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Minireview

From gut to mud: dissemination of antimicrobial resistance between animal and agricultural niches

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Summary

With increasing reports on antimicrobial resistance (AMR) in humans, animals and the environment, we are at risk of returning to a pre-antibiotic era. Therefore, AMR is recognized as one of the major global health threats of this century. Antibiotics are used extensively in farming systems to treat and prevent infections in food animals or to increase their growth. Besides the risk of a transfer of AMR between the human and the animal sector, there is another yet largely overlooked sector in the One Health triad. Human-dominated ecosystems such as agricultural soils are a major sink for antibiotics and AMR originating from livestock farming. This review summarizes current knowledge on the prevalence of AMR at the interface of animal and agricultural production and discusses the potential implications for human health. Soil resistomes are augmented by the application of manure from treated livestock. Subsequent transfer of AMR into plant microbiomes may likely play a critical role in human exposure to antibiotic resistance in the environment. Based on the knowledge that is currently available we advocate that more attention should be paid to the role of environmental resistomes in the AMR crisis.

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Introduction

'…But I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient. There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant…'

\- Alexander Fleming in his Nobel acceptance speech, 1945

In 2018, global meat production reached 342 million tons, which corresponds to an increase of 47% compared to 2000. The growing demand for animal protein makes the livestock sector the largest user of land resources and the demand is expected to more than double by 2030 (Robinson and Pozzi, 2011). Since the 1940s, livestock feed has been supplemented with non-therapeutic doses of antibiotics as they were found to improve meat production through increased feed conversion. Globally, 73% of all antibiotics sold are used in food animals and their extensive use is considered a key driver of antimicrobial resistance development in animals and spread to humans (Mohsin *et al*., 2020). However, AMR can also develop and spread in other sectors and to address AMR holistically, it is necessary to take a One Health approach. There is hardly any subject that epitomizes the principles of One Health more than AMR does (Robinson *et al*., 2016). It recognizes that the health of people is connected to the health of animals and the environment and requires collaborative efforts of multiple disciplines at multiple scales (McEwen and Collignon, 2018). Of the three domains, human health takes the spotlight. Comprehensive surveillance allowed for the estimation of the global burden of AMR on the population (WHO, 2014) and to make projections based on current trends

(O'Neill, 2016). Such estimates have only recently become available for livestock (Van Boeckel *et al*., 2020) although new resistant mutations are more likely to arise in food animals given their high biomass compared to humans (Van Boeckel *et al*., 2017). The third pillar, environmental health, is the least well understood when it comes to antibiotic resistance evolution, transmission and persistence, presumably due to perceived lower importance. However, antibiotics and antibiotic resistance have evolved in environmental microbiota (Davies, 1994; Davies, 1997) and there is some evidence that clinically relevant antibiotic resistance genes (ARGs) have originated in environmental reservoirs (Wright, 2010). These reservoirs are augmented and maintained by the influx of ARGs from livestock (Hölzel *et al*., 2010) and human waste (Reinthaler *et al*., 2003) and by the vast quantities of antibiotic residues that enter the environment from the pharmaceutical industry (Larsson *et al*., 2007), from intensive livestock farms (Ji *et al*., 2012) and hospitals (Diwan *et al*., 2010). A recent review highlights the central role of manure in the transmission of antibiotic-resistant microbes from livestock to agricultural land, crops, animals and humans (Tyrrell *et al*., 2019).

The present review focuses on the transmission of AMR from livestock production to agricultural soils, the factors driving the selection and persistence of AMR in agricultural soils, the suitability of current pretreatment option for the removal of antibiotics and AMR, pathways for the transmission of AMR from agricultural soils to humans and animals and future research needs. It summarizes the most recent knowledge by looking at studies mainly from the years 2017 to 2021, 1 year after the FDA ban on the use of antibiotics as growth promoters in livestock production.

Use of antibiotics in livestock production

The use of antibiotics in food animals is primarily associated with the practice of using sub-therapeutic doses as growth promoters or substituting more expensive hygiene measures. The benefits of sub-therapeutic levels of antibiotics on animal health and growth were reported as early as 1946 (Moore *et al*., 1946). In 1951, the U.S. Food and Drug Administration approved the use of antibiotics in animal feed without a veterinary prescription (Castanon, 2007). However, under the Council directive 70/524, antibiotics were recognized as concerning additives in animal feed and Sweden became the first to prohibit the use of antibiotic additives in animal feed in 1986 (Castanon, 2007). Despite this, recent reports from Sweden show the occurrence of resistant *Campylobacter coli* in pigs and ARGs conferring resistance to ampicillin, streptomycin, sulfamethoxazole and tetracycline in *Escherichia coli* isolated from healthy young calves of dairy herds (Sjöström *et al*., 2020; Kempf *et al*., 2017). This emphasizes the need for more intense surveillance on the use of antibiotics in livestock production. The European Union sequentially banned the use of antibiotics used as growth promoters starting with avoparcin in 1997. The last four permitted antibiotics were finally banned in 2006. In contrast, in the United States the use of antibiotics as growth promoters was still allowed until 2017 (FAO, 2020). As a consequence of the elimination of the prophylactic effect of the administered antibiotics, this ban has led to a substantial increase in the use of antibiotics for therapeutic purposes (Casewell *et al*., 2003).

In 2017, the global consumption of antibiotics in chicken, cattle and pigs was estimated to be 93 309 t of the active ingredient. The highest consumptions were recorded for China (45%), Brazil (7.9%), the United States (7.0%), Thailand (4.2%), India (2.2%), Iran (1.9%), Spain (1.9%), Russia (1.8%), Mexico (1.7%) and Argentina (1.5%) (Tiseo *et al*., 2020). Together these countries account for 75% of the total antibiotic consumption in food animals, but only 50% of the total human population. The highest amount of antibiotics was used in pigs [193 mg/population correction unit (PCU) (a kilogram of animal product) followed by chicken (68 mg/PCU) and cattle (42 mg/PCU)]. It is projected that until 2030, the total consumption will increase by 11.5% to 104 079 t with the largest increase of antibiotic usage in pigs accounting for 45% of the global increase (Tiseo *et al*., 2020). The top 10 projected consumers in 2030 are China (43%), Brazil (7.9%), United States (6.5%), Thailand (4.0%), India (2.1%), Spain (1.9%), Russia (1.9%), Mexico (1.8%), Iran (1.5%) and Argentina (1.5%) that will together use 72% of the total antibiotics consumed worldwide. About 27 different antimicrobials are used in animals (WHO, 2017a). Although macrolides, ketolides, glycopeptides, quinolones, polymyxins and cephalosporins (third to fourth generation) are listed as critically important antimicrobials for human medicine by the WHO, they are also used in livestock production. It is important to consider that there are still major gaps in the availability of reliable global data on antibiotic usage in the livestock sector, which makes it difficult to formulate and prioritize risk assessment and risk management strategies for containing AMR. In China, for example, a study from Zhang *et al*. (2015) reported usage of 84 240 t of antimicrobials in animals in 2013, while the Chinese Ministry of Agriculture estimated usage of 41 967 t for 2017 (Tiseo *et al*., 2020). This corresponds to a decrease in consumption of 49.8% in only 4 years, but China's national plan to combat AMR and reduce antimicrobial use specifically for animals was announced in 2017 only. In comparison, the Netherlands achieved a reduction of 56% of antimicrobial use in farm animals with comprehensive antimicrobial stewardship efforts over 5 years

(Speksnijder *et al*., 2015). However, China is not the only example reporting such drastic decreases in antimicrobial use, which demonstrates the need for a close examination of the reported sales data from different sources, which are the basis for projections of antimicrobial use in food animals in the future. Globally the issue of AMR caught attention when the mcr-1 gene conferring resistance to colistin, which is one of the highest priority critically important antimicrobials in human medicine, was found in pigs in slaughterhouses in China where about 12 000 t of colistin was used per year (Carnevali *et al*., 2016; Arcilla *et al*., 2016). Since then, colistin-resistant bacteria were found in humans without colistin usage in many countries of the world indicating the strong link between the human and the animal sector concerning AMR transmission and emphasizing the necessity of the One Health approach (Yacouba and Olowo-Okere, 2020).

The WHO's Global Antimicrobial Resistance Surveillance System (GLASS) for human medicine was implemented to develop a standardized approach to the collection, analysis and sharing of AMR data thereby supporting global surveillance. Such knowledge is necessary to guide decision-making and national, regional and global actions. However, there is no comparable system for supporting surveillance in animals. Scandinavian countries were not only among the first to ban the use of antibiotics in food animals, but they also took a leadership role in monitoring the prevalence of AMR in animals. Later Europe and the United States adopted similar systems (EFSA, 2014). In low and middle-income countries, however, surveillance systems are only starting to develop and point prevalence surveys have been used to map global trends in AMR in food animals (van Boeckel *et al*., 2020). These analyses showed that between 2000 and 2018, resistance levels increased in chicken and pigs and plateaued in cattle, with considerable geographic variations (van Boeckel *et al*., 2020). Hotspots of AMR were in northeastern India, northeastern China, northern Pakistan, Iran, eastern Turkey, the south coast of Brazil, Egypt, the Red River delta in Vietnam and the areas surrounding Mexico City and Johannesburg (van Boeckel *et al*., 2020). Not surprisingly, the highest resistance rates were associated with the very common classes of antimicrobials used in livestock production: tetracyclines, sulfonamides and penicillins (Van Boeckel *et al*., 2017). Given these figures, AMR in food animals needs to be ranked top priority as the high biomass of animals raised for food production and the growing demand for animal protein make them an important vehicle for the dissemination of AMR to humans and the environment. These areas demand the development of standardized universal methods and protocols which are simple and cost-effective to ensure its widespread adoption including in low- and middle-income countries.

Supplementary Table 1 enlists reports on the occurrence of AMR in livestock production in different countries. Molecular studies have advanced the identification and enumeration of ARGs genes in complex samples derived from humans, animals and the environment and highlighted livestock as an important hotspot for the emergence of AMR. Critical pathogens and multidrug-resistant strains such as *Escherichia coli*, *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, *Klebsiella Pneumoniae* and *Lactobacillus* have been found in livestock (Supplementary Table 1). A genome-wide study led to the identification of ARGs in *E. coli* resistant to tetracycline, erythromycin and kanamycin from pig farms in China and Sudan (Abdelgader *et al*., 2018). In another comparative analysis of AMR in swine and cattle-derived *E. coli*, strains from clinically healthy swine were found to be resistant to streptomycin, tetracycline and sulfamethoxazole and strains derived from clinically healthy cattle were resistant against aminoglycosides and tetracyclines (Aasmäe *et al*., 2019). A recent analysis of samples from Cambodian livestock and associated farmworkers confirmed the presence of ARGs even for last-resort antibiotics including colistin (Atterby *et al*., 2019). Antibiotic-resistant *Salmonella*, *Streptococcus*, *Prevotella*, *Fusobacterium*, *Bacteroides*, *Staphylococcus aureus*, *Pasteurella multocida*, *E. coli*, *Enterococcus faecium* are a few examples of resistant bacteria detected in pig farm samples; antibiotic-resistant *S. aureus*, *Staphylococcus* and *S. typhimurium* were identified from poultry-derived samples and methicillin-resistant *S. aureus*, *Campylobacter* and *Salmonella* have been detected in cattle-derived samples (Supplementary Table 2). The use of various antibiotics in the pig, poultry and cattle industries has been reviewed with respect to pathogens and ARGs identified in animal manure (Zalewska *et al*., 2021). These studies highlight how diverse microbes which are known human pathogens are increasingly being detected for resistance to distinct antibiotics in animal manure.

Advanced -omics techniques have facilitated the assessment of how the interaction of animals with their distinct environment affects animal health and ARGs composition (Hu *et al*., 2021). In this study, a greater mean abundance of tetracycline and macrolide resistance genes was observed in gut samples of captive mammals in comparison to wild animals. These results indicate the occurrence and persistence of animal AMR could be highly influenced by animal ecology and the relation of animals with their environment.

Antibiotics and AMR in animal manure

Even in the case of best-practice administration of antibiotics, the larger proportion (40%–90%) is excreted by the animals in the form of the parent compounds, active metabolites or conjugates that can be reconverted to the parent compound (Lamshöft *et al*., 2007; Lamshöft *et al*., 2010; Langhammer, 1989; Van Epps and Blaney, 2016; Winckler *et al*., 2004). Enrofloxacin, a fluoroquinolone, is partially metabolized to ciprofloxacin in the liver, which is also highly antimicrobially active. In contrast, small fractions of sulfonamides are converted to N4-acetylsulphonamides, which show lower antimicrobial activity than the parent compound (Anderson *et al*., 2012). Antibiotics have been detected in faeces from various animals in the range from μg kg^{-1} up to g kg^{-1} (Berendsen *et al*., 2015; Chen *et al*., 2012; Kim *et al*., 2011; Van den Meersche *et al*., 2016; Wang *et al*., 2017). The excreted amount depends on the administration route, the animal species and its life stage as well as on the physical condition of the animal (Turner *et al*., 2011). Manure was found to be highly contaminated when antibiotics are applied to complete herds for preventive purposes so that large total quantities are dispensed (Cleary *et al*., 2016). An extensive review of 104 studies from the past four decades on pharmaceuticals in animal wastes revealed the occurrence of antibiotics like enrofloxacin, oxytetracycline and chlortetracycline in the highest concentrations in both untreated and treated manure (Ghirardini *et al*., 2020). In 2015, an extensive survey of faeces samples from pigs and calves revealed the occurrence of antibiotics in the majority of the samples taken from 20 different farms. The most frequently detected antibiotics were oxytetracycline, doxycycline and sulfadiazine followed by tetracycline, flumequine, lincomycin and tylosin (Berendsen *et al*., 2015). Overall, many different compounds are used in livestock production and many of them are applied in mixed medical preparation of up to five at the same time. Among those, tetracyclines are used most frequently, followed by sulfonamides and aminoglycosides (Thiele-Bruhn, 2019). In addition to antibiotics, faeces of animals administered with antibiotics also contain resistant bacteria that have developed during the treatment (Supplementary Table 2). Because the faeces are often used as organic fertilizer on agricultural soils, soil samples are frequently found to be contaminated with antibiotics, its intermediates and resistant bacteria originating from animal guts (Ashbolt *et al*., 2018).

Antibiotic usage in livestock production is one of the main reasons for the occurrence of antibiotic-resistant bacteria in manure (Heuer and Smalla, 2007; Hölzel *et al*., 2010). In pig manure, for example, several studies detected multidrug-resistant *Salmonella enteritidis* and other *Salmonella* species (Supplementary Table 2) and *Salmonella enterica* and its serovars that are known to cause human gastroenteritis are known to originate from pigs (Kingsley and Bäumler, 2000). A 3-year study of drug resistance in cattle manure in Northern India regions revealed a high prevalence of extended-spectrum β-lactamase and carbapenemase-producing *E*. *coli* and *K*. *pneumoniae* isolates, of which several isolates exhibited co-resistance to cephalosporin and non-cephalosporin antibiotics (Devi *et al*., 2020). In another study across poultry farms in Ghana, more than 35% of the total *Staphylococcus* species isolated from the manure were resistant to antibiotics such as tetracycline, doxycycline and oxacillin (Boamah *et al*., 2017). Recent reports confirming the presence of extended-spectrum β-lactamases, as well as ARGs conferring resistance to sulfonamides, cephalosporin, erythromycin, quinolones and tetracyclines in animal manure are summarized in Supplementary Table 2. Raw manure has been shown to contain especially high levels of ARGs (Anjum *et al*., 2017; Tien *et al*., 2017; Gurmessa *et al*., 2020). However, in some countries raw manure is frequently applied to soils while in others it undergoes pretreatment such as anaerobic digestion or composting (Anjum *et al*., 2017; Ray *et al*., 2017).

Persistence of antibiotics and AMR in manure

Impact of storage conditions

For reliable environmental risk assessment, it is critical to understand which antibiotics can be expected in the environment and why. The factors determining the intrusion of antibiotics into environmental compartments are their use and their persistence in the source compartments. After use and excretion, the most important source compartment for environmental input of antibiotics and resistant bacteria is manure storage, which lasts on average for 6–9 months (Boxall *et al*., 2004). Data on the fate of antibiotics during manure storage are scarce and only a limited number of compounds have been studied. However, this information is crucial to estimate which antibiotics are likely to enter agricultural soils via manure fertilization. Studies on the fate of veterinary antibiotics in manure are optional in the assessment of the environmental impact of veterinary medicines. Only if it is demonstrated that less than 5% of antibiotics are mineralized or converted into products, the assessment is stopped in the first phase (EMA, 2011).

An investigation of antibiotics occurring in manure from pigs, calves and broilers demonstrated the long-term persistence of tetracyclines, quinolones, macrolides, lincosamides and pleuromutilins during manure storage. Their DT90 values (90% disappearance of the parent compound) ranged from 422 to 1400 days depending on the compound and the type of manure (Berendsen *et al*., 2018). In the same study, more than 10% of the initial concentrations of the antibiotics lincomycin, pirlimycin, tiamulin and most quinolones were found even after a year irrespective of the manure type. A high-throughput metagenomics approach confirmed the enrichment of pathogens *Legionella*, *Salmonella*, *Enterococcus*, *Klebsiella*, *Porphyromonas*, *Vibrio*, *Yersinia*, *Escherichia*, *Edwardsiella*, *Pseudomonas* and *Streptococcus* and ARGs during storage of manure derived from dairy cows prior to any treatment (Zhang *et al*., 2020). Resistome analysis of manure from Finnish dairy and swine farms indicated the rise in ARGs and mobile genetic elements (MGEs) during manure storage (Muurinen *et al*., 2017). However, another study investigating ARG abundance in long-term storage systems at 11 dairy farms in the United States found no indications of ARG accumulation after long-term storage (Hurst *et al*., 2019).

Effects of composting and anaerobic digestion on antibiotics and AMR

Knowing that there is a threat of AMR transmission and antibiotic contamination from untreated manure to the soil, manure pretreatment options to reduce the loads gained more attention in the past. Composting and anaerobic digestion are the most adopted cost-effective means of processing manure before its application onto agricultural soils. Both methods are used to reduce the mass and volume of manure making the handling and transport easier, improve nutrient stability, reduce odour and kill pathogens (Congilosi and Aga, 2021). In the case of anaerobic digestion, the process also yields biogas in addition to liquid fertilizer.

Composting is applied to stimulate biodegradation of chemicals of emerging concerns including pharmaceuticals, personal care products, pesticides and hormones (Bartelt-Hunt *et al*., 2013; Büyüksönmez *et al*., 2000; Ho *et al*., 2013; Xia *et al*., 2005). Therefore, it has also been suggested as a potential means to reduce the levels of antibiotics in manure before land application. However, recent studies emphasized that the removal is only incomplete. During beef and dairy manure composting, sulfamethazine and pirlimycin were almost completely removed, while chlortetracycline and tetracycline removal was in the range of 71%–84% and 66%–72% respectively (Ray *et al*., 2017). In contrast, tylosin was very recalcitrant and remained close to its initial concentrations. Overall, it seems to be difficult to draw general conclusions about the suitability of composting for the removal of antibiotics from manure as it depends on the type of antibiotics, type of manure and amendments, size of the compost pile, and the composting approach (Dolliver *et al*., 2008; Cessna *et al*., 2011; Storteboom *et al*., 2007).

The suitability of composting for the elimination of ARGs is disputed. Overall, chicken and pig manure were found to be more diverse in AMR mechanisms in comparison to bovine manure after aerobic composting (Qian *et al*., 2018). In some studies, the authors found that through composting the levels of ARGs could be reduced by 50%–70% AMR (Liebert *et al*., 1999; Partridge *et al*., 2001; Pruden *et al*., 2013). However, other studies reported an increase in the absolute abundances of sulfonamide, quinolone and tetracycline resistance genes (Riaz *et al*., 2020a; Esperón *et al*., 2020; Li *et al*., 2017). The increasing reports on detection of AMR in soils after composting of manure demonstrate the necessity to systematically assess the fate of antibiotics and ARGs in the manure of different animal origins.

Manure is a hotspot for horizontal gene transfer (HGT) events mediated by MGEs such as plasmids and transposons that contain ARGs. MGEs were found to be the most common means of AMR spread from manure to soil (Redondo-Salvo *et al*., 2020). However, MGEs often escape the composting process which has resulted in increased abundances of ARGs in agricultural soil after compost addition (Lima *et al*., 2020; Liu *et al*., 2020).

During anaerobic digestion of manure, the degradation of antibiotics is governed by the type of feedstock, inoculum sources, concentration and type of antibiotic, and process parameters (Congilosi and Aga, 2021). Conventional anaerobic digestion is found to be effective especially in the removal of β-lactams and tetracyclines but sulfonamides, fluoroquinolones and macrolides were reported to be highly persistent with removal rates as low as zero (Gurmessa *et al*., 2020). There are also no clear conclusions concerning the fate of ARGs and MGEs during anaerobic digestion of manure. Although some studies suggested anaerobic digestion as an option to reduce ARGs in manure, a complete removal has rarely been observed (Flores-Orozco *et al*., 2020a; Flores-Orozco *et al*., 2020b; Sun *et al*., 2016; Zou *et al*., 2020). Some studies even reported an increase of ARGs during the anaerobic digestion of manure from different origins (Riaz *et al*., 2020b; Agga *et al*., 2020). Similar to composting, the efficient removal of ARGs seems to be temperature-dependent. At thermophilic conditions (55°C) removal of ARGs is generally higher compared to mesophilic conditions (35°C) (Flores-Orozco *et al*., 2020b). In anaerobic digestion of manure, thermal pretreatment, pretreatment with activated carbon and microwave pretreatment were found to reduce up to 95% of ARGs conferring resistance to sulfonamides, macrolides and tetracyclines (Congilosi and Aga, 2021). Thus, AMR removal through additional measures applied as pre- or post-treatment (liquid–solid separation and drying) should be thoroughly evaluated for management of AMR in manure.

Overall, the inconsistencies concerning the removal of antibiotics and ARGs during composting and anaerobic digestion make it difficult to judge the suitability of both approaches to reduce environmental risks of manure before soil application (Gurmessa *et al*., 2020; Riaz *et al*., 2020b). However, we want to stress that a literature synthesis on all the available studies looking at the effects of composting and anaerobic digestion would be very valuable to identify general patterns and sources of disagreement among the results. The levels of ARGs post manure treatment should be watchlisted and criteria and thresholds need to be integrated into regulations for waste management. Therefore, the process efficiency of manure treatment should be inclusive of monitoring of known critical pathogens of high concern (WHO, 2017b).

Influence of manure application on soil antibiotic concentrations and soil resistomes

Manure is applied to supplement soils with macronutrients to enhance crop growth. When manure is applied to agricultural soils, contaminations with both antibiotics and resistant bacteria occur. Increasing use of antibiotics in food animal production in many regions of the world requires us to address the environmental risk resulting from the intrusion of antibiotics and AMR into soils and the threat of AMR dissemination from soils to the human and animal sector (Pérez-Valera *et al*., 2019).

Persistence of antibiotics in agricultural soils

Antibiotics in soils are subject to different abiotic and/or biotic processes. The main processes determining their fate are sorption to organic particles and degradation/transformation (Kümmerer, 2004). Sorption depends on the soil characteristics and the physicochemical properties of the antibiotics. Especially soil pH and organic matter content are the key factors determining the sorption of antibiotics in soils. Sulfonamides, for example, are mobile compounds and their speciation changes with pH. At pH values below 5, the cationic form of sulfamethazine is electrostatically attracted to the negatively charged soil particles leading to higher sorption coefficients compared to higher soil pH values at which sulfamethazine converts to the neutral and anionic forms (Wegst-Uhrich *et al*., 2014). Interaction of sulfonamides with soil organic matter is primarily driven by hydrophobic interactions (Figueroa-Diva *et al*., 2010) and several studies reported increased sorption in the presence of soil organic matter. However, recent studies demonstrated a decreased sorption of sulfonamides in presence of organic matter derived from manure due to competitive sorption of dissolved organic matter molecules blocking the access to sorption sites for the sulfonamides (Pils and Laird, 2007; Zhang *et al*., 2011; Zhang *et al*., 2021). Overall, sources, composition and quantity of soil organic matter seem to play a major role in mobilizing or retaining effects (Thiele-Bruhn and Aust, 2004; Zhang *et al*., 2021). While sorption generally reduces the mobility and, consequently, the potential leaching to ground and surface waters, it also reduces the bioavailability for microbes thereby limiting biodegradation. Overall, sorption behaviour is considered a major determinant of antibiotic persistence in soils and detailed reviews on the sorption behaviour of several antibiotics are available (Thiele-Bruhn, 2003; Wegst-Uhrich, *et al*., 2014).

Degradation and transformation of antibiotics in soils can occur through abiotic and biotic processes and is influenced by the molecular structure and physicochemical properties of the compound. Hydrolysis, which is generally considered an important abiotic degradation pathway, has been shown to play a role only for the class of β-lactams (Hou and Poole 1969; Mitchell *et al*., 2014). Recently, anaerobic microbial transformation of sulfamethoxazole has been shown in enrichment cultures from sediment of a constructed wetland and digester sludge of a wastewater treatment plant (Ouyang *et al*., 2020). However, data on the reductive or oxidative transformation of antibiotics in soils are still scarce. Photodegradation may contribute to the reduction of antibiotics mainly in aquatic environments (Batchu *et al*., 2014) and when applied to soil surfaces in thin manure layers on days with high light intensities and evaporation (Thiele-Brun and Peters 2007).

Overall, there is a huge variation in antibiotic half-lives in soil. While both amoxicillin and chlortetracycline were quickly degraded (DT50 values <1 day), azithromycin, ofloxacin and tetracyclines persisted over long periods in outdoor microcosms with half-lives of 408–3466, 866–1733 and 578 days respectively (Walters *et al*., 2010). Although there is plenty of information on degradation rates and half-lives of different antibiotics, there is a huge variation in DT50 values for antibiotics within the same group or even particular antibiotics (Cycoń *et al*., 2019). This may be due to the use of different soils with different compositions and microbial communities, different antibiotic concentrations and variations in the environmental conditions such as water content, temperature and pH among the studies.

Impact on the soil resistome

Modern-day agriculture is heavily impacted by chemical fertilizers, biocides, heavy metals and antibiotics. These pollutants provide an environment in which the microbes evolve to lower the risk of death.

Soil bacteria are a natural reservoir of ARGs, which is emphasized by the fact that ARGs can also be found in pristine environments. However, since the dramatic increase in the production of veterinary antibiotics in 1950, the levels of ARGs in soils also increased. In archived soil samples from Dutch arable field sides, for example, the relative abundance of 18 ARGs increased exponentially (Heuer *et al*., 2011a). Upon application of manure, the soil's inherent microbiome could restructure by various mechanisms depicted in Fig. 1. These include (i) incorporating the manure microbiome and resistome (Sun *et al*., 2021), (ii) selection for the natural resistome due to antibiotic or nutrient input, (Gullberg *et al*., 2011) and (iii) HGT from the manure resistome to the soil microbiome (Checcucci *et al*., 2020). Evidence of all these mechanisms has been found in different studies confirming that manure contributes largely to shaping the soil microbiome.

The addition of manure typically adds a considerable amount of bacteria carrying ARGs that may be new or increase the level of existing ones. The persistence of manure-borne ARGs is driven by the abiotic conditions prevailing in the soil and the interaction with the soil microbiome. The presence of antibiotics is considered a major determinant for the selection of AMR in the environment. After 2 years of applying antibiotic-containing manure to a field soil, the prevalence of sulfonamide-resistant isolates was increased compared to the soil before the application (Byrne-Bailey *et al*., 2009). In soil microcosm experiments, manure spiked with sulfadiazine increased the abundance of *sul1* and *sul2* resistance genes (Heuer *et al*., 2008) and repeated application of sulfadiazine-spiked manure led to an accumulation of *sul1* and *sul2* genes in the soil bacterial community, compared to manure without sulfadiazine and untreated soil (Heuer *et al*., 2011b). Owing to a dilution effect or previous degradation, typical concentrations of antibiotics are substantially smaller in soils compared to manure. However, it was shown that even very low concentrations that are up to 100-fold below the minimum inhibitory concentration can still select for resistant bacteria (Gullberg *et al*., 2011). In soils, sulfonamide concentrations as low as 0.1 mg kg^{-1} of soil were shown to have a selective effect on resistant populations (Heuer *et al*., 2008).

Resistant bacteria in manure also have the potential to spread resistance genes via MGEs to members of the

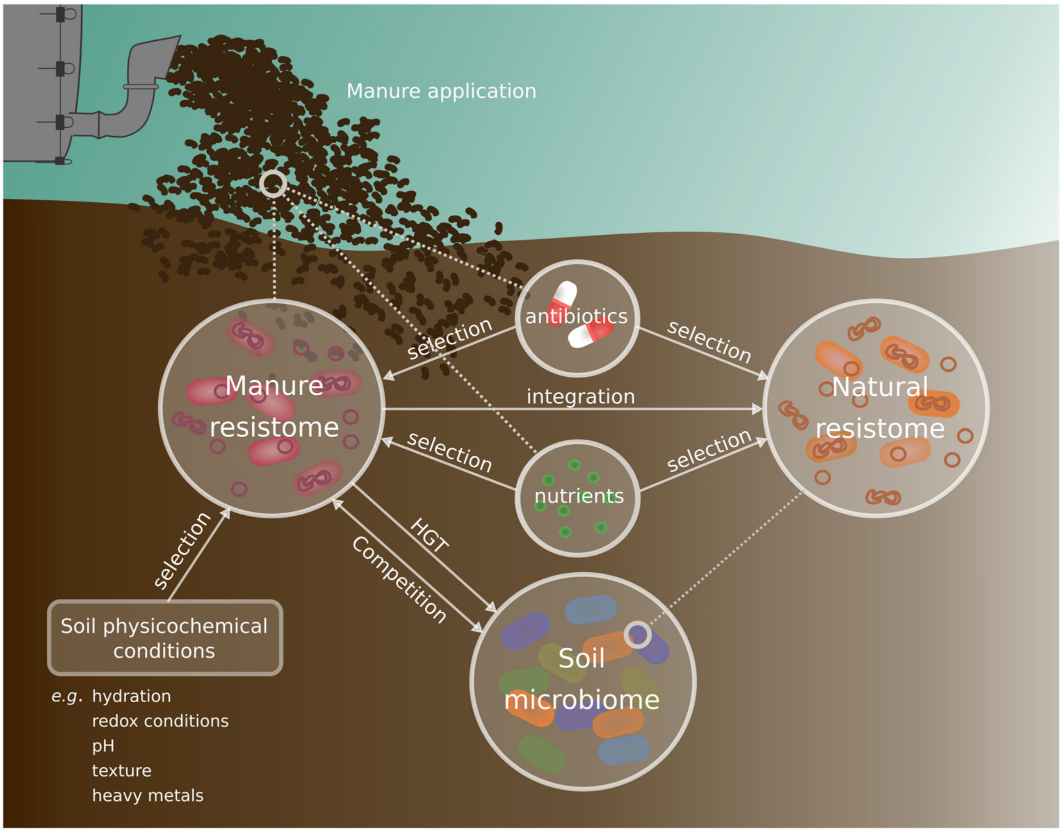

Fig. 1. Possible changes in the soil microbiome following manure application. Fertilization of agricultural soils with treated and untreated animal faeces leads to the augmentation of the soil resistome through (i) incorporation of manure-derived resistant bacteria, (ii) selection of the natural resistome and (iii) increased horizontal gene transfer from manure to soil microbiomes. Manure-derived antibiotics and nutrients and soil physicochemical parameters contribute to the selection of AMR.

soil microbiome. This can be achieved by broad-host-range plasmids or other conjugative elements (Heuer *et al*., 2011a). Horizontal transfer of ARGs via conjugation, transformation and transduction contributes to the dissemination of AMR (Lima *et al*., 2020). Chambers *et al*. (2015) reported enhanced β-lactam resistance parallel to an increase in the prevalence of HGT drivers such as phages, prophages and plasmids in cattle treated with antibiotics. The occurrence of bacteriophage-mediated dissemination of ARGs related to β-lactamase and tetracycline resistance in soil and manure has been confirmed in different studies (Anand *et al*., 2016; Lima *et al*., 2020). However, compared to the role of plasmids it still remains an understudied pathway of AMR transmission in environmental niches. Horizontal transfer of genes from manure-derived bacteria to indigenous soil bacteria might be an important factor for the long-term persistence of ARGs in soils. Bacteria from the gut of food animals may not be well adapted to the conditions prevailing in soil and studies showed their decline below detection level within weeks or months (Chee-Sanford *et al*., 2009; Hammesfahr *et al*., 2008). However, manure has been demonstrated to promote the horizontal transfer of ARGs in soils (Gotz and Smalla 1997; Zhang *et al*., 2017). In addition, sub-inhibitory levels of ciprofloxacin and levofloxacin were found to increase the selection of AMR by enhancing conjugative plasmid transfers across distinct microbial genera (Shun-Mei *et al*., 2018). Other studies demonstrated that even manure without or very low concentrations of antibiotics leads to elevated levels of ARGs in soils (Kyselková *et al*., 2013; Heuer *et al*., 2007; Zhang *et al*., 2017). This suggests that the selection of AMR in soils is not only influenced by the presence of antibiotics but also by the availability of nutrients and growth substrates (Jechalke *et al*., 2014).

Heavy metals in soils exert selective pressures which aid in co-resistance or cross-resistance of bacteria carrying ARGs (Nguyen *et al*., 2019; Ji *et al*. 2012). Co-selection occurs when the genes responsible for heavy metal resistance are located on the same MGE and cross-resistance occurs when there is tolerance to a commonly toxic substance as a consequence of exposure to a similarly acting substance (Nguyen *et al*., 2019). Heavy metals enter agricultural soils through inorganic fertilizers, manure and wastewaters used for irrigation. Heavy metals like chromium, copper, lead and mercury were found to contribute to the sustenance and transmission of AMR in soils (Yazdankhah *et al*., 2018). However, the associations seem to differ for different heavy metals (Nguyen *et al*., 2019). In *E. coli*, resistance to zinc was often associated with resistance to ampicillin, nalidixic acid and tetracycline (Becerra-Castro *et al*., 2015), while resistance to cadmium was coupled to erythromycin and tetracycline resistance (Choudhury and Kumar 1996; Roane and Kellogg 1996). Also, copper was frequently found to co-select for various ARGs conferring resistance to tetracycline, vancomycin and sulfonamides in more complex soil microbial communities (Berg *et al*., 2010; Zhang *et al*., 2018).

Establishing the missing links between AMR persistence and soil physicochemical properties is a prerequisite for evaluating the risk of AMR transmission to water, plants and humans.

Soils in a One Health perspective

The impact of environmental exposure to antibiotic resistance on human health is still largely unknown (Wuijts *et al*., 2017). Studies confirming the transmission of AMR or pathogens from a few recent studies have been enlisted in Table 1. A recent report identifies (i) fertilizers of faecal origin, (ii) irrigation and surface water for agriculture and (iii) water for aquaculture to have led to the emergence and spread of AMR in food-producing environments (ESFA 2021). This evidence indicates the critical and substantial role of agricultural soils in the spread of AMR in large ecologies and food chains. Agricultural soils comprise an important One Health interface indirectly linking the animal and the human sector. Soil microbiomes harbouring ARGs may serve as a point source of AMR transmission to other connected ecosystems and the human and animal sector via both direct and indirect pathways (Fig. 2). Nevertheless, a recent review of One Health networks highlighted that environmental health expertise is still underrepresented (Essack 2018; Khan *et al*., 2018) and should be included in national action plans for AMR (Iossa and White 2018). The environmental burden of AMR is the least well understood, although it seems likely that environmental bacteria, which are the most prevalent, form a reservoir of ARGs that may become incorporated into human and animal pathogens (Essack 2018). Of all the natural ecosystems, soils are the biggest reservoir of biodiversity. They serve as a platform for human activity, are important water filters and form the basis for agricultural production. Therefore, soils may transmit AMR to living organisms through multiple pathways including direct transmission, transmission via crops and feedstock and transmission via drinking water.

Direct transmission

Some studies found evidence for direct transmission of AMR between farm animals and farmers. One *E. coli* isolate from piglets and farmworkers harboured the gene for

Table 1. Studies confirming the transmission of antibiotic-resistant pathogens or AMR.

No.	Source of AMR/pathogen	Transmission of AMR	Type of antibiotic resistant pathogen or AMR	Reference
1	Manure-swine farms	Swine farm soil	Plasmids carrying AMR determinants in multiple *Salmonella* serotypes	Pornsukarom and Thakur (2017)
2	Chicken litter from farms	Litter to farm soil	*E. coli* and *Salmonella* sp. detected 59.1% and 15.5% respectively, 26.7% colistin-resistant *E. coli* spp. detected	Ngogang *et al*. (2021)
3	Poultry litter and cattle manure	AMR genes in grassland soils	Long-term application (14 years) of manure and assessment of AMR in grassland soil confirmed integron genes responsible for HGT and sulfonamide resistance in grassland soil	Yang *et al*. (2020)
4	Manure additions from cattle	Agricultural soil	Manure and antibiotic impacts on soil microbial communities can persist for long periods of repeated manure application	Shawver, *et al*. (2021)
5	*E. coli* in animal feeding	AMR transferred to fresh produce in farms via soils	Raw and composted manure, environment, and produce samples screened for AMR *E. coli*, its prevalence was higher in summers in all samples	Glaize *et al*. (2020)
6	Aquatic transmission routes for antibiotic-resistant organisms	Risk of human exposure	Geographic information systems to analyse the spatial distribution of sources of AMR pathogens and transmission pathways in Ireland	Chique *et al*. (2019)
7	Fertilizers of faecal origin, irrigation and surface water for plant-based food and water for aquaculture	Introduction of AMR with feed and humans confirmed	Highest priority bacteria and ARGs identified in faeces, manure, soil and water	EFSA (2021)

extended-spectrum β-lactamase and revealed similar resistance patterns, resistance genes, sequence and plasmid type (Tamta *et al*., 2020). Another study demonstrated that exposure to high-risk swine farm environments leads to taxonomic and functional remodelling of the human gut microbiota and resistome, indicating substantial interconnections between the microbiomes (Sun *et al*., 2020). However, the interconnection of soil and farmworker microbiomes and resistomes has not been studied so far and thus the risk of direct transmission from the environment to humans remains unclear.

Transmission via crops and feedstock

Bioaccumulation of antibiotics has already been observed in many different crops such as maize, cabbage, spinach, radish, corn and rice (Mullen *et al*., 2019) and phytotoxic effects of antibiotics have been identified and reviewed (Liu *et al*., 2009; Rocha *et al*., 2021). In wastewater-treated soils, non-ionic compounds were detected in higher concentrations in carrots and sweet potatoes compared to ionic compounds (Malchi *et al*., 2014). In studies with environmentally relevant concentrations of sulfamethazine, the highest tissue concentrations were in the lower nanogram range (Kang *et al*., 2013).

The plant microbiome is a major pathway for the exposure of humans to environmental resistomes. Studies on environmental resistomes have mainly focused on soil and wastewater and less attention was on the spread of AMR via plant microbiomes. However, ARGs have been identified on roots and leafy vegetables like pak choi, lettuce, radish, carrot, capsicum, tomato, maize, arugula and cilantro which indicates the risk of transmitting those ARGs to humans and animals as many of those vegetables are consumed raw (Chen *et al*., 2019). Self-transmissible multiple resistance plasmids in bacteria associated with mixed salad, arugula and cilantro were found to be transferable to *E. coli* and thus suggests that they may also have the potential to transfer to gut bacteria (Blau *et al*., 2018). There is evidence that agricultural practice not only affects soil resistomes but also that of plants. Organically produced lettuce harboured higher abundances and diversity of ARGs compared to lettuce produced conventionally (Zhu *et al*., 2017). The detected ARGs conferred resistance to nearly all antibiotics commonly used in human and veterinary medicine. In some cases, the ARGs were not detected in the surrounding soil indicating the presence of an intrinsic resistome (Chen *et al*., 2017). A comparative study of plant metagenomes assessed ARGs in root and leafy vegetables grown in soils supplied with either dairy manure,

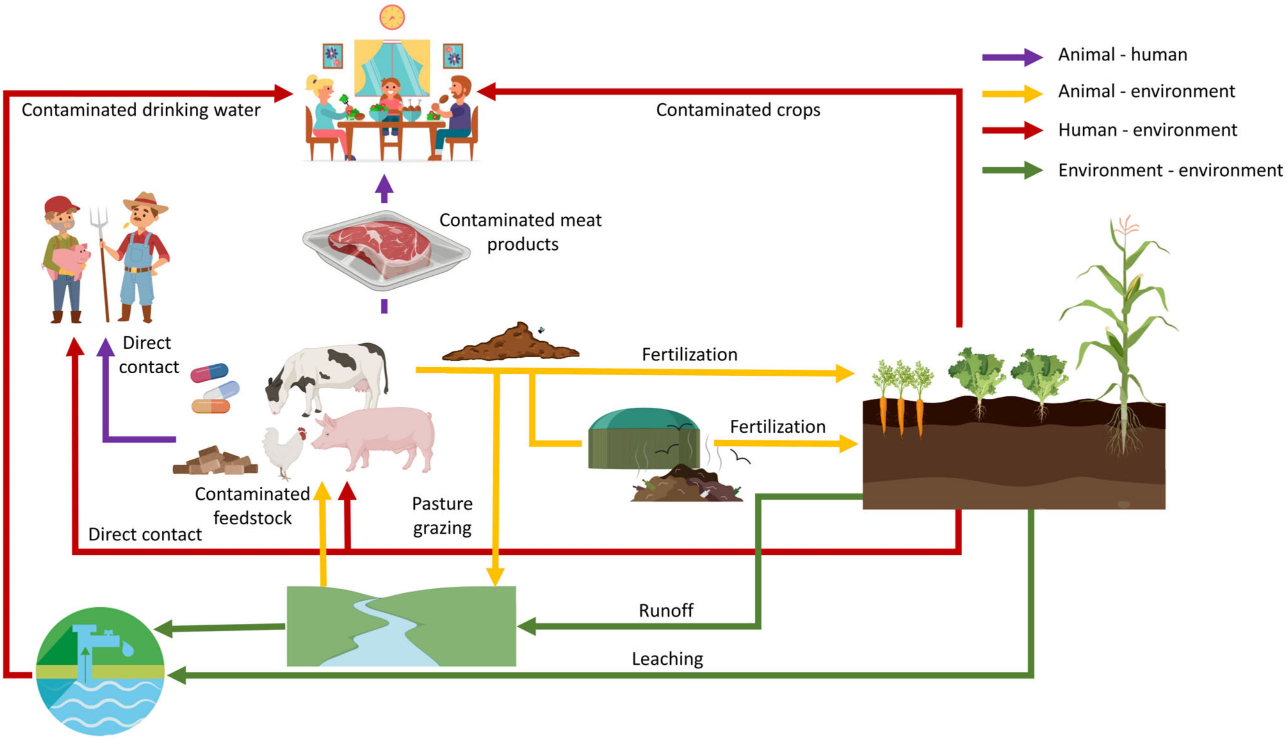

Fig. 2. AMR transmission pathways and One Health Interfaces. Antibiotic-treated livestock could transfer AMR via multiple pathways to humans and the environment. From the environment, AMR may reach humans, animals and connected environmental compartments. Transmission pathways between animals and humans (purple), animals and the environment (yellow), humans and the environment (red) and between environmental compartments (green) are indicated. Picture created with BioRender.

compost, or chemical fertilizer (Guron *et al*., 2019). In this study, factors like manure application, composting and soil type were found to influence ARG diversity in the vegetables. Although these studies analysed the transfer of antibiotics and AMR from soil to root and leafy plants, a more elaborate analysis of AMR transmission between microbiomes of soils, crops and humans is needed. For example, different *Salmonella* subtypes have been identified from poultry manure, surface waters and some leafy vegetables such as mint, lettuce and parsley, with high concordance observed between strains detected in poultry manure and parsley samples (Tarazi *et al*., 2021). Another ambiguity is whether resistance is transferred to pathogens located in the rhizosphere or phyllosphere. The microbiome of crops like sugarcane and vegetables cabbage and potato was found to be dominated by phyla Firmicutes Bacteroidetes, Proteobacteria, Chloroflexi, and Actinobacteria which are also the most dominating phyla detected in polluted waters and soil (Chen *et al*., 2019; Jadeja *et al*., 2019; Bhardawaj *et al*., 2020). The prevalent microbial phyla detected in plant microbiomes might not be pathogenic, but they could play a role in the transmission of ARGs to other bacterial genera through MGEs and HGT events (Rossi *et al*., 2014).

Transmission via drinking water

Transfer of persistent antibiotics such as tetracyclines and fluoroquinolones from soil to surface and groundwaters occurs through runoff and leaching. Groundwater samples from urban locations in Romania which included the area of a swine farm with no special waste handling system and periodical application of manure to soil were analysed for the presence of antibiotics and ARGs (Szekeres *et al*., 2018). Antibiotics like trimethoprim, cefepime and piperacillin were detected in the groundwater samples and ARGs conferring resistance to β-lactams, sulfonamides, tetracyclines and MLSB were identified. The presence of AMR contamination puts large populations at health risks as groundwater remains the major source of drinking water worldwide (Zainab *et al*., 2020). Surface waters in the vicinity of livestock farms were found to contain antibiotics like sulfadimethoxine, sulfamethoxazole, trimethoprim, sulfamerazine, sulfadiazine, lincomycin, erythromycin and monensin (Beni *et al*., 2020). Besides the latter, none of the detected antibiotics was prescribed to livestock at the farm which indicates long-term persistence of antibiotics in the environment or the need for identification of new nonpoint sources of AMR. Metagenomic analysis of samples from catch basins near cattle feedlots revealed the dominance of tetracycline and macrolide resistance genes in both faeces and water samples, which likely reflects the surface runoff of manure-associated resistant bacteria from feedlot pen floors into the catch basins (Zaheer *et al*., 2019).

Way forward

The WHO has presented a global action plan on AMR, which has been adopted as a national action plan in 58 countries (WHO 2019). However, the actual implementation of the guidelines of this plan remains questionable. In India, for example, only three out of 28 states have converted the national action plan into a state action plan on AMR and the sale of antibiotics over the counter is still widespread today (WHO 2021). Despite the 5-year FDA ban on the use of antibiotics in animal feed and the Global Action Plan guidelines on AMR, the number of deaths due to AMR is increasing, revealing the failure of existing linear approaches. The historical expertise of health systems needs to be replaced by one that is de-sectoral and inclusive of the environment. Policymakers addressing AMR need to review the implementation and practice of the standards set.

There are two important levers to reduce the burden of AMR in the environment. First, reducing the use of antimicrobials in food animals would not only counteract the increase of AMR in livestock production systems but also reduce contamination levels in manure as the main input pathway to soils. Van Boeckel *et al*. (2020) evaluated the potential effectiveness of three global policies to curb antimicrobial consumption in food animals. These policies included regulations to limit antimicrobial use, reduced meat consumption and user fees for the use of antimicrobials in animals. In combination, these measures could reduce global antimicrobial consumption in food animals by up to 80%. But even individually, each of the measures showed a reduction in antimicrobial consumption of between 9% and 66%, depending on different targets that also take into account differences between income groups. Second, the use of untreated manure for direct land application should be strongly discouraged. Manure pre-treatments such as composting and anaerobic digestion cannot yet guarantee the complete removal of AMR and the processes should be optimized accordingly. In particular, high temperatures in composting and anaerobic digestion have the potential to significantly reduce AMR levels in manure. In anaerobic digestion of manure, it was found that the addition of activated carbon and microwave pretreatment steps can reduce up to 95% of ARGs. However, further systematic studies are needed for different resistance genes. The risk of AMR spreading through manure in the environment and the possible contamination of food or drinking water requires strict surveillance, improved monitoring and the introduction of regulatory thresholds.

References

Aasmäe, B., Häkkinen, L., Kaart, T., and Kalmus, P. (2019) Antimicrobial resistance of *Escherichia coli* and Enterococcus spp. isolated from Estonian cattle and swine from 2010 to 2015. *Acta Vet Scand* **61**: 1–8.

Abdelgader, S.A., Shi, D., Chen, M., Zhang, L., Hejair, H., Muhammad, U., *et al*. (2018) Antibiotics resistance genes screening and comparative genomics analysis of commensal Escherichia coli isolated from poultry farms between China and Sudan. *Biomed Res Int* **2018**: 5327450.

Agga, G.E., Kasumba, J., Loughrin, J.H., and Conte, E.D. (2020) Anaerobic digestion of tetracycline spiked livestock manure and poultry litter increased the abundances of antibiotic and heavy metal resistance genes. *Front Microbiol* **11**: 3290.

Anand, T., Bera, B.C., Vaid, R.K., Barua, S., Riyesh, T., Virmani, N., *et al*. (2016) Abundance of antibiotic resistance genes in environmental bacteriophages. *J Gen Virol* **97**: 3458–3466.

Anderson, R., Groundwater, P.W., Todd, A., and Worsley, A. (2012) *Antibacterial Agents: Chemistry, Mode of Action, Mechanisms of Resistance and Clinical Applications*. New Jersey, United States: John Wiley and Sons.

Anjum, R., Grohmann, E., and Krakat, N. (2017) Anaerobic digestion of nitrogen rich poultry manure: impact of thermophilic biogas process on metal release and microbial resistances. *Chemosphere* **168**: 1637–1647.

Arcilla, M.S., van Hattem, J.M., Matamoros, S., Melles, D.C., Penders, J., de Jong, M.D., and Schultsz, C. (2016) Dissemination of the mcr-1 colistin resistance gene. *Lancet Infect Dis* **16**: 147–149.

Ashbolt, N., Pruden, A., Miller, J., Riquelme, M. V., and Maile-Moskowitz, A. (2018) *Antimicrobal resistance: fecal sanitation strategies for combatting a global public health threat. Global Water Pathogen Project*. URL https://www.waterpathogens.org/book/antimicrobal-resistance-fecal-sanitation-strategies-combatting-global-public-health-threat.

Atterby, C., Osbjer, K., Tepper, V., Rajala, E., Hernandez, J., Seng, S., *et al*. (2019) Carriage of carbapenemase-and extended-spectrum cephalosporinase-producing *Escherichia coli* and *Klebsiella pneumoniae* in humans and livestock in rural Cambodia; gender and age differences and detection of blaOXA-48 in humans. *Zoonoses Public Health* **66**: 603–617.

Bartelt-Hunt, S.L., Devivo, S., Johnson, L., Snow, D.D., Kranz, W.L., Mader, T.L., *et al*. (2013) Effect of composting on the fate of steroids in beef cattle manure. *J Environ Qual* **42**: 1159–1166.

Batchu, S.R., Panditi, V.R., O'shea, K.E., and Gardinali, P.R. (2014) Photodegradation of antibiotics under simulated solar radiation: implications for their environmental fate. *Sci Total Environ* **470**: 299–310.

Becerra-Castro, C., Machado, R.A., Vaz-Moreira, I., and Manaia, C.M. (2015) Assessment of copper and zinc salts as selectors of antibiotic resistance in Gram-negative bacteria. *Sci Total Environ* **530-531**: 367–372.

Beni, N.N., Snow, D.D., Berry, E.D., Mittelstet, A.R., Messer, T.L., and Bartelt-Hunt, S. (2020) Measuring the occurrence of antibiotics in surface water adjacent to cattle grazing areas using passive samplers. *Sci Total Environ* **726**: 138296.

Berendsen, B.J., Wegh, R.S., Memelink, J., Zuidema, T., and Stolker, L.A. (2015) The analysis of animal faeces as a tool to monitor antibiotic usage. *Talanta* **132**: 258–268.

Berendsen, B.J.A., Lahr, J., Nibbeling, C., Jansen, L.J.M., Bongers, I.E.A., Wipfler, E.L., *et al*. (2018) The persistence of a broad range of antibiotics during calve, pig and broiler manure storage. *Chemosphere* **204**: 267–276.

Berg, J., Thorsen, M.K., Holm, P.E., Jensen, J., Nybroe, O., and Brandt, K.K. (2010) Cu exposure under field conditions coselects for antibiotic resistance as determined by a novel cultivation-independent bacterial community tolerance assay. *Environ Sci Technol* **44**: 8724–8872.

Bhardwaj, P., Singh, K.R., Jadeja, N.B., Phale, P.S., and Kapley, A. (2020) Atrazine bioremediation and its influence on soil microbial diversity by metagenomics analysis. *Indian J Microbiol* **60**: 388–391.

Blau, K., Bettermann, A., Jechalke, S., Fornefeld, E., Vanrobaeys, Y., Stalder, T., *et al*. (2018) The transferable Resistome of produce. *mBio* **9**: 01300-01318.

Boamah, V.E., Agyare, C., Odoi, H., Adu, F., Gbedema, S. Y., and Dalsgaard, A. (2017) Prevalence and antibiotic resistance of coagulase-negative Staphylococci isolated from poultry farms in three regions of Ghana. *Infect Drug Resist* **10**: 175–183.

Boxall, A.B., Fogg, L., Blackwell, P., Blackwell, P., Kay, P., Pemberton, E., *et al*. (2004) Veterinary medicines in the environment. *Rev Environ Contam Toxicol* **180**: 1–91.

Büyüksönmez, F., Rynk, R., Hess, T.F., and Bechinski, E. (2000) Literature review: occurrence, degradation and fate of pesticides during composting: part II: occurrence and fate of pesticides in compost and composting systems. *Compost Sci Util* **8**: 61–81.

Byrne-Bailey, K., Gaze, W., Kay, P., Boxall, A., Hawkey, P., and Wellington, E. (2009) Prevalence of sulfonamide resistance genes in bacterial isolates from manured agricultural soils and pig slurry in the United Kingdom. *Antimicrob Agents Chemother* **53**: 696–702.

Carnevali, C., Morganti, M., Scaltriti, E., Bolzoni, L., Pongolini, S., and Casadei, G. (2016) Occurrence of MCR-1 colistin-resistant Salmonella isolates recovered from human and animals in Italy, 2012-2015. *Antimicrob Agents Chemother* **60**: 7532–7534.

Casewell, M., Friis, C., Marco, E., McMullin, P., and Phillips, I. (2003) The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *J Antimicrob Chemother* **52**: 159–161.

Castanon, J.I.R. (2007) History of the use of antibiotic as growth promoters in European poultry feeds. *Poult Sci* **86**: 2466–2471.

Cessna, A.J., Larney, F.J., Kuchta, S.L., Hao, X., Entz, T., Topp, E., and Mcallister, T.A. (2011) Veterinary antimicrobials in feedlot manure: dissipation during composting and effects on composting processes. *J Environ Qual* **40**: 188–198.

Chambers, L., Yang, Y., Littier, H., Ray, P., Zhang, T., Pruden, A., *et al*. (2015) Metagenomic analysis of antibiotic resistance genes in dairy cow feces following therapeutic administration of third generation cephalosporin. *PLoS One* **10**: e0133764.

Checcucci, A., Trevisi, P., Luise, D., Modesto, M., Blasioli, S., Braschi, I., *et al*. (2020) Exploring the animal waste resistome: the spread of antimicrobial resistance genes through the use of livestock manure. *Front Microbiol* **11**: 1416.

Chee-Sanford, J.C., Mackie, R.I., Koike, S., Krapac, I.G., Lin, Y.F., Yannarell, A.C., *et al*. (2009) Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. *J Environ Qual* **38**: 1086–1108.

Chen, Q.L., An, X.L., Li, H., Zhu, Y.G., Su, J.Q., and Cui, L. (2017) Do manure-borne or indigenous soil microorganisms influence the spread of antibiotic resistance genes in manured soil? *Soil Biol Biochem* **114**: 229–237.

Chen, Q.L., Cui, H.L., Su, J.Q., Penuelas, J., and Zhu, Y.G. (2019) Antibiotic resistomes in plant microbiomes. *Trends Plant Sci* **24**: 530–541.

Chen, Y., Zhang, H., Luo, Y., and Song, J. (2012) Occurrence and assessment of veterinary antibiotics in swine manures: a case study in East China. *Chin Sci Bull* **57**: 606–614.

Chique, C., Cullinan, J., Hooban, B., and Morris, D. (2019) Mapping and analysing potential sources and transmission routes of antimicrobial resistant organisms in the environment using geographic information systems—an exploratory study. *Antibiotics* **8**: 16.

Choudhury, P., and Kumar, R. (1996) Association of metal tolerance with multiple antibiotic resistance of enteropathogenic organisms isolated from coastal region of deltaic Sunderbans. *Indian J Med Res* **104**: 148–151.

Cleary, D.W., Bishop, A.H., Zhang, L., Topp, E., Wellington, E.M., and Gaze, W.H. (2016) Long-term antibiotic exposure in soil is associated with changes in microbial community structure and prevalence of class 1 integrons. *FEMS Microbiol Ecol* **1**: 92.

Congilosi, J.L., and Aga, D.S. (2021) Review on the fate of antimicrobials, antimicrobial resistance genes, and other micropollutants in manure during enhanced anaerobic digestion and composting. *J Hazard Mater* **405**: 123634.

Cycoń, M., Mrozik, A., and Piotrowska-Seget, Z. (2019) Antibiotics in the soil environment—degradation and their impact on microbial activity and diversity. *Front Microbiol* **10**: 338.

Davies, J.E. (1994) Inactivation of antibiotics and the dissemination of resistance genes. *Science* **264**: 375–382.

Davies, J.E. (1997) Origins, acquisition and dissemination of antibiotic resistance determinants. *Ciba Found Symp* **207**: 15–27.

Devi, L.S., Broor, S., Chakravarti, A., and Chattopadhya, D. (2020) Livestock manure as potential reservoir of CTX-M type extended-spectrum β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* associated with carbapenemase production. *J Pure Appl Microbiol* **14**: 171–181.

Diwan, V., Tamhankar, A.J., Khandal, R.K., Sen, S., Aggarwal, M., Marothi, Y., *et al*. (2010) Antibiotics and antibiotic-resistant bacteria in waters associated with a hospital in Ujjain, India. *BMC Public Health* **10**: 1–8.

Dolliver, H., Gupta, S., and Noll, S. (2008) Antibiotic degradation during manure composting. *J Environ Qual* **37**: 245–1253.

EFSA Panel on Biological Hazards (BIOHAZ), Koutsoumanis, K., Allende, A., Álvarez-Ordóñez, A., Bolton, D., Bover-Cid, S., *et al*. (2021) Role played by the environment in the emergence and spread of antimicrobial resistance (AMR) through the food chain. *EFSA J* **19**: e06651.

EMA. (2011) Guidelines on determining the fate of veterinary medicinal products in manure. EMA/-CVMP/ERA/430327/2009 (Revised in 2011).

Esperón, F., Albero, B., Ugarte-Ruíz, M., Domínguez, L., Carballo, M., Tadeo, J.L., *et al*. (2020) Assessing the benefits of composting poultry manure in reducing antimicrobial residues, pathogenic bacteria, and antimicrobial resistance genes: a field-scale study. *Environ Sci Pollut Res* **27**: 27738–27749.

Essack, S.Y. (2018) Environment: the neglected component of the one health triad. *Lancet Planet Health* **2**: 238–239.

European Food Safety Authority, European Centre for Disease Prevention and Control. (2014) The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2012. *EFSA J* **12**: 3547.

FAO (2020) FAO chief urges wiser antibiotic use in food animals. URL https://www.cidrap.umn.edu/news-perspective/2018/05/fao-chief-urges-wiser-antibiotic-use-food-animals.

Figueroa-Diva, R.A., Vasudevan, D., and Mackay, A.A. (2010) Trends in soil sorption coefficients within common antimicrobial families. *Chemosphere* **79**: 786–793.

Flores-Orozco, D., Patidar, R., Levin, D.B., Sparling, R., Kumar, A., and Çiçek, N. (2020a) Effect of ceftiofur on mesophilic anaerobic digestion of dairy manure and the reduction of the cephalosporin-resistance gene cmy-2. *Bioresour Technol* **301**: 122729.

Flores-Orozco, D., Patidar, R., Levin, D.B., Sparling, R., Kumar, A., and Çiçek, N. (2020b) Effect of mesophilic anaerobic digestion on the resistome profile of dairy manure. *Bioresour Technol* **315**: 123889.

Ghirardini, A., Grillini, V., and Verlicchi, P. (2020) A review of the occurrence of selected micropollutants and microorganisms in different raw and treated manure–environmental risk due to antibiotics after application to soil. *Sci Total Environ* **707**: 136118.

Glaize, A., Gutierrez-Rodriguez, E., Hanning, I., Díaz-Sánchez, S., Gunter, C., van Vliet, A.H., *et al*. (2020) Transmission of antimicrobial resistant non-O157 *Escherichia coli* at the interface of animal-fresh produce in sustainable farming environments. *Int J Food Microbiol* **319**: 108472.

Gotz, A., and Smalla, K. (1997) Manure enhances plasmid mobilization and survival of *Pseudomonas putida* introduced into field soil. *Appl Environ Microbiol* **63**: 1980–1986.

Gullberg, E., Cao, S., Berg, O.G., Ilbäck, C., Sandegren, L., Hughes, D., *et al*. (2011) Selection of resistant bacteria at very low antibiotic concentrations. *PLoS Pathog* **7**: 1002158.

Gurmessa, B., Pedretti, E.F., Cocco, S., Cardelli, V., and Corti, G. (2020) Manure anaerobic digestion effects and the role of pre-and post-treatments on veterinary antibiotics and antibiotic resistance genes removal efficiency. *Sci Total Environ* **721**: 137532.

Guron, G.K., Arango-Argoty, G., Zhang, L., Pruden, A., and Ponder, M.A. (2019) Effects of dairy manure-based amendments and soil texture on lettuce-and radish-associated microbiota and resistomes. *Msphere* **4**: 00239-19.

Hammesfahr, U., Heuer, H., Manzke, B., Smalla, K., and Thiele-Bruhn, S. (2008) Impact of the antibiotic sulfadiazine and pig manure on the microbial community structure in agricultural soils. *Soil Biol Biochem* **40**: 1583–1591.

Heuer, H., Focks, A., Lamshöft, M., Smalla, K., Matthies, M., and Spiteller, M. (2008) Fate of sulfadiazine administered to pigs and its quantitative effect on the dynamics of bacterial resistance genes in manure and manured soil. *Soil Biol Biochem* **40**: 1892–1900.

Heuer, H., Schmitt, H., and Smalla, K. (2011a) Antibiotic resistance gene spread due to manure application on agricultural fields. *Curr Opin Microbiol* **14**: 236–243.

Heuer, H., and Smalla, K. (2007) Manure and sulfadiazine synergistically increased bacterial antibiotic resistance in soil over at least two months. *Environ Microbiol* **9**: 657–666.

Heuer, H., Solehati, Q., Zimmerling, U., Kleineidam, K., Schloter, M., Müller, T., *et al*. (2011b) Accumulation of sulfonamide resistance genes in arable soils due to repeated application of manure containing sulfadiazine. *Appl Environ Microbiol* **77**: 2527–2530.

Ho, Y.B., Zakaria, M.P., Latif, P.A., and Saari, N. (2013) Degradation of veterinary antibiotics and hormone during broiler manure composting. *Bioresour Technol* **131**: 476–484.

Hölzel, C.S., Schwaiger, K., Harms, K., Küchenhoff, H., Kunz, A., Meyer, K., *et al*. (2010) Sewage sludge and liquid pig manure as possible sources of antibiotic resistant bacteria. *Environ Res* **110**: 318–326.

Hou, J.P., and Poole, J.W. (1969) Kinetics and mechanism of degradation of ampicillin in solution. *J Pharm Sci* **58**: 447–454.

Hu, T., Dai, Q., Chen, H., Zhang, Z., Dai, Q., Gu, X., *et al*. (2021) Geographic pattern of antibiotic resistance genes in the metagenomes of the giant panda. *J Microbial Biotechnol* **14**: 186–197.

Hurst, J.J., Oliver, J.P., Schueler, J., Gooch, C., Lansing, S., Crossette, E., *et al*. (2019) Trends in antimicrobial resistance genes in manure blend pits and long-term storage across dairy farms with comparisons to antimicrobial usage and residual concentrations. *Environ Sci Technol* **53**: 2405–2415.

Iossa, G., and White, P.C. (2018) The natural environment: a critical missing link in national action plans on antimicrobial resistance. *Bull World Health Organ* **96**: 858–860.

Jadeja, N.B., Purohit, H.J., and Kapley, A. (2019) Decoding microbial community intelligence through metagenomics for efficient wastewater treatment. *Funct Integr Genom* **19**: 839–851.

Jechalke, S., Heuer, H., Siemens, J., Amelung, W., and Smalla, K. (2014) Fate and effects of veterinary antibiotics in soil. *Trends Microbiol* **22**: 536–545.

Ji, X., Shen, Q., Liu, F., Ma, J., Xu, G., Wang, Y., and 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.

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

Kempf, I., Kerouanton, A., Bougeard, S., Nagard, B., Rose, V., Mourand, G., *et al*. (2017) Campylobacter coli in organic and conventional pig production in France and Sweden: prevalence and antimicrobial resistance. *Front Microbiol* **8**: 955.

Khan, M.S., Rothman-Ostrow, P., Spencer, J., Hasan, N., Sabirovic, M., Rahman-Shepherd, A., *et al*. (2018) The growth and strategic functioning of One Health networks: a systematic analysis. *Lancet Planet Health* **2**: 264–e273.

Kim, K.R., Owens, G., Kwon, S.I., So, K.H., Lee, D.B., and Ok, Y.S. (2011) Occurrence and environmental fate of veterinary antibiotics in the terrestrial environment. *Water Air Soil Pollut* **214**: 163–174.

Kingsley, R.A., and Bäumler, A.J. (2000) Host adaptation and the emergence of infectious disease: the *Salmonella* paradigm. *Mol Microbiol* **36**: 1006–1014.

Kümmerer, K. (2004) Resistance in the environment. *J Antimicrob Chemother* **54**: 311–320.

Kyselková, M., Jirout, J., Chroňáková, A., Vrchotová, N., Bradley, R., Schmitt, H., *et al*. (2013) Cow excrements enhance the occurrence of tetracycline resistance genes in soil regardless of their oxytetracycline content. *Chemosphere* **93**: 2413–2418.

Lamshöft, M., Sukul, P., Zühlke, S., and Spiteller, M. (2007) Metabolism of 14 C-labelled and non-labelled sulfadiazine after administration to pigs. *Anal Bioanal Chem* **388**: 1733–1745.

Lamshöft, M., Sukul, P., Zühlke, S., and Spiteller, M. (2010) Behaviour of 14C-sulfadiazine and 14C-difloxacin during manure storage. *Sci Total Environ* **408**: 1563–1568.

Langhammer, J.P. (1989) Untersuchungen zum Verbleib antimikrobiell wirksamer Arzneistoffe als Rückstände in Gülle und im landwirtschaftlichen Umfeld.

Larsson, D.J., de Pedro, C., and Paxeus, N. (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Hazard Mater* **148**: 751–755.

Li, H., Duan, M., Gu, J., Zhang, Y., Qian, X., Ma, J., *et al*. (2017) Effects of bamboo chroanearcoal on antibiotic resistance genes during chicken manure composting. *Ecotoxicol Environ Saf* **140**: 1–6.

Liebert, C.A., Hall, R.M., and Summers, A.O. (1999) Transposon Tn 21, flagship of the floating genome. *Microbiol Mol Biol Rev* **63**: 507–522.

Lima, T., Domingues, S., and Da Silva, G.J. (2020) Manure as a potential hotspot for antibiotic resistance dissemination by horizontal gene transfer events. *Vet Sci* **7**: 110.

Liu, C., Chen, Y., Li, X., Zhang, Y., Ye, J., Huang, H., *et al*. (2020) Temporal effects of repeated application of biogas slurry on soil antibiotic resistance genes and their potential bacterial hosts. *Environ Pollut* **258**: 113652.

Liu, F., Ying, G.G., Tao, R., Zhao, J.L., Yang, J.F., and Zhao, L.F. (2009) Effects of six selected antibiotics on plant growth and soil microbial and enzymatic activities. *Environ Pollut* **157**: 1636–1642.

Malchi, T., Maor, Y., Tadmor, G., Shenker, M., and Chefetz, B. (2014) Irrigation of root vegetables with treated wastewater: evaluating uptake of pharmaceuticals and the associated human health risks. *Environ Sci Technol* **48**: 9325–9333.

McEwen, S.A., and Collignon, P.J. (2018) Antimicrobial resistance: a One Health perspective. In *Antimicrobial Resistance in Bacteria from Livestock and Companion Animals*, Schwarz, S., Cavaco, L.M., and Shen, J. (eds). Washington, DC: American Society for Microbiology, pp. 521–547.

Mitchell, S.M., Ullman, J.L., Teel, A.L., and Watts, R.J. (2014) pH and temperature effects on the hydrolysis of three β-lactam antibiotics: ampicillin, cefalotin and cefoxitin. *Sci Total Environ* **466**: 547–555.

Mohsin, M., Shad, A.A., and Ali, J. (2020) Antimicrobial resistance, food systems and climate change. *Sustain Agric Res* **46**: 59–81.

Moore, P.R., Evenson, A., Luckey, T.D., McCoy, E., Elvehjem, C., and Hart, E.B. (1946) Use of sulfasuxidine, streptothricin, and streptomycin in nutritional studies with the chick. *J Biol Chem* **165**: 437–441.

Mullen, R.A., Hurst, J.J., Naas, K.M., Sassoubre, L.M., and Aga, D.S. (2019) Assessing uptake of antimicrobials by *Zea mays* L. and prevalence of antimicrobial resistance genes in manure-fertilized soil. *Sci Tot Environ* **646**: 409–415.

Muurinen, J., Stedtfeld, R., Karkman, A., Parnanen, K., Tiedje, J., and Virta, M. (2017) Influence of manure application on the environmental resistome under Finnish agricultural practice with restricted antibiotic use. *Environ Sci Technol* **11**: 5989–5999.

Ngogang, M.P., Ernest, T., Kariuki, J., Mouliom Mouiche, M. M., Ngogang, J., Wade, A., *et al*. (2021) Microbial contamination of chicken litter manure and antimicrobial resistance threat in an urban area setting in Cameroon. *Antibiotics* **10**: 20.

Nguyen, C.C., Hugie, C.N., Kile, M.L., and Navab-Daneshmand, T. (2019) Association between heavy metals and antibiotic-resistant human pathogens in environmental reservoirs: a review. *Front Environ Sci Eng* **13**: 46.

O'Neill, J. (2016). Tackling drug-resistant infections globally: final report and recommendations accessed at https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf [Accessed 4th June 2021].

Ouyang, W.Y., Birkigt, J., Richnow, H.H., and Adrian, L. (2020) Anaerobic transformation and detoxification of sulfamethoxazole by sulfate-reducing enrichments and *Desulfovibrio vulgaris*. *Environ Sci Technol* **55**: 271–282.

Partridge, S.R., Brown, H.J., Stokes, H.W., and Hall, R.M. (2001) Transposons Tn 1696 and Tn 21 and their integrons In4 and In2 have independent origins. *Antimicrob Agents Chemother* **45**: 1263–1270.

Pérez-Valera, E., Kyselková, M., Ahmed, E., Sladecek, F.X. J., Goberna, M., and Elhottová, D. (2019) Native soil microorganisms hinder the soil enrichment with antibiotic resistance genes following manure applications. *Sci Rep* **9**: 1–10.

Pils, J.R., and Laird, D.A. (2007) Sorption of tetracycline and chlortetracycline on K-and Ca-saturated soil clays, humic substances, and clay–humic complexes. *Environ Sci Technol* **41**: 1928–1933.

Pornsukarom, S., and Thakur, S. (2017) Horizontal dissemination of antimicrobial resistance determinants in multiple Salmonella serotypes following isolation from the commercial swine operation environment after manure application. *Appl Environ Microbiol* **83**: e01503-17.

Pruden, A., Larsson, D.J., Amézquita, A., Collignon, P., Brandt, K.K., Graham, D.W., *et al*. (2013) Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. *Environ Health Persp* **121**: 878–885.

Qian, X., Gu, J., Sun, W., Wang, X.J., Su, J.Q., and Stedfeld, R. (2018) Diversity, abundance, and persistence of antibiotic resistance genes in various types of animal manure following industrial composting. *J Hazard Mater* **344**: 716–722.

Ray, P., Chen, C., Knowlton, K.F., Pruden, A., and Xia, K. (2017) Fate and effect of antibiotics in beef and dairy manure during static and turned composting. *J Environ Qual* **46**: 45–54.

Redondo-Salvo, S., Fernández-López, R., Ruiz, R., Vielva, L., de Toro, M., Rocha, E.P., *et al*. (2020) Pathways for horizontal gene transfer in bacteria revealed by a global map of their plasmids. *Nat Commun* **11**: 1–13.

Reinthaler, F., Posch, J., Feierl, G., Wüst, G., Haas, D., Ruckenbauer, G., *et al*. (2003) Antibiotic resistance of E. coli in sewage and sludge. *Water Res* **37**: 1685–1690.

Riaz, L., Anjum, M., Yang, Q., Safeer, R., Sikandar, A., Ullah, H., *et al*. (2020a) Treatment technologies and management options of antibiotics and AMR/ARGs. In *Antibiotics and Antimicrobial Resistance Genes in the Environment*. Amsterdam, Netherlands: Elsevier, pp. 369–393.

Riaz, L., Wang, Q., Yang, Q., Li, X., and Yuan, W. (2020b) Potential of industrial composting and anaerobic digestion for the removal of antibiotics, antibiotic resistance genes and heavy metals from chicken manure. *Sci Total Environ* **718**: 137414.

Roane, T., and Kellogg, S. (1996) Characterization of bacterial communities in heavy metal contaminated soils. *Can J Microbiol* **42**: 593–603.

Robinson, T.P., Bu, D.P., Carrique-Mas, J., Fèvre, E.M., Gilbert, M., Grace, D., *et al*. (2016) Antibiotic resistance is the quintessential One Health issue. *Trans R Soc Trop Med Hyg* **110**: 377–380.

Robinson, T.P., and Pozzi, F. (2011) Mapping supply and demand for animal-source foods to 2030. Animal production and health working paper 2:1–154.

Rocha, D.C., da Silva Rocha, C., Tavares, D.S., de Morais Calado, S.L., and Gomes, M.P. (2021) Veterinary antibiotics and plant physiology: an overview. *Sci Total Environ* **767**: 144902.

Rossi, F., Rizzotti, L., Felis, G.E., and Torriani, S. (2014) Horizontal gene transfer among microorganisms in food: current knowledge and future perspectives. *Food Microbiol* **42**: 232–243.

Shawver, S., Wepking, C., Ishii, S., Strickland, M.S., and Badgley, B.D. (2021) Application of manure from cattle administered antibiotics has sustained multi-year impacts on soil resistome and microbial community structure. *Soil Biol* **157**: 108252.

Shun-Mei, E., Zeng, J.M., Yuan, H., Lu, Y., Cai, R.X., and Chen, C. (2018) Sub-inhibitory concentrations of fluoroquinolones increase conjugation frequency. *Microb Pathog* **114**: 57–62.

Sjöström, K., Hickman, R.A., Tepper, V., Olmos Antillón, G., Järhult, J.D., Emanuelson, U., *et al*. (2020) Antimicrobial resistance patterns in organic and conventional dairy herds in Sweden. *Antibiotics* **9**: 834.

Speksnijder, D.C., Mevius, D.J., Bruschke, C.J.M., and Wagenaar, J.A. (2015) Reduction of veterinary antimicrobial use in The Netherlands. The Dutch success model. *Zoonoses Public Health* **62**: 79–87.

Storteboom, H.N., Kim, S.C., Doesken, K.C., Carlson, K.H., Davis, J.G., and Pruden, A. (2007) Response of antibiotics and resistance genes to high-intensity and low-intensity manure management. *J Environ Qual* **36**: 1695–1703.

Sun, J., Liao, X.P., D'Souza, A.W., Boolchandani, M., Li, S. H., Cheng, K., *et al*. (2020) Environmental remodeling of human gut microbiota and antibiotic resistome in livestock farms. *Nat Commun* **11**: 1–11.

Sun, W., Qian, X., Gu, J., Wang, X.J., and Duan, M.L. (2016) Mechanism and effect of temperature on variations in antibiotic resistance genes during anaerobic digestion of dairy manure. *Sci Rep* **6**: 30237.

Sun, Y., Snow, D., Walia, H., and Li, X. (2021) Transmission routes of the microbiome and resistome from manure to soil and lettuce. *Environ Sci Technol* **55**: 1102–11112.

Szekeres, E., Chiriac, C.M., Baricz, A., Szőke-Nagy, T., Lung, I., Soran, M.L., *et al*. (2018) Investigating antibiotics, antibiotic resistance genes, and microbial contaminants in groundwater in relation to the proximity of urban areas. *Environ Pollut* **236**: 734–744.

Tamta, S., Kumar, O.R.V., Singh, S.V., Pruthvishree, B.S., Karthikeyan, R., Rupner, R., *et al*. (2020) Antimicrobial resistance pattern of extended-spectrum β-lactamase-producing *Escherichia coli* isolated from fecal samples of piglets and pig farm workers of selected organized farms of India. *Vet World* **13**: 360–363.

Tarazi, Y.H., Al Dwekat, A.F., and Ismail, Z.B. (2021) Molecular characterization of Salmonella spp. isolates from river and dam water, irrigated vegetables, livestock, and poultry manures in Jordan. *Vet World* **14**: 813–819.

Thiele-Bruhn, S. (2003) Pharmaceutical antibiotic compounds in soils–a review. *J Plant Nutr Soil Sci* **166**: 145–167.

Thiele-Bruhn, S. (2019) Environmental risks from mixtures of antibiotic pharmaceuticals in soils—a literature review. Report for the German Environment Agency 32.

Thiele-Bruhn, S., and Aust, M.O. (2004) Effects of pig slurry on the sorption of sulfonamide antibiotics in soil. *Arch Environ Con Tox* **47**: 31–39.

Thiele-Brun, S., and Peters, D. (2007) Photodegradation of pharmaceutical antibiotics on slurry and soil surfaces. *Landbauforschung Volkenrode* **57**: 13.

Tien, Y.C., Li, B., Zhang, T., Scott, A., Murray, R., Sabourin, L., *et al*. (2017) Impact of dairy manure pre-application treatment on manure composition, soil dynamics of antibiotic resistance genes, and abundance of antibiotic-resistance genes on vegetables at harvest. *Sci Total Environ* **581**: 32–39.

Tiseo, K., Huber, L., Gilbert, M., Robinson, T.P., and Van Boeckel, T.P. (2020) Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030. *Antibiotics (Basel, Switzerland)* **9**: 918.

Turner, P.V., Brabb, T., Pekow, C., and Vasbinder, M.A. (2011) Administration of substances to laboratory animals: routes of administration and factors to consider. *J Am Assoc Lab Anim Sci* **50**: 600–613.

Tyrrell, C., Burgess, C.M., Brennan, F.P., and Walsh, F. (2019) Antibiotic resistance in grass and soil. *Biochem Soc Trans* **47**: 477–486.

Van Boeckel, T., Pires, J., Silvester, R., Zhao, C., Song, J., Criscuolo, N., *et al*. (2020) Global trends in antimicrobial resistance in animals in low- and middle-income countries. *Int J Infect Dis* **101**: 19.

Van Boeckel, T.P., Glennon, E.E., Chen, D., Gilbert, M., Robinson, T.P., Grenfell, B.T., *et al*. (2017) Reducing antimicrobial use in food animals. *Science* **357**: 1350–1352.

Van den Meersche, T., Van Pamel, E., Van Poucke, C., Herman, L., Heyndrickx, M., Rasschaert, G., *et al*. (2016) Development, validation and application of an ultra high performance liquid chromatographic-tandem mass spectrometric method for the simultaneous detection and quantification of five different classes of veterinary antibiotics in swine manure. *J Chromatogr* **1429**: 248–257.

Van Epps, A., and Blaney, L. (2016) Antibiotic residues in animal waste: occurrence and degradation in conventional agricultural waste management practices. *Curr Pollut Rep* **2**: 135–155.

Walters, E., Mcclellan, K., and Halden, R.U. (2010) Occurrence and loss over three years of 72 pharmaceuticals and personal care products from biosolids–soil mixtures in outdoor mesocosms. *Water Res* **44**: 6011–6020.

Wang, H., Chu, Y., and Fang, C. (2017) Occurrence of veterinary antibiotics in swine manure from large-scale feedlots in Zhejiang Province, China. *Bull Environ Contam Toxicol* **98**: 472–477.

Wegst-Uhrich, S.R., Navarro, D.A., Zimmerman, L., and Aga, D.S. (2014) Assessing antibiotic sorption in soil: a literature review and new case studies on sulfonamides and macrolides. *Chem Cent J* **8**: 1–12.

WHO. (2014) *Antimicrobial Resistance: Global Report on Surveillance*. Geneva, Switzerland: World Health Organization.

WHO. (2017a) *WHO Guidelines On Use of Medically Important Antimicrobials in Food-producing Animals*. Geneva, Switzerland: World Health Organization.

WHO. (2017b) *Critically Important Antimicrobials for Human Medicine: Ranking of Antimicrobial Agents for Risk Management of Antimicrobial Resistance due to Non-human Use*. Geneva, Switzerland: World Health Organization.

WHO. (2019) *Library of national action plans*. URL http://www.who.int/antimicrobial-resistance/national-action-plans/library/en.

WHO. (2021) *Antimicrobial resistance*. URL https://www.who.int/india/health-topics/antimicrobial-resistance.

Winckler, C., Engels, H., Hund-Rinke, K., Luckow, T., Simon, M., and Steffens, G. (2004) Verhalten von Tetrazyklinen und anderen Veterinärantibiotika in Wirtschaftsdünger und Boden: (Wirkung von Tetrazyklinen und anderen Tierarzneimitteln auf die Bodenfunktion); Forschungsbericht 200 73 248. Umweltbundesamt.

Wright, G.D. (2010) Antibiotic resistance in the environment: a link to the clinic? *Curr Opin Microbiol* **13**: 589–594.

Wuijts, S., Van Den Berg, H.H., Miller, J., Abebe, L., Sobsey, M., Andremont, A., *et al*. (2017) Towards a research agenda for water, sanitation and antimicrobial resistance. *J Water Health* **15**: 175–184.

Xia, K., Bhandari, A., Das, K., and Pillar, G. (2005) Occurrence and fate of pharmaceuticals and personal care products (PPCPs) in biosolids. *J Environ Qual* **34**: 91–104.

Yacouba, A., and Olowo-Okere, A. (2020) Global trends and current status in colistin resistance research: a bibliometric analysis (1973–2019). *F1000Res* **9**: 856.

Yang, Y., Ashworth, A.J., DeBruyn, J.M., Durso, L.M., Savin, M., Cook, K., *et al*. (2020) Antimicrobial resistant gene prevalence in soils due to animal manure deposition and long-term pasture management. *PeerJ* **8**: e10258.

Yazdankhah, S., Skjerve, E., and Wasteson, Y. (2018) Antimicrobial resistance due to the content of potentially toxic metals in soil and fertilizing products. *Microb Ecol Health Dis* **29**: 1548248.

Zaheer, R., Lakin, S.M., Polo, R.O., Cook, S.R., Larney, F. J., Morley, P.S., *et al*. (2019) Comparative diversity of microbiomes and Resistomes in beef feedlots, downstream environments and urban sewage influent. *BMC Microbiol* **19**: 1–17.

Zainab, S.M., Junaid, M., Xu, N., and Malik, R.N. (2020) Antibiotics and antibiotic resistant genes (ARGs) in groundwater: a global review on dissemination, sources, interactions, environmental and human health risks. *Water Res* **187**: 116455.

Zalewska, M., Błażejewska, A., Czapko, A., and Popowska, M. (2021) Antibiotics and antibiotic resistance genes in animal manure–consequences of its application in agriculture. *Front Microbiol* **12**: 640.

Zhang, F., Zhao, X., Li, Q., Liu, J., Ding, J., Wu, H., *et al*. (2018) Bacterial community structure and abundances of antibiotic resistance genes in heavy metals contaminated agricultural soil. *Environ Sci Pollut Res* **25**: 9547–9555.

Zhang, Q., Yang, C., Dang, Z., and Huang, W. (2011) Sorption of tylosin on agricultural soils. *Soil Sci* **176**: 407–412.

Zhang, Q.Q., Ying, G.G., Pan, C.G., Liu, Y.S., and Zhao, J. L. (2015) Comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance. *Environ Sci Technol* **49**: 6772–6782.

Zhang, X., Ma, C., Zhang, W., Li, W., Yu, J., Xue, D., *et al*. (2020) Shifts in microbial community, pathogenicity-related genes and antibiotic resistance genes during dairy manure piled up. *J Microbial Biotechnol* **13**: 1039–1053.

Zhang, Y., Cheng, D., Zhang, Y., Xie, J., Xiong, H., Wan, Y., *et al*. (2021) Soil type shapes the antibiotic resistome profiles of long-term manured soil. *Sci Total Environ* **786**: 147361.

Zhang, Y.J., Hu, H.W., Gou, M., Wang, J.T., Chen, D., and He, J.Z. (2017) Temporal succession of soil antibiotic resistance genes following application of swine, cattle and poultry manures spiked with or without antibiotics. *Environ Pol* **231**: 1621–1632.

Zhu, B., Chen, Q., Chen, S., and Zhu, Y.G. (2017) Does organically produced lettuce harbor higher abundance of antibiotic resistance genes than conventionally produced? *Environ Int* **98**: 152–159.

Zou, Y., Xiao, Y., Wang, H., Fang, T., and Dong, P. (2020) New insight into fates of sulfonamide and tetracycline resistance genes and resistant bacteria during anaerobic digestion of manure at thermophilic and mesophilic temperatures. *J Hazard Mater* **384**: 121433.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supplementary Table 1. Studies on use of antibiotics and AMR in livestock

Supplementary Table 2. Studies on AMR in pig, poultry, and cattle manure published between 2017–2021.