Introduction

Antimicrobial drugs are fundamental and critically important components of the veterinarian’s tool kit for managing clinical cases. Not only are they used to treat infectious diseases, but they are also utilized to prevent and mitigate illness among patients at high risk of infection such as those that are immunocompromised or undergoing surgical procedures. Thus, it is in the interest of veterinary practitioners to maintain the efficacy of these treatments to better the health and welfare of their patients. However, bacteria are becoming increasingly resistant to antimicrobial therapies, largely due to the continuous selection pressure provided by frequent use of antimicrobials in healthcare and animal production settings. It is estimated that nearly 5 million human deaths are attributed to antimicrobial resistance (AMR) globally each year, a number that is expected to increase to 10 million by 2050. In the US alone, AMR causes an estimated 2.9 million infections and 36,000 deaths/y. While similar estimates are difficult to ascertain in veterinary medicine, recent surveys suggest that approximately 20% or more of clinical diagnostic samples can contain antimicrobial-resistant bacteria (ARB). The AVMA recognizes AMR as a significant animal health issue in which resistance is a concern for a spectrum of bacterial pathogens that affect domestic species. To address the continually evolving and complex issue of AMR, the AVMA emphasizes a One Health approach: one that integrates human, animal, and environmental disciplines and measures to comprehensively assess and combat AMR. Understandably, much of this approach is centered on relationships between humans and animals—raising awareness of the issue among human and veterinary healthcare workers, influencing prescribing habits that decrease the frequent use of antimicrobials in clinical and population settings, and monitoring AMR among commensal and pathogenic bacteria—to understand the emergence and mitigation of AMR.
While these are all important, we are growing increasingly aware of the impact the environment has on the emergence, amplification, dissemination, and persistence of ARB and genes that affect our veterinary patients. Despite this, the environment is often the most neglected component of the One Health triad when considering AMR epidemiology from the clinical practitioner’s perspective. In this review, we examine the issue of environmental AMR contamination and its impact on animal populations in livestock, clinical, and ecosystem settings and evidence-based mitigation strategies implemented at the practitioner level to reduce AMR contamination and its consequences.

Environmental AMR Contamination on the Farm

Approximately 11.1 million kg of antimicrobial drugs intended for use in food-producing animals are sold in the US every year, of which nearly 6 million kg (approx 54%) are considered medically important, as they are also used to treat human infections. While the public value and health impact of antimicrobial drugs as they are currently applied in food-producing animal populations are somewhat contentious, it is well established that antimicrobial use can drive the emergence and amplification of ARB in the food-producing animal’s microbiome. In vitro analysis showed that the use of common β-lactam antimicrobials in livestock influences the dynamics of ARB populations in ways that can foster the emergence of rare and novel AMR genotypes. Temporal trends in AMR show that, with continual use, the recovery of ARB from populations of livestock animals can range from 30% to 100% of individuals. In addition to antimicrobial use, livestock species can be exposed to ARB through other pathways like consumption of contaminated feed products. Once colonized, livestock animals can broadly disseminate ARB into natural or production environments through their feces.

In population-dense livestock facilities, environmental spread of ARB from waste can be easily transmitted across pens and between holding areas, creating a homogenous microbiome and resistome on a farm. Studies evaluating the livestock environment have recovered commensal and pathogenic bacterial species that harbor a diverse array of genes that confer resistance to antimicrobials of medical importance. For example, a recent study found the novel resistance gene blAmpc-64 among coliform bacteria recovered from sows and piglets and their farm environment. Contaminated livestock environments then serve as persistent reservoirs of ARB, as some bacteria can survive in the bedding, air ducts, fans, dust, flooring, and air for up to years while maintaining their resistance genes. Exposure to these environments is a risk to animals that may develop AMR infections that decrease productivity and welfare, to humans who interact with the animals and their environments, and to downstream consumers of their food products (Figure 1).

Livestock waste can also disseminate ARB into natural environments through a number of pathways. Runoff from fields where animals are housed or livestock waste is applied as fertilizer can result in ARB contamination of natural environments. The application of livestock waste as fertilizer significantly increases the quantity of antimicrobial resistance genes (ARG) in the soil. Rainfall on these fields or open barnyards can disseminate these ARB to the subsurface soil, where they can enter the groundwater. Furthermore, rainfall can disseminate ARB through surface runoff that enters small streams and headwaters. Flooding, a phenomenon that is becoming increasingly familiar, can exacerbate surface runoff on an exponential scale. Once disseminated beyond livestock facilities, ARB can impact the natural ecosystem of surface water streams, promoting their environmental persistence and spread to broader communities including humans and animals.

Environmental Contamination in Companion Animal Healthcare Settings

Similar to livestock and humans, healthy companion animals are frequently colonized with ARB. Many of the antimicrobials used in companion animals are considered medically important and bacteria that resist these antimicrobials pose a...
risk to both animal and human health. While ARB are not nearly as prevalent in the companion animal flora as compared to humans, these ARB can share resistant genotypes and phenotypes to common and last-resort antimicrobials used in humans. For example, carbapenem-resistant Enterobacter sp causing infections among companion animals has been reported. In 2021, an Escherichia coli strain harbored the blanDM-5 carbapenemase gene encoding for resistance to nearly all β-lactam drugs, including the carbapenem antimicrobials, producing an outbreak among companion animals in Pennsylvania. Companion animals frequently share their enteric flora with humans and vice versa, as humans are often in close contact with animals, either as companions or via occupational exposure. Because of this, the colonization and spread of ARB via companion animals is a One Health risk.

Companion animals shed ARB in their feces, and these bacteria can contaminate veterinary hospital environments. An active surveillance effort over multiple years found that a number of hospital surfaces including drains, transportation gurneys, holding areas, and scales can be contaminated in veterinary hospitals. This work has been extended to veterinary private practices, where similar ARB can be found, albeit at lesser frequency. High-contact surfaces in treatment and triage areas of private companion animal practices, including wet tables and countertops, can be contaminated with ARB. Both animal-host and human-host resistant bacteria, such as methicillin-resistant Staphylococcus pseudintermedius and Staphylococcus aureus (MRSA) can be found in exam rooms where clients often accompany their pets. Infection prevention in companion animal hospitals is not always practiced at the same level that we expect in human healthcare. In addition, animals are intimately in contact with the veterinary hospital environment. These behaviors can facilitate the spread of ARB in the veterinary hospital environment even when strict environmental disinfection is practiced. Moreover, once in the environment, bacterial organisms possess a number of adaptations to survive including the formation of biofilms on hospital surfaces. Similar to human healthcare, these bacteria can attach to environmental niduses, like drains, where they can serve as persistent reservoirs that are recalcitrant to disinfection.

Environmental contamination with ARB in veterinary hospitals represents a threat to both patients and the veterinary workforce in these facilities (Figure 2). Hospital-acquired infections are known to be associated with increased morbidity and mortality, financial cost, and client/patient dissatisfaction. Analysis of common healthcare-acquired pathogens such as the Enterobacteriales have found genomic evidence for hospital-acquired clonal strains. A year-long study of MRSA in a veterinary tertiary care facility showed that for nearly 5 months, 1 pulsotype of MRSA circulated through patients and environments across multiple departments within the hospital. In addition to hospital items like carts and gurneys that can move pathogens, a social network analysis identified veterinarians and veterinary assistants as key personnel that move ARB and pathogens within environments. This finding is corroborated by studies in human healthcare indicating that restricting doctor movement within hospitals can significantly reduce the length of infectious disease outbreaks. The overwhelming evidence that humans frequently spread ARB in healthcare settings indicates a threat to both our animal patients and veterinary staff since most of these bacteria are capable of cross-species transfer. Moreover, these bacteria have been found on personal items like cell phones that can spread ARB beyond healthcare and into the community.

**Contamination of the Natural Environment**

Natural environments, especially surface waters, act as collection sites receiving continuous inputs from a variety of sources. Some, like treated wastewater originating from human healthcare facilities or agricultural waste runoff, can be laden with pathogens, ARB, and mobile genetic elements harboring ARG that can be readily transmitted between bacteria. While natural environments can be impacted by both human and agricultural sources, the impact of human enteric bacteria discharged in treated wastewater disproportionately contributes diversity to the resistome that impacts natural environments. Screening of treated community wastewater demonstrates the magnitude and diversity of ARG that are discharged into surface waters. Our research
has shown that surface water, especially that which receives treated wastewater from metropolitan regions with large urban wastewater systems, is polluted with ARG that confer resistance to carbapenem antimicrobials. Moreover, common gram-negative enteric organisms like *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* complex that harbor mobile carbapenemase genes are routinely isolated from surface water receiving treated wastewater. Similarly, livestock waste can contribute nutrients, ARB, pathogens, and pharmaceutical metabolites, all of which contribute to One Health risk.

Once disseminated into surface waters, ARB can concentrate in stream sediment and incorporate in aquatic biofilms, called periphyton, where they can flourish and persist in nutrient-dense environments. Antimicrobial-resistant bacteria are also consumed by fish and other aquatic organisms, in which they can colonize the gastrointestinal tract. Once colonized, fish can facilitate the spread of ARB upstream and downstream of the point source of contamination, exposing naïve segments of the stream to ARB. Widespread dissemination of ARB within streams and other water sources used by terrestrial wildlife can propagate the spread to naïve land-based ecosystems. For example, we previously reported β-lactam-resistant and carbapenemase-producing bacteria colonizing white-tailed deer populations in Ohio. We concluded that the most likely source of the deer’s exposure to ARB was via surface water that received treated wastewater discharge and untreated wastewater from combined sewer overflows.

Antimicrobial-resistant bacteria in natural environments represent a potentially important risk to animal and human health. Surface waters are utilized by agriculture in a variety of ways, including as a drinking water source for livestock or to irrigate crops that will subsequently be consumed by humans or animals. Our preliminary data investigating the flow of ARG throughout an Ohio watershed found that bacterial carbapenem resistance genes could be recovered from crops irrigated with river water contaminated with those same genes. Moreover, contaminated surface waters pose a risk to humans and companion animals that are directly exposed for recreation including water sports and fishing. Humans or animals that consume the fish may be at an even greater risk, as fish are frequently contaminated with ARB and ARG of urgent public health concern. While widespread risk assessments have not been conducted investigating water exposure and ARB colonization, the “Beach Bum” study found that surfers who spent more time in contaminated ocean water were more likely to harbor ARB compared to nonsurfers. The natural environment serves as a nexus between the contamination upstream by humans and animals as well as a source of spread back to humans and animals following a cyclic One Health pathway: a cyclic pathway of AMR involving human, animal, and environmental health (Figure 3).

Managing the emergence and dissemination of ARB and ARG once they enter the natural environment poses numerous challenges that are difficult to overcome. Standard wastewater treatment methods including ozone, UV light, and hypochlorite bleach are capable of reducing ARB populations; however, ARB still escape into the natural environment via treated wastewater effluent. Similarly, methods to reduce ARB loads in livestock feces applied to natural environments through stockpiling or composting are largely ineffective at eliminating ARB and their resistance genes. While emerging technologies are being investigated to address ARB spread in human and animal waste, we do not currently have the infrastructure to sterilize all the waste that is generated. Collectively, these findings suggest that mitigation efforts prior to wastewater treatment are necessary to address AMR spread from healthcare and farms to the watershed and natural environment.

A One Health approach that is frequently emphasized to reduce the spread of AMR is the judicious use of antimicrobials. For example, in Ohio a program is underway to train livestock producers and farm workers in antimicrobial stewardship by increasing knowledge and awareness of appropriate antimicrobial use and AMR. The impact of these programs on the colonization of livestock and environmental contamination of livestock facilities remains to be characterized. Although these types of programs are relatively new, preliminary results show that antimicrobial stewardship programs reduce the
Antimicrobial treatment incidence in dairy cows and calves and alter the producer’s behavior, increasing their sensitivity for detecting cases that require antimicrobial therapy. Collectively, these alterations in prescribing behaviors will decrease the frequency of use of antimicrobials that promote animal colonization and environmental contamination.

Antimicrobial stewardship programs in companion animal hospitals also offer an opportunity to reduce environmental reservoirs of AMR. Antimicrobial stewardship programs are widespread in human healthcare, but their full adoption by companion animal veterinary medicine is still emerging. In collaboration with The Ohio State Wexner Medical Center, The Ohio State College of Veterinary Medicine implemented a veterinary antimicrobial stewardship program that includes comprehensive antimicrobial use guidelines and enhanced infection control, with a goal to support clinicians and students to confidently make judicious antimicrobial use decisions in companion animal medicine. The program also limits the use of “last resort” antimicrobials (those that are used to treat multidrug-resistant, invasive infections like the carbapenems and linezolid) to maintain their efficacy in life-threatening situations. Limiting the emergence of AMR by decreasing the frequency of antimicrobial therapy should hypothetically decrease the risk of spreading ARB and ARG into the environment. Antimicrobial stewardship programs also establish environmental surveillance efforts to monitor high-risk surfaces for ARB that can serve as human and veterinary health risks. These programs are known to reduce patient stays, hospital costs, and the spread of hospital-acquired AMR pathogens within and beyond healthcare environments.

Regulatory mechanisms to engage judicious use of antimicrobials have also been implemented in both companion and food-producing animals. For example, the AMDUCA of 1994 reduces extralabel use of approved animal and human drugs by requiring specific provisions to be met and a veterinarian prescription within the context of the veterinarian-client-patient relationship. Moreover, AMDUCA provides a list of antimicrobials and other drugs that are specifically prohibited for extralabel use in food-producing animals. More recently, the FDA enacted the Veterinary Feed Directive (Guidance for Industry No. 213) and Guidance for Industry No. 263. The Veterinary Feed Directive involves veterinarians in the framework and oversight of medically important antimicrobials delivered through feed for livestock patients. Guidance for Industry No. 263 transitions medically important over-the-counter antimicrobials that are approved for companion and/or food-producing animals to antimicrobials requiring the oversight of a veterinarian. While publicly available data on antimicrobial usage on farms are limited in the US, data aggregated by the FDA on the sale of medically important drugs from 2013 to 2022 show a 32% reduction in antimicrobial sales from nearly 9.2 million kg in 2013 to 6.25 million kg in 2022. In addition, government policies regulating antimicrobial use at the international level have been efficacious in reducing resistant bacteria recovered from livestock and food-producing animals. These programs support antimicrobial stewardship in veterinary settings, requiring more judicious use of medically important drugs approved for veterinary species. Hypothetically, these efforts will also limit the inputs that result in AMR emergence and amplification, local contamination, and dissemination to downstream environments.

The One Health Cycle of AMR

Antimicrobial-resistant bacteria readily expand and disseminate when antimicrobial drugs are frequently applied to individuals in population-dense environments. This situation often exists in healthcare institutions and animal agriculture. Resistant bacteria that are amplified in healthcare can escape in municipal wastewater flows and are transported to treatment facilities, where they are reduced but not eliminated. The remaining ARB are discharged into nearby surface waters, where they disseminate into the downstream watershed. Humans, wildlife, or domestic animals, including livestock, in direct or indirect (eg, crop irrigation) contact with these waters may become colonized with the ARB that originated in a healthcare environment. In this way, ARB with novel resistance genes can be introduced into animal agriculture, where they may again expand and disseminate. Resistant bacteria that are amplified in animal agriculture can escape in human and animal food products and colonize healthy individuals and their pets in the community. Colonization with these ARB does not generally impact the individual or the community until the colonized individual enters a healthcare (human or veterinary) environment, where they contribute ARB that may again be amplified. This continuous nature of the One Health cycle of resistance implies that there is no single point of attribution that can serve as a focus of mitigation efforts. Instead, we must recognize that we all play some role in this cycle and therefore can contribute to the solution (Figure 4).

Call to Action: Veterinarians and the Profession

Veterinary antimicrobial use is not the cause of AMR problems, but it does play a role in maintaining the One Health cycle of resistance. As a result, veterinarians can contribute directly to the solution to AMR by implementing effective mitigation efforts in the veterinary clinical environment. Structured antimicrobial stewardship programs that are supported by the AVMA and AVMA specialty colleges are an important contribution by veterinarians. In addition, clear and concise consensus guidelines are needed for the diagnoses, treatment, and management of common infectious diseases in companion and livestock animals, like reproductive, respiratory, ear, skin, and urinary tract infections that are easily accessible to front-line practitioners. These guidelines should not only be developed by individuals...
with extensive clinical knowledge like veterinary internists and dermatologists but also clinical veterinary microbiologists and veterinary pharmacists who have intimate knowledge of the pathogens and antimicrobials used in veterinary medicine. Training programs that promote the education and development of veterinary clinical microbiologists, pharmacists, and antimicrobial stewards will prepare future generations of veterinarians to tackle this ever present and growing problem of AMR. The ultimate goal is to preserve the effectiveness of antimicrobial drugs for future generations of patients. To accomplish this goal, we must find ways to interrupt the One Health cycle of resistance today.

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References


