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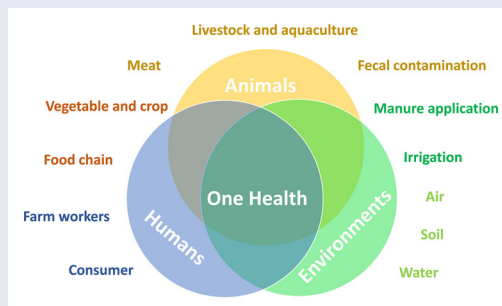
Antibiotic resistome in the livestock and aquaculture industries: Status and solutions

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ABSTRACT

Since the introduction of antibiotics into clinical practices in the 1940s, antibiotics have become an integral part of animal production to meet the increasing human demand for animal-derived foods. As a result, industrial-scale animal production has emerged as a hotspot for the evolution and dissemination of antibiotic resistance genes (ARGs), thereby potentially contributing to a looming public health crisis. The knowledge of ARGs in livestock systems has been greatly expanded with the recent development of rapid molecular tools. However, comprehensive reviews on ARGs in the animal industry and possible mitigation solutions are still lacking from a One Health perspective. Here we provide this review focusing on human health risks associated with the antimicrobial (antibiotic and metal) usages, ARGs in livestock animals and aquaculture systems in a One Health perspective to untangle the complexities of ARGs across animals, environments and humans. Specifically, this review covers (1) antimicrobials usages in the animal industry, (2) ARGs in animals affected by selective agents, (3) animal-to-human direct/indirect ARG transmission pathways, and (4) mitigation approaches. We highlighted the burden of using antimicrobials in animals for public and environmental health, and also the urgent needs for mitigating the spread of antibiotic resistance from the livestock and aquaculture industries.



KEYWORDS Antibiotic; antibiotic resistance; antibiotic resistance genes

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1. Introduction

Antibiotics are specific types of antimicrobial substances that either kill or inhibit the growth of bacteria. As the most important types of antibacterial agents, antibiotics are widely used in the treatment and prevention of bacterial infections. The discovery of penicillin in 1928 and the introduction to the medical industry in the 1940s marked the beginning of the antibiotic era (Fleming, 2001). Antibiotics have significantly transformed modern medical procedures, saved countless lives from infectious diseases and extended the average human lifespan (McDermott & Rogers, 1982). Most antibiotics are naturally occurring substances initially developed for treating infections in humans, but the use was quickly extended to disease treatment and prevention in food animals (Van Boeckel et al., 2015). Apart from therapeutic use of antibiotics, the animal feed has commonly been supplemented with low concentrations of antibiotics as growth promoters in many countries to improve the feed efficiency, weight gain and animal health (Cuong et al., 2018). High doses of metals, particularly copper (Cu) and zinc (Zn), were also found to enhance the growth of animals (Poole, 2017). Due to this feature, high concentrations of metals are also frequently supplemented into the feed for animal growth promotion and disease control.

Antibiotic resistance (AMR, also known as antimicrobial resistance) is currently recognized as one of the biggest threats to public health (Laxminarayan et al., 2013). According to the World Health Organization (WHO), we are at the brink of entering a post-antibiotic era (Alanis, 2005; Laxminarayan et al., 2013), in which the arrival of multidrug-resistant pathogens will decrease the effectiveness of antibiotics for treating bacterial infections. Antibiotic resistance genes (ARGs) are the culprit and now widely recognized as emerging environmental pollutants (Amy, 2006; Sanderson et al., 2016). Similar to most antibiotics, ARGs are ancient and naturally occurring substances. However, they are currently accumulating in human-impacted environments (Berendonk et al., 2015; Gao et al., 2018; McCann et al., 2019; Qiao et al., 2018; Zhu et al., 2017), which could be largely attributed to the intensive anthropogenic usage of antibiotics in the last few decades (Knapp et al., 2010). According to a recent modeling study, antibiotic resistance could continue to grow across countries in the coming years (Oliveira Hashiguchi et al., 2019). Meanwhile, it should be noted that metals are also contributing as co-selective agents driving the enrichment of genetic elements harboring both metal resistance genes and ARGs in the microbiomes of animals and agroecosystems (Baker-Austin et al., 2006; Poole, 2017; Zhao et al., 2019).

The human demand for animal-derived food sources is rising globally due to the increasing global population and economic growth (Tilman

et al., 2011). Combined with the increased urbanization and globalization, these developments have driven a massive growth of the industrial-scale animal food production during the past decades. For instance, the annual global growth in the fish consumption has been twice as high as the population growth over the past decades, and the global fish production peaked at about 171 million tonnes in 2016, according to the Food and Agriculture Organization (FAO, 2018). China, as the world's largest farmed food fish producer and exporter, produced more than 69 million tonnes of aquatic products in 2017 accounting for two-thirds of the cultured seafood production globally (Cao et al., 2015; USDA Foreign Agricultural Service, 2017). To meet the high market-driven demands, the antibiotic use has become an integral part of the modern industrial-scale animal production to the extent that the vast majority of antibiotics are now being used for animals rather than humans (Tang et al., 2017). The United States Food and Drug Administration (FDA) estimated that almost 80 percent of the total antibiotics consumed in the United States was used for farm animals, and ~83% of feedlots administered antibiotics for prophylaxis or growth promotion (McEwen & Fedorka-Cray, 2002). Hence, more public attention to antibiotic usage in animals and its potential risks are required to respond to antibiotic resistance issue under One Health framework (Hernando-Amado et al., 2019; Tiedje et al., 2019).

Production animal farms are complex ecosystems, where bacteria originating from production animals or humans (farm workers) and the farming environments are constantly mixed due to the manure application on farmlands and the feeding of animals with harvested forage from the manure-fertilized fields. Moreover, ARGs from farmed animals receiving antibiotics or metals can also be transmitted to humans directly via farm animals by human contact or indirectly via animal-environment-human pathways (Figure 1) (Alban et al., 2017; Ashbolt et al., 2013; Hao et al., 2014). Various anthropogenic activities play key roles for the environmental transmission of ARGs including the manure application, farm wastewater discharge, etc. These above-mentioned factors make our livestock systems not only a rich reservoir but also one of a significant ARG hotspot constituting risks to both environmental and public health worldwide (Brandt et al., 2015; Larsson et al., 2018).

The knowledge of antimicrobial (antibiotic and metal) usage for food animals, ARG pollution in livestock systems, its intricate environmental transmission and potential mitigation approaches have been dramatically expanded with the recent development of rapid molecular tools such as high-throughput qPCR chips and metagenomic sequencing. Previous publications have reviewed the global antibiotic use in animals (Cuong et al., 2018; Lulijwa et al., 2020; Van Boeckel et al., 2015), reported the antibiotic

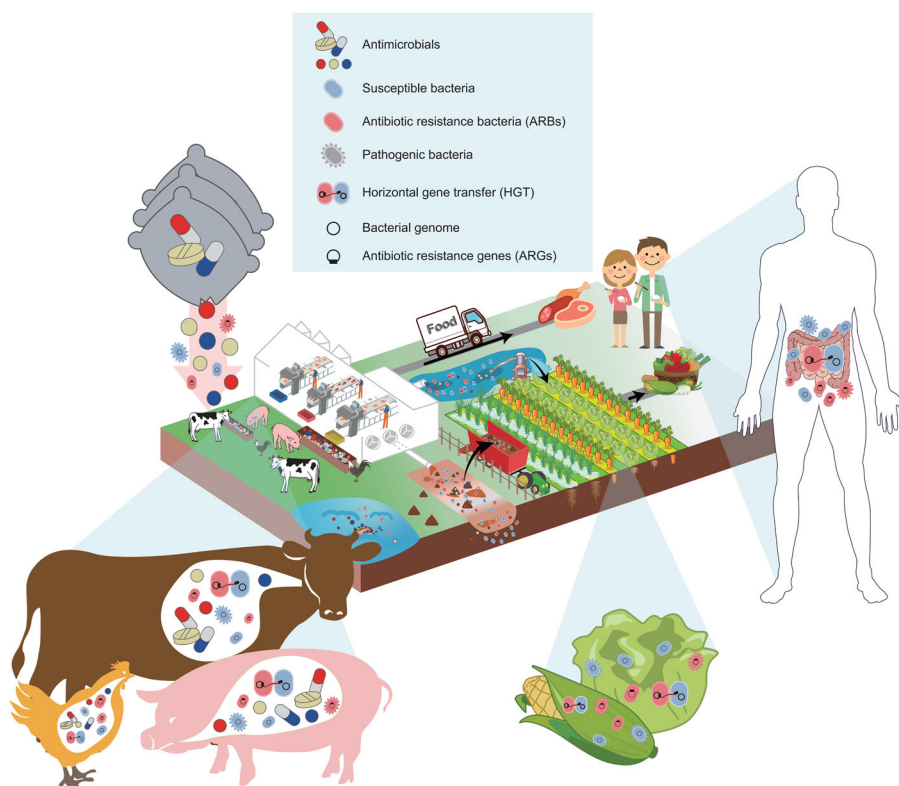


Figure 1. Animal-to-human ARGs/ARBs transmission pathways in the One Health framework. Arrows reflect the potential transmission pathways of ARGs/ARBs original from the animal industry.

resistance in the animal industry at various scales (Anjum et al., 2019; Argudin, 2017; DANMAP, 2013; Klase et al., 2019; Looft et al., 2012; Moore, 2019; Van Boeckel et al., 2019; Zhao et al., 2018; Zhu et al., 2013) and monitored their dissemination into environments (Cerqueira et al., 2019; Han et al., 2018; Heuer et al., 2011; Klase et al., 2019; Larsson et al., 2018; Lhermie et al., 2019; Xie et al., 2018). However, comprehensive reviews covering the updated status of ARGs or antibiotic-resistant bacteria (ARBs) in the livestock and aquaculture industries as linked to potential human health and their potential mitigation approaches are still lacking. Based on a One Health perspective, this review covers (1) the antimicrobial (antibiotic and metal) use in the animal industry, (2) the ARGs/ARBs in animals affected by selective agents, (3) both direct and indirect animal-to-human ARG transmission pathways, and (4) mitigation approaches for reducing human health risks.

2. Usage of antibiotics and metals for food animals

Industrial-scale animal food production relies heavily on the use of antibiotics (Van Boeckel et al., 2015). Antibiotics are not only utilized in animals

for therapeutic use to treat the infectious diseases and prevent postsurgery infections but also can be added in low concentrations to the animal feed as growth promoters or as prophylaxis to increase the farm productivity and the profitability (Hao et al., 2014; Turnidge, 2004). Enteric diseases such as weaning diarrhea can usually be prevented by feeding a sub-therapeutic dosage of antibiotics (Hao et al., 2014; Turnidge, 2004). Low dose usage of tetracyclines has for instance been common practised around the globe and is still being practised in many countries to reduce the morbidity and help the animal weight gains (Hao et al., 2014). Such non-therapeutic antibiotic consumption is economically beneficial but commonly administered via feed to the entire group of animals in livestock systems or aquaculture operations.

2.1. Historical perspectives of antibiotic use in animals

The consumption of antibiotics in animals has changed over time, which has been driven by the market but also by changes in local regulations. Sweden was the first pioneer of banning antibiotic growth promoter (AGP). During 1980–1986, the total usage of antibiotics in Sweden for animals was increased from 41 to 50.5 tons per year (Stein, 2002). This number dramatically dropped to 25.8 in 1986, when Sweden first banned the AGP in the animal feed (Stein, 2002). However, this first ban led to a slight increase of the total antibiotic use in the following years (increased to 30 tons per year during 1988–1994) since more occurrence of the postweaning diarrhea. By 1996, the total consumption of antibiotics in animals in Sweden was reduced to 20 tons by introducing more metals into animal diets for disease prevention and growth promotion (Stein, 2002). However, the global consumption of antibiotics in animals has been dramatically increasing with the human demand for the animal food, with the lack of regulation or intervention in mainly developing countries, and the consumption will probably continue to grow due to the upcoming shifting production practices from extensive farming systems to large-scale industrial systems in middle-income countries (Van Boeckel et al., 2015). Van Boeckel et al. estimated that 67% increase of the global consumption of antibiotics in animals (from 63,151 tons of antibiotics to 105,596 tons) would happen in the period from 2010 to 2030 (Van Boeckel et al., 2015).

2.2. Antibiotic use by countries

Antibiotic consumptions in the animal industry are country-specific and largely impacted by the local regulations. Since the banning of AGPs in Sweden (1986), Finland (1996) and Denmark (1998) (Levy, 2014),

restrictions on feed-grade antibiotics have been implemented in several countries to combat the spread of antibiotic resistance. AGPs were banned in the United Kingdom and other European Union (EU) countries in 2006, resulting in subsequent lower antibiotic consumption especially for tetracycline and colistin (Cogliani et al., 2011). Up to date, an updated regulation on the veterinary medication in the EU proposed the limit of antibiotic use in the prophylaxis and metaphylaxis was confirmed by the EU Council and European Parliament in 2018 (Council of the European Union, 2018). In 2017, subtherapeutic antibiotics in feed and water to improve animal growth and feed efficiency became illegal in the United State via legislative change enacted by the FDA (U.S. Food & Drug Administration, 2018).

Despite the regulatory efforts (notably in the EU and more recently in the United States), antibiotics are still widely administered to animals resulting in an increase in ARGs in animals and agroecosystem microbiomes (Van Boeckel et al., 2019). In other parts of the world (notably many low- or middle-income countries), antibiotic usage remains inadequately regulated causing significant risks for the environmental development and transfer of AMR due to the release of antibiotics and ARGs to soils and water bodies affected by animal farming operations (Argudín et al., 2017; Moore, 2019; Van Boeckel et al., 2019). Based on a One Health framework, a Global Action Plan on AMR was launched in 2015 by the World Organization for Animal Health (OIE), over 100 countries have now established their National Action Plans against AMR in animals (Góchez et al., 2019).

China started to use antibiotics as feed additives in the mid-1970s, but the consumption for food-animal has been rapidly increasing in recent decades. Nearly half of the annual antibiotic production in China went into the animal industry with a total amount of 105,000 tons (Collignon & Voss, 2015). In 2017, the Chinese government published “The National Action Plan on controlling antibiotic-resistant bacteria on animal origins (2016–2020)” integrated with the One Health concept for public health and food safety. As a result, colistin was first banned according to the Exit Plan, which aims to achieve the full drop of antibiotics as growth promoters in China (Xiao & Li, 2016).

Antibiotic usage per animal biomass produced varies between countries. In South Korea, relatively high usage of antibiotics for livestock production was reported in 2007 (0.91 kg per ton of livestock) comparing to the use in Japan (0.35 kg/ton), USA (0.14 kg/ton), New Zealand (0.04 kg/ton), Denmark (0.04 kg/ton), and Sweden (0.03 kg/ton) (Won-Sup, 2007). However, different metrics have been used for the measurement of antibiotic consumption in animals and there is thus a need for the

standardization of the dose definition to better inform on the effectiveness of antimicrobial use regulations in specific countries for tackling the global AMR crisis (Cuong et al., 2018). To this end, the World Organization for Animal Health (OIE) has built a global database on antibiotic agents intended for the use in animals, and published the methodology for the data collection in 2019 for the global development of monitoring and surveillance in line with OIE international standards (Góchez et al., 2019).

2.3. Antibiotic use by animal species

The consumptions of antibiotics are not uniform among animal species. A recent review in 2018 summarized the antibiotic use for the animal production in low- and middle-income countries and highlighted the dosage of antibiotics used was the highest in chickens (138 doses/1000 animal-days), followed by swine (40) and dairy cattle (10) (Van Boeckel et al., 2015). In contrast, over 80% of antibiotic consumption in animals went to pigs and cattle in Denmark, whereas only 1% went to chickens (DANMAP, 2013). Concerning aquaculture, substantial evidence for overuse and misuse of antibiotics has been reported in 2017, especially in low- and middle-income countries with weak regulations on antibiotic use (Watts, 2017). Salmon aquaculture provides a compelling case, in Chile, the world's second-largest salmon provider after Norway, the intensive use of antibiotics in the salmon aquaculture has become one of the highest per ton of harvested fish in the world (Miranda et al., 2018). A total of 382.5 tonnes of antibiotics were used in Chilean salmon farms in 2016, which resulted in approximately 0.53 kg of antibiotics used per tonne of salmon, while only 0.0008 kg of antibiotics were used in Norway (Cabello et al., 2013; Miranda et al., 2018). The consumption of antibiotics in the Chilean salmon industry has increased by 56% from 2005 to 2015, as compared to a 23% increase in salmon production during the same period (Miranda et al., 2018). However, the Organization for Economic Cooperation and Development (OECD) predicted that the consumption of antibiotics in all livestock systems would continue to increase and dramatically rise by 67% by 2030, with China and the United States contributing about 40% to the total growth (Van Boeckel et al., 2015).

2.4. Antibiotic use by antibiotic classes

Several classes of antibiotics have been or are used for food animals including both narrow- (e.g., macrolides and penicillin G) and broad-spectrum antibiotics (e.g., most aminoglycosides, sulfonamides and tetracyclines). The WHO has declared a list of “critically important antibiotics” used to

combat life-threatening resistant infections in humans. Critical antibiotics include several aminoglycosides, tetracyclines, quinolones, macrolides and carbapenems, some of which have also been approved for the use in veterinary medicines or as growth promoters (e.g., amikacin from the aminoglycoside class, macrolide tylosin from the macrolide class and nalidixic acid from the quinolone class) (Collignon et al., 2009). Using these human-associated antibiotics for animals can potentially lift the possibility of occurrence of resistant human pathogens, therefore raises high concerns. A recent report revealed that more than 20 different antibiotics had been applied in Chinese aquaculture farms, including the chloramphenicol, ciprofloxacin and erythromycin, which are also for the clinic use for humans (Liu et al., 2017). According to the US Department of Agriculture survey of antibiotic treatment practices, the monensin, lasalocid, neomycin and virginiamycin were commonly used as growth promoters in the US feedlots (McEwen & Fedorka-Cray, 2002). Meanwhile, chlortetracycline was administered on 51.9% of feedlots in the United States, chlortetracycline-sulfamethazine combination on 16.8%, oxytetracyclines on 19.3% and a macrolide type tylosin on 20.3% (McEwen & Fedorka-Cray, 2002). Olaquinox was also frequently found as feed additives for Chinese swine (concentrations up to 1159 µg per kg of dry feed), while the florfenicol in the feed was found up to 16.5 µg/kg (Zhao et al., 2018). The most frequently used antibiotics in Chilean salmonid farms were florfenicol and oxytetracycline for controlling piscirickettsiosis caused by Gram-negative pathogen *Piscirickettsiosis salmonis* (Lozano, 2018). In Bangladesh, at least seven different antibiotics including sulfadiazine, erythromycin and trimethoprim have been administered with the feed (about 70%) or applied directly (23%) to the fish and shellfish aquaculture for the disease treatment, as well as growth promoters (Ali et al., 2016). It should be noted that in most developing countries, there is little monitoring and intervention regarding the use of antibiotics in livestock systems, as a consequence, using the types of antibiotics that are not authorized for animals may occur.

2.5. Metal use in food animals

Apart from antibiotics, metals (e.g., copper, zinc, or arsenic) have been or are also supplemented in the animal feed for non-therapeutic purposes. Since the restriction on antibiotics as growth promoters in Europe, there has been increasing attention on using metals as feed supplements with concentrations exceeding the nutritional requirement of animals. Primarily Cu and Zn can be used as alternatives to in-feed antibiotics for the beneficial effect of disease prevention and growth promotion (Debski, 2016).

Both Cu and Zn are essential trace elements for animals and have been found in animal feeds in a wide range of concentrations for various animal species (Debski, 2016; Yazdankhah et al., 2014; Zhao et al., 2018; Zhu et al., 2013). However, the use of Cu and Zn for animals depends on the regulations and differs among animal species and their body weights. For instance, in feed samples collected from Chinese pig farms in 2016–2017, Cu and Zn were reported at concentrations of 2.3–1137.1 mg/kg and 37.4–598.3 mg/kg respectively (Zhang et al., 2012; Zhao et al., 2018). Meanwhile, Cu and Zn at concentrations of 2.73–114.7 mg/kg and 11.1–346.1 mg/kg were reported in feeds for Chinese cattle, while Cu of 2.9–98.1 mg/kg and Zn of 52.6–151.0 mg/kg for Chinese chickens (Zhang et al., 2012). In the United States, a wide range of metals in various animal feeds in Texas during 2012–2015 was reported, with the concentration of Cu averaging at 169.9, 37.8, 132.7, and 29.5 mg/kg for swine, cattle, chicken, and fish respectively (Dai et al., 2016). In a European perspective, Cu (copper sulfate) was or has been usually added in diets at levels between 150 and 175 mg/kg while Zn (zinc oxide) between 2000 and 4000 mg/kg (Stein, 2002). In 2017, the EU Commission decided that the use of medicinal Zn will be phased out in the pig production by 2022 due to the potential side effects (European Commission, 2017) and restrictions for Cu addition to animal feeds became effective in 2019 (European Commission, 2018).

2.6. The potential risks associated with the antibiotic and metal use in animals

The use of antibiotics in animals appears to promote the occurrence of resistant bacteria in animal farming systems. In-feed antibiotics and possible also metals, can select for ARGs and mobile genetic elements (MGEs) in the animal gut microbiomes (Ghosh & LaPara, 2007; Xiao et al., 2016; Yazdankhah et al., 2014; Zhao et al., 2018). However, there is debate whether the low concentration of AGPs presents a significant risk of the increasing resistance in human pathogens (Ashbolt et al., 2013; Turnidge, 2004). The proponents for AGP argue the selection of such low dosage antibiotics on ARGs might not even occur, or the effect is minimal, and more importantly, the advantages associated with AGPs outweigh the risks (Turnidge, 2004). The opponenets believe that considerable fractions of the antibiotics fed to animals are excreted as bioactive molecules in animal feces along with selected ARGs, ARBs, and MGEs (Berendonk et al., 2015). Consequently, the antibiotic residues end up in ecosystems connected with livestock production operations. Once in the environment, there is a risk that antibiotic residues may release on-site selection pressure on local

bacteria and induce the environmental development and transfer of ARGs to human pathogens (Ashbolt et al., 2013; Chee-Sanford et al., 2009). Recent studies suggest that the dispersal of ARGs/ARBs from hotspots including animal farms is the more significant contributor to the environmental dissemination of ARGs than the in situ environmental selection (Brandt et al., 2015; Karkman et al., 2019; Zhu et al., 2017). Nevertheless, there is yet no consensus on the risk associated with low, sub-inhibitory concentrations of antibiotics regarding their abilities to select antibiotic resistance and increase rates of bacterial evolvability e.g., via increased emergence of multidrug-resistant mutants (Gillings & Stokes, 2012; Karkman et al., 2019).

A recent study systematically reviewed the previous publications for the current evidence of the AMR transfer to humans from food animals (Muloi et al., 2018). Their report concluded that 74% of the studies provided evidence of animal-human AMR transmission with 18% indicating transmission from animals to humans, whereas no direction of transmission could be determined for the remaining 56% of the studies (Muloi et al., 2018). Regardless, it remains a challenge to estimate the human health risks posed by antibiotics used in animals as it depends on the antibiotic in question and several other factors (Subbiah et al., 2016). Better understanding of the human health risks associated with the antimicrobial use in animals is needed for improving the risk mitigation in animal production. In the remaining part of this paper we review the most important human health risk processes in more depth.

3. Antibiotic resistance in animals affected by selecting agents

3.1. The global increase of ARGs in animals

Production animal farms are considered the hotspots for the AMR development and dissemination, with the animal microbiome comprising a rich reservoir of ARGs (Argudín et al., 2017). A wide array of ARGs present in diverse bacterial hosts has been found in animal guts and manure, and ARG prevalence can clearly be linked to the use of antibiotics or other selecting agents in animals (Looft et al., 2012; Van Boeckel et al., 2019; Zhao et al., 2018). Tetracycline and sulfonamide resistance genes have been widely investigated and most frequently reported in animal farms from various countries previously using the traditional quantitative polymerase chain reaction (qPCR) (Ghosh & LaPara, 2007; Olonitola et al., 2015). However, with the recent development of DNA-based comprehensive tools including high-capacity (also known as high-throughput) qPCR and metagenomics, the rapid development and dissemination of antibiotic resistome were revealed for a significantly broader spectrum of ARGs (Munk et al.,

2018; Su et al., 2017; Xiao et al., 2016). Hundreds of ARGs conferring resistance to various antibiotic classes (aminoglycoside, chloramphenicol, fluoroquinolones, streptomycin, penicillin, sulfonamide, tetracycline, vancomycin, etc.) have been detected in the animal production systems in studies published in the 2000s (Looft et al., 2012; Wang, Zhang, et al., 2017; Xiao et al., 2016). The antibiotic resistomes in pigs from China and Europe were identified to comprise several shared ARGs conferring resistance to bacitracin, cephalosporin, macrolide, streptogramin B and tetracycline (Xiao et al., 2016). Plasmid-mediated resistance gene *mcr-1*, conferring resistance to colistin, a last-line drug for some multidrug-resistance infections, has been considered to be of animal origin and has been widely investigated to understand the complexities of AMR across animals, humans and other environments (Liu et al., 2016; Wang et al., 2017).

The ARG levels in farmed animals and livestock systems are globally increasing and reflect the history of antibiotic use (Moore, 2019). Low- and middle-income countries (LMICs) are of great concern due to their unregulated antibiotics use (Van Boeckel et al., 2019). For instance, a recent metagenomic analysis of the gut microbiome of 287 pigs from China, France and Denmark showed that the continuously low doses of antibiotic use in China had distinguished the ARG profile in Chinese pig guts by harboring higher abundances of ARGs than that in French and Danish pigs (over 10-fold changes) (Xiao et al., 2016). However, a comprehensive data collection at a global scale remains a challenge, due to poor documentation of ARGs, lack of access to national and regional survey data, and lack of standardized methodology. A recently published study managed to collect 901 published data on ARGs from low- and middle-income countries in Asia, Africa, and Americas during 2000 to 2018 to map the global trends of ARGs in farmed animals (Van Boeckel et al., 2019). Over 50% increase of resistance was identified in LMICs with 0.13 to 0.34 in pigs, 0.15 to 0.41 in chickens, and 0.12 to 0.23 in cattle (Jia et al., 2017). ARGs in animals displays country-specific patterns with geographic differences. For instance, China and India were the largest hotspots of ARGs with local animals harboring higher abundance among all developing countries (Argudín et al., 2017). Brazil and Kenya were proposed as emerging hotspots (Argudín et al., 2017). Even though antibiotic use was low by international standards in Nordic countries, a wide variety of ARGs and MGEs were detected in Finnish dairy and swine farms (Muurinen et al., 2017).

Global ARG patterns also depend on animal species. A recent shotgun metagenomics study analyzed fecal samples from 181 pig and 178 poultry farms from nine European countries for ARG characterization and found higher ARG loads in pigs whereas poultry resistomes were more diverse (Munk et al., 2018). Furthermore, not only animal species but also breeds

can affect ARGs in animal guts due to the influence of host genetics on gut microbiota, which was confirmed by a reference gene catalogue study of the pig gut microbiome and qPCR analysis targeting ARGs in pig guts from different breeds (Xiao et al., 2016; Zhang et al., 2019).

Intensive food animal farming in China has arguably made China's animal farms one of the biggest hotspots of ARGs worldwide (Van Boeckel et al., 2019). China as the world's largest food animal producer is not only feeding over half of the world's pigs but also a prolific producer of chicken, sheep, goat, fish, etc., as a consequence, China harbors higher diversity and abundance of ARGs in their farmed animals than other countries (Van Boeckel et al., 2019; Xiao et al., 2016). High-throughput qPCR developed for ARG detection was first employed to profile the ARGs in Chinese pig farms in a study published in 2013 (Zhu et al., 2013). With a total of 295 primers for the rapid quantification of ARGs and few MGEs, it detected 149 unique ARGs against all major classes of antibiotics (aminoglycoside, beta-lactam, chloramphenicol, macrolide-lincosamide-streptogramin B, multidrug, sulfonamide, tetracycline and vancomycin) with the absolute abundance up to 1.3×10^{10} copies per gram of pig manure and the enrichment up to 28,000-fold compared to antibiotic-free farms, revealing the high levels of ARGs in Chinese swine farms induced by in-feed antibiotics and heavy metals (Zhao et al., 2018; Zhu et al., 2013). Common occurring ARGs in Chinese pigs included aminoglycosides RGs (such as *aacA*, *aacC*, *aadA*, *aadE* and *strB*), macrolide-lincosamide-streptogramin B (MLS_B) RGs (*ermFT*, *lnuB*, *mefA* and *vatE*), tetracyclines RGs (*tetL*, *tetPA*, *tetPB*, *tetQ*, *tetX*, *tetG*, *tetM*), sulfonamide RGs (*sul1*, *sul2*), and colistin RGs (*mcr-1*) (Liu et al., 2016; Zhao et al., 2018; Zhu et al., 2013). The diverse and abundant ARGs in Chinese pigs also include the genes confer resistance to antibiotic critically important for human use, e.g., macrolides RGs (*mphA* and *erm*) (Zhu et al., 2013). According to a recent study in 2019 monitoring 10 typical ARGs (3 *tet*, 2 *erm*, 2 *sul*, *bla_{CTX-M}*, *bla_{TEM}*, and *mcr-1*) in Chinese pig farms, a typical industrial pig farm with 10,000 pigs could release about $4.0 \pm 1.3 \times 10^{17}$ copies of ARGs per day, with the emission rates depending on the pig types (growing and fattening pigs > gestation sows > nursery pigs > lactation sows) (Zhang et al., 2019). Comprehensive resistome analyses on large-scale Chinese poultry farms also found ARGs prevalent in poultry fecal samples including the recently described critical ARGs *mcr-1* and *optrA* (an oxazolidinone and phenicol RG), highlighting the ARG issue in Chinese animal farms (Wang et al., 2017).

3.2. The growing concern of ARGs in aquaculture

Aquaculture is vulnerable to the introduction of ARGs/ARBs. With high diversity and intensity of bacteria, aquaculture has become a hotspot for

ARGs/ARBs (Cabello et al., 2016). It is unique animal husbandry comparing to terrestrial animal farms and is highly complicated, dynamic, interconnected, and easily influenced by environmental and anthropogenic factors. Driven by the market, aquaculture requires intensive culture systems and proportionately a higher volume of antibiotics than that applied in terrestrial animal farms. As a consequence, a large amount (nearly 80%) of antimicrobials (antibiotics and metals) used in aquaculture end up in uneaten medicated feeds; unabsorbed antibiotics and secretions of culture organisms enter aquatic environments closely related to aquaculture facilities (e.g., water, sediments and other water-borne species), therefore provides a favorable environment for the development and enrichment of persistent aquatic ARGs (Brunton et al., 2019; Henriksson et al., 2018; Seiler & Berendonk, 2012). Moreover, a comparative study on aquaculture and non-aquaculture sites in 2014 suggested the selection of antibiotics could happen even in areas far from the original site using selective agents (Shah et al., 2014). A wide range of ARGs have been identified in aquaculture, including ARGs encoding tetracycline resistance (*tetA*, *tetB*, *tetC*, *tetD*, *tetE* and *tetG*), quinolone resistance (*qnrA*, *qnrB*, *qnrS1* and *aac(6′)-Ib-cr*), macrolide resistance (*mphA* and *erm*), aminoglycoside resistance (*aph*, *aad* and *aac(6′)-Ib*), chloramphenicol resistance (*catA2*, *cml* and *floR*), β -lactams resistance (*bla_{CTX-M}* and *bla_{TEM}*), sulfonamide resistance (*sul1*, *sul2* and *sul3*) and etc (Miranda et al., 2018; Su, Liu, et al., 2017). High prevalence (81%) of resistant strains was found in a Chilean salmon farm, and the majority of strains were positive to genes resistant to tetracycline (e.g., *tetA* and *tetG*) (Shah et al., 2014).

Integrated aquaculture has been regarded as an efficient system combined with agriculture and livestock, to increase productivity and maintain ecological balance; on the other hand, integrated aquaculture seems to facilitate the dissemination of ARGs and resistant bacteria in and around aquaculture farms (Watts, 2017). In an open cage system, farm fish feces are another sources of ARGs spreading from fish farms to surrounding environments. In the study by Muzasari et al. in 2016, 20 out of 28 ARGs (e.g., aminoglycoside resistant genes *aadA1*, *aadA2*, tetracycline resistant gene *tetM*, and trimethoprim *drfA1*) and few transposons (e.g., *tnpA01-tnpA07*) were detected in both fish intestinal samples and farm sediments (Muziasari et al., 2016). Furthermore, a large number of fish pathogens carrying ARGs are zoonotic pathogens which can not only cause infections to the animal hosts but also to humans by direct contact with contaminated aquaculture facilities and indirectly by foodborne infections, such as *Listeria monocytogenes* (Skowron et al., 2018), *Aeromonas* (Syrova et al., 2018) and *Clostridium spp* (Hedberg et al., 2018).

4. Animal-to-human antibiotic resistance transmission pathways

The animal husbandry system and animal microbiome, serve as a reservoir of ARBs, ARGs and MGEs, have significant clinical relevance to public health due to the potential antibiotic resistance transmission from animals to humans (Figure 1). For example, pathogens such as methicillin resistant *Staphylococcus aureus* (MRSA, a specific human pathogen that is resistant to commonly used antibiotics) are not only a special concern for animals but also for humans since it has the ability to cause a range of different illnesses in humans from minor skin infections to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome, bacteremia, and sepsis (Collignon et al., 2009).

4.1. Direct exposure

Farmworkers, veterinarians, slaughterhouse workers and animal food handlers who are under the direct exposure with animals and their biological substances, are at high risk of being colonized with antibiotic-resistant bacteria from animals and animal farms, which subsequently may provide an opportunity for the entry of ARGs/ARBs in local communities and health care settings (Marshall & Levy, 2011; van den Bogaard et al., 2002). Reynaga et al. reported that the high prevalence (81/140, 57.9%) of pig farmworkers had been colonized or infected with livestock-associated clonal lineage ST398 of MRSA (Reynaga et al., 2016). It has been found that *E. coli* strains isolated from turkey and broiler farmers from the Netherlands were nearly resistant to all tested antibiotics (van den Bogaard et al., 2002). These livestock-associated ARGs/ARBs could further transmit from farmers to their families and the local community by human-to-human transmissions, resulting in increasing cause of colonization and infections in people with/without livestock contact (Larsen, 2015).

4.2. Food chain and food trade

Food chains are far-reaching and complicated pathways for the AMR transmission pathways from animals to humans. Numerous studies have demonstrated that the high abundance of ARGs/ARBs in animal foods, including pork, chicken, beef and fish (de Boer et al., 2009; Founou et al., 2016; Heuer et al., 2009). For instance, in a study on MRSA in meat from the retail trade, the contamination rate was found to be the highest in turkey (35%), chicken (16%), veal (15%), pork (10%) and beef (10%), and lower in final products (3%) comparing to the meat at processing (4.2%) (de Boer et al., 2009). Another example is the *mcr-1* gene, which spread from animals to humans via food chains as evidenced by the higher detection rate

in animal samples (21%) and raw meat (15%) as compared to its low prevalence in clinical samples (1%) in China (Liu et al., 2016).

The globalization of food trade in animals and animal products plays an important role in the global spread of ARGs from animals to humans. The AMR crisis in developing countries is therefore a global problem since many developing countries are the main global exporters of food animals or meat products, therefore facilitate ARGs/ARBs to transport globally (Zhu et al., 2017). For instance, Brazil as the world's largest chicken and beef exporter contributes to the global spread of *mcr-1* gene (Fernandes et al., 2016). Approximately 70% of the poultry production in Thailand is exported, and the ARBs/ARGs with Thailand origin can be further transferred all over the world via the global food trade (Boonyasiri et al., 2014).

4.3. Animal-to-human transmission via environmental compartments

The environment plays an essential role in the global transport of ARGs from food animals to humans (Graham et al., 2019; Huijbers et al., 2015). Mainly two processes are involved in this environmental dissemination from animal farms: the selection by antibiotic residues and the dispersal of ARGs/ARBs. Antibiotics and resistant bacteria have been detected in the farm dust, air current inside the feeding operations, as well as in the groundwater under the influence of animal husbandry and feedlot areas in general (Hamscher et al., 2003; McEachran et al., 2015; Sapkota et al., 2007; Seiler & Berendonk, 2012; Zhu et al., 2013). Exposure scenarios with contaminations in the farm environments also provide pathways of the ARGs transmission to humans (Marshall & Levy, 2011). It has been shown that proximity to animal feeding operations or areas with fecal contaminations can increase the risk of MRSA (Casey et al., 2013). However, transmissions of animal sourced ARGs are not occur only in the animal farming environments. To unfold the complexities of AMR across animals, environments and humans, we here propose the animal-to-human AMR transmission pathways by focusing on the environmental transmission pathways in a One Health perspective (Figure 1).

4.3.1. Via manured farmland soils

Land application of the animal manure is a major environmental dissemination pathway for antibiotic resistomes in agro-ecosystems, which potentially contributes to ARGs/ARBs in human communities through pathways associated with the exposure and external release (Heuer et al., 2011). Manure, as a fertilizer with rich nutrients and organic matters, is commonly used worldwide in agriculture for improving the soil properties and enhancing the crop growth. However, manure has become an important

reservoir of antibiotic compounds, ARBs, ARGs, and MGEs (Han et al., 2018; Karkman et al., 2019; Zhu et al., 2013). Increasing evidence shows that the manure application can remarkably increase ARGs and the selection of ARB populations in soils (Han et al., 2018; Heuer et al., 2011; Muurinen et al., 2017; Xie et al., 2018). Soil usually harbors diverse intrinsic ARGs owing to the complex microbial community and diverse antibiotic-producing resident microbes (Riesenfeld et al., 2004; Su et al., 2014; Zhu et al., 2019). Therefore, the enhanced level of ARGs after manure application is not only attributed to the introduction of novel ARGs from the fecal contamination, but also to the elevated abundance of existing resident ARGs selected by applied manure (Nikolina, 2014). Moreover, ARGs can be more established in the soil microbial community and persistent under regular manure applications (Heuer & Smalla, 2007).

ARGs in manure-impacted soils can potentially enter the food chain, and the consumption of organically produced vegetables and fruits from manured-soils is likely another route for the ARGs dissemination to humans (Berger et al., 2010; Zhang et al., 2019). Soil microbes have a profound impact on the development of bacterial communities of below- and above-ground parts of plants, shown by a sizeable functional overlap between leaf- and root-derived bacteria (Bai et al., 2015). A strong association exists between endophytic and rhizosphere bacteria, and many facultative endophytic bacteria can also survive in the rhizosphere (van der Lelie et al., 2009). Besides, the rhizosphere is known as a hotspot for the horizontal gene transfer (Elsas et al., 2003). A previous studies demonstrated that soil bacteria could survive in the interior of the root and become root endophytes (Bulgarelli et al., 2012). As a consequence, the bacterial community of plants growing on manure-amended soil can be influenced by soil bacterial communities. Manure has been shown to stimulate the horizontal transfer of ARGs in soils (Heuer et al., 2011; Zhu et al., 2013) and from soils to vegetable microbiome (Zhang et al., 2019). Previous studies have detected various ARGs in vegetables and fruits (including root endophytes, leaf endophytes and phyllosphere) after growing in the manure-amended soil (Berger et al., 2010; Marti et al., 2013; Ruimy et al., 2010; Wang et al., 2015; Zhu et al., 2017). A total of 134 ARGs were detected in the conventionally and organically produced lettuce using high-throughput quantitative PCR (HT-qPCR), and the phyllosphere of organic produce had a higher abundance of ARGs than the phyllosphere of conventionally produced lettuce (Zhu et al., 2017). Vegetables and fruits from manured soils, especially those are eaten raw, could therefore represent an important vehicle for the antibiotic resistance transmission into humans (Berger et al., 2010). In this situation, a better understanding of ARGs in the soil-plant system under manure fertilization, is crucial in helping control ARG spread.

The influence of manure application on soil ARGs also depends on agricultural practices. A Finish study revealed the only temporary increase in ARGs after manure fertilization under the restricted antibiotic use policy in Finland, implying that the negative influence of manure application on ARG contamination in soils might be mitigated under the restricted policy on antibiotic usage in animals (Muurinen et al., 2017). However, it could also be attributed to the limited manure application rates and volumes (Muurinen et al., 2017).

4.3.2. Via aquatic environments

Aquatic environments are considered an ideal setting for the acquisition and dissemination of ARGs (Marti et al., 2014). Genetic exchange and recombination can frequently occur in aquatic environments in order to shape the evolution of aquatic microbial community (Watts, 2017). The genetic plasticity of aquatic microbes enables the quick movement of ARGs in aquatic bacterial population and community to combat the potential pressure from antibiotic pollutants and/or to enhance the competitiveness. Moreover, once microbes acquired ARGs (or MGEs carrying the ARGs), the acquired ARGs tend to be more persistent in aquatic environments compared to terrestrial environments, held even with absence of the selection pressure (Manu, 2010). Aquaculture is a gateway to development and globalization of AMR in aquatic environments (Cabello et al., 2016). Large amounts of selective agents and fecal contaminations containing ARGs/ARBs from aquaculture enter our water bodies, stimulating the bacterial mutation, recombination and horizontal gene transfer, thereby increasing the level of ARGs in natural aquatic environments and risk of spreading ARGs from aquaculture to humans (Watts, 2017).

The dissemination pattern of ARGs from aquaculture varied among different aquaculture systems. In open systems, a high proportion (70%–80%) of used antibiotics end up as residues, persist and select for ARBs in aquatic ecosystems, together with ARGs excreted by fishes and other seafood animals leaving a legacy effect on aquatic microbial communities (Watts, 2017). In closed systems, farming systems are usually separated from the general environments. In near zero-discharge recirculating aquaculture closed systems (RAS), limited exchange happens between aquaculture water systems and the surrounding environments, but antibiotics accumulate in the systems promoting the ARBs on the RAS biofilter (Li, Zhang, et al., 2017). In integrated aquaculture systems, fish farming is usually connected with livestock farming or/and crops for better resource utilization. However, they also represent a high degree of ARG pollution and gene transfer in the soil-water-plant systems, providing an elevated risk of resistome transmissions to humans (Klase et al., 2019). In other regular

closed systems, antibiotics and ARGs can be reduced by waste treatments and discharge controls before reaching the environments. The wastewater containing antibiotic residues and ARGs usually either flow into aquatic environments after the wastewater treatment or being treated to produce aquaculture sludge as organic fertilizers. In some cases, the treated aquaculture effluents are used in irrigation for crops or urban parks, together with the land application of aquaculture sludge as organic fertilizer, therefore provides a pathway for ARGs from animals to soils and crops, which potentially impact downstream occupational workers, crop consumers and urban residents (Chen et al., 2016; Fahrenfeld et al., 2013; Wang et al., 2014). However, it should be noted that the great majority of the developing countries has no or minimal waste treatments in aquaculture systems or lacks regulations, thus untreated aquaculture wastewater may directly flow into the surrounding water bodies, potentially promoting the risk of spreading ARGs from aquaculture to humans via aquatic environments (U.S. Centers for Disease Control & Prevention, 2018).

4.4. The horizontal gene transfer promotes the transmission

The horizontal transfer of ARGs potentially promotes the flow of ARGs from animals to humans (Soucy et al., 2015; von Wintersdorff et al., 2016). As many environmental microbes especially aquatic bacteria from aquaculture share a large number of MGEs, e.g., plasmids, integrative conjugative elements, integrons and transposons, significant genetic exchange and recombination can occur for various purposes (Elsas et al., 2003; Marti et al., 2014; von Wintersdorff et al., 2016). Furthermore, the strong association between antibiotic resistome in soil environments and human clinical pathogens has been demonstrated showing that MGE-mediated HGT assembles tandem arrays of distinct ARGs into integrons, transposons and plasmids and then makes them mobile (Forsberg et al., 2012). These mobile ARGs and microbes can disseminate into surrounding environments and migrate into our food chains (Zhu et al., 2017; Zhu et al., 2018). ARGs transfer to human pathogens by the transduction, bacterial conjugation and with the bacterial uptake of “free” DNA can also happen (Zhu et al., 2017; Zhu et al., 2018). Therefore the Class 1 integrons, which are often physically linked to multiple resistant determinants for antibiotics, are proposed to be the most critical and widespread agents of ARGs and a useful proxy for ARGs with anthropogenic origins including the animal-food producing industry (Gaze et al., 2011; Gillings, 2018; Gillings et al., 2015). Conjugation is the transfer of DNA from a contributing cell to a recipient cell via bacterial pili or adhesins, and it has also been recognized to have a great influence on the dissemination of ARGs among the bacterial

population, compared to transformation and transduction (von Wintersdorff et al., 2016). In livestock systems especially the aquaculture, ARGs are commonly associated with conjugative plasmids, integrons or transposons (Watts, 2017). Once ARG exchange events have occurred in environmental bacteria, the ARGs can be further disseminated among local bacterial populations including human pathogens and then spread globally through the international transport of food products as well as global travelers (Cabello et al., 2016; Zhu et al., 2017; Zhu et al., 2018). Several studies have revealed that livestock environments might have contributed to the emergence of the plasmid-encoded *qnrA* gene conferring low-level resistance to quinolones, and the *qnrA* gene were associated with waterborne species *Shewanella* spp, which are widely disseminated in marine and freshwater environments (Poirel et al., 2005; Yan et al., 2017). Yang et al. investigated the resistome in sediment samples from a marine fish farm using high-throughput sequencing and observed that several contigs containing resistance genes (e.g., *strAB*, *qnrA* and *tetL*) and transposons or plasmids, were highly identical (>90%) to those from human pathogens (Yang et al., 2013). There is another interesting example that plasmid-borne *mcr* genes may have primarily originated from the aquatic systems as a result of aquaculture activities that transport *mcr* genes from aquatic bacteria to terrestrial bacteria (Cabello et al., 2017). One evidence is that amino acid sequences of *mcr-3* and *mcr-4* were significantly identical to phosphoethanolamine transferases found in fish pathogens *Aeromonas Salmonicida* (84%) (Yin et al., 2017) and *Shewanella frigidimarina* (99%) (Carattoli et al., 2017). Furthermore, a recent study showed that aquaculture is a significant reservoir of *mcr-1* gene, observed that geographical zones with low aquaculture activity have significantly lower odds of *mcr-1* positivity (odds ratio = 0.5, 95% confidence interval: 0.3–0.7) than those with high aquaculture activity (Shen et al., 2018). So far, *mcr* genes have been globally identified in animal farms, animal food products, vegetables, imported reptiles, environments (sewage and soils), and humans (Liu et al., 2016; Shen et al., 2018; Wang et al., 2017, 2018). Further public health risk arose from this gene family has emerged with subsequent global dissemination (Wang et al., 2018). This scenario is worrying, as colistin remains as a last-line antibiotic against the global emergence of MDR Gram-negative bacteria in clinical settings.

5. Mitigation approaches

5.1. Control of selective agents

Reducing and optimizing antibiotic consumption in the livestock industry is the most direct method to mitigate the animal-originated ARG dissemination. It has been shown that the restriction of antibiotic use and

intervention actions have a remarkable effect on the retard of AMR in livestock systems and its dissemination (Levy, 2014; Pruden et al., 2013; Stein, 2002; Tang et al., 2017; Xiao et al., 2016). In Denmark, halting the nontherapeutic use of antibiotics in animal industry leads to a significant decrease of ARGs/ARBs in animals and meat products within 1–2 years (Levy, 2014). This is because that the susceptible bacteria could be able to out-compete the resistant bacteria if the selective pressure from antibiotics is reduced (Andersson & Hughes, 2010). Meanwhile, improving animal health by providing better management of the livestock, better hygiene in farming settings, and using a preventive vaccine to avoid animal diseases can help reduce the consumption of antibiotics. Other additives such as phytogetic products, probiotics, and prebiotic as alternatives of antibiotics could be useful in reducing the antibiotic consumption and development of resistance in animals (Gaggia et al., 2010; Windisch et al., 2008). Antimicrobial peptides are also proposed as an effective alternative of antibiotics due to their efficacious antibiotic effects and weak resistance induction ability (Li et al., 2018). Furthermore, it is possible to reduce the antibiotics and ARGs release into the environments by prudent care with the livestock waste. When the selection driven by antibiotics lowered, the likelihood for the ARG transfer and proliferation could be reduced in different environmental niches.

5.2. Manure management

Composting can eliminate pathogens in the fresh manure, reduce the odor emission, and produce organic matters for crop production. The hyperthermophilic composting (with the temperature reaches up to 90 °C during the fermentation process) has been shown to remove ARGs and MGEs more efficiently than the conventional composting (89% and 49%, respectively) (Liao et al., 2018). This might due to the high temperature achieved during the hyperthermophilic phase, composting can effectively remove antibiotics such as tetracyclines, sulfonamides, fluoroquinolone, macrolides, ionophores, and penicillins up to 70%, thereby decreasing the potential selection for ARGs along the pathways (Pruden et al., 2013; Selvam & Wong, 2017). However, the response of ARGs varies during the composting as a result of the complex microbial ecological processes (Su et al., 2015). Aerobic composting has been shown to universally reduce ARGs in chicken and pig manures, but nearly half of the ARGs were enriched by more than 10-folds in the bovine manure (Qian et al., 2018). The ARG abundance in composted cattle and poultry manures can be decreased by 9.6% and 31.7% as compared to the corresponding raw manure (Xie et al., 2016), but certain ARGs, like *sul* genes, *tetL* and *tetX*, persisted or markedly increased after

the thermophilic composting (Qian et al., 2016; Wang et al., 2015; Xie et al., 2016; Zhang et al., 2015). In contrast, the lagoon storage was not sufficient compared to composting (Wang et al., 2012). One possible explanation could be that some persistent ARGs locate on MGEs are hard to be removed and HGT could promote their enrichment in parallel (Su et al., 2015).

Additives, such as biochar, zeolites, superabsorbent polymers, and coal gasification slags, can be applied in the composting or soils to improve the removal efficiency of ARGs (Cui et al., 2016; Lu et al., 2018; Peng et al., 2018). In particular, biochar can elevate the thermophilic composting temperature, accelerate the organic matter degradation, immobilize heavy metals, and reduce nutrient loss (Cui et al., 2016; Li, Duan, et al., 2017). More recently, it has been demonstrated that converting composted swine manures into biochar in an industrial-scale production oven can significantly remove total ARGs and MGEs, and that applying manure-derived biochar to soil did not result in the enrichment of ARGs/MGEs (Cui et al., 2016; Zhou et al., 2019). In a recent study, the vermicomposting of the swine manure using the housefly larvae significantly attenuated 94 out of 158 ARGs (by 85%) (Wang et al., 2017). Several studies have proved that biochar also has the capability of inhibiting the ARB and ARG proliferation in soils and vegetables (Duan et al., 2017; Yang et al., 2018; Ye et al., 2016), due to its porous structure, high surface-area-to-volume ratio and microbial hospitality. For instance, Duan et al. showed that the amendment of biochar reduced the accumulation of oxytetracycline, the abundance of ARGs and human pathogenic bacteria in soils and lettuces (Duan et al., 2017). Combining of the biochar amendment and polyvalent phage could effectively achieve the inactivation of antibiotic-resistant pathogenic bacteria, and reduce the ARG dissipation in soil-lettuce systems (Ye et al., 2018). This combined treatment has further been shown to have a positive effect on the restoration of the microbial community in the soils (Ye et al., 2018).

Anaerobic digestion as a commonly used livestock waste treatment process has been shown to economically and efficiently remove ARGs and ARBs (Couch et al., 2019; Czekalski et al., 2014). Certain types of ARGs like *tet* and *erm* genes could be reduced by log copies during the anaerobic digestion (Couch et al., 2019; Zhang et al., 2017). However, the efficiency of anaerobic digestion to reduce ARGs in animal waste is largely dependent on various factors such as substrate types, operating temperatures and microbial hosts of ARGs, therefore causing inconsistent results of ARGs during the anaerobic digestion in previous publications (Zhang et al., 2015, 2017; Zhang et al., 2019). Similar to composting, additives (e.g., biochar and wheat straw) can further improve the ARG removal during the anaerobic digestion by inhibiting residual antibiotics and metals (Couch et al.,

2019). Although anaerobic digestion and composting are key methods for efficiently eliminating ARGs, it should be noted that they did not completely remove ARGs and certain ARGs can still survive during treatment processes, even with an elevation of the resistance prevalence (Zhang et al., 2015). Therefore, further operations or discharge control might need to be considered to retard the potential ARG runoff.

5.3. Wastewater treatment

Treating wastewater from the livestock industry can significantly reduce the richness of ARGs/MGEs and efficiently control the dissemination of ARGs/ARB from animal farming especially the aquaculture (An et al., 2018; Gros et al., 2019; He et al., 2020). A vast majority of studies have reported a decreased level of ARGs in effluents after the wastewater treatment reactors (An et al., 2018; Bouki et al., 2013; Szczepanowski et al., 2009). One study focusing on integrons and mobile ARGs has shown the wastewater treatments significantly reduced the abundance of integrons and resistance genes in integron cassettes (An et al., 2018). Due to the high efficiency of the MGE removal, some researchers believe even there is still a fairly high concentration of ARGs in the effluent, the spread of ARGs from the wastewater treatment plants is not severe as we thought and only limited core ARGs was further disseminated into environments (Munck et al., 2015). Although wastewater treatment is shown to be a promising technology for removing ARGs, developing countries are often lack of sufficient wastewater treatment or management for animal industries, thus the wastewater may directly be discharged to surrounding waterbodies (Gros et al., 2019). Moreover, the removal of ARGs can largely depending on the treatment technology. For example, in general farms, livestock wastewater is treated in a bioreactor through a constructed wetland without a full scale wastewater treatment. In contrast, ARGs are more efficiently removed in full scale wastewater treatment plants; and the inflow volume, the type of biological treatments and the hydraulic residence time are all linked to the treatment efficiency, therefore influencing on the bacteria and ARG removal (Novo & Manaia, 2010).

5.4. Management and intervention policy

Regulatory requirements for animal farms and their waste control is essential for managing AMR problems under One Health (Lhermie et al., 2016). It is important to engage policy-makers, researchers, farmworker, animal farming stakeholders, and the general public in all countries with this AMR global problem. Standardized methods and global sharing databases for

antibiotics and ARGs/ARB in animal industries could facilitate the solution exploration and provide a better platform for decision-makers regarding the ARG threat (Góchez et al., 2019). Improving existing regulations which cause less economic losses in the animal industry might accelerate the implementation of antibiotic restrictions. To prevent the dissemination of ARGs from the animal husbandry to downstream environments and humans, surveillance and risk assessments on ARGs/ARB in animal waste and wastewater are needed before further applications. Economically and environmentally sustainable approaches are needed to be developed, improved and integrated further (Wernli et al., 2017). National and international cooperations are needed to tackle antibiotic resistance, including reinforcing recognition of the threat of antibiotic resistance and seeking more advanced technologies or effective management options to control antibiotic resistance (Wernli et al., 2017). Education and knowledge dissemination on ARGs are needed for all stakeholders and general public to improve awareness in order to change the current situation.

6. Conclusions and perspectives

By now there is clear evidence that the use of antimicrobials (antibiotics and metals) in animals leads to the selection for antibiotic resistance in animal-associated microbiomes. It is also evident that livestock systems contribute to the global dissemination of antimicrobials, food-borne pathogens and ARGs/ARBs through various transmission routes, some of which include different environmental compartments. In principle, there are no geographic boundaries when aiming to combat the global spread of ARGs from livestock systems. However, the complete high-resolution picture for ARG dissemination from animals to humans is still unclear. And specifically the human health significance of indirect transmission pathways from animals to humans via environmental compartments is still unknown. Better quantification of the relative contribution of each transmission route may help to estimate the quantitative transmission risks, and rank the human health risks posed by different transmission pathways. In the coming years, there is a significant need for continuous researches and surveillance of veterinary antibiotic consumption and resistance in both small- and large-scale livestock systems. Importantly, studying AMR from a holistic “One Health” perspective that covers the entire spectrum including humans, animals and various environmental compartments such as water, soil and air is imperative. There is also an urgent need for standardized methods and global databases to improve our understanding of the contributions of animal sectors to the increased prevalence of ARGs within human pathogenic strains at a global scale. This knowledge will be essential and provide the

foundational data for establishing better guidelines from authorities and solutions for the mitigation of the public health antibiotic resistance crisis. In compliance with the One Health approach and associated policy frameworks, we argue that a global effort is required in order to reduce the use of antimicrobials in food animals in ways that do not affect animal farm productivity.

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