

The AVMA's definitions of antimicrobial uses for prevention, control, and treatment of disease

Members of the AVMA Committee on Antimicrobials:

David R. Smith, DVM, PhD (representing American Association of Bovine Practitioners), Starkville, Miss.

Patricia S. Gaunt, DVM, PhD (representing American Association of Fish Veterinarians), Stoneville, Miss.

Paul J. Plummer, DVM, PhD (representing American Association of Small Ruminant Practitioners), Boone, Iowa.

Hector M. Cervantes, DVM, MS (representing American Association of Avian Pathologists), Watkinsonville, Ga.

Peter Davies, BVSc, PhD (representing American Association of Swine Veterinarians), Saint Paul, Minn.

Virginia R. Fajt, DVM, PhD (representing American Association of Small Ruminant Practitioners), College Station, Tex.

Erin Frey, DVM, MPH (representing American Animal Hospital Association), Raleigh, NC.

Michele T. Jay-Russell, DVM, MPVM, PhD (representing American Association of Food Safety and Public Health Veterinarians), Davis, Calif.

Terry W. Lehenbauer, DVM, MPVM, PhD (representing American Association of Bovine Practitioners), Tulare, Calif.

Mark G. Papich, DVM, MS (representing American Association of Equine Practitioners), Raleigh, NC.

Tina M. Parker, DVM, MScPH (at-large member), Gaithersburg, Md.

Erin C. Phipps, DVM, MPH (at-large member), Albuquerque, NM.

Joni M. Scheftel, DVM, MPH (representing American Association of Food Safety and Public Health Veterinarians), Mayer, Minn.

Lauren V. Schnabel, DVM, PhD (representing American Association of Equine Practitioners), Holly Springs, NC.

Randall S. Singer, DVM, PhD (representing American Association of Avian Pathologists), Saint Paul, Minn.

Janet E. Whaley, DVM (representing American Association of Fish Veterinarians), Brookeville, Md.

Jennifer K. Wishnie, DVM, MSc, MPH (representing American Association of Swine Veterinarians), San Luis Obispo, Calif.

Lindsay R. Wright, DVM (representing American Animal Hospital Association), Salt Lake City, Utah.

Michael Costin, DVM, MBA (AVMA staff consultant to the committee), Schaumburg, Ill.

Address correspondence to Dr. Smith (david.smith@msstate.edu).

This manuscript has not undergone external peer review.

Abstract

Recent state and federal legislative actions and current recommendations from the World Health Organization seem to suggest that, when it comes to antimicrobial stewardship, use of antimicrobials for prevention, control, or treatment of disease can be ranked in order of appropriateness, which in turn has led, in some instances, to attempts to limit or specifically oppose the routine use of medically important antimicrobials for prevention of disease. In contrast, the AVMA Committee on Antimicrobials believes that attempts to evaluate the degree of antimicrobial stewardship on the basis of therapeutic intent are misguided and that use of antimicrobials for prevention, control, or treatment of disease may comply with the principles of antimicrobial stewardship. It is important that veterinarians and animal caretakers are clear about the reason they may be administering antimicrobials to animals in their care. Concise definitions of prevention, control, and treatment of individuals and populations are necessary to avoid confusion and to help veterinarians clearly communicate their intentions when prescribing or recommending antimicrobial use.

In veterinary medicine, antimicrobial stewardship refers to the commitment by veterinarians and animal caretakers to preserve the effectiveness of antimicrobials without risking the health and welfare of animals or harming public or environmental health. Antimicrobial stewardship includes providing systems of care to reduce the incidence of common diseases, making evidence-based decisions about the use of antimicrobial drugs, and using antimicrobials judiciously, with ongoing evaluation of the outcomes of use and consideration for animal caretakers' available resources.

The concept of antibiosis (ie, the use of substances derived from one living organism to kill another) is as old as antiquity. However, the antimicrobial era only began in earnest in the early days of World War II,¹ and the concept of antimicrobial stewardship is nearly as old. The first volume in the USDA's "Yearbook of Agriculture" series to mention the use of antimicrobials to treat animal diseases was published in 1947 and included statements illustrating early recognition of the importance of antimicrobial stewardship.² For example, the authors stated that "[o]f course, the sulfa drugs and penicillin, like all new

drugs, should be used only as prescribed by a veterinarian; their indiscriminate use may be wasteful and actually harmful to the animal patients.”

Less than a decade later, Jones wrote that “[a] disturbing and increasingly dangerous practice of giving antibiotics promiscuously for almost any and all kinds of sickness has become increasingly common in recent years when many antibiotics became generally available. Some susceptible strains of disease-producing bacteria, especially staphylococci, may develop a total resistance because the antibiotics are improperly used. It has become apparent that when an antibiotic is used promiscuously in any given community or hospital, resistant strains of staphylococcal bacteria can be found in a significant portion of the animal or human population.”³ However, he also stated that “no patient should be deprived of the benefit of antibiotic therapy solely because of the fear of inducing resistance in the disease germ.”³

Recently, the AVMA defined antimicrobial stewardship as “the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health.”⁴ The AVMA identified 5 core principles of antimicrobial stewardship in veterinary medicine⁴:

- Commit to stewardship.
- Advocate for a system of care to prevent common diseases.
- Select and use antimicrobial drugs judiciously.
- Evaluate antimicrobial drug use practices.
- Educate and build expertise.

Central to antimicrobial stewardship is the role veterinarians play in helping animal caretakers maintain systems of husbandry that avoid common infectious diseases, thereby reducing reliance on the use of antimicrobials to maintain animal health. At times, however, therapeutic use of antimicrobials is essential for the prevention, control, or treatment of disease. However, the lack of clear definitions of the terms “prevention,” “control,” and “treatment” have led to misunderstandings and confusion about therapeutic intent when using antimicrobials.

Recent state and federal legislative actions and current recommendations from the World Health Organization seem to suggest that when it comes to antimicrobial stewardship, use of antimicrobials for prevention, control, or treatment of disease can be ranked in order of appropriateness, which in turn has led, in some instances, to attempts to limit or specifically oppose the routine use of medically important antimicrobials (ie, antimicrobials that are the same as or closely related to antimicrobials important for treatment of human diseases) for prevention of disease. For example, a California law⁵ that became effective in January 2018 defines antimicrobial stewardship as a “commitment to ... use medically important

antimicrobial drugs only when necessary to treat, control, and, in some cases, prevent disease.”

Similarly, a 2017 Maryland law⁶ provides that medically important antimicrobials can be used in cattle, swine, or poultry only for the treatment of disease, to control the spread of disease or infection, or when performing a surgical or medical procedure. However, the legislation also allows for the use of medically important antimicrobials if a licensed veterinarian judges the use necessary to address a high risk that animals will contract a particular disease or infection. Thus, this law seems to support the use of medically important antimicrobials for treatment or control of disease but causes confusion about the use of these drugs for the prevention of disease, except possibly in individual animals at high risk of infection.

In the same vein, the World Health Organization recommends that farmers stop routinely using medically important antibiotics to prevent disease in healthy animals.⁷ Also, a proposed amendment to the federal Food Drug and Cosmetic Act would allow the use of medically important antimicrobials only for the treatment of animals with documented disease or for nonroutine disease control.⁸

The sense one gets from these laws and recommendations is that the quality of antimicrobial stewardship can be evaluated on the basis of the therapeutic intent of the use (ie, whether the purpose is to prevent, control, or treat disease), such that treatment of individual animals with clinical disease represents good stewardship whereas use for the prevention of disease may not. Further, it seems that this ranking represents concerns about treating animals that are not yet exhibiting clinical signs of disease.

In contrast, the AVMA Committee on Antimicrobials believes that attempts to judge antimicrobial stewardship on the basis of therapeutic intent (ie, prevention vs control vs treatment) are misguided. Rather, we hold that antimicrobial stewardship should be evaluated on the basis of the decisions made to justify use of antimicrobials in the first place and the actions taken to maintain their effectiveness when they are used.

Thus, we believe that strategic uses of antimicrobials for prevention, control, or treatment of disease may each comply with the principles of antimicrobial stewardship. That said, we do not defend every use of antimicrobials for prevention, control, or treatment of disease, because some uses of antimicrobials, regardless of whether for prevention, control, or treatment, fail to meet stewardship guidelines. Also, important approaches to disease prevention, control, and treatment that do not involve antimicrobial use should be taken into consideration.

Misunderstandings about whether specific examples of antimicrobial use comply with the principles of antimicrobial stewardship may originate from confusion regarding the underlying therapeutic intent. For example, administration of antimicrobials in animal feed, versus by some other route of administra-

tion, may be considered to not comply with the principles of antimicrobial stewardship because of a belief that the intent of putting antimicrobials in feed is growth promotion. The practice of feeding medically important antimicrobials for growth promotion has not been legal in the United States since January 2017. However, medically important antimicrobials can be delivered in feed, according to label directions, under the order of a veterinarian, if the intent is to prevent, control, or treat a disease.

Similarly, administering antimicrobials to animals that do not currently have any clinical signs of disease might be considered the same as giving antimicrobials to healthy animals and, thus, not compliant with the principles of antimicrobial stewardship. However, this reasoning fails to recognize important distinctions between clinically evident disease, subclinical disease, and the incubation period of infection. In practice, we almost never know the infection status of individuals and cannot reliably identify all potential sources of exposure or routes of transmission. However, we often can recognize those combinations of factors that cumulatively present a reasonable risk that infection will be transmitted or disease will occur. Thus, administration of antimicrobials to animals that do not currently have clinical signs of disease may comply with the principles of antimicrobial stewardship if there is reason to believe that the animals are at risk of becoming infected, are incubating an infection, or have subclinical infection that may be transmitted to others.

In some animals, such as honeybees and catfish, it is not possible to treat only the individual animals with clinical signs of disease. In other animals, such as swine and poultry, it may not be feasible to treat only diseased individual animals. For these and other production systems, antimicrobials must be delivered to the entire group of animals.

It is important that veterinarians and animal caretakers are clear about the reasons they are administering antimicrobials to animals in their care. Concise definitions of prevention, control, and treatment of individuals and populations are necessary to avoid confusion and to help veterinarians clearly communicate their intentions when prescribing or recommending antimicrobial use.

Defining Prevention, Control, and Treatment of Disease

Disease treatment

Treatment is defined as the management and care of a patient for the purpose of combatting a disease or disorder.⁹ The use of antimicrobials to treat bacterial diseases implies that pathogenic organisms have infected tissue and are causing a disease process that can be recognized on the basis of history, physical examination findings, or results of diagnostic testing. For practical purposes, antimicrobial treatment refers

to the administration of antimicrobials to individuals with clinical or diagnostic evidence of infection.

Disease prevention

Prevention of disease has been defined in various ways, with some authors classifying disease prevention as primary, secondary, or tertiary.¹⁰ Primary prevention refers to actions that modify conditions of the environment (eg, providing proper nutrition and alleviating stress) to promote health or that specifically improve the protection of individuals or groups from disease (eg, immunization and sanitation). Secondary prevention refers to early detection and treatment of disease prior to development of clinical signs to promote a cure, slow disease progression, prevent severe sequelae, or minimize risk for transmission of the disease agent. On a population basis, secondary prevention through early treatment of infected individuals may protect other animals from exposure to the disease agent. Finally, tertiary prevention refers to those actions that limit the extent of damage after disease has already occurred.

By these definitions, the use of antimicrobials for disease prevention is conceptually aligned with secondary prevention at the individual or population level. However, these classifications do not account for the prophylactic use of antimicrobials when infection is anticipated but has not yet occurred.

Others have defined disease prevention as the actions taken to exclude infectious diseases from individuals or populations.¹¹ This implies that the disease process has not yet been established in individuals or the population. In terms of the therapeutic use of antimicrobials, the FDA defines disease prevention as the administration of an antimicrobial to animals, none of which are exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered.¹²

The use of antimicrobials for disease prevention is often referred to as prophylaxis to distinguish it from other methods of disease prevention, such as vaccination. Antimicrobials have been used to prevent infection in a variety of settings on the assumption that, if a drug is effective at eliminating established infections, then it should also be effective at discouraging infections from becoming established in the first place.¹ Thus, antimicrobials might be used prophylactically for the following purposes¹:

- To protect individuals or populations against invasion by specific bacteria to which they have been or are likely to be exposed.
- To prevent secondary bacterial infection in individuals with other conditions (eg, viral infection or immunosuppressive conditions) that may make those individuals more susceptible to infection.
- To inhibit the spread of localized infections within an individual.
- To prevent infection in individuals with accidental or surgical trauma.

The prophylactic use of antimicrobials is not effective in all clinical settings and, in some instances, may harm individual animals (eg, when antimicrobial use results in superinfection) or cause collective harm to the population (eg, when antimicrobial use selects for antimicrobial-resistant bacteria).¹ On the other hand, the strategic use of antimicrobials for prophylaxis may be the most prudent approach in situations where timely use of antimicrobials eliminates infections that would be more difficult or impossible to treat once disease is established or that could become more widely spread among animals in a group in the absence of timely administration. Examples of prophylactic uses of antimicrobials include intramammary infusion of an antimicrobial in dairy cows at the end of the lactation period to prevent new infections and administration of an antimicrobial in any species in conjunction with dental procedures or orthopedic or gastrointestinal surgery.

Disease control

Control of disease refers to the actions taken to reduce the frequency of existing disease. In individual animals, disease control is conceptually analogous to tertiary disease prevention; that is, infection exists in the individual animal and actions are being taken to limit the extent of damage.¹⁰ More often, disease control refers to reducing the frequency of disease in a population.¹⁰ In this context, administration of antimicrobials to a group of animals to reduce the incidence of bacterial disease within the group, sometimes referred to as metaphylaxis, represents a type of disease control.^{13,14}

The AVMA's Definitions

The US Government Accountability Office and, more recently, World Organisation for Animal Health (OIE) have developed definitions of antimicrobial uses for prevention, control, and treatment of disease (**Appendix**).^{15,16} However, these definitions do not fully distinguish between antimicrobial administration to individual animals versus groups of animals and are ambiguous about administration of antimicrobials to animals with evidence of disease other than observable clinical signs. This latter issue is important because not all bacterial infections result in obvious clinical signs, and disease might be diagnosed on the basis of evidence other than clinical signs, such as results of laboratory testing. Therefore, the AVMA Committee on Antimicrobials has recommended specific definitions of antimicrobial use for the prevention, control, and treatment of disease to the AVMA Board of Directors, which recently approved the definitions as AVMA policy.¹⁷

Antimicrobial use for disease prevention

For individual animals, the AVMA defines antimicrobial use for disease prevention (ie, prophylaxis) as “administration of an antimicrobial to an individual animal to mitigate the risk for acquiring a disease or

infection that is anticipated on the basis of history, clinical judgement, or epidemiological knowledge.”¹⁷

To mitigate the risk for disease or infection within a group of animals, the AVMA defines antimicrobial use for disease prevention as “administration of an antimicrobial to a group of animals, none of which have evidence of disease or infection, when transmission of existing undiagnosed infections, or the introduction of pathogens, is anticipated based on history, clinical judgement or epidemiological knowledge.”¹⁷

Antimicrobial use for disease control

For individual animals, the AVMA defines antimicrobial use for disease control (ie, metaphylaxis) as “administration of an antimicrobial to an individual animal with a subclinical infection to reduce the risk of the infection becoming clinically apparent, spreading to other tissues or organs, or being transmitted to other individuals.”¹⁷

To prevent additional new cases of infectious disease within groups of animals, the AVMA defines antimicrobial use for disease control as administration of an antimicrobial “to reduce the incidence of infectious disease in a group of animals that already has some individuals with evidence of infectious disease or evidence of infection.”¹⁷

Antimicrobial use for disease treatment

For individual animals, the AVMA defines antimicrobial use for disease treatment as “administration of an antimicrobial as a remedy for an individual animal with evidence of infectious disease.”¹⁷

To remedy disease in groups of animals, the AVMA defines antimicrobial use for disease treatment as “administration of an antimicrobial to those animals within the group with evidence of infectious disease.”¹⁷

A Matter of Perspective

It is difficult to use therapeutic intent to determine whether antimicrobial use in any particular situation complies with the principles of antimicrobial stewardship because whether the use represents treatment, control, or prevention depends, at least to some extent, on whether the intent is viewed from the perspective of individual animals or groups of animals. For example, the use of antimicrobials to control infectious disease in a population simultaneously includes administration of antimicrobials for treatment of individuals with clinical signs of the disease, control of infection in individuals with subclinical disease, and prevention of infection in individuals that have not yet acquired the infection.

Further, when antimicrobials are administered to a group of animals, the therapeutic intent for each individual in the group could be prevention, control, or treatment of disease. Consider, as a hypothetical example, a situation where several cows in a herd die

of anthrax following an episode of flash flooding. A veterinarian could reasonably advise the herd owner to administer antimicrobials to all the remaining cattle in the herd, even though they were not showing clinical signs of anthrax, because they may have been exposed to anthrax spores. In this case, the veterinarian's recommendation represents use of antimicrobials to control a disease known to exist in the herd. The veterinarian may also recommend that the owner of a neighboring herd administer antimicrobials to all the cattle in that herd, even though none of the cattle had died or developed clinical signs of anthrax, because the cattle had a similar risk for exposure to anthrax organisms as a result of the flooding. In this case, the veterinarian's recommendation represents use of antimicrobials for disease prevention. In both herds, some cattle may already be incubating anthrax organisms, and antimicrobial administration for these individual animals represents disease treatment. For individual cattle that are not yet infected, however, antimicrobial administration represents disease prevention.

To continue the hypothetical scenario, if, over the next several days, other herds also experience cattle deaths because of anthrax, a regulatory veterinarian may recommend antimicrobial administration, perhaps in conjunction with vaccination, for other affected and unaffected herds to reduce the incidence of disease in the region. In this case, the regulatory veterinarian's recommendation represents antimicrobial use for regional disease control. However, those herds in the region that had already had cattle die of anthrax are using antimicrobials for disease control, which includes both treatment and prevention for individual cattle. And, herds in the region that had not had any cattle die of anthrax are using antimicrobials for disease prevention.

For all of these antimicrobial uses, whether the therapeutic intent was disease treatment, control, or prevention depends on whether one views that use from the perspective of the individual cattle, the individual herds, or all herds in the region. Regardless, in this scenario, withholding antimicrobial use until clinical signs were observed would not be a responsible approach.

Conclusion

Since the dawn of the antimicrobial era, the health-care professions have recognized the critical importance of antimicrobial stewardship. The basis of antimicrobial stewardship is to preserve the effectiveness of antimicrobials for prevention, control, and treatment of bacterial diseases. Antimicrobial use practices are better evaluated on the basis of whether they comply with the principles of antimicrobial stewardship—specifically, whether decisions are based on optimizing therapeutic efficacy while minimizing the risk of antimicrobial resistance, not on the basis of whether the therapeutic intent of use is for the prevention, control, or treatment of disease.

Acknowledgments

The authors thank Dr. Kathie Elizabeth Bjork, Dr. Mike J. Murphy, Dr. Megin Nichols, and Mr. Ron Phillips for providing advice to the AVMA Committee on Antimicrobials. The authors also thank AVMA Board of Directors liaison Dr. Charles Alfred Lemme for providing expertise and support in the preparation of this report.

References

1. AVMA. Antimicrobial stewardship definition and core principles. Available at: www.avma.org/KB/Policies/Pages/Antimicrobial-Stewardship-Definition-and-Core-Principles.aspx. Accessed Sep 25, 2018.
2. Weinstein L. *Chemotherapy of microbial diseases*. 5th ed. New York: MacMillan Publishing Co Inc, 1975.
3. Giltner LT. Animal diseases. In: *Science in farming, the yearbook of agriculture, 1943-1947*. Washington, DC: US Government Printing Office, 1947;81-94.
4. Jones LM. Antibiotics. In: *Animal diseases, the yearbook of agriculture, 1956*. Washington, DC: US Government Printing Office, 1956;94-96.
5. Livestock: use of antimicrobial drugs. State of California. SB-27. Available at: leginfo.ca.gov/faces/billNavClient.xhtml?bill_id=201520160SB27. Accessed Sep 30, 2018.
6. Keep Antibiotics Effective Act of 2017. State of Maryland. SB0422 (CH0788). Available at: mgaleg.maryland.gov/web-mga/frmMain.aspx?pid=billpage&stab=02&id=sb0422&tab=subject3&ys=2017RS. Accessed Sep 30, 2018.
7. *WHO guidelines on use of medically important antimicrobials in food-producing animals*. Geneva: World Health Organization, 2017.
8. Preservation of Antibiotics for Medical Treatment Act of 2017. H.R.1587. 115th Congress (2017-2018). Available at: www.congress.gov/bill/115th-congress/house-bill/1587/text. Accessed Dec 26, 2018.
9. *Dorland's illustrated medical dictionary*. 25th ed. Philadelphia: WB Saunders Co, 1974.
10. Mausner J, Kramer S. Measurement of morbidity and mortality. In: *Epidemiology: an introductory text*. 2nd ed. Philadelphia: WB Saunders Co, 1985;43-54.
11. Martin SW, Meek AH, Willeberg P. Rationale, strategies, and concepts of animal disease control. In: *Veterinary epidemiology*. Ames, Iowa: Iowa State University Press, 1987;245-257.
12. FDA. Guidance for industry #209: the judicious use of medically important antimicrobial drugs in food-producing animals. Available at: www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf. Accessed Sep 18, 2018.
13. Apley MD, Fajt VR. Feedlot therapeutics. *Vet Clin North Am Food Anim Pract* 1998;14:291-313.
14. Thomson DU, White BJ. Backgrounding beef cattle. *Vet Clin North Am Food Anim Pract* 2006;22:373-398.
15. Antibiotic resistance: agencies have made limited progress addressing antibiotic use in animals. GAO-11-801. In: *Report to the ranking member, Committee on Rules, House of Representatives*. Washington, DC: US Government Accountability Office, 2011;6-7.
16. World Organisation for Animal Health. Terrestrial animal health code. Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals. Available at: www.oie.int/index.php?id=169&L=0&htmfile=chapitre_antibio_monitoring.htm. Accessed Sep 25, 2018.
17. AVMA. Definitions of antimicrobial use for treatment, control and prevention. Available at: www.avma.org/KB/Policies/Pages/AVMA-Definitions-of-Antimicrobial-Use-for-Treatment-Control-and-Prevention.aspx. Accessed Nov 14, 2018.

For all Viewpoint articles, opinions expressed are those of the authors and do not necessarily reflect the official policy of the AVMA.

Appendix

Definitions of antimicrobial uses for the prevention, control, and treatment of disease provided by the US Government Accountability Office (GAO)¹⁴ and the World Organisation for Animal Health (OIE).¹⁵

Antimicrobial use	US GAO	OIE
Prevention	Disease prevention: administered to a group of animals, none of which is exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered.	“To prevent”: means to administer an antimicrobial agent to an individual or a group of animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the drug is not administered.
Control	Disease control: administered to a group of animals when a proportion of the animals in the group exhibit clinical signs of disease.	“To control”: means to administer an antimicrobial agent to a group of animals containing sick animals and healthy animals (presumed to be infected), to minimize or resolve clinical signs and to prevent further spread of the disease.
Treatment	Disease treatment: administered only to animals exhibiting clinical signs of disease.	“To treat”: means to administer an antimicrobial agent to an individual or a group of animals showing clinical signs of an infectious disease.