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Antimicrobial Resistance Arising from Food-Animal Productions and Its Mitigation

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1. Introduction

Antibiotics are routinely used in livestock production to treat and prevent diseases, or more often to promote growth of animals at sub-therapeutic doses. However, the huge amount of antibiotics used selects for resistant bacteria, resulting in development of antimicrobial resistance (AMR) mostly in intestinal microbiota of food animals. Therefore, animal manure constitutes the single largest reservoir of AMR. Although most of the AMR is carried by commensal bacteria, AMR genes can be transferred to pathogens of both animals and humans through horizontal gene transfer (HGT). Therefore, animal manure is a source of AMR contamination and poses a potential risk to human health. Because animal manure is the largest reservoir of AMR, management and treatment of animal manure provide an opportunity to contain and destruct AMR arising from food animal production. Several technologies are available for management and disposal of animal manure, including lagoon storage, intensive biological treatments, composting, and land application. These technologies differ in containing and reducing AMR as they create different physiochemical and biological conditions, which affect the survival of bacteria including antimicrobial-resistant bacteria. In this chapter, we discuss the development and occurrence of AMR arising from food animal production, as well as strategies and technologies to mitigate dissemination of AMR off farms to broad environment.

2. Use of antibiotics in food animal industry and development of antimicrobial resistance

In commercial food animal production, large quantities of antimicrobials are used to treat and prevent diseases and to promote animal growth (Prescott, 2008). In the latter case, antimicrobials are added to feed or drinking water at subtherapeutic levels. The Union of Concerned Scientists (UCS) reported that 11,200 metric tons of antimicrobials were used annually in the swine, poultry, and cattle industries for nontherapeutic purposes alone (Mellon *et al.*, 2001). In the United States and other countries as well, up to 50% of the

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antibiotics produced annually are used in food-animal production at therapeutic and subtherapeutic (for prophylaxis and growth promotion) levels (Barton, 2000; Teuber, 2001). Antimicrobials of almost all classes have been used in animal production. Some classes are primarily used for disease treatment or prevention, such as quinolones, lincosamides, and aminoglycosides, while others are used for both growth promotion and disease treatment/prevention, such as penicillins, macrolides, polypeptides, streptogramins, and tetracyclines. A survey by the American Health Institute (AHI, 2001) showed that among the antimicrobials used also in human medicine, tetracyclines leads the usage with an assumption of 3,239 tons per year followed by a combination of macrolides, lincosamides, polypeptides, streptogramins, and cephalosporins with an annual usage of 1,937 tons (Chee-Sanford *et al.*, 2009). Such usage of antimicrobials creates selective pressure for development of AMR.

Most of the bacteria carried by individual animals are within the intestinal tract, reaching a density of 10^{11} bacteria/g fecal content. In mammalian animals, bacteria account for about 50% of the feces. Most of the intestinal bacteria are commensal bacteria belonging to several hundred species (Andremont, 2003). Because antimicrobials were fed to animals for extended periods of time (weeks or months), intestinal bacteria are under persistent selective pressure to develop resistance to the antimicrobials used. As a result, AMR develops primarily in the intestinal tract and feces becomes the single largest reservoir of AMR arising from food animal production (Chee-Sanford *et al.*, 2009; Chen *et al.*, 2008). It is estimated that 180 million dry tons of livestock and poultry manure is generated annually in the US (Roe & Pillai, 2003). That can be translated into 90 dry tons of bacteria, many of which can be resistant to one or more antimicrobials. Although the majority of AMR present in animal manure is carried by commensal bacteria, the resistance genes can be transferred to bacteria pathogenic to animals and/or humans (Brody *et al.*, 2008; Witte, 2000). Figure 1 illustrates the dissemination of AMR to broad environments through vertical gene transfer (VGT) and horizontal gene transfer (HGT).

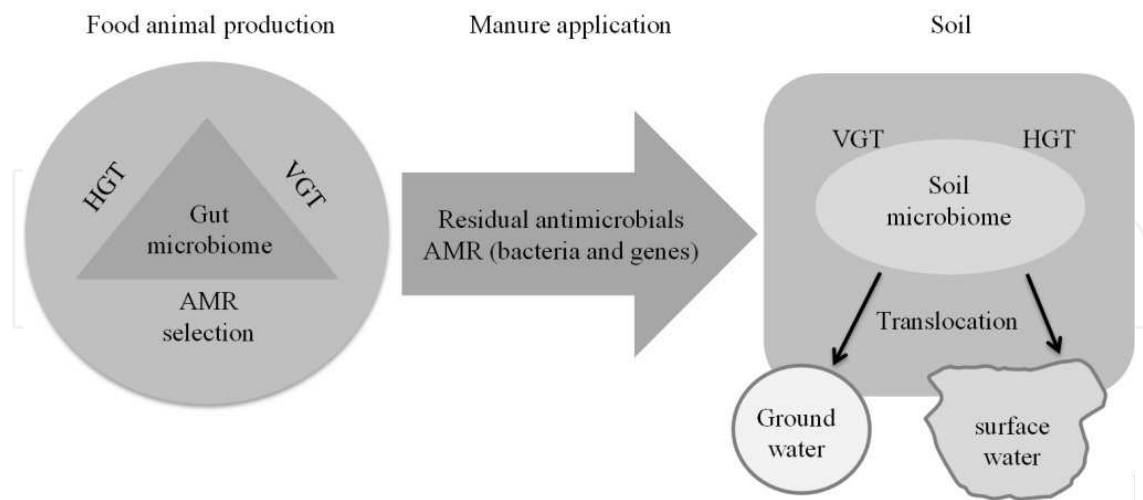


Fig. 1. Conceptualized view showing the possible fates of antimicrobial resistance (AMR) and residual antimicrobials after land application of animal manure (modified based on Chee-Sanford, *et al.*, 2009).

It has been well documented that bacteria resistant to antimicrobials abound in the intestinal tract and manure (Chen *et al.*, 2008). Antibiotic resistance was detected in *E. coli* isolated from

animals soon after antibiotics were introduced to animal husbandry in the 1950s. Tetracycline-resistant *E. coli* was first found in chickens and pigs fed tetracycline in UK (Smith, 1967). With increasing use of various antimicrobials in food animals, AMR has been on the rise (Prescott, 2008). Numerous studies have been reported that examined the relationship between usage of antimicrobials and development of AMR in food animals. Although no precise quantitative relationship has been established, the accumulating body of data indicates a positive correlation between antimicrobial use and AMR development in food animals (Aarestrup *et al.*, 2008; Mathew *et al.*, 2007). As one example, in two farms where tylosin was used for growth promotion or treatment of diseases, 59% and 28%, respectively, of the *E. coli* isolates were resistant to tylosin, while only 2% of the *E. coli* isolated from an organic farm were resistant (Jackson *et al.*, 2004). In another study, as much as 71% of the *Enterococcus faecalis* isolated from swine manure was resistant to tetracycline (Haack & Andrews, 2000). These high levels of prevalence of AMR highlight the magnitude of AMR problem from animal manure.

The severity of AMR is also reflected by the wide occurrence of AMR to many drugs important to both animals and humans. Resistance has been seen to almost all kinds of veterinary antibiotics, including aminoglycoside, sulfadiazine, ampicillin, erythromycin, chloramphenicol, streptomycin, sulphonamide and tetracycline (Agustin *et al.*, 2005; Dubel *et al.*, 1982; Dunlop *et al.*, 1998; Hendriksen *et al.*, 2008; Hendriksen *et al.*, 2008; Lundin *et al.*, 2008). Additionally, AMR is distributed in many bacterial species. For example, resistance to tetracycline has been found in 26 different bacterial genera and in 60 species from swine manure (Stine *et al.*, 2007). Furthermore, with the wider use of antibiotics, multiple drug resistance often develops (Chen *et al.*, 2008; D'Lima *et al.*, 2007; Luangtongkum *et al.*, 2006). A study conducted in the 1980s on swine manure showed low levels of multiple drug resistance (Hanzawa *et al.*, 1984). However, there has been a rapid emergence of multiple drug resistance concomitant with widespread use of antimicrobials in both human medicine and animal husbandry in the past 10 to 15 years (Hawkey & Jones, 2009; Huang *et al.*, 2009).

Multiple drug resistance stems from clustering of multiple AMR genes together, primarily on mobile genetic elements. As a consequence, selection by one antibiotic drug can co-select multiple drug resistance. The selection of tetracycline resistance in beef cattle fed tylosin, a macrolide drug, (Chen *et al.*, 2008) attests this notion. Also, because multiple AMR genes are physically located on the same mobile genetic elements, multiple drug resistance can be readily transferred to other bacteria through HGT. Binh *et al.* investigated the types of transferable plasmids that carry multiple AMR genes in piggery manure (Binh *et al.*, 2008) and found many of the 81 plasmids carry multiple AMR genes. Transposons and integrons were also found to carry multiple AMR genes (Barlow *et al.*, 2008; D'Lima *et al.*, 2007). This finding corroborates the potential risk posed from food animal production where antimicrobials are routinely used.

3. Impact of AMR in livestock manure on the development of AMR in environment

Animal manure from food animals is primarily applied to land either directly or after initial treatment or storage in on-farm animal facilities. Antimicrobial-resistant bacteria are, therefore, introduced to soil and disseminated to both soil and aquatic environments. Some studies have been carried out to determine the survival of manure bacteria after land application. Data from human pathogens, such as *Salmonella* and *Campylobacter*, *Yersinia*

enterocolitica and *Escherichia coli* O157:H7, showed that their survival in water, soil and manure slurry varies dramatically, ranging from one day to longer than one year (Buswell *et al.*, 1998; Guo *et al.*, 2002; Santo Domingo *et al.*, 2000; Tauxe, 1997; Wang & Doyle, 1998). Although the survival of these manure bacteria remains to be determined, likely depending on the physiological and ecological features of the resistant bacteria, the resistance genes can be transferred to indigenous soil bacteria. AMR can then be further disseminated to other environments, such as groundwater and surface water through seepage and run off, respectively. Eventually, resistant bacteria can enter the food chain through crops grown on the affected land (Boehme *et al.*, 2004). There is a great interest in assessing the likelihood of AMR transfer from manure impacted soil to produce, especially ready-to-eat vegetables (Egea *et al.*, 2011; Rizek *et al.*, 2011).

The impact of AMR from animal manure to soil is also reflected at genetic level. Numerous studies have demonstrated the dissemination of AMR genes from manure to soil after land application. Although most of the manure bacteria may not survive long after manure application, the large number of manure bacteria and soil bacteria can create frequent HGT by which AMR genes are transferred to bacteria indigenous to soil (Sengeløv *et al.*, 2003). These researchers also detected increased levels of tetracycline resistance gene (*tet*) with increased application of pig manure slurry to soil. Our own data also demonstrated an increase in *tet* genes and erythromycin resistance genes (*erm*) in soil impacted by the use of antimicrobials in swine production (unpublished data).

Both surface water and groundwater can also be contaminated by AMR arising from food animal production. Groundwater downstream of a swine manure lagoon was found to contain a much higher level of *tet* genes than the groundwater upstream of the swine lagoon (Koike *et al.*, 2007). Seepage from the lagoon was responsible to the increase in *tet* genes in the groundwater. By the same token, AMR can be readily disseminated to groundwater and surface water following manure application to land and rainfall.

Significant portion (25-75%) of the antibiotic drugs consumed by food animals are excreted by the animal (Chee-Sanford *et al.*, 2009). The half-life of these excreted antimicrobials varies depending on the drugs concerned and the abiotic and biotic conditions that drugs come in contact. A few studies have found that some residual antimicrobials can persist in waste treatment systems and in the environment for long periods of time (Zilles *et al.*, 2005). It is not well understood to what extent the antimicrobials from animal manure can contribute to development of AMR in environment. However, some researchers showed that microbial populations in soil and water bodies could be affected by antimicrobial-containing manure (Campagnolo *et al.*, 2002; Kong *et al.*, 2006; Martinez, 2009).

Antimicrobial resistance is becoming an increasing health concern because antimicrobial-resistant commensal bacteria function as a huge resistance reservoir and can spread AMR to the environment and humans. Antimicrobial resistance can be transferred to human by bacteria that can survive in both animals and humans. And greater concerns come from the possibility of AMR transfer from bacteria of animal origin to those in humans. Additionally, the microbiomes present in water, soil, and crops should also be taken into consideration because the dynamics and population structure of their microbial communities can be affected by animal wastes. Although it remains to be determined if environmental AMR reservoir can serve as an intermediate between AMR genes between bacteria of animals and humans (Canton, 2009; Wright, 2010), some *in-vitro* studies did indicate possible exchange of

AMR genes between soil bacteria and bacterial of animal origin via broad host-range plasmids (Heuer & Smalla, 2007; Smalla *et al.*, 2000). Horizontal transfer of AMR genes can occur among bacteria that are not phylogenetically closely related, and such HGT aggravates the concern. In recent years, numerous studies have been reported on the emergence of multiple drug resistance and its linkage to the mobile genetic elements. Although no proof has been found of exchange of genes between environmental bacteria and human intestinal microbiota, the risk remains.

Cases of food contaminated with common pathogenic bacteria (e.g., *Campylobacter jejuni*, *E. coli*, *Salmonella* and *Enterococcus faecium*) carrying resistant genes have been reported (Yan & Gilbert, 2004; Zhao *et al.*, 2003). The possible aftermath of AMR mediated via food chain could have two ramifications. First, the colonization of zoophilic resistant bacteria in human gut could compromise the therapeutic effect of treatment of human infections because most antibiotics either are used both in humans and animals or share the same resistance mechanism. Second, there is the risk of gene exchange between colonized exogenous resistant bacteria and bacteria indigenous to human intestines (Hammerum & Heuer, 2009; Luangtongkum *et al.*, 2009; Walsh & Fanning, 2008). Although it remains to be determined if colonization of pathogens of animal origin in human gut results in transfer of their resistant gene to human intestinal microbiome, the potential warrants careful examination in future studies.

Antimicrobial resistance arising from animals can also spread to humans by contact. Akwar *et al.* (Akwar *et al.*, 2007) indicated that occupational exposure of farmers to animals carrying resistant bacteria may constitute a source of AMR in humans. Ahmad *et al.* (Ahmad *et al.*, 2011) reported that insects, which can move freely over long distance, could acquire multi-drug (mainly tetracycline and erythromycin) resistant enterococci from swine manure and transfer them among animal production farms and from farms to food.

4. Mobile genetic elements and horizontal resistance gene transfer

Horizontal gene transfers (HGT), which is primarily mediated by mobile genetic elements, play an essential role in dissemination of AMR genes. Conjugative plasmids, transposons, integrons, phages, and insertion elements have all been implicated in horizontal resistance gene transfer (Barlow, 2009). Since *tet* genes were found on plasmids in the 1960s, most of the known AMR genes have been found residing on mobile genetic elements (Barlow *et al.*, 2008; Lawley *et al.*, 2000; Nandi *et al.*, 2004; Rice, 1998). By analyzing resistant strains isolated from a conventional swine farm, Stine *et al.* (Stine *et al.*, 2007) found recombination of *tet* genes and multiple different *tet* genes carried in single bacterial isolates. HGT is primarily responsible for the development of multiple drug resistance (Hawkey & Jones, 2009).

It should be noted that HGT can occur between bacteria that belong to different species. As such, AMR genes can be transferred from manure bacteria to indigenous bacteria, which are adapted to the soil environment and amplify the AMR through proliferation (i.e. vertical gene transfer). Additionally, because transformation does not need a live donor, AMR released from dead bacteria can also contribute to HGT through natural transformation. Thus, AMR genes inside of dead bacteria or released from dead bacteria also constitute a portion of the AMR reservoir and should be included in risk assessment of AMR arising from animal production. Additionally, most bacteria in soil or manure are viable but not

culturable. In the case of soil bacteria, as much as 99% may not be cultured (Torsvik *et al.*, 1990). Therefore, most AMR is carried by unculturable bacteria, and AMR present in both culturable and unculturable bacteria should be examined to account for the entire AMR reservoir.

5. Mitigation of AMR arising from animal production

Although antibiotics are widely thought to be the most successful drug in human medicine, risk of AMR to human health emerged from the early clinical practices (Gezon & Cryst, 1948; Rutherford *et al.*, 1946). As elaborated above, extensive use of antimicrobials in livestock production made AMR situation worse. The potential but great risk precipitated the ban, at first partially and now completely, of antimicrobials as growth promoters in Europe (Casewell *et al.*, 2003). The ban led to significant decrease in AMR though not completely eliminated AMR from animal husbandry (Dibner & Richards, 2005). Although there is much debate about the total ban of antimicrobials as growth promoters and AMR prevalence, antimicrobials are still used as growth promoters outside of Europe. Therefore, there is a need to effectively control the dissemination of AMR off animal farms, and management and disposal of animal manure provide a critical control point in containing and reducing AMR arising from animal production systems.

5.1 Lagoons

In most swine and dairy farms, animal manure is typically collected from the barn into a pit and then pumped into an on-farm lagoon. The manure is stored in the waste lagoon for extended period of time (varying from weeks to months depending on seasons) until being applied to crop land. Such lagoons are large to ensure enough capacity to store the manure from large confined animal feeding operations (CAFOs). Quite a few studies have detected high levels of AMR in animal waste lagoons (Fox, 2004; Koike *et al.*, 2007; Macauley *et al.*, 2007; Mezriouia & Baleuxb, 1994). The bottom of animal waste lagoons is rarely lined by any impermeable material, and thus lagoon water, together with some compounds, bacteria, including antimicrobial-resistant ones, can seep into the aquifer underneath and be translocated into groundwater. Thus, this type of treatment, which is thought to be improper in many aspects, can lead to serious pollutions. Several studies have examined the impact of swine lagoons on AMR in groundwater. By comparing AMR profiles of *E. coli* in groundwater underneath swine waste lagoons with those in groundwater of crop farms, Anderson *et al.* showed that swine waste lagoon dramatically increased the prevalence *E. coli* and its multiple drug resistance (Anderson & Sobsey, 2006). Using PCR assays, AMR genes arising from swine waste lagoons were also found to be disseminated to groundwater (Chee-Sanford *et al.*, 2001; Koike *et al.*, 2007). Irrigation of crop land with the lagoon water and subsequent run off can disseminate AMR further to soil and surface water.

A number of studies have examined the potential of livestock waste lagoons to reduce AMR present in the animal manure. By analyzing fecal streptococci using a cultivation-based method, several *tet* gene classes by PCR, and methylation of 23S rRNA by probe hybridization, Jindal *et al.* found that swine waste lagoons had high prevalence of AMR (Jindal *et al.*, 2006). By comparing the abundance of both *tet* and *erm* genes, between swine manure and corresponding waste lagoons, swine waste lagoons were not found to be effective in reducing AMR appreciably (Chen *et al.*, 2008; Chen *et al.*, 2007; Wang *et al.*, 2011;

Yu *et al.*, 2005). Actually, some AMR can increase during lagoon storage (Wang *et al.*, 2011). This is consistent with the previous finding that AMR can increase in lagoons that store sewage (Mezriouia & Baleuxb, 1994).

Currently, there is no regulation on animal waste lagoons, but the potential risk posed by such lagoons is of great concern. Recognizing the potential risk, several research groups have investigated reduction of manure by tertiary treatments that have been used in municipal wastewater treatments. Macauley *et al.* (Macauley *et al.*, 2006) examined the effect of chlorine, ultraviolet light and ozone on swine lagoon bacteria. They found that these treatments at enough concentration or strengths dramatically decreased total bacteria present in swine lagoons, and a combination of chlorine and tetracycline killed all bacteria. Because antimicrobial resistant bacteria have similar ecological and physiological traits than as their susceptible peers, except for their AMR ability, these treatments should equally kill antimicrobial resistant bacteria and thereby reducing AMR present in lagoons. However, additional cost associated with these tertiary treatments probably prevents them from being applied in farms. Indeed, few farms have adopted these treatments.

5.2 Aerobic and anaerobic treatments

Intensive treatments have been implemented on a few animal farms, especially swine farms. These treatments use biological and/or chemical processes to reduce organic strength of the wastewater from CAFOs. The influent and the effluent of an Ekokan upflow biofilter system implemented at a swine farm were found to contain similar levels of both *erm* and *tet* genes (Chen *et al.*, 2010; Chen *et al.*, 2007). Based on a laboratory-scale study, Chenier *et al.* also concluded that aerobic treatments were ineffective in preventing AMR from being disseminated to the environments (Chenier & Juteau, 2009; Chenier & Juteau, 2009). The survival of aerobic and facultative anaerobic resistant bacteria and HGT were suggested as possible reasons for the persistence of AMR during aerobic treatments. It should be noted, however, that aerobic treatments can alter the prevalence of individual resistant bacteria as bacterial species can differ in AMR they carry and in survival during the same aerobic treatments.

Anaerobic digestion of animal manure is increasingly being implemented. The ability of an anaerobic sequencing batch reactor (ASBR) to decrease the AMR present in swine waste was assessed by Angenent *et al.* (Angenent *et al.*, 2008). Although the anaerobic treatment was effective in reducing the tylosin present in the swine manure, both the content and the effluent of the ASBR had substantially higher levels of AMR than that the waste stream fed to this system. In a full-scale anaerobic digester, Chen *et al.* (Chen *et al.*, 2010) also found that multiple classes of *erm* genes and *tet* genes present in swine manure did not reduce substantially during anaerobic digestion even though some classes of *erm* and *tet* genes reduced to some extent. Similar results were obtained by Ma *et al.* (Ma *et al.*, 2011) who used a laboratory-scale digester to digest municipal sludge at both mesophilic and thermophilic temperatures. The similar conditions (mesophilic temperature and anaerobic environments) in anaerobic digester might explain the inability to reduce AMR. However, anaerobic digesters differ in design (complete mixed, plug-flow, etc.) and operation (organic loading rate, hydraulic retention time, temperature, etc.). More studies are warranted to examine persistence of AMR in different anaerobic digesters operated under different conditions.

5.3 Composting

Composting has been used in management and treatment of livestock manure to produce fertilizer with reduced pest and disease incidence (Deluca & Deluca, 1997; Kashmanian & Rynk, 1995; Litterick *et al.*, 2004). Compost has been shown to be effective to kill pathogens and indicator bacteria present in livestock manure (Grewal *et al.*, 2007; Grewal *et al.*, 2006; Jiang *et al.*, 2003; Lemunier *et al.*, 2005; Tiquia, 2005). In surveying abundance of a large number of *tet* genes and *erm* genes, composted manure was found to contain much less AMR genes, up to seven orders of magnitude, than fresh manure or manure treated by other technologies, including lagoon, aerobic treatment, and anaerobic treatments (Chen *et al.*, 2010; Chen *et al.*, 2007; Yu *et al.*, 2005). In a field study using windrows of beef cattle manure, *E. coli* resistant to ampicillin and tetracycline substantially reduced in the initial two weeks (Sharma *et al.*, 2009). Multiple classes of both *tet* and *erm* genes also exhibited significant reduction in abundance, however, the magnitude of the reduction was much smaller, even after 11 weeks. Nevertheless, the *tet* and *erm* genes differed in dynamics during the 18-week composting, with *tet*(A,C) and *erm*(A) increased marginally by week 11 relative to weeks 0 and 5, while *tet*(G), RPP *tet*, *erm*(B), *erm*(C), *erm*(F), *erm*(T), and *erm*(X) decreasing at most time points analyzed. The relatively cold ambient temperature (September to November in Alberta, Canada) prevented the temperature from reaching 55°C inside of the windrows and might have contributed to the relatively small magnitudes of decrease in the *tet* and *erm* genes.

The intensity of composting management can affect the reduction of AMR and degradation of antimicrobials during composting because composting management can dramatically affect the microbial activities within composting windrows. This was exemplified in a pilot study using horse manure (Storteboom *et al.*, 2007) where high-intensity management (including amending with alfalfa and dried leaves, and regularly watering and turning) was found to degrade antimicrobials (i.e. chlortetracycline, tylosin, and monensin) and reduce *tet*(O) gene more rapidly than low-intensity management (no amendment or watering or turning). However, *tet*(W) increased in both the composting treatments after 141 days of treatment. More classes and types of AMR genes need to be examined to determine to what extent intensities of composting management affect AMR persistence during composting treatment. By comparing the dynamics of *tet*(W) and *tet*(O) genes between beef cattle manure containing high levels of AMR and dairy manure containing low level of AMR, this pilot study also showed that manure that contains high levels of AMR requires a longer time to achieve significant reduction of AMR. Increased HGT in the presence of high levels of AMR might be one of the explanations in the observed difference in the AMR dynamics.

The temporal changes in AMR carried by both cultivated and uncultivated bacteria present in swine manure during simulated composting at 55°C (the typical temperature achieved inside of large compost windrows) were compared to a simulated lagoon treatment at room temperature in a recent study (Wang *et al.*, 2011). Over a 48-day period cultivated aerobic heterotrophic tetracycline-resistant bacteria and erythromycin-resistant bacteria decreased by more than 7 and 4 logs, respectively, in the simulated composting treatment, while only 1 to 2 logs for both resistant bacterial groups in the simulated lagoon treatment. In the above study, the dynamics of six classes each of *erm* and *tet* genes, including *erm*(A), *erm*(B), *erm*(C), *erm*(F), *erm*(T), *erm*(X), *tet*(A/C), *tet*(G), *tet*(M), *tet*(O), *tet*(T), and *tet*(W), were also monitored. Except *erm*(B) and *tet*(A/C), all the resistance gene classes analyzed declined

marginally during the first 17 days of the composting treatment, but dramatically thereafter within 31 days of the composting treatment. The observed decreases in AMR were not attributed to decrease in overall bacterial population, which did not decrease in the course of the composting treatment (Wang *et al.*, 2011). It remains to be determined why different AMR genes decreased at varying rates during composting. Two plausible explanations were offered to explain why cultured resistant bacteria decreased to a greater extent than the AMR genes analyzed: first, some resistant bacteria lost culturability or viability during composting, but their genetic materials, including the AMR genes, persisted. Second, not all the AMR genes were accounted for, as not all AMR genes could be detected by any existing real-time PCR assays. However, it is also possible that AMR might be more prevalent among culturable bacteria than among unculturable bacteria. Future studies are needed to test this hypothesis.

Different classes of *tet* or *erm* genes were found to have different persistence during composting treatment. For example, *tet*(W) was reduced slower than *tet*(O) irrespective of intensity of composting treatment of horse manure (Storteboom *et al.*, 2007). Wang *et al.* also showed that *erm*(B) and *tet*(A/C) were more persistent than *erm*(A), *erm*(B), *erm*(C), *erm*(F), *erm*(T), *erm*(X), *tet*(A/C), *tet*(G), *tet*(M), *tet*(O), *tet*(T), or *tet*(W). Difference in host ranges of AMR genes and ecology and physiology of resistant bacterial hosts are major factors contributing to the variations in persistence of AMR genes. However, more detailed investigation is needed to elucidate the mechanism that affecting persistence of different AMR.

The high efficacy of composting in reducing AMR was hypothesized to be attributed to several reasons (Chen *et al.*, 2010; Wang *et al.*, 2011). First, livestock manure is dominated by mesophilic anaerobic bacteria, which can be killed by the thermal aerobic conditions created in compost. Second, compost has relatively low water content and thus water activity. As such, proliferation of bacteria, including antimicrobial-resistant bacteria, can be greatly reduced within compost piles or windrows. Third, horizontal transfer of resistant genes is hindered because of the phylogenetic distance between aerobic thermophiles and the anaerobic mesophiles (Chenier & Juteau, 2009; Chenier & Juteau, 2009). Indeed, Guan *et al.* (Guan *et al.*, 2010; Guan *et al.*, 2007) showed that although resistant mobile plasmids carried by *E. coli* could survive and be transferred during chicken manure composting, higher temperature helped prevent spread of the plasmids in the environment. The relatively low water activity and the solid state within compost matrix should also reduce HGT (Wang *et al.*, 2011). Taken together, composting is an effective technology to reduce AMR and should help mitigate dissemination of AMR arising from animal production. .

6. Concluding remarks

Although the role(s) of AMR to bacteria is a matter of debate (Aminov, 2009; Davies, 2006; Yim *et al.*, 2007; Yim *et al.*, 2006), it is a fact that the widespread of AMR poses a risk to human health and livestock manure from CAFOs is a large source of AMR. Reduced use of antimicrobials in animal production is an option in decreasing development of AMR, but the perceived negative effects on productivity make it not likely, at least in the near future, to ban Antibiotic growth promoter (AGP) in many countries. Therefore, manure treatment and management should be considered as a critical control point to reduce dissemination of AMR off animal farms. Lagoon storage is probably the poorest in terms of reducing AMR

present in animal manure, while compost is the most effective. Aerobic biological treatments do not effectively reduce total AMR, but shift the resistant bacterial populations. Anaerobic treatment operated at thermophilic temperature, but not at mesophilic temperature, is another option to mitigate AMR present in animal manure. However, because the current conclusions are based on studies on either a few select cultured bacteria (e.g. *E. coli*, *Enterococcus*, *Staphylococcus* and *Streptococcus*) or select AMR genes (mostly *tet* genes and *erm* genes), future studies are warranted to include more AMR so that the conclusions will be applicable to AMR in general.

Understanding the AMR genes and the corresponding resistant bacteria is essential to assess the risk posed to health of both humans and animals. DNA-based techniques (e.g. real-time PCR) enable measurement of AMR carried in both cultured and uncultured bacteria; however, these techniques typically do not allow identification of AMR-carrying bacteria. To complement this limitation cultivation-based studies are needed. Additionally, metagenomics empowered by massively parallel DNA sequencing provide an alternative in identifying the genes and bacteria in resistant populations.

No treatment technology is practical that can completely eliminate AMR present in animal manure. The surviving AMR will eventually find its way to the environments. In a recent study, we analyzed the cultured bacteria resistant to tetracyclines or erythromycin that were recovered from swine manure before and after composting treatment in a comparative manner. We observed considerable shifts in resistant bacterial populations, AMR genes (i.e. *tet* and *erm* genes), carriage of multiple AMR per isolate, and plasmids (unpublished data). This type of studies is needed to identify the surviving resistant bacteria and their ecology upon land application of composted manure.

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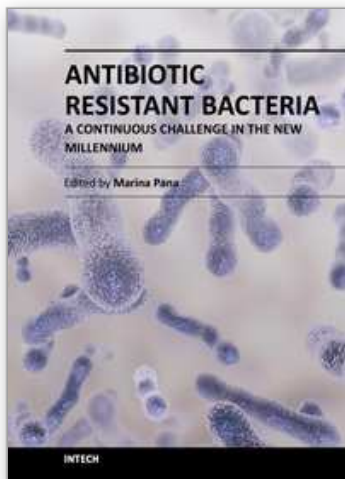
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Antibiotic-resistant bacterial strains remain a major global threat, despite the prevention, diagnosis and antibiotherapy, which have improved considerably. In this thematic issue, the scientists present their results of accomplished studies, in order to provide an updated overview of scientific information and also, to exchange views on new strategies for interventions in antibiotic-resistant bacterial strains cases and outbreaks. As a consequence, the recently developed techniques in this field will contribute to a considerable progress in medical research.

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