W-Y, Yang X-P, Li Q, Wu L-H, Shen Q-R, Zhao F-J (2016) Changes in antibiotic concentrations and antibiotic resistome during commercial composting of animal manures. *Environ Pollut* 219:182–190
45. Johnson TA, Stedtfeld RD, Wang Q, Cole JR, Hashsham SA, Looft T, Zhu Y-G, Tiedje JM (2016) Clusters of antibiotic resistance genes enriched together stay together in swine agriculture. *MBio* 7:e02214–e02215
46. Ma L, Li AD, Yin XL, Zhang T (2017) The prevalence of integrons as the carrier of antibiotic resistance genes in natural and man-made environments. *Environ Sci Technol* 51:5721–5728
47. Zhu YG, Gillings M, Simonet P, Stekel D, Banwart S, Penuelas J (2017) Microbial mass movements. *Science* 357:2
48. Marti R, Tien Y-C, Murray R, Scott A, Sabourin L, Topp E (2014) Safely coupling livestock and crop production systems: how rapidly do antibiotic resistance genes dissipate in soil following a commercial application of swine or dairy manure? *Appl Environ Microbiol* 80:3258–3265
49. Qian X, Sun W, Gu J, Wang XJ, Sun JJ, Yin YN, Duan ML (2016) Variable effects of oxytetracycline on antibiotic resistance gene abundance and the bacterial community during aerobic composting of cow manure. *J Hazard Mater* 315:61–69
50. Van Elsas JD, Turner S, Bailey MJ (2003) Horizontal gene transfer in the phytosphere. *New Phytol* 157:525–537
51. Flörke M, Kynast E, Bärlund I, Eisner S, Wimmer F, Alcamo J (2013) Domestic and industrial water uses of the past 60 years as a mirror of socio-economic development: A global simulation study. *Glob Environ Chang* 23:144–156
52. Mateo-Sagasta J, Raschid-Sally L, Thebo A (2015) Global wastewater and sludge production, treatment and use. In: Drechsel P, Qadir M, Wichelns D (eds) *Wastewater: economic asset in an urbanizing world*. Springer, Dordrecht, pp 15–38
53. Gatica J, Cytryn E (2013) Impact of treated wastewater irrigation on antibiotic resistance in the soil microbiome. *Environ Sci Pollut Res Int* 20:3529–3538
54. Pan M, Chu LM (2018) Occurrence of antibiotics and antibiotic resistance genes in soils from wastewater irrigation areas in the Pearl River Delta region, southern China. *Sci Total Environ* 624:145–152
55. Jechalke S, Broszat M, Lang F, Siebe C, Smalla K, Grohmann E (2015) Effects of 100 years wastewater irrigation on resistance genes, class I integrons and IncP-1 plasmids in Mexican soil. *Front Microbiol* 6:163
56. Kapanen A, Vikman M, Rajasärkkä J, Virta M, Itävaara M (2013) Biotests for environmental quality assessment of composted sewage sludge. *Waste Manag* 33:1451–1460
57. Raheem A, Sikarwar VS, He J, Dastyar W, Dionysiou DD, Wang W, Zhao M (2018) Opportunities and challenges in sustainable treatment and resource reuse of sewage sludge: a review. *Chem Eng J* 337:616–641
58. Yang G, Zhang G, Wang H (2015) Current state of sludge production, management, treatment and disposal in China. *Water Res* 78:60–73

59. An X-L, Su J-Q, Li B, Ouyang W-Y, Zhao Y, Chen Q-L, Cui L, Chen H, Gillings MR, Zhang T, Zhu Y-G (2018) Tracking antibiotic resistome during wastewater treatment using high throughput quantitative PCR. *Environ Int* 117:146–153
60. Su JQ, Wei B, Ou-Yang WY, Huang FY, Zhao Y, Xu HJ, Zhu YG (2015) Antibiotic resistome and its association with bacterial communities during sewage sludge composting. *Environ Sci Technol* 49:7356–7363
61. Zhang J, Sui Q, Tong J, Buhe C, Wang R, Chen M, Wei Y (2016) Sludge bio-drying: Effective to reduce both antibiotic resistance genes and mobile genetic elements. *Water Res* 106:62–70
62. Gaze WH, Zhang L, Abdouslam NA, Hawkey PM, Calvo-Bado L, Royle J, Brown H, Davis S, Kay P, Boxall AB, Wellington EM (2011) Impacts of anthropogenic activity on the ecology of class 1 integrons and integron-associated genes in the environment. *ISME J* 5:1253–1261
63. Chen H, Zhang M (2013) Occurrence and removal of antibiotic resistance genes in municipal wastewater and rural domestic sewage treatment systems in eastern China. *Environ Int* 55:9–14
64. Threedeach S, Chiemchaisri W, Watanabe T, Chiemchaisri C, Honda R, Yamamoto K (2012) Antibiotic resistance of *Escherichia coli* in leachates from municipal solid waste landfills: Comparison between semi-aerobic and anaerobic operations. *Bioresour Technol* 113:253–258
65. Zhou Z, Raskin L, Zilles JL (2010) Effects of Swine manure on macrolide, lincosamide, and streptogramin B antimicrobial resistance in soils. *Appl Environ Microbiol* 76:2218–2224
66. Ma Y, Wilson CA, Novak JT, Riffat R, Aynur S, Murthy S, Pruden A (2011) Effect of various sludge digestion conditions on sulfonamide, macrolide, and tetracycline resistance genes and class I integrons. *Environ Sci Technol* 45:7855–7861
67. Gao M, Jia R, Qiu T, Han M, Wang X (2017) Size-related bacterial diversity and tetracycline resistance gene abundance in the air of concentrated poultry feeding operations. *Environ Pollut* 220:1342–1348
68. Dungan RS (2010) Fate and transport of bioaerosols associated with livestock operations and manures. *J Anim Sci* 88:3693–3706
69. Morselli L, Olivieri P, Brusori B, Passarini F (2003) Soluble and insoluble fractions of heavy metals in wet and dry atmospheric depositions in Bologna, Italy. *Environ Pollut* 124:457–469
70. Flanner MG, Zender CS, Randerson JT, Rasch PJ (2007) Present-day climate forcing and response from black carbon in snow. *J Geophys Res* 112(D11)
71. 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. *Environ Sci Technol Lett* 5:74–79
72. Fahrenfeld N, Knowlton K, Krometis LA, Hession WC, Xia K, Lipscomb E, Libuit K, Green BL, Pruden A (2014) Effect of manure application on abundance of antibiotic resistance genes and their attenuation rates in soil: field-scale mass balance approach. *Environ Sci Technol* 48:2643–2650
73. Gou M, Hu HW, Zhang YJ, Wang JT, Hayden H, Tang YQ, He JZ (2018) Aerobic composting reduces antibiotic resistance genes in cattle manure and the resistome dissemination in agricultural soils. *Sci Total Environ* 612:1300–1310
74. Burch TR, Sadowsky MJ, LaPara TM (2014) Fate of antibiotic resistance genes and class 1 integrons in soil microcosms following the application of treated residual municipal wastewater solids. *Environ Sci Technol* 48:5620–5627
75. Zhang J, Sui Q, Tong J, Zhong H, Wang Y, Chen M, Wei Y (2018) Soil types influence the fate of antibiotic-resistant bacteria and antibiotic resistance genes following the land application of sludge composts. *Environ Int* 118:34–43
76. Joy SR, Bartelt-Hunt SL, Snow DD, Gilley JE, Woodbury BL, Parker DB, Marx DB, Li X (2013) Fate and transport of antimicrobials and antimicrobial resistance genes in soil and runoff following land application of swine manure slurry. *Environ Sci Technol* 47:12081–12088
77. Chen Z, Zhang W, Wang G, Zhang Y, Gao Y, Boyd SA, Teppen BJ, Tiedje JM, Zhu D, Li H (2017) Bioavailability of soil-sorbed tetracycline to *Escherichia coli* under unsaturated conditions. *Environ Sci Technol* 51:6165–6173

78. McKinney CW, Pruden A (2012) Ultraviolet disinfection of antibiotic resistant bacteria and their antibiotic resistance genes in water and wastewater. *Environ Sci Technol* 46:13393–13400
79. Burch TR, Sadowsky MJ, Lapara TM (2013) Aerobic digestion reduces the quantity of antibiotic resistance genes in residual municipal wastewater solids. *Front Microbiol* 4:17
80. Chee-Sanford JC, Mackie RI, Koike S, Krapac IG, Lin YF, Yannarell AC, Maxwell S, Aminov RI (2009) Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. *J Environ Qual* 38:1086–1108
81. Chee-Sanford JC, Aminov RI, Krapac IJ, Garrigues-Jeanjean N, Mackie RI (2001) Occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine production facilities. *Appl Environ Microbiol* 67:1494–1502
82. Koike S, Krapac IG, Oliver HD, Yannarell AC, Chee-Sanford JC, Aminov RI, Mackie RI (2007) Monitoring and source tracking of tetracycline resistance genes in lagoons and groundwater adjacent to swine production facilities over a 3-year period. *Appl Environ Microbiol* 73:4813–4823
83. Kroer N, Barkay T, Sorensen S, Weber D (1998) Effect of root exudates and bacterial metabolic activity on conjugal gene transfer in the rhizosphere of a marsh plant. *FEMS Microbiol Ecol* 25:375–384
84. Zhu YG, Zhao Y, Li B, Huang CL, Zhang SY, Yu S, Chen YS, Zhang T, Gillings MR, Su JQ (2017) Continental-scale pollution of estuaries with antibiotic resistance genes. *Nat Microbiol* 2:16270
85. Rahube TO, Romain M, Andrew S, Yuan-Ching T, Roger M, Lyne S, Yun Z, Peter D, Lapen DR, Edward T (2014) Impact of fertilizing with raw or anaerobically digested sewage sludge on the abundance of antibiotic-resistant coliforms, antibiotic resistance genes, and pathogenic bacteria in soil and on vegetables at harvest. *Appl Environ Microbiol* 80:6898–6907
86. Xu FL, Wang JP, Guo YC, Fu P, Zeng HW, Li ZG, Pei XY, Liu XM, Wang S (2018) Antibiotic resistance, biochemical typing, and PFGE typing of *Bifidobacterium* strains commonly used in probiotic health foods. *Food Sci Biotechnol* 27:467–477
87. Chen QL, An XL, Zhu YG, Su JQ, Gillings MR, Ye ZL, Cui L (2017) Application of struvite alters the antibiotic resistome in soil, rhizosphere, and phyllosphere. *Environ Sci Technol* 51:8149–8157
88. Yang L, Liu W, Zhu D, Hou J, Ma T, Wu L, Zhu Y, Christie P (2018) Application of biosolids drives the diversity of antibiotic resistance genes in soil and lettuce at harvest. *Soil Biol Biochem* 122:131–140
89. Hao Z, Li X, Yang Q, Sun L, Yang X, Zhou M, Deng R, Bi L (2017) Plant growth, antibiotic uptake, and prevalence of antibiotic resistance in an endophytic system of pakchoi under antibiotic exposure. *Int J Environ Res Public Health* 14:1336
90. Verraes C, Van BS, Van ME, Van CE, Butaye P, Catry B, de Schaetzen MA, Van HX, Imberechts H, Dierick K (2013) Antimicrobial resistance in the food chain: a review. *Int J Environ Res Public Health* 10:2643–2669
91. Bais HP, Weir TL, Perry LG, Gilroy S, Vivanco JM (2006) The role of root exudates in rhizosphere interactions with plants and other organisms. *Annu Rev Plant Biol* 57:233–266
92. Berendsen RL, Pieterse CM, Bakker PA (2012) The rhizosphere microbiome and plant health. *Trends Plant Sci* 17:478–486
93. Smalla K, Cook K, Djordjevic SP, Kluemper U, Gillings M (2018) Environmental dimensions of antibiotic resistance: assessment of basic science gaps. *FEMS Microbiol Ecol* 94(12):fy195
94. Cruz-Loya M, Kang TM, Lozano NA, Watanabe R, Tekin E, Damoiseaux R, Savage VM, Yeh PJ (2019) Stressor interaction networks suggest antibiotic resistance co-opted from stress responses to temperature. *ISME J* 13:12–23
95. Graham DW, Olivares-Rieumont S, Knapp CW, Lima L, Werner D, Bowen E (2011) Antibiotic resistance gene abundances associated with waste discharges to the Almendares river near Havana, Cuba. *Environ Sci Technol* 45:418–424
96. Poole K (2012) Stress responses as determinants of antimicrobial resistance in Gram-negative bacteria. *Trends Microbiol* 20:227–234

97. Jechalke S, Heuer H, Siemens J, Amelung W, Smalla K (2014) Fate and effects of veterinary antibiotics in soil. *Trends Microbiol* 22:536–545
98. Van Zwieten L, Kimber S, Morris S, Chan KY, Downie A, Rust J, Joseph S, Cowie A (2010) Effects of biochar from slow pyrolysis of papermill waste on agronomic performance and soil fertility. *Plant and Soil* 327:235–246
99. Jia M, Wang F, Jin X, Song Y, Bian Y, Boughner LA, Yang X, Gu C, Jiang X, Zhao Q (2016) Metal ion-oxytetracycline interactions on maize straw biochar pyrolyzed at different temperatures. *Chem Eng J* 304:934–940
100. Vithanage M, Rajapaksha AU, Zhang M, Thiele-Bruhn S, Lee SS, Ok YS (2015) Acid-activated biochar increased sulfamethazine retention in soils. *Environ Sci Pollut Res* 22:2175–2186
101. Han XM, Hu HW, Shi XZ, Wang JT, Han LL, Chen D, He JZ (2016) Impacts of reclaimed water irrigation on soil antibiotic resistome in urban parks of Victoria, Australia. *Environ Pollut* 211:48–57
102. Lehmann J, Rillig MC, Thies J, Masiello CA, Hockaday WC, Crowley D (2011) Biochar effects on soil biota – a review. *Soil Biol Biochem* 43:1812–1836
103. Nguyen BT, Lehmann J, Hockaday WC, Joseph S, Masiello CA (2010) Temperature sensitivity of black carbon decomposition and oxidation. *Environ Sci Technol* 44:3324–3331
104. Cui E, Wu Y, Jiao Y, Zuo Y, Rensing C, Chen H (2017) The behavior of antibiotic resistance genes and arsenic influenced by biochar during different manure composting. *Environ Sci Pollut Res* 24:14484–14490
105. Tang X, Lou C, Wang S, Lu Y, Liu M, Hashmi MZ, Liang X, Li Z, Liao Y, Qin W, Fan F, Xu J, Brookes PC (2015) Effects of long-term manure applications on the occurrence of antibiotics and antibiotic resistance genes (ARGs) in paddy soils: Evidence from four field experiments in south of China. *Soil Biol Biochem* 90:179–187
106. Kang K, Ni Y, Li J, Imamovic L, Sarkar C, Kobler MD, Heshiki Y, Zheng T, Kumari S, Wong JCY, Archana A, Wong CWM, Dingle C, Denizen S, Baker DM, Sommer MOA, Webster CJ, Panagiotou G (2018) The environmental exposures and inner- and intercity traffic flows of the metro system may contribute to the skin microbiome and resistome. *Cell Rep* 24:1190
107. Vincent AT, Trudel MV, Paquet VE, Boyle B, Tanaka KH, Dallaire-Dufresne S, Daher RK, Frenette M, Derome N, Charette SJ (2014) Detection of variants of the pRAS3, pAB5S9, and pSN254 plasmids in aeromonas salmonicida subsp salmonicida: multidrug resistance, inter-species exchanges, and plasmid reshaping. *Antimicrob Agents Chemother* 58:7367–7374
108. Bragazza L, Bardgett RD, Mitchell EAD, Buttler A (2015) Linking soil microbial communities to vascular plant abundance along a climate gradient. *New Phytol* 205:1175–1182
109. Gomez-Sagasti MT, Alkorta I, Becerril JM, Epelde L, Anza M, Garbisu C (2012) Microbial monitoring of the recovery of soil quality during heavy metal phytoremediation. *Water Air Soil Pollut* 223:3249–3262
110. Xiao K-Q, Li B, Ma L, Bao P, Zhou X, Zhang T, Zhu Y-G (2016) Metagenomic profiles of antibiotic resistance genes in paddy soils from South China. *FEMS Microbiol Ecol* 92(3): fiv023
111. Wu N, Qiao M, Zhang B, Cheng W-D, Zhu Y-G (2010) Abundance and Diversity of Tetracycline Resistance Genes in Soils Adjacent to Representative Swine Feedlots in China. *Environ Sci Technol* 44:6933–6939
112. Hunter PR, Wilkinson DC, Catling LA, Barker GC (2008) Meta-analysis of experimental data concerning antimicrobial resistance gene transfer rates during conjugation. *Appl Environ Microbiol* 74:6085
113. Stepanauskas R, Glenn TC, Jagoe CH, Tuckfield RC, Lindell AH, King CJ, McArthur JV (2006) Coselection for microbial resistance to metals and antibiotics in freshwater microcosms. *Environ Microbiol* 8:1510–1514
114. Yazdankhah S, Rudi K, Bernhoft A (2014) Zinc and copper in animal feed – development of resistance and co-resistance to antimicrobial agents in bacteria of animal origin. *Microb Ecol Health Dis* 25:25862
115. Ji X, Shen Q, Liu F, Ma J, Xu G, Wang Y, Wu M (2012) Antibiotic resistance gene abundances associated with antibiotics and heavy metals in animal manures and agricultural soils adjacent to feedlots in Shanghai; China. *J Hazard Mater* 235:178–185

116. Zhao Y, Cocerva T, Cox S, Tardif S, Su JQ, Zhu YG, Brandt KK (2019) Evidence for co-selection of antibiotic resistance genes and mobile genetic elements in metal polluted urban soils. *Sci Total Environ* 656:512–520
117. Wright MS, Peltier GL, Stepanauskas R, McArthur JV (2006) Bacterial tolerances to metals and antibiotics in metal-contaminated and reference streams. *FEMS Microbiol Ecol* 58:293–302
118. Ding C, Pan J, Jin M, Yang D, Shen Z, Wang J, Zhang B, Liu W, Fu J, Guo X, Wang D, Chen Z, Yin J, Qiu Z, Li J (2016) Enhanced uptake of antibiotic resistance genes in the presence of nanoalumina. *Nanotoxicology* 10:1051–1060
119. Qiu Z, Yu Y, Chen Z, Jin M, Yang D, Zhao Z, Wang J, Shen Z, Wang X, Qian D, Huang A, Zhang B, Li J-W (2012) Nanoalumina promotes the horizontal transfer of multiresistance genes mediated by plasmids across genera. *Proc Natl Acad Sci U S A* 109:6
120. Zhu D, Zheng F, Chen QL, Yang XR, Christie P, Ke X, Zhu YG (2018) Exposure of a soil collembolan to Ag nanoparticles and AgNO₃ disturbs its associated microbiota and lowers the incidence of antibiotic resistance genes in the gut. *Environ Sci Technol* 52:12748–12756
121. Li J, Zhang K, Zhang H (2018) Adsorption of antibiotics on microplastics. *Environ Pollut* 237:460–467
122. Sun M, Ye M, Jiao W, Feng Y, Yu P, Liu M, Jiao J, He X, Liu K, Zhao Y, Wu J, Jiang X, Hu F (2018) Changes in tetracycline partitioning and bacteria/phage-mediated ARGs in microplastic-contaminated greenhouse soil facilitated by sphorolipid. *J Hazard Mater* 345:131–139
123. Arias-Andres M, Kluemper U, Rojas-Jimenez K, Grossart H-P (2018) Microplastic pollution increases gene exchange in aquatic ecosystems. *Environ Pollut* 237:253–261
124. Crofts TS, Gasparini AJ, Dantas G (2017) Next-generation approaches to understand and combat the antibiotic resistome. *Nat Rev Microbiol* 15:422–434
125. Graham DW, Knapp CW, Christensen BT, McCluskey S, Dolfing J (2016) Appearance of beta-lactam resistance genes in agricultural soils and clinical isolates over the 20th century. *Sci Rep* 6:21550
126. Lau CH-F, Van Engelen K, Gordon S, Renaud J, Topp E (2017) Novel antibiotic resistance determinants from agricultural soil exposed to antibiotics widely used in human medicine and animal farming. *Appl Environ Microbiol* 83:e00989–e00917
127. Forsberg KJ, Reyes A, Wang B, Selleck EM, Sommer MOA, Dantas G (2012) The shared antibiotic resistome of soil bacteria and human pathogens. *Science* 337:1107–1111
128. Luby E, Ibekwe AM, Zilles J, Pruden A (2016) Molecular methods for assessment of antibiotic resistance in agricultural ecosystems: prospects and challenges. *J Environ Qual* 45:441–453
129. Martinez JL, Coque TM, Baquero F (2015) What is a resistance gene? ranking risk in resistomes. *Nat Rev Microbiol* 13:116–123
130. Ghaly TM, Chow L, Asher AJ, Waldron LS, Gillings MR (2017) Evolution of class 1 integrons: Mobilization and dispersal via food-borne bacteria. *Plos One* 12:e0179169
131. Blau K, Bettermann A, Jechalke S, Fornefeld E, Vanrobaeys Y, Stalder T, Top EM, Smalla K (2018) The transferable resistome of produce. *MBio* 9:e01300–e01318
132. Carnevali C, Morganti M, Scaltriti E, Bolzoni L, Pongolini S, Casadei G (2016) Occurrence of *mcr-1* in colistin-resistant *Salmonella enterica* isolates recovered from humans and animals in Italy, 2012 to 2015. *Antimicrob Agents Chemother* 60:7532–7534
133. Roberts KD, Azad MA, Wang J, Horne AS, Thompson PE, Nation RL, Velkov T, Li J (2015) Antimicrobial activity and toxicity of the major lipopeptide components of polymyxin B and colistin: last-line antibiotics against multidrug-resistant gram-negative bacteria. *ACS Infect Dis* 1:568–575
134. Hu Y, Liu F, Lin IYC, Gao GF, Zhu B (2016) Dissemination of the *mcr-1* colistin resistance gene. *Lancet Infect Dis* 16:146–147
135. Arnold S, Gassner B, Giger T, Zwahlen R (2004) Banning antimicrobial growth promoters in feedstuffs does not result in increased therapeutic use of antibiotics in medicated feed in pig farming. *Pharmacoepidemiol Drug Saf* 13:323–331

136. Edgar R, Friedman N, Molshanski-Mor S, Qimron U (2012) Reversing bacterial resistance to antibiotics by phage-mediated delivery of dominant sensitive genes. *Appl Environ Microbiol* 78:744–751
137. Jang HM, Lee J, Kim YB, Jeon JH, Shin J, Park MR, Kim YM (2018) Fate of antibiotic resistance genes and metal resistance genes during thermophilic aerobic digestion of sewage sludge. *Bioresour Technol* 249:635–643
138. Ghosh S, Ramsden SJ, LaPara TM (2009) The role of anaerobic digestion in controlling the release of tetracycline resistance genes and class 1 integrons from municipal wastewater treatment plants. *Appl Microbiol Biotechnol* 84:791–796
139. Zhang J, Chen M, Sui Q, Wang R, Tong J, Wei Y (2016) Fate of antibiotic resistance genes and its drivers during anaerobic co-digestion of food waste and sewage sludge based on microwave pretreatment. *Bioresour Technol* 217:28–36
140. Qian X, Sun W, Gu J, Wang XJ, Zhang YJ, Duan ML, Li HC, Zhang RR (2016) Reducing antibiotic resistance genes, integrons, and pathogens in dairy manure by continuous thermophilic composting. *Bioresour Technol* 220:425–432
141. Zhang CM, Xu LM, Wang XC, Zhuang K, Liu QQ (2017) Effects of ultraviolet disinfection on antibiotic-resistant *Escherichia coli* from wastewater: inactivation, antibiotic resistance profiles and antibiotic resistance genes. *J Appl Microbiol* 123:295–306
142. Zhang T, Yang Y, Pruden A (2015) Effect of temperature on removal of antibiotic resistance genes by anaerobic digestion of activated sludge revealed by metagenomic approach. *Appl Microbiol Biotechnol* 99:7771–7779
143. Guo A, Gu J, Wang X, Zhang R, Yin Y, Sun W, Tuo X, Zhang L (2017) Effects of superabsorbent polymers on the abundances of antibiotic resistance genes, mobile genetic elements, and the bacterial community during swine manure composting. *Bioresour Technol* 244:658–663
144. Cui E, Wu Y, Zuo Y, Chen H (2016) Effect of different biochars on antibiotic resistance genes and bacterial community during chicken manure composting. *Bioresour Technol* 203:11–17
145. Zhang Y, Li H, Gu J, Qian X, Yin Y, Li Y, Zhang R, Wang X (2016) Effects of adding different surfactants on antibiotic resistance genes and *intI1* during chicken manure composting. *Bioresour Technol* 219:545–551
146. Peng S, Li H, Song D, Lin X, Wang Y (2018) Influence of zeolite and superphosphate as additives on antibiotic resistance genes and bacterial communities during factory-scale chicken manure composting. *Bioresour Technol* 263:393–401
147. Zhang J, Wang Z, Wang Y, Zhong H, Sui Q, Zhang C, Wei Y (2017) Effects of graphene oxide on the performance, microbial community dynamics and antibiotic resistance genes reduction during anaerobic digestion of swine manure. *Bioresour Technol* 245:850–859
148. Neshat SA, Mohammadi M, Najafpour GD, Lahijani P (2017) Anaerobic co-digestion of animal manures and lignocellulosic residues as a potent approach for sustainable biogas production. *Renew Sustain Energy Rev* 79:308–322
149. Sun W, Gu J, Wang X, Qian X, Peng H (2019) Solid-state anaerobic digestion facilitates the removal of antibiotic resistance genes and mobile genetic elements from cattle manure. *Bioresour Technol* 274:287–295
150. Zhang H, Chang F, Shi P, Ye L, Zhou Q, Pan Y, Li A (2019) Antibiotic resistome alteration by different disinfection strategies in a full-scale drinking water treatment plant deciphered by metagenomic assembly. *Environ Sci Technol* 53:2141–2150
151. Dodd MC (2012) Potential impacts of disinfection processes on elimination and deactivation of antibiotic resistance genes during water and wastewater treatment. *J Environ Monit* 14:1754–1771
152. Guo M-T, Yuan Q-B, Yang J (2015) Distinguishing effects of ultraviolet exposure and chlorination on the horizontal transfer of antibiotic resistance genes in municipal wastewater. *Environ Sci Technol* 49:5771–5778