Review

The contribution of manure to antibiotic resistance and the spread of antibiotic resistance genes in soil: a review

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Abstract

The intensive use of antibiotics, worldwide, in animal husbandry, has led to the development and enrichment of different environments in antibiotic-resistant bacteria (ARB) and antibiotic-resistance genes (ARGs). Moreover, the subsequent application of manure contributes to the emergence of antimicrobial resistance (AMR) in soil. The spread of ARB and ARGs through trophic networks and potential human transmission indicate the need for innovative treatment approaches and strategies to reduce manure contaminants.

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Introduction

Excessive use of antibiotics in zootechnics poses a great risk to sustainable agriculture and human health worldwide. Antibiotic resistance (AR) is a typical "One Health" problem, affecting humans, animals and the environment [1,2,3]. In recent decades, the intensive use of antibiotics, worldwide, in livestock farming, has led to the development and enrichment of various environments in antibiotic-resistant bacteria (ARB) and antibiotic-resistance genes (ARGs), and the subsequent application of manure contributes to the high resistance to antibiotics in the soil [1]. Approximately 58% of the antibiotics consumed in the veterinary sector are excreted in the environment, more than half reaching the soil, where antibiotic residues can negatively affect microbial processes in the environment [4].

The development of large-scale animal feeding operations increased the need for widespread use of antibiotics in the treatment of veterinary infections, disease prevention and growth promotion. Antibiotics have been often included in the past in feed additives in small doses to promote the growth of animals used for meat, being excreted in non-metabolized forms or as active metabolites [5,6]. Antibiotics administered to animals offer selective advantages for ARB that develop in the animal intestine being eliminated in feces and possibly in the environment. The AR can rapidly spread among microbial populations by horizontal gene transfer (HGT), facilitated by mobile genetic elements (MGE), such as plasmids, integrons, transposomes and genetic tapes [5].

Manure composting is a common practice which could effectively reduce the relative abundance of ARGs and MGE, however, the field application of compost may still pose potential risks to humans and crops due to the presence of antibiotic residues, ARGs and pathogens.

In this context, in this paper we will present the diversity of resistant enteric pathogens with zoonotic potential present in manure, the determining factors for reducing the risks of human exposure to antimicrobial resistance (AMR) and the evaluation of different strategies of intervention on manure to reduce the risk of exposure to AMR.

Antibiotics, ARB and the abundance of ARGs in soil and manure

Antibiotics are a heterogeneous group of chemicals that have a low molecular weight, and are produced by microorganisms through biosynthesis processes, which stop or inhibit the microbial growth and multiplication [7]. The synthesis of antibiotics has thus evolved as an ecological competitive mechanism. Microorganisms from the group of actinomycetes, Gram-positive bacilli and microscopic fila-

mentous fungi are the main antibiotic producers [7]. Different antibiotics act differently, given the nature of their structure and the degree of affinity to certain target sites in the bacterial cell [8,7,9]. Some antibiotics inhibit the synthesis of cell walls (e.g., beta-lactams and vancomycin) blocking the functioning of enzymes involved in the synthesis of peptidoglycans. Another category of antibiotics changes the permeability of the plasma membrane (e.g., gramicidin, polymyxin, nystatin). Most classes of antibiotics interfere with protein synthesis (e.g., tetracyclines and aminoglycosides) disrupting bacterial metabolism, resulting in microbial death or growth and multiplication inhibition. There are also antibiotics that interfere with the synthesis of nucleic acids (e.g., fluroquinolones, rifamycin) [10].

Since the early 50s, antimicrobials have been widely adopted for non-human applications, most importantly as feed additives [11].

Farm animal husbandry has intensified the need for widespread use of veterinary antibiotics in the treatment of infections, prevention of diseases and promotion of the growth of animals used for meat [12, 13, 14]. According to "The State of the World's Antibiotics", two-thirds of all antibiotics produced each year worldwide (65,000 tons out of 100,000 tons) are used to treat and raise farm animal [15]. In the global top of sales of antibiotics for animal use in 2009 are macrolides, penicillins and tetracyclines, which are very important for human medicine [16]. The most common antibiotics present in manure from pigs and turkeys are tetracyclines, tylosin, sulfamethazine, monesin, penicillin and nicarbazine [17,18, 19].

Antibiotic-resistant bacteria that are constantly found in animal feces can also be found in manure (e.g., *Extended-Spectrum Beta-Lactamase-producing E. coli* (ESB) and *Methicillin-Resistant Staphylococcus aureus* (MRSA) [20,21]. In soil and surface waters, antibiotics have been identified, such as macrolides, sulfonamides, sulfadimethoxine, tetracycline, lincomycins, chloramphenicol, chlortetracycline, sulfamethazine, trimethoprim [1]. The use of antibiotics in livestock production is equal to or even higher than in the human population, thus, the Union of Researchers reported that around 11 million kg of antibiotics were used for non-therapeutic purposes in the pig, poultry and cattle industries as growth promoters. This aggressive use clearly suggests the idea that large amounts of antibiotics end up in wastewater treatment plants and manure, and that is why environmental reservoirs are seen as the main hotspots for various microorganisms to achieve antibiotic resistance [22].

Manure from animals treated with antibiotics is a direct source of antibiotics and ARB, and thus the application of manure on the soil increases the level of BRA and ARGs in

the soil [23]. When animals consume antibiotics, they are released into the feces and up to 90% urine [12, 24]. In a study performed in the Netherlands on pig and cattle farms, the most common recovered antibiotics were oxytetracycline, doxycycline and sulfadiazine, followed by tetracycline, lincomycin and tylosin. More than a third of the fecal samples contained more than one antibiotic. The authors concluded that the sum of the concentrations of different antibiotics in a sample exceeded the concentrations required to select antibiotic resistance.

The indiscriminate and abusive use of antibiotics has led to the accumulation of higher concentrations of antibiotics in the environment. The sources by which antibiotics can be released into the environment are diverse, including human waste streams, as well as waste from veterinary use and animal husbandry [25,26]. Antibiotics used for prophylaxis or therapy in humans contaminate human waste streams, also antibiotics used in animals to promote growth, prevent and treat diseases, also contaminate animal waste streams. Thus, they are considered the main sources of antibiotic release into the environment [27, 15]. This is due to the fact that the administered antibiotics are not completely metabolized and are released unchanged in the environment, that is, water, manure or soils. Depending on the specific antibiotic and the dose administered, as well as the species and age of the animals, the amount and speed with which antibiotics are released into the environment are different [28], [29].

Antibiotics and their metabolites contained in manure from farm animals can leak through the pile to surface and groundwater, as well as into the soil. This phenomenon often occurs with antibiotics with high affinity in water or that are soluble in water, thus making their spread and ecotoxicity in the environment faster, and widely [30]. In fact, antibiotics can also be introduced into the environment by fertilizing the soil with raw animal manure, irrigation with wastewater generated from farmed activities or by accidental release through runoff from the farm [31,26]. Even the dust can be contaminated with antibiotics from farms and could serve equally as another way of their release into the environment [32]. Chee-Sanford et al. [33] also highlighted the release of antibiotics into the environment through the dispersion of food and the accidental spill of products [26].

Antibiotic resistance genes from the soil can enter the food chain through contaminated crops or groundwater, and can have serious consequences for human health. Studies evaluating the impact of fertilization with organic fertilizers have shown that excessive use of sulfonamides can lead to increase abundance of ARGs in the soil, but such increases are fleeting when manure is applied at recommended rates. The application of manure can affect the composition and functional properties of microbial communities in the soil. A number of researches have been conducted using RT-qPCR on ARGs associated with agriculture to quantify several resistance genes groups, such as tetracycline resistance genes (e.g., *tetG*, *tetM*, *tetPB*) and sulfonamide resistance genes (e.g. *sul1*, *sul2*). Also based on quantitative PCR (HT-qPCR) analyses, it has been shown that hundreds of ARGs encoding resistance to aminoglycosides, tetracycline, macrolides, multidrug, chloramphenicol, beta-lactams and sulfonamide can be investigated simultaneously in manure and composts [34,35,5].

Antibiotics and heavy metals as selection agents for antimicrobial resistance in manure

The consumption of antibiotics is the main determinant of the emergence of new mechanisms of antimicrobial resistance. It should be noted that antimicrobial resistance is a natural phenomenon, preceding the modern selective pressure of the clinical use of antibiotics, as many BRA and ARGs have been identified in original environments [36]. Residues of antibiotics or other categories of substances (such as heavy metals and biocidal products) together with a large and diverse population of antimicrobial-resistant microorganisms, both both pathogens and environmental and commensal bacteria belonging to the intestinal microbiota, can also form an environment conducive to the emergence of new forms of resistance [37-43].

Resistance gives the bacterium the ability to survive at cytotoxic concentrations of antibiotic. In the presence of antibiotics, resistant bacteria can survive and even multiply. The bacteria have developed a remarkable ability to develop resistance to every antibiotic introduced into the clinic. With the introduction into the clinic of a new antibiotic, the development of resistance is inevitable, and the rate of appearance of bacterial strains resistant to new drugs is of the order of 1%, but after 8-12 years of intensive use of antibiotics in the human clinic and in animal husbandry, bacterial strains with multiple resistance have become very frequent [7]. After the application of fertilizers, the abundance of ARGs increased, which indicates a transfer of resistance genes from manure into the soil [44]. The vertical flow of genes involves the transmission of genetic information in successive generations of cells, along with the division, while the HGT is achieved by transferring genetic information between bacteria, in other ways than by division [7]. The HGT can be achieved between the donor bacterium, phages, free DNA or from dead cells and living cells through three different mechanisms, i.e. conjugation, transformation and transduction, occurring both in the clinic and in the natural environment [44,45,46].

The acquisition of resistance genes by human pathogens from environmental bacteria has been demonstrated in several cases, such as the *CTX-M*, a gene encoding for an extended spectrum β-lactamase, which originated from environmental bacteria [47,48,49,50].

An important reservoir for transferable plasmids carrying ARGs is the manure from pigs, used to fertilize the soil. A study by Binh et al. in Germany on pig manure demonstrated the frequent presence of plasmid *bla-TEM*, *sul1*, *sul2* and *sul3* [51]. The presence of selective agents such as antibiotics, heavy metals and disinfectants combined with ARGs, MGEs and various microorganisms create an ideal environment for generating resistance through mutation or genetic transfer [22].

The literature on investigating ARB and ARGs in manure has shown that most studies have focused on investigating pathogenic strains such as *Escherichia coli* and *Salmonella spp.*, and few studies have focused on investigating other genera such as *Campylobacter* sp. and *Enterocccus* sp. [52].

In cattle manure have been identified bacterial strains belonging to the *multi-resistant Enterobacteriaceae (*specifically *Salmonella spp.), Campylobacter, methicillin-resistant Staphylococcus aureus (MRSA)* and *vancomycin-resistant Enterococci (VRE)* (53-56).

Heavy metal contamination functions as a selective agent for AMR. The agricultural practices are a major source of soil contamination with moderate to highly toxic metals, such as mercury, lead, cadmium, copper, and zinc [5], which can accumulate at critical concentrations and may trigger co-selection of AMR [57]. Heavy metals such as iron, cobalt, manganese, copper and zinc are used as nutritional additives in animal feed.

Heavy metals together with antibiotics used in agriculture, discharged into the environment can cause a combined selection and co-selection effect for ARB, and therefore manure-enriched soils from antibiotic-treated animals can play an important role in evolution of ARB [58].

Antibiotics and heavy metal products are frequently used by farmers during feeding, in the treatment of infections and to limit the spread of infections to animals [59]. Exposure to these substances may increase the likelihood of RA selection and co-selection.

The toxicity of heavy metals differs from one bacterial species to another, being involved mainly in different physiological functions, but their toxicity depends very much on the concentration.

Environmental conditions greatly influence the toxicity of heavy metals. The pH value, the concentration of organic matter and the redox potential could affect the concentration and bioavailability of heavy metals in soil, sediments and water. For example, the amount of O_2 influences the redox potential and therefore affects the solubility of some heavy metals. The decomposition in water of high concentrations of organic matter leads to a decrease in oxygen levels to anaerobicity, which decreases the solubility of cadmium and zinc. Low pH values increase the solubility of lead, cadmium and zinc [60].

It has been shown that bacteria in the environment can adapt to the ecological conditions of the environment, manifesting different degrees of sensitivity to toxic metals. The sensitivity of bacteria to the action of heavy metals is quite complex, studies haing shown that Gram-positive bacteria are more sensitive to heavy metals than Gram-negative bacteria, but this sensitivity may differ even in bacteria belonging to the same genus [58].

To avoid cellular degradation caused by heavy metal toxicity, bacteria have developed tolerance mechanisms for heavy metals. The formation or complex sequestration of toxic metals shows that during metal binding, the concentration of free toxic ions in the cytoplasm is minimized. Biosorption of toxic metals takes place at the level of cell membranes, cell walls and extracellular polymeric substance (EPS) of biofilms [61, 62, 63].

Another mechanism of tolerance to heavy metals is detoxification by reducing the intracellular ions [64]. A well-understood example is the mercury reductase (*Mer A*) protein encoded by the *merA* gene. This *MerA* protein reduces Hg^{2+} to the less toxic Hg^0, that will diffuse from the cell due to its low evaporation point [65, 66].

Extrusion of toxic ions by efflux systems is another mechanism by which bacteria tolerate the heavy metal [66]. The outflow of inorganic metal anionic arsenite is mediated by a membrane protein in Gram-positive bacteria, while in the Gram-negative ones it requires an additional ATPase subunit.

The relationship between soil resilience and human health

Human health has been directly correlated with the environment (i.e., habitat and its components, including plants, animals, microorganisms, and other human beings) and the food quality [67, 68]. Given the human population constant growing and living conditions changing, food shortages and growing demands for increased production of animal protein for human consumption around the world, there is an acute need for improving agricultural and industrial productivity [69]. The use of antibiotics in agriculture to meet the needs of the growing human population has been associated with several benefits and thus, it is anticipated that in the future almost all animals slaughtered and consumed as food will

be treated with antibiotics [70]. However, the consumption of meat, milk and eggs contaminated with antibiotic residues usually has an extraordinary negative impact on human health. Effects of antibiotic contamination can be direct or indirect, due to the high dose of residues, which could accumulate over an extended period [70]. They can manifest as hypersensitivity reactions to drugs, aplastic anemia, carcinogenic, mutagenic, immunological and teratogenic effects, nephropathy, hepatotoxicity, disruption of normal intestinal microbiota etc. [26].

The literature demonstrates the transmission of ARB and ARGs from animals to humans [71, 72, 73]. A recent review of the literature suggests that only 5% of the studies claim that there is no link between antibiotic use and AMR in humans, while 72% of the studies provided evidence in favor of transmitting AMR to humans [74].

Through the frequent use of the same antibiotics with similar modes of action, both for animal and human purposes, the transferability of AMR from animals to humans is very probable [75]. Resistance can be transferred from animal to animal or animal to human, either by direct contact or indirectly through the food chain, water, mud-fertilized soils and manure [76]. Contamination with ARB and ARGs can be achieved directly by immediate exposure to animals and biological substances, including urine, feces, milk, and saliva, or indirectly by contact or ingestion of contaminated animals and food derived from them [77, 26]. On the other hand, ARB can be transmitted from humans, including farm workers and their families, to food-bearing animals because it has been observed that the digestive tract and skin of these people contain a large number of commensal bacteria, especially *S. aureus* [78]. However, the risk of transmission depends on geographical location, ethnic / cultural practices, religion, hygiene status, farm size and type of integrated agriculture [79, 26].

Manure together with wastewater are among the main environmental reservoirs of AMR. Following direct spreading on the ground, ARB and ARGs may be released into the environment by penetration into surface waters, aerosolization or through crops (foodborne infections), all of which increasing the risk of human or animal exposure [14].

Animal husbandry operations on farms that use antibiotics are closely linked to the development of ARM in animal caregivers, meat processors and residents close to females [23].

After Woolhouse et al. [80], AMR in animal husbandry can be viewed from four different points of view considered as part of a farm described as an ecosystem [78]: farm animals (cattle, pigs, poultry, sheep), animal products, farm workers, farm environmental sites (water, soil, feed, wastewater, sewage, lagoon, manure and sludge after treatment).

Farm animals are an essential component in understanding the interaction between humans, animals and the environment in terms of bacteria, antibiotics and the movement of antibiotic resistance genes [80]. The digestive tract of animals and farm workers is colonized with various microorganisms, including bacteria and resistant forms, thus being the most important reservoir of microorganisms that play a vital role in disseminating and acquiring resistant bacteria and resistance genes [78, 26].

In a study conducted on a number of 1872 farmers and residents in the vicinity of farms in Germany, a country with a high density of closed animal farms, B. Bisdorff et al. demonstrated that 1% of the general population and 24 of the investigated farmers were positive for MRSA ST398. The risk factor for MRSA-ST398 strain colonization in the neighboring population was the repeated contact of a family member with animals, as well as regular visits to private farms. Contact with pigs has been the main risk factor for colonization among farmers [81]. The highest exposure for farmers was found in poultry farms [82].

Recent studies have shown that multi-drug-resistant *S. aureus* isolates have been identified in aerosols inside chicken farms, and over 80% of these isolates carry the *mecA* gene. For employees and local residents, inhaling bacteria from the air was the direct route of exposure, indicating a significant health risk associated with aerosol exposure [83].

The impact of manure treatment on the persistence and proliferation of AMR

Treatment methods used to limit the occurrence and spread of AMR should lead to inactivation of pathogens and, in addition, to the destruction of ARGs [84]. Composting and anaerobic digestion techniques are widely used for manure recycling.

Aerobic composting is a controlled process by which various groups of microorganisms decompose organic materials, producing secondary and inorganic organic compounds [85]. This method uses the biological oxidation process, an aerobic, thermophilic process of decomposition and microbial synthesis of organic substances from organic waste of plant or animal origin.

Aerobic composting lasts about 45 days, and the temperatures reached during this process are 65-70ºC. Degradation of ARGs requires longer exposure to high temperatures. Laboratory studies have shown that temperatures above 70ºC completely degrade bacterial DNA, ARGs are reduced, and therefore hyperthermophilic composting is more efficient than conventional composting, during which temperatures can reach 90ºC [86].

Some studies have shown that exposure to higher temperatures and longer duration of the thermophilic phase greatly increases the effectiveness of reducing antibiotics during composting. Thus, composting has been suggested as a practical and economical intervention strategy to reduce the concentration of antibiotics in manure, before its application in the field [27]. In 2012, Kim showed in a study that composting reduced the concentration of extractable tetracycline by up to 96%, sulfonamides by 99% and macrolides by 95% [87].

There is limited information on the degradation of antibiotics during composting. A study conducted by Van Dijk and Keukens (2000) showed that the concentration of sulfochloropyramine in poultry manure decreased by 58-82% after 8 days of composting. Following the storage of the same manure after composting, for 3 months, an additional 33% reduction in the concentration of antibiotics was observed [27].

A study by Min Gou et al. in 2018 aimed to examine a broad spectrum of ARGs during the aerobic composting process and compare the effects of manure and compost application on the abundance, diversity and dynamics of these ARGs and bacteria associated with organic fertilizers and compost after a period of 4 months in the laboratory microcosm incubated in the soil taken from the field. Quantitative PCR analyzes detected a total of 144 ARGs in all soil samples, from untreated manure and composted manure, with multidrug-resistance and resistance to macrolide-lincosamide-streptogramin B, aminoglycosides, tetracycline, β- lactam. By incubating the microcosm for 120 days in the laboratory, the diversity and abundance of ARGs in manure-treated soils were significantly higher than in composted manure-treated soils. The level of AMR decreased rapidly over time in all samples of composted manure. The network analysis revealed interactions between ARGs and MGE in manure-treated soils compared to compost-treated soils, suggesting that the ARGs mobility potential was lower in compost-modified soils [88].

Anaerobic digestion is another biological method recommended to treat the manure before its application in the field. Elimination of the antibiotic during such an operation is due to temperature-dependent abiotic processes, such as adsorption and degradation [89, 90].

Another effective strategy to reduce the abundance and spread of ARGs in the soil is the application of biochar on the soil. Recently, the effects of biochar action on soil ARGs were studied and, based on the results, a significant change was observed in the microbial communities after the addition of biochar to soil. Different types of agricultural or household waste prepared from different raw materials cause different changes in the structures of the microbial community. The change in bacterial phylogenetic compositions can result in a change in ARGs and, therefore, the addition of different biofuels to composting manure can have effects on the relative abundance of ARGs in the soil [91].

Conclusions

Soil is a natural source of antibiotics and ARGs, and their excessive use increases the risk of spreading AMR through manure. The presence and release of heavy metals in the environment trigger co-selection of antibiotic resistance in bacteria. Further, horizontal gene transfer mediated by mobile genetic elements increases the risk of spreading ARGs from soil microorganisms to human pathogens. Thus, well-managed aerobic compost treatments that reach higher peak temperatures (> 60°C) are more effective in reducing antibiotic residues. Similarly, thermophilic anaerobic digesters that operate under steady state may be more effective at reducing antibiotic residues than mesophilic or anaerobic lagoons. ARGs often persist through these systems, although optimal management and higher temperature are a feasible method to more efficiently reduce the abundance of ARGs due to additional dehydration of the compost pile [92, 93].

Biochar added to a composting system favors the optimization of the composting process and its final quality, by stabilizing and reducing toxicity. Recent studies have shown that the combined application of biochar and compost decreases the bioavailability and absorption of contaminants in compost [94, 91].

Additional research leading to the development of sensitive and accurate analytical techniques to measure the concentrations of antibiotic residues, but also the clarification of the routes of antibiotic-associated contaminants in the ecosystem. In-depth research is required for optimization of the anaerobic digestion process of liquid manure, with emphasis on the elimination of antibiotic residues, streamlining the composting procedure to minimize AMR in manure and the subsequent dissemination of environmental ARGs in the food chain, as well the development of management programs for risk assessment regarding the research of minimum threshold concentrations that induce or support the spread of AMR in the environment.

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Conflicts of Interest

The authors declare no conflict of interest

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