



Current status and future perspective of antimicrobial-resistant bacteria and resistance genes in animal-breeding environments

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ABSTRACT. The emergence and spread of antimicrobial-resistant bacteria (ARB) and antimicrobial resistance genes (ARGs) are a global public health concern. ARB are transmitted directly or indirectly from animals to humans. The importance of environmental transmission of ARB and ARGs has recently been demonstrated, given the relationships between compost, livestock wastewater, insects, and wildlife. In addition, companion animals and their surrounding environments (veterinary hospitals and homes with companion animals) should be considered owing to their close relationship with humans. This review discusses the current status and future perspectives of ARB and ARGs in animal-breeding environments.

KEYWORDS: animal, antimicrobial resistance, environment, One Health

The emergence and spread of antimicrobial-resistant bacteria (ARB) and antimicrobial resistance (AMR) genes (ARGs) are considered a global public health concern [80], given the potential transfer of ARB and ARGs to humans and the reduced effectiveness of antimicrobial therapy in humans. According to a review on AMR [57], neglecting the growing AMR could result in an estimated 10 million deaths per year worldwide by 2050, owing to the ineffectiveness of antimicrobial therapy. Antimicrobials are used to treat both animals and humans [25]. According to a survey conducted by the World Organization for Animal Health (OIE), the global consumption of veterinary antimicrobials was 104,779 tons in 2015, with the highest consumption noted in Asia and Oceania, followed by American, European, and African countries. Previous studies have shown that the selection of ARB and ARGs is related to antimicrobial usage [2, 5, 7]. Data from various countries have revealed a high rate of ARB derived from swine, which are among livestock species that necessitate the highest use of antimicrobials [14, 52].

Surveillance of antimicrobials in humans and animals has been undertaken in Japan [50, 54]. Although livestock farming is not prevalent in Japan, several antimicrobials are employed for livestock, with 646 tons used in 2018 [71]. Reportedly, the number of antimicrobials used in livestock in Japan is higher than that in humans [71]. According to the Japanese Veterinary Antimicrobial Resistance Monitoring reports, the antimicrobial susceptibilities of indicator bacteria, such as *Escherichia coli* and enterococci, and foodborne bacteria, such as *Salmonella* and *Campylobacter*, derived from cattle, pigs, and broilers, are monitored [54]. The transmission routes of ARB and ARGs from livestock via meat have been a research focus. Several domestic and international surveys have examined ARB and ARGs in commercial meat products [30, 40, 55, 70]. In 2018, the Ministry of Agriculture, Forestry and Fisheries initiated the monitoring of ARB derived from companion animals [54], which are in close contact with humans and receive not only veterinary antimicrobials but also human antimicrobial therapy [49]. Therefore, ARB can be transmitted directly or indirectly from animals to humans. In addition, breeding environments are considered a potential source of ARB contamination in humans and animals.

The importance of environmental transmission of ARB and ARG has recently been demonstrated (as determined by the relationship between compost, livestock wastewater, insects, and wildlife; Fig. 1). Regarding the public health threat of ARB/ARGs in the environment, the World Health Organization (WHO) published a global action plan in 2015 based on the “One Health” approach [80]. The WHO integrated the global surveillance of extended-spectrum β -lactamase (ESBL)-producing *E. coli* [79]. The Codex Alimentarius Commission has suggested that livestock environments should also be considered during sampling for AMR surveillance

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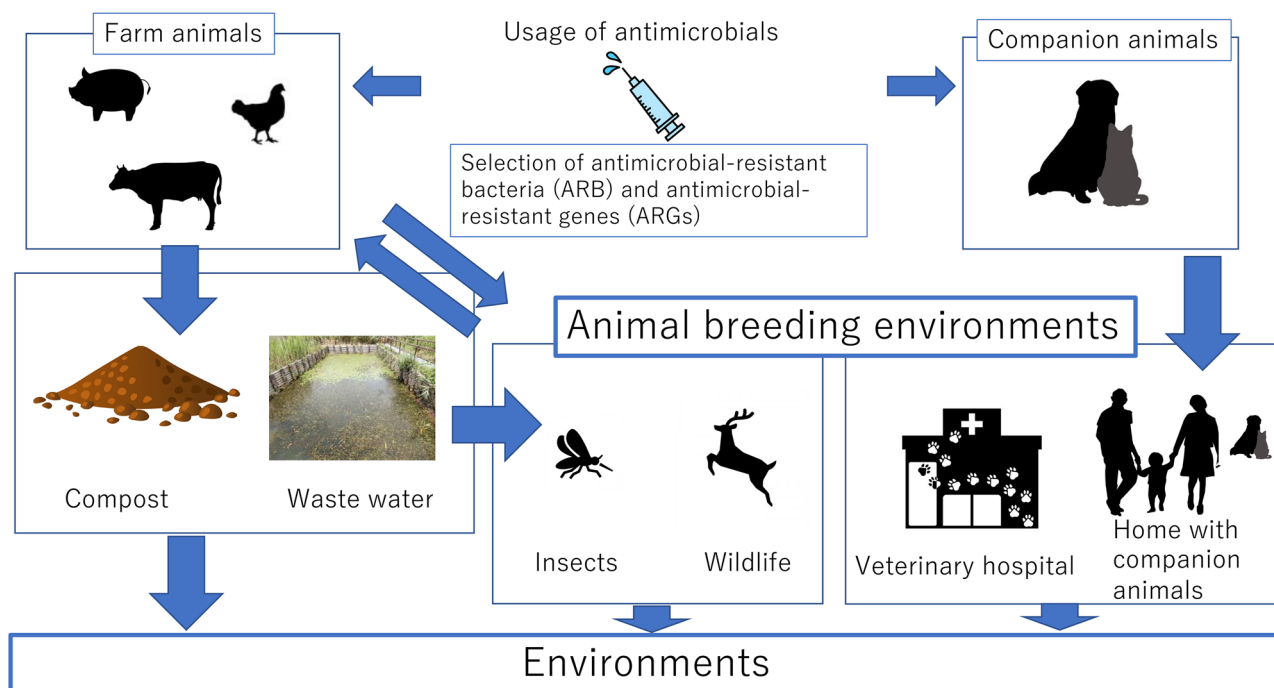


Fig. 1. Potential transmission routes of antimicrobial-resistant bacteria and antimicrobial resistance genes, focusing on breeding environments.

[12]. Furthermore, companion animals and their surrounding environments (veterinary hospitals and homes with companion animals; Fig. 1) should be examined, owing to their close contact with humans.

In this context, the WHO has demonstrated the importance of the “One Health” approach. This review presents the current status and future perspectives of ARB and ARGs in the breeding environment as a “One Health” approach.

IMPORTANCE OF THE LIVESTOCK ENVIRONMENTS AS A RESERVOIR OF ARB AND ARGs

Animal husbandry for meat production is based on cattle, swine, poultry, and aquaculture industries and is a human activity with environmental impacts such as antimicrobial release and AMR spread. Van Boeckel *et al.* [77] estimated that the global average annual consumption of antimicrobials per kilogram of animal produced in 2010 was 45, 172, and 148 mg/kg for cattle, pigs, and chickens, respectively. Tetracyclines are the most common antimicrobials used in swine populations worldwide [45]. The amount of ARB and ARGs differed across animal species, largely because of the distinct amounts of antimicrobials employed in different animal species.

Antimicrobials are bioactive substances that effectively function at low concentrations and are excreted after a short duration of action. Although the amount of antimicrobials excreted varies with the substance type, dose, animal species, age, and application method [43], most antimicrobials are poorly absorbed and metabolized in animal bodies, followed by fecal or urinary excretion, mostly in their original or unchanged form [43, 65]. In addition, some antimicrobials can be converted into metabolites, which undergo elimination or transformation into their precursor compounds. For example, some antimicrobials are converted into conjugated forms, such as acetylated metabolites, which are rendered inactive and analytically undetectable. However, the acetyl group can be cleaved in manure, thereby reconstituting the precursor compound [11]. According to Kemper [43], thousands of tons of antimicrobials are excreted annually by animal husbandries worldwide. Therefore, these agents may be present in wastewater and animal manure in an active form and consequently distributed in several environmental compartments, including soil, surface, and groundwater, depending on their physicochemical properties [10]. In addition, insects and wildlife in livestock environments can come into contact with ARB, ARGs, and residual antimicrobials, potentially functioning as reservoirs of ARB and ARGs. Therefore, it is important to understand the current status of ARB and ARGs in these environmental components (compost, wastewater, insects, and wildlife) and establish suitable countermeasures (Fig. 1).

MANURE COMPOSTING

Considering the growth in livestock globally [67], the therapeutic use of veterinary antimicrobials is expected to approach 100,000 tons by 2030 [77]. Moreover, the total amount of manure has expanded along with the increased number of animals globally. Regionally, the annual production of livestock manure has reached approximately 3.8 billion tons in China [23] and 1.4 billion tons per year in 27 European member states. In the United States, more than 1 billion tons of manure are produced annually [24]. Raw manure is frequently applied to soils in some countries, whereas it undergoes pretreatment in others. Untreated manure contains

numerous pathogenic bacteria, ARB, ARGs, and residual antimicrobials [48]. Thus, the direct use of manure as fertilizer can pose serious environmental concerns, as well as contaminate domesticated plants with ARB and ARGs (Fig. 1).

Aerobic composting and anaerobic digestion are commonly adopted cost-effective strategies for processing manure before application to agricultural soils. Both methods can reduce the mass and volume of manure, facilitate handling and transport, improve nutrient stability, reduce odor, and kill pathogens [13]. In addition to liquid fertilizer, biogas is produced during anaerobic digestion.

Most livestock feces are treated through aerobic composting and spread on the soil. Aerobic composting is the most frequently employed method in Japan. It can convert various organic materials into more stable and eco-friendly substances and is a promising strategy for reducing the ecological risk of multiple pollutants [46]. Several reports have indicated that proper composting can effectively prevent ARB [48]. We have previously reported that aerobic composting reduces ARB abundance [83]. Comparing the abundance of ARGs in compost can be challenging, given that their fate during composting can be impacted by various material sources and different operating conditions; however, their abundance typically decreases with aerobic composting [42]. In addition, veterinary antimicrobial residues were detected in compost even after treatment, potentially inducing ARB and ARGs [83].

Anaerobic digestion has been one approach for general organic waste management, and it has been evaluated for ARB, ARGs, and veterinary antimicrobial removal from manure [13]. This method is considered valuable for energy production and environmental risk reduction [82]. Anaerobic digestion was found to be highly effective for decreasing levels of ARB and ARGs when compared with aerobic composting [13, 24, 39]. However, anaerobic digestion was widely reported to be inefficient for completely removing antimicrobials or ARGs, suggesting the need for a comprehensive approach to this pathway [24].

If animal manure could be transformed into a low-risk organic fertilizer, it would markedly improve land productivity and alleviate the global resource crisis. Various additives (e.g., activated carbon and zeolite, mainly in China) have been formulated as an effective method for aerobic composting to repress ARB and ARGs [62, 86]. Hyperthermophilic composting has also been reported to effectively reduce ARB and ARGs [47]. Additional research assessing these treatment methods is warranted to further minimize the risk of ARB and ARGs in manure on livestock farms. Furthermore, continuous AMR profiling of compost could determine the risk of human transmission.

LIVESTOCK WASTEWATER

The presence of ARB, ARGs, and antimicrobials in aquatic environments has become a global concern, given their adverse effects on aquatic organisms and humans. Livestock wastewater is an important source of antimicrobials in municipal wastewater [29, 61, 78, 85] and surface water [9, 15, 31, 36] (Fig. 1). Jiang *et al.* [37] also indicated that the overall antimicrobial contamination was more significant in suburban areas than in urban sites, owing to intensive livestock activities in suburban areas along the river. Furthermore, swine wastewater is an important source of antimicrobials in the environment, attributed to its large-scale application in the swine industry. Yang *et al.* suggested a high prevalence of ARGs in piggery wastewater [81].

Typically, livestock wastewater undergoes treatment with activated sludge. Biological treatment is the most common strategy for livestock wastewater treatment, given its proven robustness, high cost-effectiveness, and low environmental impact [9]. Decreased levels of ARB and ARGs have been reported in effluents after wastewater treatment [1, 4, 68]. Although wastewater treatment was found to be a promising technology for ARB and ARG removal, developing countries often lack sufficient wastewater treatment or management for animal industries, potentially resulting in the direct discharge of wastewater into surrounding waterbodies [22]. Untreated livestock wastewater poses a significant AMR risk [8]. Therefore, developing more effective and inexpensive treatment methods is required, especially in developing countries, where high concentrations of ARB and ARGs have been reported in livestock wastewater, attributed to insufficient treatment and inappropriate treatment practices. Accordingly, AMR monitoring of livestock wastewater may be useful for determining appropriate treatment processes for livestock wastewater.

INSECTS

Insects commonly associated with food-producing animals represent a direct and important link between animal farms and urban communities in terms of AMR traits. Houseflies and cockroaches reportedly carry ARB identical to those found in animal manure [75, 87]. In contrast, ARB were rarely isolated from insects captured at locations with a limited number of animals, such as downtown areas [64] and parks and universities in urban areas [58]. These results suggest that insects carry ARB from their environment (Fig. 1).

We have previously examined the role of houseflies as ARB and ARG reservoirs in farm environments [16]. Houseflies are frequently found in diverse habitats and move freely owing to their strong flying ability. We isolated *E. coli* from houseflies and livestock feces on farms as an indicator of bacterial species, and the properties and genetic homology of the isolates were evaluated. The results revealed that houseflies might receive ARB and ARGs from livestock feces and transmit ARB and ARGs to other farms and environments [75, 76]. In addition, given the dense and diverse community of intestinal bacteria, including pathogenic strains, the conjugation transfer of plasmids harboring ARGs may occur in the intestinal tract of flies. Therefore, we administered antimicrobial-resistant *E. coli* to houseflies in the laboratory and observed that ARGs were transferred to the housefly intestinal tract by performing a conjugation transfer test [17]. This finding revealed that ARG transmission occurred in the intestinal tract of houseflies. In addition, flies reportedly act as reservoirs in farm environments by maintaining ARB and ARGs from generation to generation [19], and houseflies can contaminate food by contact [18]. These results revealed that houseflies play an important role as vectors and reservoirs in ARB and ARG transmission, maintenance, and contamination. Therefore, the management of insects, including houseflies, is crucial to reduce the risk of emergence and spread of ARB and ARGs in farm environments.

WILDLIFE

Despite the growing literature on AMR in medical and veterinary settings, the wildlife compartment remains poorly explored [72]. Herein, we review a few reported studies on AMR in wildlife.

Wildlife animals, such as field mice and deer, have minimal contact with humans and rarely harbor ARB [3, 35, 69]. However, some small mammals, such as rodents, can be found in farm environments. In our previous study, we isolated ARG-coding *E. coli* (*bla*_{CTX-M1}-harboring *E. coli*) from a rat captured on a farm; a similar ARB was isolated from egg-laying hens on the same farm [3]. A survey of Okinawa rail, a protected species, also reported a high rate of ARB isolated from individuals in the vicinity of a farm [33]. The *bla*_{CTX-M-14} plasmid was found to be transmitted between farm animals and weasels captured around animal facilities [84]. These results suggest that ARB/ARGs are transmitted from livestock to wildlife. In addition, wild boars are considered ARB carriers, owing to their frequent interactions with livestock and human garbage [21, 73]. Wild foxes and badgers have been reported to harbor ARB [6, 56], as they may be in contact with farm environments. Moreover, intraspecies dissemination of quinolone-resistant *E. coli* was detected in a high-density deer population inhabiting an urban area, which may pose a potential risk to public health [32]. Therefore, wildlife may also act as a reservoir of ARB and ARGs (Fig. 1).

In addition, wild birds are considered reservoirs of ARB and ARGs. ARB prevalence has been reported in various wild birds in Japan [38, 51, 74]. Tetracycline-, streptomycin-, and sulfa-drug-resistant bacteria have frequently been isolated from wild birds, suggesting their role as ARB reservoirs. In addition, wild ducks and geese could become ARB spreaders, given their capacity for long-distance movements [63]. We have previously reported that wild migratory birds could carry ARB harboring transferable ARGs [20]. Conversely, the prevalence of ARB differs between non-migratory birds, such as the Great Cormorant, and migratory birds [59].

Although it is difficult to completely thwart the cross-transmission of infectious diseases and pathogens in livestock and wildlife, extensive countermeasures are required to prevent contact between these species. Recently, the standards of rearing hygiene management have been strengthened in Japan to prevent the emergence of critical animal diseases, such as classical swine fever and avian influenza. These efforts could help prevent the spread of ARB and ARGs in farm environments.

COMPANION ANIMALS AND RELATED FACILITIES

Considering third-generation cephalosporins and fluoroquinolones, the AMR rate of Enterobacterales (*E. coli*, *Klebsiella* spp., *Enterobacter* spp.) derived from companion animals was 30–40% [27, 28]; These rates were higher than those derived from livestock. ESBL-producing bacteria were more frequently observed in *Klebsiella* spp. and *Enterobacter* spp. than in *E. coli*. The possible transmission of these ARB to humans is of great concern to public health.

In addition, broad-spectrum cephalosporin-resistant *E. coli* derived from companion animals or humans have been comparatively analyzed [60]. Although a poor clonal relationship was observed between companion animals and human isolates, plasmids harboring the β -lactamase gene (*bla*_{CMY-2}) were similar in some canine and human samples. In addition, Kawamura *et al.* reported that *bla*_{CTX-M-14} and *bla*_{CTX-M-15}-harboring plasmids were frequently isolated from *E. coli* derived from companion animals [41]. Additionally, 36% of these ESBL-producing *E. coli* were sequence type (ST) 131, the most frequently isolated ST of ESBL-producing *E. coli* in human clinical cases. These results indicate that interspecies diffusion of cephalosporin-resistant *E. coli* occurs between companion animals and humans.

To clarify ARB transmission between companion animals and humans, the characteristics of *E. coli* strains derived from dogs and their owners were compared. The results revealed that the transfer of *E. coli* between owners and their dogs occurred in 3 of 34 tested participants (8.8%) [26]. This finding suggests that ARB are transmitted to companion animals in home environments (Fig. 1).

In 2008, we documented a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in veterinarians (23%) in Sapporo, Japan [34]. Although the “Manual for preventing nosocomial infection of MRSA in animal hospitals” was established in 2009, the prevalence of MRSA among veterinarians remained elevated (15%) when examined in 2016 [66]. MRSA remains persistent in veterinary hospitals; however, its origin remains unclear [66]. These results suggest that veterinary hospitals are MRSA reservoirs (Fig. 1). Therefore, it is imperative to improve the sanitary environments of veterinary hospitals. Given that the “Manual for preventing nosocomial infection of MRSA in animal hospitals” remains insufficiently disseminated, further promotion and awareness-raising for veterinarians is warranted.

The use of antimicrobials can be a selective pressure for ARB in homes with companion animals and in veterinary hospitals [44]. In Japan, the “Guide for prudent use of antimicrobials for companion animals” has been published to spread awareness among veterinarians regarding the importance of prudent antimicrobial use and to educate owners [53]. The guide recommends avoiding excessive skin-to-skin contact with companion animals to prevent ARB transmission. Therefore, raising AMR awareness among owners (by distributing the guide and pamphlets related to AMR) is an important measure for future prevention.

CONCLUSION

Currently, there is an overwhelming lack of data on the precise environment of animals as sources of ARB and ARG transmission. However, ARB and ARGs are present in the environment, and their risks must be reduced as feasible. Given that breeding animals are the primary origin of ARB and ARGs in the environment, the first step is to avoid the emergence and increased prevalence of ARB and ARGs in these animals. In addition, continuous monitoring and surveillance are essential for maintaining the safety of breeding environments and establishing strategies against ARB and ARGs. Effective countermeasures will be proposed in the future based on AMR-related monitoring data in breeding environments.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

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