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Review

Mitigating Antibiotic Resistance at the Livestock-Environment Interface: A Review

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The rise of antimicrobial resistance (AR) is a major threat to global health. The food animal industry contributes to the increasing occurrence of AR. Multiple factors can affect the occurrence and dissemination of AR in the animal industry, including antibiotic use and farm management. Many studies have focused on how the use of antibiotics in food-producing animals has led to the development of AR. However, a few effective mitigating strategies for AR have been developed in food-producing animals, especially those exposed to the environment. The aim of this review is to summarize potential strategies applicable for mitigating AR at the environment-livestock interface.

Keywords: Antibiotic resistance, beef cattle, grazing, mitigation

Introduction

Antibiotic resistance (AR) is a crucial challenge to the effectiveness of antibiotic treatments for both humans and animals. The increasing prevalence of resistance and the emergence of multi-drug resistant pathogens pose major threats to communities. More than 2 million people are infected, and at least 23,000 estimated people die every year, because of AR in the US [1]. By 2050, it is estimated that 10 million deaths annually will be attributable to AR, and a cumulative economic cost of $100 trillion globally may accrue if no actions are taken [2]. The World Health Organization published its very first list of antibiotic-resistant “priority pathogens” in 2017 [3], which included 12 antibiotic resistant microorganisms (ARMs), to address the importance of these ARMs and to urge new antimicrobial therapy development. The gastrointestinal tract of humans and animals, especially those receiving antibiotics, serve as a significant reservoir of AR [4]. The transmission of ARMs can occur easily via contaminated water, food, waste, or any other environment. The animal industry can play a crucial role in the emergence and transmission of ARMs as in developed countries about 50-80% of total antibiotic use is attributed to livestock, in which the use of antimicrobials was the greatest in poultry, followed by swine and dairy cattle [5, 6], and the highest resistance rates are detected in antibiotics commonly used in the animal industry, such as tetracyclines, sulfonamides, and penicillins [7].

Though the prevalence of ARMs in animal farms and the surrounding environment has been extensively reported [8−11], few studies have focused on mitigation strategies of ARMs for livestock operations, especially at the environment-livestock interface. The United States is the world’s largest beef producer, however, before entering feedlot facilities, most cattle are raised in grazing operations, where the animals have greater opportunities to interact with the environment. This type of supply chain, which spans many different types of natural habitats, creates a challenge to control ARMs dissemination. The aim of this review is to summarize the recent advances in ARMs mitigation and propose strategies that can further control ARMs at the environment-livestock interface.

Antimicrobial Stewardship

Antimicrobial stewardship is defined as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance” [12]. Similar to human medicine, antimicrobial stewardship should also be applied to the animal industry. It is frequently suggested that the use of antibiotics in food animals for purposes of disease treatment and prevention, and growth promotion are associated with the global rise of AR. It is estimated that global antibiotic consumption in 2010 was 63,151 ± 1,560 tons, and by 2030, this number will increase by 67% [13]. In addition, an association was identified between restricted antibiotic use and a corresponding decrease in the prevalence of ARMs [14]. The use of not only antibiotics, but also antimicrobial metal ions contributes to the rise of AR through co-selection [15]. Copper and zinc are often fed to cattle as antimicrobials for growth promotion and high feed efficiency. However, feeding high concentrations of copper and zinc contributed to the increased AR of fecal bacteria [16]. Moreover, copper resistant bacteria showed a significantly higher incidence of resistance to antibiotics such as ampicillin and sulfanilamide [17]. Chromium, nickel, lead, and iron also promote the acquisition of specific antibiotic resistant genes (ARG) [15]. Therefore, it is important to decrease the overall use of antimicrobials in the animal industry. To achieve this goal, it is necessary to limit the use of antibiotics for growth promotion, regulate clinically-important antibiotic use, and optimize the current antibiotic therapy dose and duration.

However, in grazing beef cattle operations, the use of antimicrobials may not serve as a major cause of ARMs [18]. Mir *et al.* described that in 7 different herds where the cattle never received cefotaxime treatments, the prevalence of cefotaxime resistant bacteria (CRB) ranged from 4.5% to 30% [19]. In another study, by tracking a herd of calves without antibiotic exposure history for one year, the authors discovered that 92% of the calves were colonized by CRB at least once [20]. Moreover, a survey questionnaire study, enrolled 17 commercial beef farms in north and central Florida, showed that in 82.4% of the farms, 5% or less of the cattle received antibiotic treatments annually in cow/calf operations [8]. In the same study, no significant correlation was identified between the prevalence and concentration of CRB and antibiotic use in these 17 farms [8]. These findings suggest that ARMs colonization in beef cattle can occur dynamically in the absence of antibiotic exposure, and these ARMs may originate from the environment. Recently, it is widely known that ARMs can be isolated from the environment. For example, the prototype of extended spectrum β-lactamase (ESBL) gene, CTX-M, was originated from environmental *Kluyvera* strains [21]. Therefore, for grazing operations, mitigation strategies should focus on environmental transmission routes in addition to antibiotic use.

Farm Management

Although the occurrence of ARMs is possibly naturally happening in some cases, certain farm management practices can help control the load of ARMs acquired by animals. For example, the correlation between ARMs prevalence in cattle and animal management, including different farm characteristics, feeding practices, and farm hygiene were the most investigated factors.

Farm size was found to correlate with the prevalence of ARMs. Hille *et al.* analyzed samples from 60 beef production units and found that less intensive farming, combined with better hygiene in beef cattle, was associated with a lower prevalence of CRB [10]. The low intensive farm management factors include only one stable for cattle, duration of fattening more than 18 months, feeding hay, and cleaning of stables exclusively with a pitchfork. Markland *et al.* also reported that small to medium farms (< 500 cattle) had lower CRB prevalence when compared to large farms (> 500 cattle) [8]. Similarly, Schmid *et al.* identified that farms purchasing more cattle had a higher detection rate of ESBL-producing *E. coli* [11]. In summary, farms with smaller numbers of cattle tend to harbor a lower prevalence of ARMs.

When examining feeding practices, it was found that supplementing cattle with ionophores correlated with a lower prevalence of CRB. One hypothesis of this phenomenon is that ionophores reduced the overall intake of cattle and decreased the interaction between cattle, soil, and forage [8]. In another study, feeding waste milk to calves tended to correlate with a higher prevalence of ESBL-producing *E. coli* [11]. Di Labio *et al.* consistently found that feeding milk byproducts to calves and administering antibiotics through feed increased the risk of ARMs [22].

Another critical farm management practice is farm hygiene. Isolating sick animals, burying deceased cattle, and cleaning drinking water troughs more than once a month are practices that are associated with a lower prevalence of CRB [8]. The best hygiene practices also include control of livestock insect pests. For example, flies are known to spread CRB in livestock farms [23]. Some farm environments are excellent habitats for houseflies (*Musca domestica*), stable flies (*Stomoxys calcitrans L.*), and German cockroaches (*Blattella germanica L.*), which disseminate fecal bacteria due to their unrestricted movement and mode of feeding [24]. Flies from cattle farms were found to carry ESBL-producing *E. coli,* and multi-drug resistant *E. coli* O157:H7, and they are involved in the spread of these ARMs [9, 23]. Therefore, a better implemented pest control program will favor the reduction of ARMs in any farm. Another study in Switzerland collected questionnaires from 100 Swiss veal farms and found that farms with both external calf purchase and larger finishing groups had higher concentration of CRB [22].

Water Treatment

The emergence of ARG in water bodies is well documented, including hospital wastewater, animal production wastewater, sewage, wastewater treatment plants, surface water and groundwater [25, 26]. After antibiotics are used in both human hospitals and in veterinary settings, the antibiotics are excreted and enter the sewage system; some of antibiotics and their metabolites are then released into natural water bodies, which then may promote the rise of ARMs. For instance, Jiang *et al.* detected 12 antibiotics and 6 metabolites in river water samples, in which sulfonamides (8.59−158.94 ng/l) and their metabolites were detected [27]. These antibiotics- and ARMs-contaminated water is eventually drunk by animals or used in agriculture systems. One study in Italy isolated 273 *E. coli* from wastewater used in agriculture, in which 22.71%, 19.41%, 16.84%, 14.28%, and 24.17% were resistant to ampicillin, tetracycline, sulfamethoxazole, streptomycin, or multi-drug resistant, respectively [28]. Many of these isolates carried class 1 integrons and R plasmids, suggesting that when these bacteria occur in wastewater, they may serve as a reservoir of plasmid-mediated ARGs. In Ireland, antimicrobial resistant *E. coli*, including ESBL-producing *E. coli*, was recovered from the effluent of a wastewater treatment plant; this means that the non-eliminated ARMs may enter the natural water environment after being expelled into urban sanitation pathways [29]. In addition, ARGs have been frequently detected in the environments. For example, Volkmann *et al.* reported that *vanA* and *ampC* genes were detected in 21% and 78% of the samples, respectively [30]. These results suggested that water bodies are a major transmission route of ARG from human activities to agriculture systems. Therefore, to minimize the contamination of water sources by ARMs, it is essential to incorporate proper water treatment strategies.

To date, there is no available water treatment that can completely remove ARMs in water for use on animal farms. Only one patent described a comprehensive waste treatment system that creates a pathogen-free liquid effluent which can be reused [31], however, the inventors did not test ARG for the patent. For agricultural water, the effect of treatment strategies on ARMs have been summarized [32]. The water treatment strategies include disinfectants, biodegradation, and nanoparticles. Some of these strategies may be incorporated for animal farm water treatment.

Chlorine is the most commonly used disinfectant, as it is easily accessible and effective at inactivating ARMs. Other effective oxidants are ozone, Fenton's reagent, and photocatalytic systems [32]. UV light has also been tested. The radicals in these oxidants react rapidly and are responsible for damage to bacterial DNA and RNA [32]. Notably, killing the ARG-carrying bacteria does not necessarily mean the elimination of its ARG [33]. The remaining intact DNA from the killed bacteria may still confer resistance genotypes to other bacteria via transformation or transduction. Therefore, the disinfectants can inactivate ARMs and degrade bacterial DNA will ensure the deactivation of AR completely.

In biodegradation, a widely used technique is constructed wetlands (CW). The CW are a man-made, small semi-aqua ecosystem that can remove organics and nutrients efficiently. The CW were able to inactivate coliforms, *Enterococcus* spp., and *Staphylococcus* spp. [34, 35]. CW with surface flow can reduce ARG productively with the highest removal rate being 99% [32]. For example, Chen *et al.* detected that the predominant ARGs in the influent of CW were *sul1*, *sul2*, *tetM*, and *tetO*, and the CW system reduced the ARGs by more than 95% [36]. Vegetated CW showed a higher capacity to remove ARMs in a cost effective manner [34]. The removal rate is dependent upon the substrate and hydraulic loading. Both microbial degradation and physical sorption are involved in the destruction of antibiotic residues and ARG in CW [37].

Lastly, nanoparticles, especially metal nanoparticles, have shown antimicrobial activity against ARMs mostly in medical settings. However, in one study, nanoalumina treatment actually promoted the horizontal conjugative transfer of ARG [38], which indicates that the nanotech strategy needs to be further developed before application in the real world.

Wildlife Control

ARMs have been widely detected in many wildlife species. Back in the 90s, a high prevalence of antimicrobial resistant Gram-negative organisms were found in woodland rodents that had never been exposed to antibiotics [39]. In recent years, the existence of ARMs has been discovered from birds, wolf, lynx, wild boars, foxes, deer, bats and rodents, which was summarized by Lee *et al.* (Lee *et al.*, under review). These wild animals, especially migratory birds, serve as potential reservoirs of ARMs and have a critical role in spreading ARMs globally [40]. Furthermore, flies which surround grazing animals in farms also carry ARMs. Although antibiotics are not applied to wildlife intentionally, wildlife can acquire ARMs interacting with the environment, where wildlife species inhabit and there are many antibiotics through multiple routes. For instance, in the environment, antibiotics are produced naturally by microorganisms, causing the evolution of bacteria to gain resistance. Moreover, the antibiotics used in human hospitals can reach the environment mostly via irrigation water for forage. Veterinary antibiotics are also dispersed into the environment from manure and slurry originating from treated animals. The antibiotics and their metabolites continue their transmission dynamically among surface water, ground water, and soil, which contributes to the promotion of ARMs in the environment resulting in the increasing exposure of ARMs to wildlife.

It would be ideal to have full control over livestock-wildlife interactions to decrease the transmission of ARMs, but no practical strategies are available because grazing cattle stay in open environments most of the time. Innovative ideas need to be brought up to minimize the interaction between wildlife and livestock.

Fencing is typically used in either small or large-scale farms to segregate wildlife from cattle. The barriers play an important role in farm biosecurity. Judge *et al.* reported that simple exclusion measures including sheet metal gates, adjustable metal panels for gates, sheet metal fencing, feed bins, and electric fencing, completely prevented Eurasian badger (*Meles meles*) from entering farm buildings and reduced their visits to the rest area of the farms, which potentially decreases the transmission of *Mycobacterium bovis*, the cause of bovine tuberculosis (TB) [41]. Another effective management tool that facilitates the reduction of disease transmission from wildlife is livestock protection dogs (LPD), which were originally developed to protect goats and sheep from predators. One study found that a male-female pair of dogs per farm that are bonded strongly with cattle, but not humans, were effective in blocking wolf, coyote, and deer visits to livestock pastures [42]. The use of LPD may also prevent the interaction of livestock and migrating birds, which serve as one of major ARMs carrier and transmit ARMs worldwide [43].

The control of wildlife populations is another way to prevent potential transmission of ARMs between livestock and wildlife; because overpopulation of wildlife can result in an increased population of ARMs carriers and contact rates between livestock and wildlife. Management actions such as feeding bans or increased culling of animals can be applied to control overabundant wildlife [44]. Supplemental feeding has been provided to wildlife to deal with ecological and socio-economic purposes, however, providing food to wildlife through feeding or baiting has negative effects on animal health and disease transmission [45]. Supplemental feeding of white-tailed deer (*Odocoileus virginianus*) was associated with the increased prevalence of TB and the TB prevalence was declined when deer were dispersed, indicating that feeding bans can control the number of hosts with TB [46]. In addition, increased culling of wildlife can regulate the number of wildlife. Simulation models showed that control of the badger population through culling was effective to reduce the prevalence of TB [47]. Similarly, culling effects have been demonstrated on the prevalence of TB on wild boar [48]. Since wildlife are one of the important carriers of ARMs, transmission of ARMs between wildlife and livestock can be prevented by controlling wildlife populations and their contact rates with livestock. However, it should be noted that sometimes the effects of wildlife population control can be unpredictable and these measures are often controversial in light of ethics and ecology [44]. For instance, studies have shown that the effect of culling animals on the incidence of TB is dependent upon the culling area and the elimination of specific species which can then influence the populations of other species [44, 49]. Therefore, multiple routes of ARMs transmission should be considered to reduce potential interaction between livestock and wildlife [49].

Manure Treatment

With current technology and farm management, it is not likely that farmers will treat manure from cattle on pastures due to the tremendous additional cost and labor to collect the feces. However, shedding of ARMs in feces is one of the most important transmission routes because this process releases ARMs into the environment and then contaminate water, soil, plants, and wildlife [50, 51]. If certain methods can be developed to collect manure on a daily basis, then current strategies to reduce pathogen loads in dairy or feedlot farms also can be applied to cow/calf operations. Possible future solutions include developing an automatic feces collector that can pick up manure from the pasture routinely, or a diaper which can collect feces directly before they drop to the ground. Once collected, the manure can be disposed to biodigesters. An anaerobic digestion process can be used to produce biogas and biofertilizer while reducing microbial dissemination to the surrounding environment [52].

Animal Microbiome

Though rarely studied, manipulating the gastrointestinal microbiota of livestock has the potential to become a new strategy to reduce ARMs and pathogens. Recently Fan *et al.* [53] reported that an animal's genetics is associated with their intestinal microbiota, which is in turn related to antibiotic resistance. With a unique multibreed Angus-Brahman herd, the authors revealed that in postweaning heifers, the hindgut microbiota differed among different breed groups. The heifers with more Brahman proportion showed higher abundance of β-lactam antibiotic resistance. Specifically, the cattle with more Brahman proportion were enriched with β-lactam resistant genes including β-lactamase class C (*ampC*), membrane fusion protein (acrA multidrug efflux system), and penicillin-binding protein 2. It was proposed that host genetics may drive the shift of hindgut microbiota and thereby alter the antimicrobial resistance profile. Additionally, Mir *et al.* discovered the differences in intestinal microbiota of calves with or without CRB colonization [20]. In the CRB positive calves, a higher abundance of Fusobacteria, Elusimicrobia, Chlamydia, and Cyanobacteria and a lower abundance of Spirochetes were detected, indicating the possible role of microbiota in determining ARMs presence in cattle.

The influence of animal microbiota on the colonization of ARMs has been shown in other studies as well. Munk *et al.* [54] investigated the fecal resistome of slaughter pigs and broilers to understand the abundance, diversity, and structure of the pig and broiler resistomes in Europe. The abundance of ARGs was positively associated with veterinary antimicrobial usage in both pigs and poultry [54]. Furthermore, the resistome of pigs and broilers significantly correlated with their bacterial composition, and the animals with similar taxonomic compositions showed similar resistome compositions. During the early life of dairy calves, dietary transition and animal age contributed to the change of gut microbiota, and these transitions influenced the fecal resistome [55]. The change of diet from colostrum to milk replacer caused the functional changes of the gut fecal community: the composition of carbohydrate associated enzymes increased significantly over time, and the relative abundance of bacteria that encoded the most ARGs (*e.g.*, Enterobacteriaceae) decreased [55]. In humans, fecal microbiota transplantation (FMT) has been used to decolonize ARMs in patients' gut based on the knowledge of interactions between gut microbiota and ARMs [56]. The fecal material obtained from healthy donors was transplanted to the patients colonized by ARMs [57]. Fifteen participants out of 20 (75%) experienced complete decolonization of ARMs without adverse events [57]. Therefore, based on the interactions between animal microbiota and ARMs, microbiota engineering may be a promising tool to decrease the load of ARMs in the future.

Development of New Therapies

To reduce the risk of increasing ARMs on farms, alternative antimicrobial therapies should be developed and applied in food-producing animals. Indeed, the transition from current antibiotic practices to new antimicrobial applications cannot be straightforward due to the efficiency, cost, and labor required. In cattle farms, antibiotics are used mainly to treat and prevent diseases. The current alternative options for these purposes, similar to human medicine, include: prebiotics and probiotics, phage therapy, vaccines, antimicrobial peptides (AMPs), antimicrobial polymers, and synergistic antibiotic combinations.

Prebiotics, probiotics, and their combination, called synbiotics, have been well-established with various commercial products available to prevent disease. However, the efficacy of these feed additives is variable. The application of probiotics and prebiotics were reviewed by Gaggia *et al.* [58]. The most frequently used probiotics include *Lactobacillus*, *Enterococcus*, *Bacillus*, and *Saccharomyces*. The activity of probiotics depends upon dosage, timing, duration, and strains. The most frequently studied prebiotics are oligosaccharides, such as fructooligosaccharides, galactosyl-lactose, cellooligosaccharide, and mannanoligosaccharide [58, 59]. Though some evidence shows that prebiotics, probiotics, and synbiotics can outcompete pathogens, no study has yet evaluated if they decrease the prevalence of ARMs in animal gastrointestinal tracts.

Phage therapy has gained more and more attention nowadays due to the dramatic increase of multi-drug resistant pathogens. Phage therapy studies have shown very promising results in both animal and human trials [60]. Compared to antibiotics, they harbor the advantages of species- or strain-specificity, self-amplification, biofilm degradation, and low toxicity in animals and human [60]. For instance, phage strains were reported being able to rescue mice infected with vancomycin-resistant *E. faecium* [61], ESBL-producing *E. coli* [62], and imipenem-resistant *Pseudomonas aeruginosa* [63]. Moreover, phage lysin, a bacterial cell wall hydrolase, is able to cause cell lysis independently [64], which has great potential as an alternative therapeutic.

Vaccines also play a key role in animal disease prevention. By reducing the burden of animal disease, effective vaccines also favor the reduction of antibiotic use. In beef cattle, researchers have attempted to develop new vaccines against tick infestation, parasites, bovine respiratory disease, and liver abscesses [65−68]. Though some of the vaccines have been commercialized, most of them still lack reliable results and need further exploration. In cow/calf operations, most of the antibiotics are used to treat upper respiratory infections [8], therefore, if a dependable vaccine is available, it will decrease the use of antibiotics in grazing operations significantly.

AMPs are immune effectors produced by multicellular organisms to kill microbes. Depending on their physio-chemical structure, AMPs either form pores on the bacterial cell wall or penetrate into the cells and target intracellularly [69]. Studies found that the AMPs which disrupt the cell wall have major advantages over antibiotics. The majority of this type of AMPs display broad-spectrum antibacterial activity, do not increase bacterial mutation rates and are less likely to cause resistance [70]. In addition, the AR of bacteria usually leads to collateral sensitivity (enhanced sensitivity) to the cell wall-targeting AMPs [71]. AMPs have been increasingly studied in animal trials [72, 73], however, to the best of our knowledge, the application of AMPs in cattle has never been investigated.

Antimicrobial polymers, especially those in micro- and nanoscale, share similar properties with AMPs. They bind to the bacterial cell wall and cause cell lysis, allowing the polymers to have broad-spectrum antimicrobial activity with low odds of causing antimicrobial resistance [74]. Though not many antimicrobial polymers have been tested in food animals, one of them is chitosan microparticles [74]. Chitosan microparticles were able to decrease *E. coli* O157:H7 shedding in cattle [75], cure metritis as effectively as ceftiofur in dairy cows [76], and reduce *Vibrio* spp. concentration in oysters (*Crassostrea virginica*) [77]. However, in the food animal industry, the application of polymers as antimicrobials is relatively new and will need further investigation to ensure their safety and efficacy before they can be widely recommended for use.

Another way to mitigate ARMs is by using combination therapies. The combination of two or more antibiotics, or antibiotic and non-antibiotic compounds (*e.g.*, antimicrobial polymers, AMPs, or adjuvants altering host biology) can provide a new transitional therapy during the era in which no new classes of antibiotics are being developed [78]. As the combination therapies have higher efficiency to kill pathogens, especially the ARMs with resistance to one type of antibiotics, these pathogens have less opportunity to survive and transmit from infected animals to other animals or the environment. One classic example of antibiotic-antibiotic adjuvant combination is the application of β-lactam antibiotics with β-lactamase inhibitors. Currently only the pair of amoxicillin and clavulanic acid has been commercialized in human clinics. Back in the 90s, a combination of thiamphenicol and tylosin was tested to treat bovine respiratory disease, and the administration of 10 mg/kg thiamphenicol with 4 mg/kg tylosin increased the cure rate significantly compared with giving 20 mg/kg thiamphenicol alone or 10 mg/kg ampicillin [79]. However, not much progress has been made within the animal industry for investigating combination therapies.

Risk Analysis

Mathematical modeling for risk analysis has been applied extensively in public health settings to help us understand the evolution and dissemination of ARMs, factors contributing to the emergence of ARMs, and the knowledge gap needs to be filled [80]. With these models, better decisions can be made towards fighting ARMs. A few studies have incorporated similar approaches in the cattle industry. One study developed a pharmacokinetic model to understand the antimicrobial residue concentration in beef cattle after feeding chlortetracycline, by counting the antibiotic degradation, absorption, excretion, and cattle intestinal volume change during growth, which favors the estimation of selective pressure on enteric bacteria [81]. In addition, Volkova *et al.* built a model to assess the dynamics of plasmid-mediated ceftiofur resistance in enteric *E. coli* of dairy cattle [82]. The model suggested that $bla_{\text{CMY-2}}$ mediated ceftiofur resistance can persist in enteric *E. coli* between ceftiofur therapies and parenteral ceftiofur treatment decreases the number of antibiotic-sensitive enteric *E. coli*. Because many ARMs dissemination routes have been identified at the livestock-environment interface (*e.g.*, wildlife, water, and soil), it would be very beneficial to assess the spread of ARMs using mathematical models, which will provide insights of the interactions among microbes, animals, and the environment, and then guide further research directions.

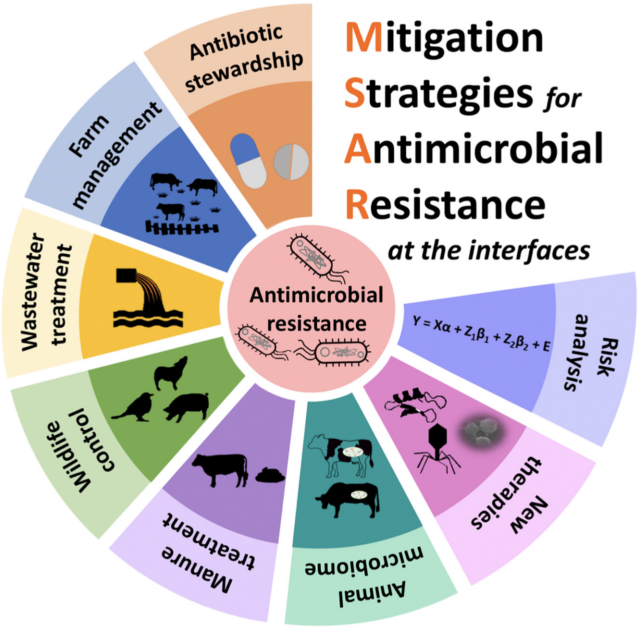

Fig. 1. The mitigation strategies for antibiotic resistance at the interfaces of environment and livestock.

Animal industry plays a critical role in the increased occurrence of antibiotic resistance. At the interfaces, food-producing animals acquire antibiotic resistant microorganisms (ARMs) via antibiotic usage, forage, soil, water, and the interaction with wildlife. Some effective strategies to reduce the burden of ARMs at the interfaces include farm management improvement, wastewater treatment, wildlife control, manure treatment, antibiotic usage reduction and development of new antimicrobial therapies. In the near future, with more advanced technology, animal microbiome manipulation will also serve as a promising option to control ARMs. Meanwhile, risk assessment with modeling is needed to provide up-to-date evaluation of ARM dissemination and guide mitigation strategy development.

Conclusions

The burden of ARMs is continuously growing. Increased attention has been focused on understanding the dissemination of ARMs and developing antibiotic alternatives to address the ARMs problem. Unfortunately, there are currently limited mitigation strategies available in the food-producing animal industry, especially in grazing cattle operations. This review identified effective strategies and proposed some possible solutions that may be used in the future. A summary of the mitigation strategies is presented in Fig. 1. However, to best facilitate the reduction of ARMs, knowledge needs to be deepened and refined on the origin and transmission of ARMs. To minimize the impact of ARMs upon both food-producing animals and people, further strategies need to be developed in the near future.

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Conflict of Interest

The authors have no financial conflicts of interest to declare.

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