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Antibiotic Residues in Animal Waste: Occurrence and Degradation in Conventional Agricultural Waste Management Practices

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Abstract The presence of antibiotics in animal manure represents a significant concern with respect to the introduction of antibiotic residues to the environment and the development of antibiotic-resistant pathogens. In this review, we have (1) compiled reported detections of antibiotics in poultry litter, swine manure, and cattle manure; and (2) discussed the treatment of antibiotics during conventional agricultural waste management practices. The most reported antibiotics in animal manure were fluoroquinolones, sulfonamides, and tetracyclines, all of which the World Health Organization has listed as critically important for human health. Relatively high treatment efficiencies were observed for antibiotics in composting, anaerobic digestion, and aerobic/anaerobic lagooning. Interestingly, active management of compost piles did not demonstrate a significant increase in antibiotic degradation; however, low- and high-intensity compost systems exhibited high treatment efficiencies for most antibiotics. Anaerobic digestion was not effective for some key antibiotics, including lincosamides and select sulfonamides and fluoroquinolones. Given the potential for energy recovery during anaerobic digestion of agricultural waste, efforts to optimize antibiotic degradation represent an important area for future research. Lagoons also exhibited fairly high levels of antibiotic treatment, especially for aerobic systems; however, the operational costs/complexity of these systems inhibit utilization at the full-scale. No overall trends in antibiotic treatment efficiency during these three agricultural waste management practices were observed. Finally, we posit that increased efforts to include analysis of antibiotic residues in animal manure in national surveillance programs will provide important information to address concerns over the continued use of antimicrobials in animal feeding operations.

Keywords Antibiotics · Agricultural waste · Animal manure · Composting · Anaerobic digestion · Antimicrobial resistance

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Introduction

The discovery of antibiotics in the 1940s [1–4] spurred a new era of human health. Extension of the benefits and advantages of antibiotics to food animals occurred almost immediately. By 1951, the antibiotic additive market for manufactured animal feeds was $17.5 million [5]. Ten years later, $24 million of antibiotics were used for disease control, and an additional $19 million of antibiotics were employed for nutrition and feed efficiency (i.e., growth promotion) [5]. The animal antibiotics and antimicrobials market reached $3.3 billion in 2013 and is expected to exceed $4.1 billion by 2018 [6]. The extreme growth of this industry stems from two major factors: (1) increased animal production over the past half century and (2) concentration of animal feeding operations. For example, the total US availability (millions of tons) of beef, pork, and chicken from 1951 to 2013 was 3.18–8.47, 3.48–6.88, and 1.16–9.13, respectively [7]; for reference, the US population doubled over the same period. The transition from traditional farms to concentrated animal feeding operations (CAFOs), which produce hundreds of thousands to millions of animals per farm each year, has necessitated increased antibiotic use to prevent the spread of disease among animals raised in close confines.

Several concerns arise from the use of antibiotics in animal feeding operations: incorporation of antibiotics into animal products, development of single- and multidrug resistance, introduction of resistant bacteria to the environment, and discharge of antibiotic residues to environmental systems. The recent bans on organoarsenical use in the USA were instigated by detection of arsenic in poultry meat [8, 9]. Development of new microbiological tools and high-throughput sequencing has spurred a significant body of literature on the presence of antibiotic-resistant organisms and antimicrobial resistance genes in animal manure [10–12]. Land application of agricultural waste containing antibiotic residues is an emerging concern, since this practice facilitates the spread of antibiotic resistance [13–15]. For example, one study found that *Enterococcus* spp. sampled from 82 farms on the poultry-intensive eastern shore of Maryland were resistant to lincosamides, macrolides, and tetracyclines [16]. Moreover, a number of studies have detected antibiotics in animal waste [17–22]; however, synthesis of reported antibiotic concentrations in animal waste is needed to design and test treatment technologies that ensure degradation of antimicrobials in animal waste before use as fertilizers and soil amendments. To date, the most commonly employed agricultural treatment systems involve biological processes, such as composting, anaerobic digestion, and anaerobic/aerobic lagooning [23].

The main objectives of this review are as follows:

1. Describe antibiotics employed in production of the three leading food animals (i.e., poultry, swine, and cattle) and compile detections of these antibiotics in manure
2. Identify degradation of antibiotics during composting, anaerobic digestion, and anaerobic/aerobic lagooning of agricultural waste

Antibiotic Presence in Agricultural Waste

Antibiotic Use in Food Animals

As indicated above, antibiotic use in animal feeding and production operations began in the 1940s. Antibiotics are primarily added to animal feed for three purposes: to treat disease (therapeutic levels), to prevent disease (subtherapeutic levels), and to promote animal growth (subtherapeutic levels). In the USA, "subtherapeutic" use of antibiotics is defined as concentrations less than 2 g/t feed over a time course longer than 2 weeks [24]. In half of the world's countries, primary antibiotic use stems not from therapeutic use but from prophylactic needs (i.e., mitigating infection and spread of disease) and growth promotion (i.e., growing bigger animals faster) [25]. The benefits of feeding subtherapeutic levels of antibiotics to animals have been known since the mid-1940s. A 1946 report from Moore et al. [26] identified increased chick growth with sulfasuxidine (sulfonamide), streptothricin (streptothricin), and streptomycin (aminoglycoside) treatment; a marked reduction in coliform bacteria was also observed in the cecal contents. Gaskins et al. [27] summarized four mechanisms responsible for the effects of growth-promoting antibiotics: inhibition of subclinical infections, reduction of growth-depressing microbial metabolites, reduction of microbial use of nutrients, and enhanced uptake and use of nutrients. While the use of antimicrobial growth promoters has consistently increased since the 1950s, a growing number of developed countries have restricted the use of antimicrobials for growth promotion due to antimicrobial resistance concerns [28].

Antibiotic doses in animal feed vary by compound, animal, and country. Bolan et al. [29] assembled a list of antimicrobial doses for poultry production, which included maximal doses of 77 mg/kg amprolium (coccidiostat), 26 mg/kg chlortetracycline (tetracycline), 152 mg/kg nicarbazin (coccidiostat), 29 mg/kg oxytetracycline (tetracycline), and 25 mg/kg penicillin (beta-lactam). McEwen and Fedorka-Cray [30] reported that growth promoters are typically administered at 2.5–125 mg/kg. However, measured concentrations of antibiotics in manure regularly exceed these levels, indicating the widespread misuse of antimicrobial feed additives. A US Department of Agriculture (USDA) study from 1999 found that 83 % of cattle feedlots administered subtherapeutic levels of at least one antibiotic to cattle [24]. Using data from 710 farms and 3328 animal feeds, Dewey et al. [31] found that 699 feeds used antimicrobial additives incorrectly, that is at higher than recommended concentrations or on the incorrect class of pig. The dominant antimicrobial additives in that study were tetracyclines (1898 feeds; 79 % labeled use), followed by penicillins (468 feeds; 88 % labeled use) and carbadox, an anti-dysentery drug used in swine (410 feeds; 67 % labeled use) [31]. Broilers are often grown in flocks as large as 100, 000 birds, precluding single-bird-based treatment. For that reason, antimicrobials are administered through the water supply [30]. This process may result in differential dosing across the flock and result in elevated antibiotic levels in poultry litter.

According to the US Food and Drug Administration (FDA), 18 classes of antimicrobials are approved for use in food-producing animals [32]. These classes include the following: aminocoumarins, aminoglycosides, amphenicols, cephalosporins, diaminopyrimidines, fluoroquinolones, glycolipids, ionophores, lincosamides, macrolides, penicillins, pleuromutilins, polymyxins, polypeptides, quinoxalines, streptogramins, sulfonamides, and tetracyclines. In general, these antimicrobials are introduced to animals through feed or water; however, a small fraction of antimicrobials are injected or administered by intramammary, oral, or topical means. Chee-Sanford et al. [33] assembled a list of antibiotic classes used in production of poultry, swine, and cattle using available data from the US Government Accountability Office (GAO) and USDA. These animal-class pairs are summarized below:

- Poultry: aminocoumarins, aminocyclitols, aminoglycosides, beta-lactams, fluoroquinolones, glycolipids, ionophores, lincosamides, macrolides, polypeptides, quinolones, streptogramins, sulfonamides, tetracyclines
- Swine: aminocyclitols, aminoglycosides, beta-lactams, carbadox, glycolipids, lincosamides, macrolides, polypeptides, streptogramins, sulfonamides, tetracyclines
- Cattle: aminoglycosides, beta-lactams, chloramphenicol, fluoroquinolones, glycolipids, ionophores, macrolides, quinolones, streptogramins, sulfonamides, tetracyclines

Consumption of antimicrobials is not equal between classes. The Animal Health Institute [34] conducted a survey of antibiotic use in animal production. Findings from that survey indicated that ionophores/arsenicals (40 % of total use) and tetracyclines (37 %) were the most consumed classes, followed by penicillins (9.4 %), sulfonamides (3.1 %), aminoglycosides (1.3 %), and fluoroquinolones (0.002 %). Current use is likely to deviate from these survey results as a result of the 2013 banning of organoarsenicals, including roxarsone, carbarsone, and arsanilic acid, in the USA [35]; nitarsone was banned in 2015 [36]. Recent bans on other antimicrobial growth promoters may also be shifting global trends.

Like humans, animals do not fully metabolize antibiotics. Kumar et al. [37] assembled a list of excretion factors for various antibiotic classes, demonstrating that 75–80 % of tetracyclines, 60 % of lincosamides, and 50–90 % of macrolides are excreted unchanged. These levels are fairly similar to urinary excretion factors in humans for tetracyclines (tetracycline, 58 ± 8 %) but higher than those for macrolides (erythromycin, 12 ± 7 %) and lincosamides (lincomycin, 5–15 %) [38]. Due to high consumption and incomplete metabolism, agricultural waste is expected to contain high levels of antibiotics; this hypothesis has been confirmed by numerous studies for a variety of animals [17–22]. The following subsections discuss the detection of antibiotics in poultry ("Poultry Litter"), swine ("Swine Manure"), and beef cattle ("Cattle Manure") manure.

Poultry Litter

Antibiotics have been widely detected in poultry litter. Detected concentrations of fluoroquinolones, sulfonamides, and tetracyclines varied over several orders of magnitude, as observed in Fig. 1. In fact, our assembled list of reported concentrations includes 29 different antibiotics. The highest detected antibiotics in poultry litter were fluoroquinolones, and enrofloxacin, in particular [39]. A list of antibiotics from the three most represented classes detected in poultry litter is as follows:

- Fluoroquinolones: ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, fleroxacin, lomefloxacin, norfloxacin
- Sulfonamides: sulfachloropyradazine, sulfadiazine, sulfadimidine, sulfaguanidine, sulfamerazine, sulfamethoxazole, sulfamonomethoxine, sulfanilamide
- Tetracyclines: chlortetracycline, doxycycline, methacycline, oxytetracycline, tetracycline

Fluoroquinolones The highest fluoroquinolone concentrations were detected in poultry litter from China. Detected concentrations varied over six orders of magnitude, indicating that different practices between farms and countries significantly impact antibiotic residues in manure. For example, the maximum enrofloxacin concentrations in poultry litter from China, Egypt, and Austria were 1421, 31, and 8 mg/kg, respectively [18, 39, 40]. Regardless, detection of enrofloxacin was consistent across these studies, with enrofloxacin being detected in 35, 30, and 25–38 % of litter from China, Egypt, and Austria, respectively. Ciprofloxacin, which is a known metabolite of enrofloxacin [60–63], was also detected in the Chinese and Egyptian studies, with maximum concentrations of 46 and

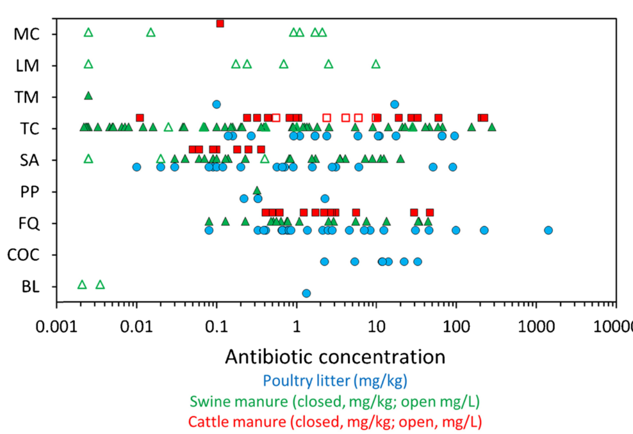

Fig. 1 Antibiotic concentrations detected in poultry, swine, and beef cattle manure. Data was aggregated from available reports [13, 16, 18, 21, 39–59]. Antibiotic class codes on the *y*-axis are as follows: *MC* macrolide, *LM* lincosamide, *TM* trimethoprim, *TC* tetracycline, *SA* sulfonamide, *PP* polypeptide, *FQ* fluoroquinolone, *COC* coccidiostat, *BL* beta-lactam. For clarity, only the minimum and maximum antibiotic concentrations from individual studies were included here. This list is not exhaustive but is meant to convey the relative antibiotic detection and concentration ranges in animal manures

2 mg/kg, respectively [18, 39]. These findings are important since ciprofloxacin is a human-use antibiotic. In fact, of the seven fluoroquinolones detected in poultry litter, only three (i.e., danofloxacin, difloxacin, and enrofloxacin) are classified for veterinary use. The widespread utilization of human-use antibiotics in animal feeding operations may contribute to increased rates of resistance development in human pathogens. This area requires additional research to safeguard the efficacy of human-use medicine.

Sulfonamides The reporting of sulfonamides in poultry litter is more limited than fluoroquinolones. This scenario may stem from low use of sulfonamides in poultry feed additives or from a dearth of studies that have investigated sulfonamide residues in poultry litter. Overall, sulfonamide consumption in animal feeds is higher than fluoroquinolones [34]; however, fluoroquinolones are more persistent in the environment. Discovery of sulfonamides occurred rapidly in the 1940s and 1950s, and widespread use in the decades since then has resulted in high levels of resistance [64]. For that reason, a decreasing dependence on sulfonamide use in food animals seems likely. The low detection frequencies (e.g., 5.6 % for sulfadimidine; 7.4 % for sulfamethoxazole) observed for sulfonamide antibiotics reinforce the idea that antibiotic use is shifting away from sulfonamides and to other classes. In any case, Zhao et al. [39] and Martinez-Carballo et al. [40] detected sulfonamide concentrations as high as 6 mg/kg sulfadimidine and 51 mg/kg sulfadiazine in chicken litter. Trimethoprim, which is usually co-dosed with sulfamethoxazole, has also been detected in poultry litter [40].

Tetracyclines Tetracycline residues were reported in poultry litter from Austria, China, Egypt, and the USA. The median detection frequency of tetracycline antibiotics (~28 %) was similar to fluoroquinolones (~28 %) and higher than sulfonamides (~7 %). Given the AHI consumption trends [34] identified above for tetracyclines (37 % consumption) and fluoroquinolones (0.002 % consumption), similar detection rates for tetracyclines and fluoroquinolones in poultry litter are surprising. Nevertheless, some studies have shown high detection frequency for tetracyclines. For example, Furtula et al. [13] reported chlortetracycline concentrations as high as 66 mg/kg in US poultry litter samples with a detection frequency of 60 %. Tetracycline resistance is common; however, tetracyclines are still widely used in human medicine and listed as critically important [65]. For that reason, the extensive detection of tetracycline residues in animal waste is a public health concern.

Beta-lactams and Polypeptides Few reports [13] were available on beta-lactam presence in poultry litter; however, penicillins and other beta-lactams are readily metabolized and are, therefore, not expected to be widely present in poultry litter. In addition, these molecules are quickly degraded in environmental matrices, decreasing long-term persistence concerns. Polypeptides are similar in this respect. Two polypeptides, bacitracin and virginiamycin, were reported at concentrations of 0.22–2.3 mg/kg in US poultry litter [13]. The relatively low concentrations of these antibiotic classes in poultry litter suggest that the use of fluoroquinolones, sulfonamides, and tetracyclines may be of greater concern; however, increased surveillance of less-consumed antibiotics will provide much needed information to verify this postulation.

Coccidiostats This antimicrobial class is used in animal production to prevent protozoan infections [66]. A number of coccidiostats, including monensin, narasin, nicarbazin, and salinomycin, were detected in poultry litter. In general, the magnitude of detected concentrations of coccidiostats in poultry litter (i.e., 2.3–33 mg/kg) is similar to that of fluoroquinolones, sulfonamides, and tetracyclines. Consider that monensin, narasin, nicarbazin, and salinomycin were detected in US poultry litter at concentrations as high as 11.8, 32.96, 22.4, and 14.1 mg/kg [13]. However, the detection frequency of coccidiostats tended to be less than 20 %, whereas 20–40 % was observed for fluoroquinolones, sulfonamides, and tetracyclines. Because coccidiostats are not used in human medicine, the development of resistance may be less relevant from a public health standpoint when compared to fluoroquinolones, sulfonamides, tetracyclines, beta-lactams, and polypeptides, among others. However, the influence of coccidiostats on development of multidrug resistance is an important knowledge gap given the high use in animal feed.

Organoarsenicals One important class of veterinary antibiotics missing from Fig. 1 is the organoarsenicals. As indicated above, these chemicals are banned in the USA and European Union due to concerns arising from not only arsenic incorporation into meat products [8, 9] but also arsenic presence in the resulting manure. Organoarsenicals are, however, still used in other parts of the world [67]. Degradation of this unique class of antimicrobials has been investigated using a variety of techniques: biological processes [68, 69], UV irradiation/advanced oxidation [70], and adsorption [71, 72]. Due to the incorporation of arsenic moieties in organoarsenicals, transformation-based processes (i.e., oxidation and metabolism, among others) do not represent effective treatment options and phase-change (i.e., sorption, ion exchange) processes are necessary. Given the phase-out of these chemicals in the USA and European Union, they were not included in this discussion; however, Mangalgiri et al. [67] provided a comprehensive review of the use of these chemicals in poultry applications.

The widespread detection of antimicrobials in poultry litter is important in the domestic and global markets. In the USA, poultry is the number one meat product. Beef consumption has been decreasing since the mid-1970s, whereas poultry consumption has increased consistently since the 1950s. The per capita availability of poultry exceeded pork in 1996 and beef in 2010 [7]. In 2013, the per capita availability of poultry was 57.7 lb, compared to 53.6 lb beef and 43.4 lb pork [7]. On the global market, broiler production rose by 6.6 % between 2011 and 2014 [73]. Unlike swine and cattle manure, poultry litter is a dry waste material; therefore, antibiotic residues may be more persistent in environmental systems. For this reason, the fate of diverse antimicrobial classes in conventional and advanced treatment systems is a critical question.

Swine Manure

The concentrations of antibiotics reported in swine manure are presented in Fig. 1. In general, the antibiotic classes and distribution of detected concentrations in swine manure align fairly well with those in poultry litter. Like poultry litter, the fluoroquinolone, sulfonamide, and tetracycline classes have been detected most widely. A number of human- and veterinary-use fluoroquinolone antibiotics, including ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, fleroxacin, lomefloxacin, and norfloxacin, have been detected in swine manure and lagoons at concentrations as high as 44 mg/kg [39, 40]. Similarly, 11 sulfonamides have been detected in swine manure from Austria, China, Germany, Switzerland, and the USA [16, 39–42]. Tetracycline antibiotics, and key metabolic products, have been widely reported in swine manure with detection frequencies as high as 73 % in Austria [40]. The concentration distribution for all three classes mostly ranges between 0.01 and 100 mg/kg (or mg/L).

Relatively few reports documented the presence of other antimicrobial classes in swine manure. Macrolides (i.e., erythromycin and tylosin) have been detected over a wide concentration range, namely 0.001 to 10 mg/L [16, 43–45, 74, 75]. All of these detections came from US swine manure. Penicillin G was also detected at microgram per liter levels in US swine lagoons [16]. While sulfamethoxazole and trimethoprim demonstrated reasonably similar concentration ranges in poultry litter, reported concentrations for trimethoprim (2.5 μg/L) in swine lagoons were lower than sulfamethoxazole (400 μg/L) [16]. Two lincosamides, lincomycin and spectinomycin, were identified in swine manure from US and Canadian farms [16, 46, 76]. Kuchta and Cessna also demonstrated that lincomycin and spectinomycin are persistent in swine manure lagoons, increasing exposure of native microbial populations to high concentrations of lincosamides. For this reason, increased surveillance of antibiotic residues from these lesser consumed antimicrobial classes represents an important knowledge gap, especially with respect to the development of antimicrobial resistance.

Antimicrobial loads in swine manure vary from operation to operation. For example, Qiao et al. [21] measured five tetracycline antibiotics, and several metabolites, in swine manure from three Chinese farms. One manure demonstrated a total mass concentration of tetracyclines of 117 μg/kg (dry weight), whereas another exhibited over 15,200 μg/kg [21]. The two farms with elevated tetracycline content in swine manure showed predominant use of either chlortetracycline or oxytetracycline. Other reports show more consistent antibiotic levels. For example, Angenent et al. [43], Stone et al. [47], and Loftin et al. [44] all identified maximum tylosin concentrations of 1.1–2.1 mg/L in swine manure from US farms.

The diversity of antimicrobials detected in US swine manure includes the following: penicillin G, lincomycin, erythromycin, tylosin, bacitracin, sulfadimethoxine, sulfamethazine, sulfamethoxazole, chlortetracycline, oxytetracycline, and trimethoprim [16, 43–45, 47–49]. This diversity is concerning as the complex mixture of antimicrobials in swine manure/lagoons may more readily lead to the development of multidrug-resistant pathogens. Compounding this threat is the increased demand for pork products in the USA. In the 1990–2013 period, total pork production has consistently increased from 11.6 billion lb to 13.8 billion lb [7]. As swine production continues to increase, effective treatment of antibiotic residuals is an important need.

Cattle Manure

Less information is available for antibiotic concentrations in manure from beef cattle. Our analysis demonstrated that the number of antimicrobial classes used in beef cattle was more restricted compared to poultry and swine. As expected, fluoroquinolones, sulfonamides, and tetracyclines were all detected; however, other antibiotic classes have not been widely reported. De Liguoro et al. [50] detected 0.11 mg/kg of tylosin (macrolide) in US beef cattle manure. The corresponding concentrations of antibiotics identified in cattle manure are presented in Fig. 1. In general, the concentration distributions for fluoroquinolones and tetracyclines in cattle manure were consistent with those observed in poultry litter and swine manure (i.e., 0.1 to 100 mg/kg), but sulfonamide levels were lower.

In a comprehensive study, Zhao et al. [39] measured seven fluoroquinolones, eight sulfonamides, and four tetracyclines in manure from large-scale animal feedlots in China. With the exception of three sulfonamides, each of the 16 other investigated antibiotics were detected in cattle manure. Chlortetracycline and enrofloxacin exhibited detection frequencies of 82.1 and 64.3 %, respectively [39]. In general, fluoroquinolones and tetracyclines were detected more frequently and at higher concentrations than sulfonamides. The maximum detected concentrations were as follows: oxytetracycline, 59.59 mg/kg; enrofloxacin, 46.70 mg/kg; ciprofloxacin, 29.59 mg/kg; and chlortetracycline, 27.59 mg/kg [39]. An important aspect of these findings is the similarity of antimicrobial detections in poultry litter, swine manure, and cattle manure. For that reason, it may be useful to consider these four molecules as priority pollutants that can be used as chemical markers for the fate and transport of antimicrobials in agricultural settings or in agricultural waste management practices.

Other studies primarily reported tetracycline presence in cattle manure. Chlortetracycline was identified in cattle manure from China, Germany, and Turkey at concentrations ranging from 0.011 to 208 mg/kg [39, 51, 52, 77, 78]. The other dominant tetracycline used in cattle production was oxytetracycline. Identified oxytetracycline levels in cattle manure were 0.32 to 225 mg/kg [39, 50, 53–55]. Arikan and coworkers [51, 54, 78] detected metabolic products from oxytetracycline and chlortetracycline in cattle manure; however, these levels were generally lower than the corresponding parent antimicrobials. Identification of other metabolites from the fluoroquinolone and sulfonamide classes, among others, in animal manure is a critical knowledge gap. This need is especially important when metabolic products retain antimicrobial activity and the ability to instigate development of antimicrobial resistance.

In the USA, per capita beef consumption has dropped from 64.5 lb/person in 2000 to 53.6 lb/person in 2013 [7]. However, global beef (and veal) consumption increased about 1 % between 2011 and 2015 [73]. This trend, along with the increased use of antibiotics in animal production, is expected to lead to increased antibiotic loading to sensitive watersheds. That scenario may result in the development and spread of antimicrobial resistance. In fact, a number of efforts have already demonstrated the impact of CAFOs on discharge of antimicrobial resistance genes [79]. Furthermore, this situation may be enhanced in developing countries with less stringent environmental regulations. Consider that Brazil, China, and India produced approximately 35 % of global beef/veal in 2015 [73]; in addition, these countries accounted for about 38 % of beef/veal exports. An important question for the continued development and integration of global meat markets involves the ability of animal feeding operations to minimize antibiotic residues and resistance.

Identification of Priority Antibiotics

The USDA Economic Research Service has reported the per capita availability of beef, pork, and chicken since 1909 [7]. Using those data with the annual US population and average meat production per animal (i.e., 5.9 lb/chicken, 283 lb/pig, and 1300 lb/cow [80]), we computed the equivalent animal production. Typical lifetime manure production values for poultry, swine, and beef cattle are 11, 1287, and 20,300 lb/animal, respectively [80]. With this information, the total US manure production was calculated. From the literature used to generate Fig. 1, the median reported fluoroquinolone, sulfonamide, and tetracycline concentrations for each animal were determined: [fluoroquinolone] = poultry, 2.13 mg/kg; swine, 0.93 mg/kg; cattle, 2.43 mg/kg; [sulfonamide] = poultry, 0.62 mg/kg; swine, 0.19 mg/kg; cattle, 0.095 mg/kg; [tetracycline] = poultry, 2.39 mg/kg; swine, 0.36 mg/kg; cattle, 2.40 mg/kg. The median reported frequency of detection for each class-animal pair was also collected. The total manure production was multiplied by the median antibiotic concentration and median detection frequency to yield the total estimated antibiotic loads in poultry, swine, and cattle manure (Fig. 2).

From Fig. 2, it is clear that the estimated antibiotic load in animal manure has increased since 1990. Note that antibiotic use was not deconvoluted with time; therefore, the trends in total estimated antibiotic loads directly follow animal production trends. Nevertheless, it is interesting to note that FDA data has shown consistent increases in antimicrobial use in animal production. For example, between 2009 and 2013, total antimicrobial use increased 17 %, from 12.6 million kg to 14.8 million kg [32]. For that reason, the estimated antibiotic loads shown in Fig. 2 may be conservative.

Many of the antibiotics identified above have been identified as "critically important antimicrobials" by WHO [81]. This classification involves meeting two criteria:

Criterion 1 An antimicrobial agent, which is the sole (or one of limited) available therapy, to treat serious human disease

Criterion 2 An antimicrobial agent that is used to treat diseases caused by either: (1) organisms that may be transmitted to humans from nonhuman sources, or (2) human diseases caused by organisms that may acquire resistance genes from nonhuman sources

Those antibiotics that meet one criterion are deemed "highly important," whereas those compounds that meet neither requirement are "important" [81]. Table 1 provides a summary of antibiotics detected in animal manure, including the WHO classification and maximum detections in poultry litter, swine manure, and cattle manure. While the use of critically important antibiotics in animal production may be cause for concern regarding food quality, the presence of critically important antibiotics in animal manure may represent an even larger threat due to potential introduction of antibiotic residues, antibiotic-resistant bacteria, and antimicrobial resistance genes to environmental systems. For this reason, effective treatment of antibiotics in agricultural waste treatment systems is paramount.

Degradation of Antibiotics in Agricultural Waste Management

In many cases, animal manure is directly applied to land as a fertilizer or soil amendment. However, in other scenarios, treatment processes are employed prior to land application of

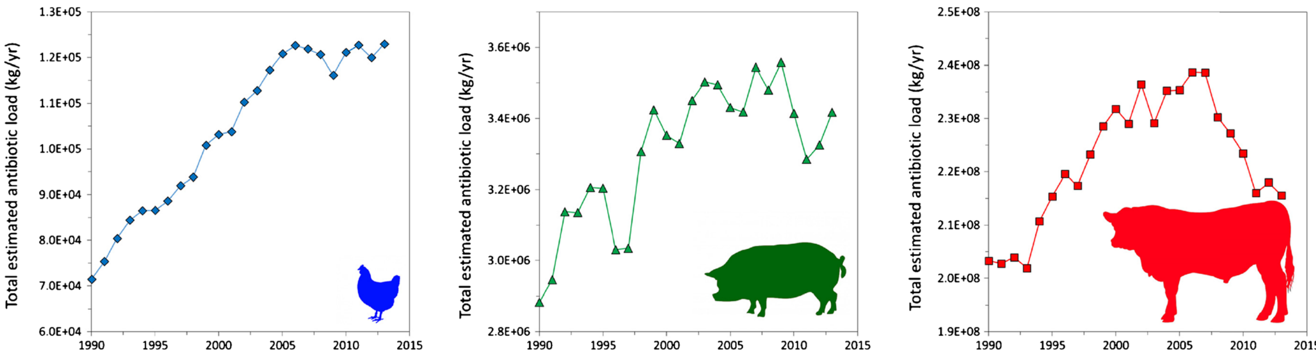

Fig. 2 Total estimated antibiotic load from US poultry, swine, and beef cattle production. The total pounds of meat available from poultry, swine, and beef cattle were collected from the USDA Economic Research Service [7]. These amounts were divided by the average weight of broilers (5.9 lb), hogs (283 lb), and beef cattle (1300 lb) at slaughter to determine the number of animals produced [80]. Average lifetime manure production was estimated at 11, 1287, and 20,300 lb/animal for poultry, swine, and beef cattle, respectively [80]. The total manure production for each animal was multiplied by the median concentrations and frequencies of detection for fluoroquinolone, sulfonamide, and tetracycline antibiotics (from data used to generate Fig. 1). Other antibiotics are not included in this analysis. Differences in antibiotic feeding rates are not included for the 1990–2013 period

agricultural waste. Manure treatment has a variety of objectives, including reducing the volume of waste and converting it to usable products, such as a nutrient-rich fertilizer or biogas [82, 83]. Treatment options range from relatively straightforward practices, such as those that occur in manure piling, low-intensity composting, or storage in anaerobic lagoons, to treatment processes that require greater management (e.g., high-intensity composting, anaerobic digestion, and aerobic lagooning).

The USDA's *Agricultural Waste Management Field Handbook* [23] reviews typical waste management systems for many animal handling facilities, including dairy, beef, swine, and poultry operations. The preferred treatment option largely depends on the solids content of the manure. In many cases, solid-liquid separation is performed, and the two waste streams are treated separately. Separated solids are typically composted. Poultry litter, which is a relatively dry waste, can be directly composted. The liquid fraction of manure streams is typically treated in anaerobic or aerobic lagoons. In some cases, the complete manure (i.e., no solid-liquid separation) or the separated liquid component are treated by anaerobic digestion. These USDA descriptions are generally consistent with the findings from a survey of 100 farms in northeast Spain, which found that composting was the most commonly employed treatment practice, and that while only two farms currently employed anaerobic digestion, new facilities were planned and under construction [84]. A comprehensive discussion of the fate of antibiotics in the three most common types of manure treatment, namely composting, anaerobic digestion, and lagooning, follows in the below sections.

Composting

Composting covers a range of manure management activities that take advantage of microbial processes to aerobically degrade organic material, stabilize the waste, and reduce odor and pathogens. In some cases, the manure pile is mixed with organic materials, such as sawdust or dried leaves, that help with balancing nutrient conditions and enhancing aeration; furthermore, the compost may be turned to increase oxygen availability within the pile [23]. In all cases, microbial processing during composting raises the temperature of the manure pile.

A number of studies have found that the presence of various antibiotics (i.e., chlortetracycline, oxytetracycline, and tetracycline) does not significantly affect the composting process [51, 53, 85, 86]. These findings have been confirmed using the temperature profile, the normalized mass of carbon dioxide produced, the volatile solids content, pH changes, moisture content, and the carbon to nitrogen ratio in the compost pile.

As shown in Table 2, a majority of studies have found antibiotic treatment efficiencies of ≥90 %. Those studies have investigated the following antimicrobials: chlortetracycline [21, 51, 56, 77, 85, 87, 89–91], doxycycline [21], iso-chlortetracycline (a metabolite of chlortetracycline) [51, 77], methacycline [21], monensin [91], oxytetracycline [21, 53, 77, 85, 91], salinomycin [88], sulfadiazine [89], sulfamethazine [90]; tetracycline [21, 85, 91], and tylosin [90, 91]. Lower treatment efficiencies have been reported for chlortetracycline [56], ciprofloxacin [89], monensin [87], sulfamethazine [87], and tylosin [87] in select studies, indicating a dependence on composting technique and management. Furthermore, a variety of manure types have been investigated, including swine [21, 56, 85, 89, 90], poultry [56, 85, 87, 88], cattle [51, 53, 77, 91], and horse [91]. Antimicrobial treatment efficiencies were highest during the early, high-temperature thermophilic phase of composting [53, 56, 77, 88, 89].

Arikan et al. [51] found negligible chlortetracycline and iso-chlortetracycline residuals in composted mixtures and sterilized mixtures that were incubated at 55 °C. However, lower treatment efficiencies were observed in mixtures

Table 1 Overview of antibiotic classes used in animal production

Class	Antibiotic	Primary use	WHO classification	Max. conc. (mg/kg) in poultry litter	Max. conc. (mg/kg or mg/L) in swine manure	Max. conc. (mg/kg or mg/L) in cattle manure	References
Beta-lactam	Penicillin	Human	Critically important	1.33	0.0035		[13, 16]
Coccidiostat	Monensin	Veterinary	n/a	11.8			[13]
Coccidiostat	Narasin	Veterinary	n/a	32.96			[13]
Coccidiostat	Nicarbazin	Veterinary	n/a	22.4			[13]
Coccidiostat	Salinomycin	Veterinary	n/a	14.1			[13]
Fluoroquinolone	Ciprofloxacin	Human	Critically important	45.59	33.98	29.59	[39]
Fluoroquinolone	Danofloxacin	Veterinary	Critically important	2.48	2.92	3.06	[39]
Fluoroquinolone	Difloxacin	Veterinary	Critically important	12.38	2.51	2.63	[39]
Fluoroquinolone	Enrofloxacin	Veterinary	Critically important	1420.76	33.26	46.7	[39]
Fluoroquinolone	Fleroxacin	Human	Critically important	99.43	7.46	2.22	[39]
Fluoroquinolone	Lomefloxacin	Human	Critically important	7.03	44.16	5.53	[39]
Fluoroquinolone	Norfloxacin	Human	Critically important	225.45	5.5	2.76	[39]
Lincosamide	Lincomycin	Human	Highly important		9.78		[46]
Lincosamide	Spectinomycin	Human	Important[a]		0.686		[46]
Macrolide	Erythromycin	Human	Critically important		0.0025		[16]
Macrolide	Tylosin	Veterinary	Critically important		2.1	0.11	[43, 50]
Polypeptide	Bacitracin	Human	Important	2.27	0.32		[13, 48]
Polypeptide	Virginiamycin	Veterinary	Highly important	0.33			[13]
Sulfonamide	Sulfachloropyridazine	Human	Highly important[b,c]	0.71	3.51	0.36	[39]
Sulfonamide	Sulfadiazine	Human	Highly important[c]	91	11.3		[40, 41]
Sulfonamide	Sulfadimethoxine	Human	Highly important[c]		0.0025		[16]
Sulfonamide	Sulfadimidine	Human	Highly important[c]	6.04	20	0.18	[39, 40]
Sulfonamide	Sulfaguanidine	Human	Highly important[b,c]	0.57	1.55	0.25	[39]
Sulfonamide	Sulfamerazine	Human	Highly important[c]	0.66	0.14	0.09	[39]
Sulfonamide	Sulfamethazine	Human	Highly important[b,c]		8.9		[42]
Sulfonamide	Sulfamethoxazole	Human	Highly important[c]	2.8	0.84		[39]
Sulfonamide	Sulfamonomethoxine	Human	Highly important[b,c]	0.9	4.08	0.06	[39]
Sulfonamide	Sulfanilamide	Human	Highly important[c]	1.59	0.04		[39]
Sulfonamide	Sulfathiazole	Human	Highly important[c]		12.4		[42]
Tetracycline	Chlortetracycline	Human	Highly important[a]	94.71	281	208	[51, 56, 57]
Tetracycline	Doxycycline	Human	Highly important[a]	10.91	1.35	1.05	[21, 39]
Tetracycline	Methacycline	Human	Highly important[a]	5.86	5.43	0.96	[39]
Tetracycline	Oxytetracycline	Human	Highly important[a]	10.56	59.06	225	[39, 53]
Tetracycline	Tetracycline	Human	Highly important[a]	2.394	41.2		[41, 58]
Trimethoprim	Trimethoprim	Human	Highly important[c]	17	0.0025		[16, 40]

[a] Criterion 2 met in some countries

[b] Expected to be "highly important" but not explicitly listed in the WHO document

[c] Criterion 1 met in some countries

incubated at colder temperatures. For these reasons, antibiotic treatment is attributed to temperature-dependent abiotic processes, such as sorption and degradation. Kim et al. [90] attributed the ≥95 % treatment efficiencies of chlortetracycline, sulfamethazine, and tylosin to sorption mechanisms; however, the authors noted that microbial processes within compost piles produce a variety of compounds that interact and complex with antibiotics. Thus, while the sorption process is abiotic, antibiotic removal from the aqueous phase may be aided by biotic processes that co-occur in the compost pile. Furthermore, the authors [90] asserted that removal of charged molecules from the aqueous phase, such as tylosin which is predominantly cationic below pH 7.2, is enhanced through ionic mechanisms. Li et al. [92] investigated sorption of tetracyclines in swine manure to compost and attributed ≥97 % of the removal to the high organic content and cation exchange capacity of the

Table 2 Overview of antibiotic removal in composting studies

Compound	Percent removal	Initial concentration (μg/kg)	$t_{1/2}$ (days)	Length of experiment (days)	Scale of experiment	Type of manure	Reference
Coccidiostats							
Monensin	54–76	11,900	22	35	Lab-scale	Turkey	[87]
Monensin	54–76	11,900	11	22	Lab-scale	Turkey	[87]
Monensin	54–76	11,900	19	35	Lab-scale	Turkey	[87]
Monensin	90	250	14.7	141	Pilot-scale	Horse	[77]
Monensin	90	250	30.1	141	Pilot-scale	Horse	[77]
Salinomycin	100	22,000	1.3	38	Lab-scale	Poultry	[88]
Fluoroquinolones							
Ciprofloxacin	69	2000	–	56	Lab-scale	Swine	[89]
Ciprofloxacin	83	20,000	–	56	Lab-scale	Swine	[89]
Macrolides							
Tylosin	54–76	3700	23	35	Lab-scale	Turkey	[87]
Tylosin	54–76	3700	19	22	Lab-scale	Turkey	[87]
Tylosin	54–76	3700	16	35	Lab-scale	Turkey	[87]
Tylosin	95	2000	–	40	Lab-scale	Swine	[90]
Tylosin	95	10,000	–	40	Lab-scale	Swine	[90]
Tylosin	95	20,000	–	40	Lab-scale	Swine	[90]
Tylosin	95	–	–	80	Full-scale	Swine	[90]
Tylosin	100	180	4.2	141	Pilot-scale	Horse	[77]
Tylosin	100	230	9.8	141	Pilot-scale	Horse	[77]
Sulfonamides							
Sulfadiazine	100	2000	–	56	Lab-scale	Swine	[89]
Sulfadiazine	100	20,000	–	56	Lab-scale	Swine	[89]
Sulfamethazine	0	10,800	–	35	Lab-scale	Turkey	[87]
Sulfamethazine	0	10,800	–	22	Lab-scale	Turkey	[87]
Sulfamethazine	0	10,800	–	35	Lab-scale	Turkey	[87]
Sulfamethazine	99	2000	–	40	Lab-scale	Swine	[90]
Sulfamethazine	99	10,000	–	40	Lab-scale	Swine	[90]
Sulfamethazine	99	20,000	–	40	Lab-scale	Swine	[90]
Sulfamethazine	99	–	–	80	Full-scale	Swine	[90]
Tetracyclines							
Chlortetracycline	100	7.9	–	–	Full-scale	Swine	[21]
Chlortetracycline	0	67.4	–	–	Full-scale	Swine	[21]
Chlortetracycline	96.3	8992	–	–	Full-scale	Swine	[21]
Chlortetracycline	98.5	60,000	–	45	Lab-scale	Hen	[85]
Chlortetracycline	97.3	60,000	–	45	Lab-scale	Swine	[85]
Chlortetracycline	>99	1500	1		Lab-scale	Turkey	[87]
Chlortetracycline	>99	1500	0.8	22	Lab-scale	Turkey	[87]
Chlortetracycline	>99	1500	0.9	35	Lab-scale	Turkey	[87]
Chlortetracycline	96	2000	–	40	Lab-scale	Swine	[90]
Chlortetracycline	96	10,000	–	40	Lab-scale	Swine	[90]
Chlortetracycline	96	20,000	–	40	Lab-scale	Swine	[90]
Chlortetracycline	96	–	–	80	Full-scale	Swine	[90]
Chlortetracycline	100	330	5.1	141	Pilot-scale	Horse	[77]
Chlortetracycline	100	330	8.4	141	Pilot-scale	Horse	[77]
Chlortetracycline	100	250	13.4	182	Field-scale	Beef cattle	[77]
Chlortetracycline	100	300	13.5	182	Field-scale	Beef cattle	[77]
Chlortetracycline	100	20	5.8	182	Field-scale	Dairy cattle	[77]
Chlortetracycline	100	20	6.8	182	Field-scale	Dairy cattle	[77]
Chlortetracycline	100	10,000	–	56	Lab-scale	Swine	[89]
Chlortetracycline	100	100,000	–	56	Lab-scale	Swine	[89]
Chlortetracycline	92.6	94,710	11.0	42	Lab-scale	Broiler	[56]
Chlortetracycline	100	53,100	4.39	42	Lab-scale	Layer-hen	[56]
Chlortetracycline	100	100,000	12.0	42	Lab-scale	Layer-hen	[56]
Chlortetracycline	100	150,300	12.2	42	Lab-scale	Layer-hen	[56]
Chlortetracycline	27	879,600	86.6	42	Lab-scale	Swine (hog)	[56]
Chlortetracycline + 4-epi-chlortetracycline	99.4	113,000	4	30	Lab-scale	Beef cattle	[51]
Chlortetracycline + 4-epi-chlortetracycline	99.7	192,000	2.6	28	Lab-scale	Beef cattle	[77]
Chlortetracycline + 4-epi-chlortetracycline	99.7	192,000	3.0	28	Lab-scale	Beef cattle	[77]
Chlortetracycline + 4-epi-chlortetracycline	97.6	192,000	3.8	28	Lab-scale	Beef cattle	[77]

Table 2 (continued)

Compound	Percent removal	Initial concentration (μg/kg)	$t_{1/2}$ (days)	Length of experiment (days)	Scale of experiment	Type of manure	Reference
Chlortetracycline + 4-epi-chlortetracycline	96	192,000	4.0	28	Lab-scale	Beef cattle	[77]
Doxycycline	100	5.1	–	–	Full-scale	Swine	[21]
Doxycycline	99.8	1351	–	–	Full-scale	Swine	[21]
Doxycycline	93.9	1223	–	–	Full-scale	Swine	[21]
Iso-chlortetracycline	100	36,800	–	28	Lab-scale	Beef cattle	[77]
Iso-chlortetracycline	100	36,800	–	28	Lab-scale	Beef cattle	[77]
Iso-chlortetracycline	100	36,800	–	28	Lab-scale	Beef cattle	[77]
Iso-chlortetracycline	100	36,800	–	28	Lab-scale	Beef cattle	[77]
Iso-chlortetracycline	97.5	12,000	–	30	Lab-scale	Beef cattle	[51]
Methacycline	100	12	–	–	Full-scale	Swine	[21]
Methacycline	100	71.1	–	–	Full-scale	Swine	[21]
Oxytetracycline	13.0	74.9	–	–	Full-scale	Swine	[21]
Oxytetracycline	97.2	2544	–	–	Full-scale	Swine	[21]
Oxytetracycline	40.8	39.2	–	–	Full-scale	Swine	[21]
Oxytetracycline	97.2	60,000	–	45	Lab-scale	Hen	[85]
Oxytetracycline	96.2	60,000	–	45	Lab-scale	Swine	[85]
Oxytetracycline	100	1000	15.2	182	Field-scale	Beef cattle	[91]
Oxytetracycline	100	800	31.1	182	Field-scale	Beef cattle	[91]
Oxytetracycline	100	250	9.8	182	Field-scale	Dairy cattle	[91]
Oxytetracycline	100	200	17.7	182	Field-scale	Dairy cattle	[91]
Oxytetracycline	98.3	18,000	4.7	28	Lab-scale	Beef cattle	[77]
Oxytetracycline	98.3	18,000	4.7	28	Lab-scale	Beef cattle	[77]
Oxytetracycline	97.8	18,000	5.6	28	Lab-scale	Beef cattle	[77]
Oxytetracycline	91.1	18,000	7.5	28	Lab-scale	Beef cattle	[77]
Oxytetracycline	99.8	115,000	3.2	35	Lab-scale	Beef cattle	[53]
Tetracycline	0	2.2	–	–	Full-scale	Swine	[21]
Tetracycline	55.1	122	–	–	Full-scale	Swine	[21]
Tetracycline	95.8	1210	–	–	Full-scale	Swine	[21]
Tetracycline	93.8	60,000	–	45	Lab-scale	Hen	[85]
Tetracycline	95.7	60,000	–	45	Lab-scale	Pig	[85]
Tetracycline	100	65	6.5	182	Field-scale	Beef cattle	[91]
Tetracycline	100	30	17.2	182	Field-scale	Beef cattle	[91]
Tetracycline	100	5	–	182	Field-scale	Dairy cattle	[91]
Tetracycline	100	7	–	182	Field-scale	Dairy cattle	[91]

compost. Chlortetracycline sorbed more strongly than oxytetracycline and tetracycline due to the electron withdrawing characteristics of the chlorine atom, which results in higher polarity.

Kim et al. [90], Selvam et al. [89], and Bao et al. [56] found comparable treatment efficiencies during composting processes with different initial antibiotic concentrations. However, Selvam et al. [89] reported that high initial antimicrobial concentrations (i.e., 50 mg/kg of chlortetracycline and 10 mg/kg each of sulfadiazine and ciprofloxacin) resulted in a lag phase before degradation. Conversely, Qiao et al. [21] observed treatment efficiencies of approximately 25 % when initial antibiotic concentrations were less than 0.12 mg/kg compared to 91–94 % treatment at higher initial antibiotic concentrations. The authors concluded that additional removal of antibiotics at such concentrations is difficult in composting systems.

Ramaswamy et al. [88] and Dolliver et al. [87] found comparable antibiotic treatment efficiencies between managed composting (i.e., turning and adjustment of the moisture content) and piling practices with no additional management. These findings come despite the higher temperatures achieved in more intensive manure management. Storteboom et al. [91] found that the impact of management intensity varied by antibiotic: no significant differences were observed for monensin, but improved treatment efficiencies were reported for chlortetracycline and tylosin in managed compost piles. For all three antibiotics, the rate of degradation was higher with more intensive management practices. Arikan et al. [77] investigated different arrangement strategies for manure piles, including placing the pile on straw to reduce heat loss, covering the pile with straw to reduce heat loss, and mixing straw into the pile to increase aeration. In all cases, comparable degradation was reported and these removals were not significantly different than the control pile, which was placed directly on the floor, uncovered and unamended. Thus, low-intensity management practices may still achieve substantial treatment of antibiotics.

Anaerobic Digestion

Anaerobic digestion is a two-step process, in which a fraction of the organic content of the manure is first hydrolyzed and converted into volatile fatty acids (VFAs) by acidogenic bacteria [93]. Methanogenic bacteria then convert VFAs into methane [93]. In comparison to composting or long-term storage of manure in lagoons, anaerobic digestion is a more sensitive process that requires operational precision. Nevertheless, anaerobic digestion provides certain advantages, including production of methane, which offsets energy costs, reduces greenhouse gas emissions, and increases the economic sustainability of farm operations [94].

As summarized in Table 3, removal of various antibiotics during anaerobic digestion has been investigated for swine [43, 47, 96–99] and cattle manure [54, 78, 95] in 20–216-day experiments. Nearly all analyses were performed at mesophilic temperatures [43, 54, 78, 95–99], although psychrophilic [47] temperatures have been examined in select studies. Anaerobic sequencing batch reactors, which decouple the solids' residence time and hydraulic retention time and allow for smaller reactor footprints [100], have also been explored for the removal of antibiotics [43, 101, 102]. Nearly complete removal was observed for the following antimicrobials: ampicillin [95], florfenicol [95], sulfadimethoxine [97], sulfamerazine [97], sulfamethoxazole [97], sulfamethoxydiazine [98], tetracycline [98], trimethoprim [97], and tylosin [43, 47, 95]. Negligible removals were identified for iso-chlortetracycline [78] and sulfathiazole [97]; furthermore, less than 20 % removal was reported for spectinomycin [96] and sulfamethazine [95, 97]. One study observed 57 % degradation of chlortetracycline at psychrophilic temperatures [47] compared to 74–92 % at mesophilic temperatures. Sara et al. [96] found that thermal pretreatment prior to anaerobic digestion enhanced antibiotic removal. These findings indicate that antibiotic biodegradation efficiencies are temperature dependent, with increased removal at higher temperatures.

Angenent et al. [43] attributed high treatability of tylosin A to biodegradation. Sara et al. [96] also concluded that observed removals of ceftiofur, danofloxacin, lincomycin, and spectinomycin were largely attributable to biodegradation. Metabolites of ampicillin [95], chlortetracycline [78], florfenicol [95], sulfadiazine [97], and tylosin [95] have been reported, reinforcing the contribution of biodegradation processes. Wang et al. [45] found a lower reduction in methane production when tylosin A was added directly to manure before anaerobic digestion than when tylosin A was fed to animals, even when the influent tylosin concentrations to the digesters were identical. This difference was attributed to the presence of metabolites in the manure. However, biodegradation may be class- and compound-specific. For example, Mitchell et al. [95] found minimal biodegradation of sulfamethazine and 20 % removal by sorption.

In general, the preponderance of the literature [49, 55, 74, 96, 101–113] focuses on the effects of antibiotics on the anaerobic digestion process rather than the fate of antibiotics during treatment. Individual antibiotics demonstrate a range of impacts on biogas production, from no effect to complete inhibition. Ampicillin [95], carbadox [102], cefazolin [113], ceftiofur [96], chloramphenicol [109], chlortetracycline [49, 109], erythromycin [109], lincomycin [102], oxytetracycline [107], sulfamethazine [95, 102], and tylosin [43, 47, 102, 109] did not reduce biogas production (under the tested conditions). Varel and Hashimoto [108] found that monensin completely inhibited methane production, although they proposed that microbial adaptation could occur. A number of studies reported partial inhibition of biogas production by amoxicillin [107]; ampicillin [105]; chloramphenicol [105]; chlortetracycline [47, 99, 103, 104, 108]; danofloxacin [96]; enrofloxacin [103]; florfenicol [95]; micospectone [96], which is a combination of spectinomycin and lincomycin; oxytetracycline [54, 99, 105, 111, 113, 114]; penicillin [102, 105]; sulfamethoxydiazine [98]; tetracycline [98, 102, 105]; thiamphenicol [107]; and tylosin [45, 95, 101]. Unsurprisingly, greater inhibitory effects have been identified at higher antibiotic concentrations for several antibiotics: chlortetracycline [99, 103, 104], enrofloxacin [103], florfenicol [95], oxytetracycline [55, 99, 111], and tylosin [101].

The mechanism of antibiotic impacts on anaerobic digestion is convoluted. While the presence of antibiotics can reduce biogas production, substantial evidence exists that antimicrobial compounds (at some concentrations) do not affect process stability as measured by biogas composition [47, 54, 55, 105], pH [45, 102, 104, 113], VFA concentrations [102, 113], soluble organic content in the digestion process [54, 102], volatile solids removal [43, 102], or nitrogen content [45, 103]. However, the presence of antibiotics has, under certain conditions, been shown to affect acetate uptake [101, 104], pH [47], chemical oxygen demand [47, 109], volatile solids removal [47, 105], VFA levels [47, 105, 109], or methane content [104, 105]. While biogas production rates [95, 106] and composition [49] may initially be affected by the presence of antibiotics, this impact can be overcome by implementing an acclimation period. This scenario is reinforced by identified changes in microbial communities following introduction of chlortetracycline [47, 103, 104], oxytetracycline [111], and tylosin [45, 47]; however, Bauer et al. [103] found that enrofloxacin did not alter the microbial community structure. Again, these results suggest a dependence of microbial population changes on antimicrobial class. With the advent of high-throughput analytical techniques, future research efforts to document the impacts of antimicrobials on microbial community structure and function will help elucidate impacts on digester performance and antibiotic degradation.

Anaerobic and Aerobic Lagoons

Lagoons are a common means of manure storage. Some lagoons are emptied twice a year [46], while others are designed to never be emptied and rely on evaporation or infiltration for dissipation of the liquid content, with gradual accumulation of solids [115]. Treatment of antibiotics in anaerobic lagoons [44, 46, 48, 116, 117] has been

Table 3 Summary of antibiotic removal by anaerobic digestion

Compound	Percent removal	Initial concentration (mg/L)	$t_{1/2}$ (days)	Temperature (°C)	Configuration	Type of manure	Reference
Amphenicols							
Florfenicol	100	0.36	–	37	Batch (40 days)	Cattle	[95]
Florfenicol	100	3.6	–	37	Batch (40 days)	Cattle	[95]
Florfenicol	100	36	–	37	Batch (40 days)	Cattle	[95]
Florfenicol	100	180	–	37	Batch (40 days)	Cattle	[95]
Florfenicol	100	360	–	37	Batch (40 days)	Cattle	[95]
Beta-lactams							
Ampicillin	100	0.35	–	37	Batch (40 days)	Cattle	[95]
Ampicillin	100	3.5	–	37	Batch (40 days)	Cattle	[95]
Ampicillin	100	35	–	37	Batch (40 days)	Cattle	[95]
Ampicillin	100	175	–	37	Batch (40 days)	Cattle	[95]
Ampicillin	100	350	–	37	Batch (40 days)	Cattle	[95]
Ceftiofur	72.35	1.7	–	37	Batch (60 days)	Swine	[96]
Ceftiofur	72.46	6.9	–	37	Batch (60 days)	Swine	[96]
Ceftiofur	73.77	13.8	–	37	Batch (60 days)	Swine	[96]
Ceftiofur	80.22	13.8	–	37	Batch (60 days)	Swine	[96]
Ceftiofur	79.71	13.8	–	37	Batch (60 days)	Swine	[96]
Fluoroquinolones							
Danofloxacin	33.95	1.1	–	37	Batch (60 days)	Swine	[96]
Danofloxacin	28.17	4.3	–	37	Batch (60 days)	Swine	[96]
Danofloxacin	32.27	8.5	–	37	Batch (60 days)	Swine	[96]
Danofloxacin	45.55	8.5	–	37	Batch (60 days)	Swine	[96]
Danofloxacin	41.94	8.5	–	37	Batch (60 days)	Swine	[96]
Lincosamides							
Spectinomycin	17.61	9.2	–	37	Batch (60 days)	Swine	[96]
Spectinomycin	18.46	37	–	37	Batch (60 days)	Swine	[96]
Spectinomycin	16.26	73.9	–	37	Batch (60 days)	Swine	[96]
Spectinomycin	18.78	73.9	–	37	Batch (60 days)	Swine	[96]
Spectinomycin	18.54	73.9	–	37	Batch (60 days)	Swine	[96]
Lincomycin	32.81	4.6	–	37	Batch (60 days)	Swine	[96]
Lincomycin	34.32	18.5	–	37	Batch (60 days)	Swine	[96]
Lincomycin	33.86	37	–	37	Batch (60 days)	Swine	[96]
Lincomycin	34.6	37	–	37	Batch (60 days)	Swine	[96]
Lincomycin	34.27	37	–	37	Batch (60 days)	Swine	[96]
Macrolides							
Tylosin	99.4	1.6	0.10	25	ASBR	Swine	[43]
Tylosin	99.1	1.1	–	10–20	Batch (216 days)	Swine	[47]
Tylosin	100	0.92	–	37	Batch (40 days)	Cattle	[95]
Tylosin	100	9.2	–	37	Batch (40 days)	Cattle	[95]
Tylosin	100	92	–	37	Batch (40 days)	Cattle	[95]
Tylosin	100	460	–	37	Batch (40 days)	Cattle	[95]
Tylosin	100	920	–	37	Batch (40 days)	Cattle	[95]
Sulfonamides							
Sulfadimethoxine	99.6	0.40	–	37	Batch (34 days)	Swine	[97]
Sulfadimethoxine	99.6	2.0	–	37	Batch (34 days)	Swine	[97]
Sulfamerazine	100	0.40	–	37	Batch (34 days)	Swine	[97]
Sulfamerazine	100	2.0	–	37	Batch (34 days)	Swine	[97]
Sulfamethazine	20	0.28	–	37	Batch (40 days)	Cattle	[95]

Table 3 (continued)

Compound	Percent removal	Initial concentration (mg/L)	$t_{1/2}$ (days)	Temperature (°C)	Configuration	Type of manure	Reference
Sulfamethazine	20	2.8	–	37	Batch (40 days)	Cattle	[95]
Sulfamethazine	20	28	–	37	Batch (40 days)	Cattle	[95]
Sulfamethazine	20	140	–	37	Batch (40 days)	Cattle	[95]
Sulfamethazine	20	280	–	37	Batch (40 days)	Cattle	[95]
Sulfamethazine	0	0.40	–	37	Batch (34 days)	Swine	[97]
Sulfamethazine	0	2.0	–	37	Batch (34 days)	Swine	[97]
Sulfamethoxazole	99.9	0.40	–	37	Batch (34 days)	Swine	[97]
Sulfamethoxazole	99.9	2.0	–	37	Batch (34 days)	Swine	[97]
Sulfamethoxydiazine	100	50.0	–	25	Batch (20 days)	Swine	[98]
Sulfamethoxypyridazine	72.3	0.40	–	37	Batch (34 days)	Swine	[97]
Sulfamethoxypyridazine	72.3	2.0	–	37	Batch (34 days)	Swine	[97]
Sulfathiazole	0	2.0	–	37	Batch (34 days)	Swine	[97]
Tetracyclines							
4-Epi-chlortetracycline	39.0	4.11	39	35	Batch (33 days)	Beef cattle	[78]
4-Epi-chlortetracycline	30.4	0.56	50	35	Batch (33 days)	Beef cattle	[78]
Chlortetracycline	57.0	28	–	10–20	Batch (216 days)	Swine	[47]
Chlortetracycline	74	5.86	18	35	Batch (33 days)	Beef cattle	[78]
Chlortetracycline	75	0.98	18	35	Batch (33 days)	Beef cattle	[78]
Chlortetracycline	90.8	9.8	–	35	Batch (21 days)	Swine	[99]
Chlortetracycline	91.3	46.1	–	35	Batch (21 days)	Swine	[99]
Chlortetracycline	89.9	74.0	–	35	Batch (21 days)	Swine	[99]
Iso-chlortetracycline	0	2.36	–	35	Batch (33 days)	Beef cattle	[78]
Iso-chlortetracycline	0	0.28	–	35	Batch (33 days)	Beef cattle	[78]
Oxytetracycline	59	9.8	56	35	Batch (64 days)	Beef cattle	[54]
Oxytetracycline	57.8	13.5	–	35	Batch (21 days)	Swine	[99]
Oxytetracycline	53.2	56.9	–	35	Batch (21 days)	Swine	[99]
Oxytetracycline	67.6	95.0	–	35	Batch (21 days)	Swine	[99]
Tetracycline	100	50	–	25	Batch (20 days)	Swine	[98]
Trimethoprim							
Trimethoprim	100	0.56	–	37	Batch (34 days)	Swine	[97]
Trimethoprim	100	2.8	–	37	Batch (34 days)	Swine	[97]

evaluated for swine and dairy manure. Bacitracin, chlortetracycline, oxytetracycline, spectinomycin, and tylosin have demonstrated 70–100 % treatment efficiencies in studies lasting 12–240 days [44, 46, 48, 116]. In most cases, removal was biphasic, with a period of rapid concentration change in the first week followed by a prolonged second stage. Lincomycin diverged from this pattern: 40 % was removed within the first 6 days, but concentrations were stable thereafter [46]. Less than 50 % of tetracycline was degraded in an 8-day experiment [117]. Pei et al. [116] found that temperature affected sulfamethoxazole treatment in lagoons: 25 % degradation was observed at 4 °C, but 85 % occurred at 20 °C. A similar experiment carried out with oxytetracycline showed complete removal at 4 and 20 °C.

Loftin et al. [44] inhibited microbial activity in samples with high solids content and found that a significant proportion of tylosin removal occurred via sorption. However, the authors observed faster treatment kinetics in uninhibited samples, thereby indicating the additional contribution of biodegradation processes, which is consistent with the biodegradability of tylosin demonstrated for anaerobic digestion [43]. Evaluation of antibiotic effects on biological processes in anaerobic lagoons has been correlated to methane production. Loftin et al. [44] found that chlortetracycline, lincomycin, oxytetracycline, sulfadimethoxine, sulfamethazine, sulfathiazole, tetracycline, and tylosin reduced methane production by 10–65 %. In addition, lagoons treating manure from farms with a history of antibiotic consumption were found to experience less inhibition of methane production than lagoons with limited antibiotic exposure. These results further verify that microbial populations can acclimate to manure containing antibiotics over long timeframes.

Limited data is available on antibiotic treatment in aerated lagoons, which are more difficult to manage due to higher operational costs associated with mixing, maintenance, and aeration. In laboratory studies with swine and dairy cattle manure, monensin [116], oxytetracycline [116], and tylosin [44] were completely removed over the course of 12–150 days. Treatment efficiencies of less than 70 % were observed for tetracycline in an 8-day experiment [117]. As in anaerobic lagoons, a temperature dependence was observed for sulfamethoxazole with complete removal at 20 °C, but only 35 % at 4 °C; complete removal of oxytetracycline occurred at both conditions [116].

Loftin et al. [44], Kühne et al. [117], and Pei et al. [116] evaluated treatment of oxytetracycline, sulfamethoxazole, tetracycline, and tylosin in anaerobic and aerobic lagoons, effectively establishing a baseline for comparing performance. Oxytetracycline was fully removed for both conditions, but treatment efficiencies for sulfamethoxazole, tetracycline, and tylosin were higher at aerobic conditions. The half-life, or $t_{1/2}$, for tetracycline [117] and the time required for a 90 % decrease in tylosin concentration under aerobic conditions were approximately half of those calculated for anaerobic conditions, indicating that aerobic lagoons are more effective at treating antibiotic residues; however, the operational complexity and maintenance costs associated with aerobic lagooning may limit implementation.

Pei et al. [116] and Loftin et al. [44] compared antimicrobial degradation in both anaerobic and aerobic lagoons with and without sodium azide (to inhibit biological activity) and found conflicting results. Pei et al. reported higher treatment efficiencies of monensin, oxytetracycline, sulfamethoxazole, and tylosin in the uninhibited experiments, indicating that biodegradation played a significant role in removal. On the other hand, Loftin et al. observed similar removal efficiencies for both conditions, suggesting that biodegradation played a relatively minor role in tylosin treatment. For these reasons, the contribution of biodegradation to overall removal likely depends on the physicochemical characteristics of individual antibiotics and lagoon conditions. Analysis of settled solids in operating lagoons at eight different animal (i.e., poultry, swine, and cattle) feeding operations [118] demonstrated tetracycline concentrations of ≥3000 μg/kg (dry weight) and sulfonamide levels of ≥800 μg/kg (dry weight). Ciprofloxacin, enrofloxacin, lincomycin, trimethoprim, and tylosin A were also detected, although at lower levels. These detections indicate that antimicrobial sorption to lagoon solids plays a significant role in the removal of these antibiotics from lagoon effluent. Similarly, Peak et al. [119] evaluated tetracycline presence in full-scale, functioning lagoons from eight cattle farms and found concentrations as high as 17 μg/L. These farms were categorized as "high use" for tetracycline, indicating that high treatment efficiencies are likely (although initial concentrations were not reported). These findings also establish that antibiotic residues are present in lagoon effluent, which is often land-applied as a soil amendment and/or fertilizer.

Comparison of Treatment Methods

Tables 2, 3, and 4 show that chlortetracycline, oxytetracycline, tetracycline, and tylosin have been widely evaluated in composting, anaerobic digestion, and lagoon studies. Direct comparison of these studies obfuscates conclusions about the most effective treatment method. Tetracycline was completely removed from the treated effluent in one anaerobic digestion study while demonstrating a treatment efficiency of >90 % in most composting studies; however, lower removals were reported in aerobic and anaerobic lagoons. For chlortetracycline, treatment was highest (generally 90–100 %) in composting systems. Chlortetracycline removal from the treated effluent in anaerobic digestion and anaerobic lagoons reached 90 % in some cases but tended to be lower overall. Complete removal of oxytetracycline was observed in anaerobic/aerobic lagoons and nearly all composting studies, but lower treatment efficiencies were reported for anaerobic digestion. Similar findings are observed for tylosin, which was completely removed in most anaerobic digestion and aerobic lagoon studies, but not all of the composting investigations.

In general, antibiotic treatment efficiencies during composting were more consistent and higher in comparison to anaerobic digestion and lagoons. However, given that observed removals rely on sorption, antibiotics are not transformed through the composting process, and thus antibiotic residues remain in composted manure. The resulting bioavailability of antibiotics, following land application, depends on the reversibility of the sorption reaction. On the other hand, biodegradation is more prominent in anaerobic digestion, and both sorption and biodegradation are relevant in lagoons. In both processes, antibiotic transformation occurs, resulting in lower antibiotic concentrations in treated manure and process effluent; however, the presence of biologically active metabolites in treated manure needs to be more fully investigated. This area has been partially investigated for some fluoroquinolones and tetracyclines, but for other antibiotics, identification of degradation products in agricultural waste management is a primary research gap.

Anaerobic lagoons are the most common means of manure management due to the low maintenance needs and costs. However, our aggregate analysis has shown that anaerobic lagoons offer the lowest antibiotic treatment efficiencies. Thus, continued use of anaerobic lagoons ensures that antibiotics remain in manure solids and lagoon effluent during field application. For that reason, manure from facilities that

Table 4 Antibiotic removal in anaerobic and aerobic lagoon systems

Compound	Percent removal	Initial concentration (mg/L)	$t_{1/2}$ (days)	Length of experiment (days)	Temperature (°C)	Conditions	Type of manure	Reference
Coccidiostats								
Monensin	100	20	–	–	20	Aerobic	Dairy cattle	[116]
Lincosamides								
Lincomycin	37.7	0.053	–	154	20	Anaerobic	Swine	[46]
Spectinomycin	100	0.387	–	154	20	Anaerobic	Swine	[46]
Macrolides								
Tylosin	90	10[a]	9.7	40	37	Anaerobic	Swine	[48]
Tylosin	>70	20	12.9[b]	12	22	Anaerobic	Swine	[44]
Tylosin	>90	20	1.7[b]	12	22	Anaerobic	Swine	[44]
Tylosin	>90	195	1.7[b]	12	22	Anaerobic	Swine	[44]
Tylosin	99	12	–	240	22	Anaerobic	Swine	[44]
Tylosin	100	20	0.5–1.1[b]	12	22	Aerobic	Swine	[44]
Tylosin	100	20	0.5–1.1[b]	12	22	Aerobic	Swine	[44]
Polypeptides								
Bacitracin F	100	50[a]	1.9	40	37	Anaerobic	Swine	[48]
Sulfonamides								
Sulfamethoxazole	25	20	–	150	4	Anaerobic	Dairy cattle	[116]
Sulfamethoxazole	35	20	–	150	4	Aerobic	Dairy cattle	[116]
Sulfamethoxazole	85	20	–	150	20	Anaerobic	Dairy cattle	[116]
Sulfamethoxazole	100	20	–	150	20	Aerobic	Dairy cattle	[116]
Tetracyclines								
Chlortetracycline	>80	300[a]	1	40	37	Anaerobic	Swine	[48]
Oxytetracycline	100	20	–	150	4	Anaerobic	Dairy cattle	[116]
Oxytetracycline	100	20	–	150	4	Aerobic	Dairy cattle	[116]
Oxytetracycline	100	20	–	75	20	Anaerobic	Dairy cattle	[116]
Oxytetracycline	100	20	–	75	20	Aerobic	Dairy cattle	[116]
Tetracycline	49.1	200	9	8	Ambient	Anaerobic	Swine	[117]
Tetracycline	68.7	200	4.5	8	Ambient	Aerobic	Swine	[117]

[a] Milligram per kilogram dry weight basis

[b] t_{90} (time for 90 % removal)

employ antimicrobial growth promoters contains antibiotic residues, commensurate with additive doses. This situation results in antibiotic introduction to the environment.

Discussion

Detection of antibiotic residues in manure from the three most consumed animals, as well as incomplete removal in typical waste management practices, is an emerging concern given increasingly globalized food markets. This scenario is complex as increasing populations, developing countries, and urbanization demand more food resources and often involve increasingly meat-centered diets. However, for the same reasons, the efficacy of medicine is of grave importance, especially in rapidly developing countries like Brazil, China, and India. Molton et al. [120], among others, argue that infection control, surveillance, and antimicrobial stewardship (i.e., the topic of concern for this review) are the most important tools against the spread of antibiotic resistance. The cost of developing new pharmaceuticals, including antibiotics, hinders the ability to address this crisis through discovery of novel drugs. Currently, 39 antibiotics are in development, with 12 in phase 3 trials. Due to the eventual development of resistance to these compounds, some have advocated for the development and use of antimicrobial peptides [121, 122] and other alternative treatments [123, 124].

Antimicrobial Resistance

Here, we have focused on synthesizing reports on antibiotic residues in animal manure and documenting the removal of antibiotics in conventional agricultural waste treatment processes. Nevertheless, increased understanding of the fate of antibiotic-resistant bacteria and antimicrobial resistance genes in such practices is also valuable. Runoff from conventional agricultural waste management (i.e., poultry litter piles, manure lagoons, etc.) has been widely implicated in the spread of antimicrobial resistance [10, 13, 125, 126]. A number of previous reviews have tackled issues relating to antimicrobial resistance and animal production [127–131]. For the sake of brevity, those issues are not revisited here; however, critical knowledge gaps remain with respect to the impact of treatment processes on inactivation of resistant bacteria and destruction of antimicrobial resistance genes.

The connection between antibiotic residues and antibiotic resistance has been highlighted in popular news outlets in recent years, especially with respect to antibiotic use in animal production [132–134]. For example, many fast food producers/outlets, including Perdue, Panera, McDonald's, Tyson, and Chipotle, have vowed to eliminate or reduce antibiotic use in animal production. Regardless, antimicrobial drug sales and distribution data reported by the FDA demonstrates that antimicrobial use has consistently risen from 2009 to 2014. In fact, antimicrobial use in the USA rose from 12.6 million kg in 2009 to 15.4 million kg in 2014. Key increases were noted among lincosamides (150 % growth from 2009 to 2014), cephalosporins (57 % increase), and aminoglycosides (36 % increase). Ionophores and tetracyclines remain the most consumed classes of antimicrobials with over 4.7 and 6.6 million kg, respectively, used in 2014. The preponderance of antibiotic use in animal production amid widespread levels of antimicrobial resistance indicates the need for increased regulation of antibiotic use in agriculture.

Regulations

The discussion over banning the use of antimicrobials in animal feeding operations is not new. In 1969, the Swann Committee (UK) recommended a ban on subtherapeutic use in animal feed based on concerns about development of antimicrobial resistance in human pathogens [135]. Similar reports were made in the USA throughout the 1980s [24]. In 1997, the World Health Organization (WHO) published a report linking antimicrobial use in food animals to antimicrobial resistance in human pathogens [136]. WHO has released several reports since that time further documenting the spread of antimicrobial resistance and connections to antibiotic use in animal production [25, 28, 65, 137]. The foreword of the 2014 WHO report, *Antimicrobial Resistance: Global Report on Surveillance*, indicates that a post-antibiotic era is a real possibility in the twenty-first century due to the alarming rate of development and spread of antibiotic resistance [25].

Currently, 11 countries have surveillance programs for antimicrobial resistant bacteria (i.e., *Salmonella*, *Campylobacter*, *Escherichia coli*, *Enterococci*, and animal pathogens) in healthy/diseased animals, food, and healthy/diseased humans [25]. Only Denmark monitors all scenarios. Eight countries, namely Denmark, Finland, France, Italy, Japan, Norway, USA, and Sweden, monitor antibiotic-resistant bacteria in food. Currently, widespread programs focused on the preponderance of antibiotic residues, antibiotic-resistant bacteria, and/or antimicrobial resistance genes in animal manure are not available. These data may provide important insight into the fate and transport of antibiotics in agriculturally intense areas. Furthermore, efforts to quantify antibiotic residues in food products may help to ensure food safety and public health.

Seventeen years after Swann's recommendation to ban subtherapeutic use of antimicrobials in animal feed, Sweden became the first country to eliminate antimicrobial use for growth promotion [138]. In other countries, regulations against the use of antimicrobials in animal feed were enacted beginning in the late 1990s. The European Union banned avoparcin, a glycopeptide, in 1997 [28]. In 1998, Denmark banned the use of virginiamycin. Shortly thereafter, a voluntary ban on all antimicrobial growth promoters was enacted in Danish poultry, swine, and cattle [28]. A number of other antimicrobials, including bacitracin (cyclopeptide), spiramycin (macrolide), tylosin (macrolide), and virginiamycin (streptogramin), were banned in the European Union in 1999. Other antimicrobials, including carbadox, avilamycin (orthosomycin), olaquindox (quinoxaline), and salinomycin (ionophores), are banned in select countries. In 2006, the European Union instituted an overall ban on the use of antibiotic growth promoters [139]; Mexico and Taiwan also have national bans on the use of antimicrobial growth promoters [140]. Although subtherapeutic use of antimicrobial growth promoters is prohibited in the European Union [141, 142], the use of these chemicals in other countries is still common. Given the increased globalization of food production and markets, international agreements limiting the use of antimicrobials in animal production may be an important step to reducing the continued development and spread of resistance. This strategy is especially true in countries where human-use antimicrobials are used in animal production.

Conclusions

The twenty-first century is a critical period in the use of antimicrobials. After 60+ years of antibiotic use in human and veterinary medicine, many pathogens have developed resistance mechanisms. Furthermore, multidrug-resistant bacteria have been increasingly identified, generating concerns over superbugs that cannot be treated with conventional antibiotics. In this review, we have focused on describing the presence of antimicrobials in animal manure and the ability of conventional agricultural waste management systems to treat antibiotic residues, thereby, decreasing the selective pressure for development of resistance. Concluding thoughts, along with areas for continued research, are summarized below:

- Fluoroquinolones, sulfonamides, and tetracyclines have been widely identified in poultry litter, swine manure, and cattle manure. These detections include human-use compounds that have been labeled as "critically important" for human medicine. Increased efforts to identify metabolic products of these antibiotics will contribute to a better understanding of the total antimicrobial load in manure streams.
- Fewer detections of antimicrobials from other classes (e.g., beta-lactams, lincosamides, macrolides, and polypeptides, among others) have been reported; however, as pressure increases to reduce the use of fluoroquinolones, sulfonamides, and tetracyclines in animal feeding operations, efforts to identify residues from these other antibiotics are critical. The continued development of novel analytical methods for measurement of large suites of antibiotics in complex matrices, like manure, will facilitate continued efforts in this area.
- For many antibiotics, increased management of compost piles (i.e., turning, aeration, etc.) does not significantly affect antimicrobial degradation. High treatment efficiencies were observed regardless of management intensity. However, observed removals are believed to rely on sorption and thus antibiotics in manure may not be transformed into benign products through composting.
- Anaerobic digestion exhibited relatively high treatment efficiencies for most antimicrobials, with the exception of lincosamides, select sulfonamides, and danofloxacin. To date, most research efforts have focused on the impacts of antimicrobials on biogas production; however, efforts to optimize digesters for antibiotic degradation would facilitate improved removal of antimicrobials from agricultural waste.
- Increased management of lagoons, namely operating under aerobic conditions, resulted in higher antibiotic removal efficiencies. Regardless, the additional operational complexity and costs inhibit widespread adoption of this practice. Antibiotic stability in sediment from aerobic/anaerobic lagoons remains an area of interest, because accumulation of antibiotics in lagoons may increase the rate of single- and multidrug resistance development.
- Available data for antibiotic degradation during composting, anaerobic digestion, and aerobic/anaerobic lagooning did not elucidate any overall trends in treatment. This finding highlights the diversity of antibiotic molecules. Optimization of agricultural waste management for priority antibiotics (identified from concentrations in manure and potential threat to human health) represents an important area for future research. Furthermore, efforts that integrate treatment of antimicrobials and resource recovery may provide the best option for incorporation into full-scale operations.
- While a number of countries contain surveillance programs for antibiotic-resistant bacteria in animals, food, and humans, concerted efforts to measure antibiotic residues in manure are equally important, especially because land application of manure represents a major avenue of antibiotic introduction to environmental systems and water supplies.

Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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