

## ACVIM Consensus Statement

J Vet Intern Med 2015

Consensus Statements of the American College of Veterinary Internal Medicine (ACVIM) and European College of Equine Internal Medicine (ECEIM) provide the veterinary community with up-to-date information on the pathophysiology, diagnosis, and treatment of clinically important animal diseases. The ACVIM Board of Regents oversees selection of relevant topics, identification of panel members with the expertise to draft the statements, and other aspects of assuring the integrity of the process. The statements are derived from evidence-based medicine whenever possible and the panel offers interpretive comments when such evidence is inadequate or contradictory. A draft is prepared by the panel, followed by solicitation of input by the ACVIM membership which may be incorporated into the statement. It is then submitted to the *Journal of Veterinary Internal Medicine*, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

## ACVIM Consensus Statement on Therapeutic Antimicrobial Use in Animals and Antimicrobial Resistance

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The epidemic of antimicrobial resistant infections continues to challenge, compromising animal care, complicating food animal production and posing zoonotic disease risks. While the overall role of therapeutic antimicrobial use in animals in the development AMR in animal and human pathogens is poorly defined, veterinarians must consider the impacts of antimicrobial use in animal and take steps to optimize antimicrobial use, so as to maximize the health benefits to animals while minimizing the likelihood of antimicrobial resistance and other adverse effects. This consensus statement aims to provide guidance on the therapeutic use of antimicrobials in animals, balancing the need for effective therapy with minimizing development of antimicrobial resistance in bacteria from animals and humans.

**Key words:** Antibiotics; Antimicrobial stewardship; Public health; Therapeutics.

Development of antimicrobials was one of the landmark achievements in medicine. Availability of effective antimicrobial therapy has had a profound impact on human and animal health, improved human and animal welfare, and fostered production of safe and economical production of food. Antimicrobial therapy has allowed for medical advances such as surgery and chemotherapy that would otherwise be impossible, and without these drugs, human and veterinary medicine would bear little resemblance to their current states. However, as warned by Sir Alexander Fleming in his

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Submitted December 1, 2014; Revised January 21, 2015; Accepted January 27, 2015.

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DOI: 10.1111/jvim.12562

### Abbreviations:

AMR	antimicrobial resistance
CLSI	Clinical and Laboratory Standards Institute
ESBL	Extended spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	food and drug association
FDA-CVM	FDA Center for Veterinary Medicine
ICU	intensive care unit
MDR	multidrug resistant
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MRSP	methicillin-resistant <i>Staphylococcus pseudintermedius</i>
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
PK-PD	pharmacokinetic-pharmacodynamic
USP	united states pharmacopeia

Nobel Prize address,<sup>1</sup> use of antimicrobials can, and will, lead to resistance. While warnings of the end of the “antibiotic era” might be excessive, antimicrobial resistance (AMR) poses important challenges and has resulted in tremendous impacts on human and animal health, and the economics of both medicine and agriculture.

Concern has been expressed about the use, and perceived overuse, of antimicrobials in animals and the consequences for animal and human health, just as there are concerns about antimicrobial use and AMR in humans. This highly contentious and complex area will not be easily resolved, but it is clear that there is a need for improved antimicrobial use practices in veterinary medicine, human medicine and animal production, to reduce the prevalence and implications of AMR. While

it is important to engage other sectors, it is equally important for veterinarians to focus on areas where they can have the most direct impact, that being antimicrobial use in animals. In 2005, the first ACVIM consensus statement on antimicrobial therapy was published.<sup>2</sup> The principles put forth in that statement still apply. However, new issues continue to arise and knowledge continues to advance, giving rise to the need to expand on those principles. Accordingly, the objective of this consensus statement was to provide guidance on the therapeutic use of antimicrobials in animals, balancing the need for effective therapy and minimizing development and dissemination of antimicrobial resistance in bacteria from animals and humans.

### Statement Development Process

The statement was developed using an iterative process with various Committee members leading discussion and drafting initial text. This was then discussed and revised by the broader Committee. After development of the final draft, an objective evaluation process was used for each statement. Committee members used a 5-point Likert scale to rank each statement. For a statement to be adopted,  $\geq 75\%$  of members must have indicated that they strongly agreed (score = 1) or agreed (score = 2) with the statement.<sup>3</sup>

### Antimicrobial Use and Antimicrobial Resistance

Any use of antimicrobials, whether considered therapeutic or not, and prudent or otherwise, exposes bacterial pathogens and the commensal microbiota to varying concentrations of antimicrobial drug for variable times. This creates a selection pressure that can result in emergence of resistance or, if a resistant subpopulation is present, an increase in the abundance of resistant bacteria.

This statement was not created to ascertain the relative roles of antimicrobial use in humans and animals on AMR. This is a complex area that is hampered by important data gaps, although it is undeniable that antimicrobial use can result in AMR in the species that is being treated and that some resistant pathogens or resistance via plasmids can be transmitted bi-directionally between animals and humans. While the emphasis of this statement is on clinical aspects of antimicrobial use in veterinary medicine, some discussion of other aspects of antimicrobial use and AMR is required.

#### *What is the Relative Contribution of Therapeutic Use of Antimicrobials in Animals to Resistance among Human Pathogens?*

There is strong evidence that antimicrobial use in animals can promote resistance in some zoonotic pathogens,<sup>4</sup> yet data are far from conclusive and the relative impact of antimicrobial use in various animal species on AMR in human pathogens is inadequately quantified. It has previously been stated that, "Although some

antibiotics are used both in animals and humans, most of the resistance problem in humans has arisen from human use".<sup>5</sup> The Committee agrees that antimicrobial use in a single animal species (or humans) is the main force behind development of AMR in bacteria infecting or colonizing that species, but that does not mean that interspecies transmission is not important. Indeed, transmission of resistant bacteria from animals to humans is an important concern, albeit one that is inadequately understood.

#### *Does Therapeutic Antimicrobial Use (Prudent or Otherwise) in Humans Contribute to Resistance Among Animal Pathogens?*

While direct evidence is often lacking, there is key circumstantial evidence indicating human origin, human-to-animal, or both modalities of transmission of some antimicrobial resistant pathogens, particularly in horses and household pets,<sup>6-8</sup> but also in livestock.<sup>9</sup> Yet, once human-to-animal transmission occurs, this creates the potential for further transmission back to humans or to other animals. Examples include the presence of human epidemic clones of methicillin-resistant *Staphylococcus aureus* (MRSA) in household pets<sup>10-12</sup> and in horses,<sup>7,13,14</sup> identification of contact with human hospitals or children as risk factors for MRSA and *Clostridium difficile* acquisition by dogs,<sup>15</sup> identification of antimicrobial exposure of an owner as increasing the risk of *C. difficile* shedding in dogs,<sup>15</sup> the presence of common human clones of multidrug resistant enterococci, such as clonal complex 17, in pets<sup>16</sup> and multidrug resistant Gram-negative pathogens from dogs, cats, horses and people carrying the same resistant genes.<sup>17,18</sup> Human-animal transmission of MDR pathogens should not be taken as an indication that human influences are greater than veterinary influences, but rather as an indicator of the complexity of the issue.

#### *Does Therapeutic Antimicrobial Use (Prudent or Otherwise) in Animals Contribute to Resistance Among Animal Pathogens?*

Some data indicate that therapeutic antimicrobial use in various animal species contributes to antimicrobial resistance among animal pathogens, but there is a relative paucity of information compared to that in the human literature and a profound lack of information on specific drugs and drug classes that produce the greatest risk. The emergence of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) perhaps provides the most compelling argument about the potential for emerging resistance in dogs, with profound increases in MRSP carriage and infection and evidence of a role of antimicrobials in selection for this resistant opportunist.<sup>19-22</sup> Similar evidence of a role of antimicrobial exposure has been reported for methicillin-resistant *S. aureus* (MRSA) in horses.<sup>23,24</sup> As another example, the cumulative incidence of macrolide and rifampin resistance in *Rhodococcus equi* has been increasing over

the past 10 years and foals infected with resistant isolates are more likely to die than foals infected with susceptible isolates.<sup>25</sup> In recent years, strains of *Mannheimia haemolytica* and *Pasteurella multocida* that are resistant to several antimicrobials in clinical use have been isolated from cattle with respiratory disease,<sup>26–28</sup> however, there are issues with sampling bias and regional differences that hamper any broad conclusions. Yet, there are also specific examples where treatment has not typically been associated with development of resistance, such as the predictable susceptibility of *Streptococcus equi* subspecies *equi* and *S. equi* subspecies *zooepidemicus*.

More information is needed on the effect of antimicrobials on the emergence of resistance in nontarget bacteria, particularly the vast intestinal microbiota that contains myriad opportunistic pathogens and reservoirs of antimicrobial resistance. Resistance can develop in these reservoir populations, as demonstrated by detection of cefotaxime-resistant or ceftiofur-resistant fecal *E. coli* strains in dogs treated with ceftiofur or ceftiofur, respectively.<sup>29,30</sup> There are inconsistent results regarding AMR that might result from drug exposures used for treatment of clinical disease in cattle. Some experimental work suggests there can be profound shifts in the resistance prevalence for *E. coli* and increased identification of resistance genes when cattle are treated with ceftiofur.<sup>31,32</sup> However, it is unknown whether these changes represent transient or permanent shifts in the microbiota, and the effects of antimicrobial exposures in experimental settings have not always been completely predictable.<sup>33</sup> Further, associations between exposure and resistance have not been as strong or predictable in studies conducted under field conditions.<sup>34,35</sup> These various studies of resistance in cattle highlight the complexity of factors affecting microbial ecology, and the impacts of antimicrobial exposures are not fully understood at this time in any host species.

### ***Are MDR Pathogens More Virulent than their Susceptible Counterparts?***

It is commonly accepted that infections with antimicrobial-resistant organisms are generally associated with increased morbidity, increased case fatality risk, and increased treatment costs when compared to their antimicrobial-susceptible counterparts. However, the reasons behind this are complex and not entirely explained by available data, which are mostly from human studies. For example, various studies suggest that infections caused by resistant bacteria, such as MRSA, are associated with increased case fatality, morbidity and costs compared to those caused by susceptible strains, such as MSSA.<sup>36–38</sup> However, much of the discrepancy in outcomes between antimicrobial-susceptible and antimicrobial-resistant organisms is related to ineffective initial (empirical) antibiotic therapy, resulting in a delay in the control of infection, and not necessarily because of increased virulence of resistant organisms.<sup>39,40</sup> Furthermore, some studies that have compared outcomes of infection with resistant organisms to that caused by

their susceptible counterparts have not shown significant differences in outcome *once appropriate antimicrobial therapy was administered*.<sup>41,42</sup>

Veterinary data evaluating the clinical impact of antimicrobial-resistance are limited. No difference in outcome has been reported in studies of methicillin-resistant versus methicillin-susceptible staphylococcal infections in dogs,<sup>22,42,43</sup> yet those studies have been relatively small or dominated by conditions that are unexpected to develop severe complications or death, for instance, pyoderma in dogs.

The Committee recognizes that infection with antimicrobial-resistant organisms might be associated with worse outcomes in some instances; however, this is most likely because of delayed onset of appropriate antimicrobial therapy and not because of increased inherent virulence. Most infections caused by MDR pathogens should be no more virulent than those caused by their susceptible counterparts *if the resistant pathogen is promptly identified and appropriate antimicrobial therapy is initiated*. Thus, it is critical for proper diagnostic testing, including bacterial culture and susceptibility testing, to be performed early in disease, whenever possible, to facilitate rapid initiation of appropriate therapy. Further, the Committee emphasizes that simple identification of a resistant pathogen does not necessarily mean that the bacterium is the cause of disease or that a different treatment response is required (aside from selection of an appropriate drug). The presence of a multidrug resistant pathogen alone is not an indication for the use of more recently developed drugs versus earlier antimicrobials to which the bacterium might be susceptible, or longer durations of the treatment.

The economic impact of antimicrobial resistance remains to be adequately investigated. It is likely that infections caused by resistant pathogens will increase the cost of treatment for animal owners, at least in some situations. Increased costs occur because of the expense related to follow-up visits, follow-up culture and susceptibility tests and for costly treatments that must be used to treat some multidrug resistant pathogens where no other alternatives exist. In addition, some antimicrobials that are required for the treatment of MDR pathogens, such as chloramphenicol, might have greater risk of injury to the kidney, liver, or bone marrow, necessitating monitoring for adverse effects of treatment.

### **What Action should be Taken to Reduce the Risk and Occurrence of Antimicrobial Resistance Related to Therapeutic Use of Antimicrobials in Veterinary Medicine?**

#### ***General Methods to Reduce Antimicrobial Resistance***

There are 3 main general approaches that have been recommended for limiting AMR; preventing disease occurrence, reducing overall antimicrobial drug use and improved antimicrobial drug use. Preventing disease is a critical aspect of antimicrobial stewardship and one that is often overlooked. Quite simply, if disease occurrence

can be reduced, the pressure to use antimicrobials therapeutically can be similarly reduced. This involves aspects including good animal care and husbandry, including appropriate use of efficacious vaccines, use of infection control measures in veterinary hospitals and on farms and other basic disease prevention and control approaches. Difficult-to-treat, resistant infections often occur in association with invasive therapies and intensive treatment of sick animals, and veterinarians must take increasing notice of the importance of practices that can decrease risks for infection in these animals. Full discussion of disease prevention methods is beyond the scope of this Statement but the importance of these measures cannot be overemphasized.

Efforts to reduce and improve antimicrobial drug use are receiving increasing attention, particularly in human healthcare. It is reasonable to assume that reduced antimicrobial use in animals might reduce emergence and dissemination of AMR in some situations, something that has been suggested through voluntary or mandatory restriction of certain antimicrobials in food animals.<sup>4,44</sup> However, the association is not absolute and unintended consequences must be considered. For example, use of high levels of dietary zinc as an alternative to antimicrobials for prevention of postweaning diarrhea in pigs can result in as strong a selection pressure for MRSA as administration of tetracycline, because of colocation of zinc and methicillin-resistance genes.<sup>45,46</sup> Further, if reduced prophylactic use of antimicrobials results in increased disease rates and therapeutic use of newer antimicrobials with more profound impacts on the commensal microbiota, the net benefit of overall antimicrobial reduction can be lost. The Committee emphasizes the need to reduce the reliance on antimicrobials but also the need to study the impacts and ensure that there are no unintended increases in resistance associated with interventions.

### ***Controlling Disease without Antimicrobials***

Not all animals that are ill have bacterial infections and not all bacterial infections require treatment with systemic, or indeed any, antimicrobials. Further, worsening disease states of critically ill animals is not necessarily a reason to escalate antimicrobial treatments. Consideration of these basic points can reduce overall antimicrobial use while optimizing animal care. Viral infections, immune-mediated conditions, inflammatory conditions such as pancreatitis and neoplasia can cause fever and other signs often attributed to bacterial infection. Early diagnostic intervention as a substitute for the empiric use of antimicrobials can help to resolve this question. Further, it is uncommon for most types of bacterial infections to occur without a predisposing condition, and repeated treatment with antimicrobial drugs without attention to the underlying cause might ultimately be futile clinically and lead to increased risk of AMR. Attention to the underlying cause alone might lead to resolution of a secondary bacterial infection, without the need for antimicrobial drugs. Therefore, the Committee emphasizes the need for veterinarians to

pursue appropriate diagnostic testing, whenever possible, and to counsel animal owners and producers about the importance of diagnostic testing. Ultimately, time and money spent on diagnostic testing can likely reduce morbidity, case fatality and overall treatment costs in many situations.

Even when bacterial infections are identified, systemic antimicrobial therapy might not be the optimal approach. Incision and drainage is the preferred method for treatment of localized abscesses, with no evidence that concurrent antimicrobial therapy is necessary for resolution. Local therapy with biocides or antimicrobial drugs might be equally (or more) effective in some situations, such as the use of chlorhexidine bathing for treatment of superficial folliculitis in dogs. Additionally, the prudence of treating moribund animals with antimicrobial drugs must also be questioned. Antimicrobial drugs, especially those of critical importance to human health, should never be used without reasonable expectation that they will favorably impact the course of disease.

### ***Should Access to Some Antimicrobials be Restricted?***

The Committee strongly supports a recommendation that all antimicrobials intended for use in animals (excluding ionophores) should be available only by prescription by a veterinarian with a valid veterinarian/client/patient relationship. Over-the-counter (OTC) access to antimicrobials from sites such as feed supply stores or pet stores is contrary to basic concepts of prudent and effective antimicrobial use and could constitute an animal welfare concern if sick animals do not receive proper veterinary care. Furthermore, nonprescription use of some drugs can presumably increase the risk of resistance, result in ineffective therapy and unnecessary animal suffering and increase the risk of drug residues in food animals.

In some regions of the world, prescription and use of selected antimicrobials are restricted or banned in veterinary medicine based on residue or antimicrobial resistance concerns, and willingness of regulatory bodies to restrict veterinary access to certain antimicrobial classes appears to be increasing, particularly in northern Europe. This is a highly contentious topic because of the need to balance animal health and welfare, the human-animal bond and public health, most often with limited objective data. These factors are vastly different in food animals compared to companion animals and horses, yet these differences are often not considered. Additionally, postrestriction surveillance data are often lacking to determine whether these restrictions will have an impact on resistance in animal and human pathogens, which translates to adverse impacts on public health. Whether or not restriction or prohibition policies are scientifically justifiable is a subject of considerable debate because of the lack of evidence or conflicting evidence, a debate that gets complicated with concerns about animal welfare, food safety, the “right” or responsibilities of veterinarians to use antimicrobials in an off-label manner and perceived overuse in human medicine.

The Committee considers regulatory restriction or prohibition of use of selected antimicrobials by licensed veterinarians to be a complex and unresolved issue that is lacking in adequately rigorous scientific data. In the absence of clear evidence, the Committee supports a cautious approach (the “precautionary principle”) to the use of antimicrobials in animals but emphasizes the need to consider animal welfare, economic and human-animal bond issues, new evidence and unintended consequences. Any restrictive policy should be accompanied by a robust surveillance plan to evaluate the impact of the intervention on antimicrobial resistance, as well as animal health and welfare and public health. Further, clear data are lacking regarding antimicrobial use in companion animals in most regions with respect to both overall volume and drug-specific use, and better tracking mechanisms are required to facilitate assessment of the risk to public health of antimicrobial use in food and companion animals.

The Committee believes that voluntary restriction is a preferable approach as it can allow for regionally relevant approaches that balance animal care and antimicrobial resistance concerns. The exceptions are those antimicrobials for which the regulatory authorities (e.g. FDA-CVM in the United States) have banned in food-producing animals because of concerns of harmful residues (eg, chloramphenicol, nitroimidazoles and nitrofurans) or are restricted because the agency believes that they pose a risk for causing antimicrobial resistance that can be transferred to people (eg, glycopeptides, extra-label use of fluoroquinolones and cephalosporins and extra-label use of sulfonamides in dairy cattle). A voluntary approach is only effective if guidelines are adequately rigorous, based on sound evidence, and if there is good compliance. Therefore, if veterinary medicine cannot, or will not, take serious measures to foster prudent use of certain drug classes, regulatory restrictions would be justifiable. To avoid mandatory restrictions by regulatory bodies, the Committee believes that the veterinary profession must be proactive in its approach to control the use of antimicrobial agents in animals. This could take the form of national, regional (state/province) or practice-specific guidelines and antimicrobial stewardship programs to foster reduced overall antimicrobial use and to provide specific criteria that must be fulfilled before a “critically important antimicrobial” might be used. To facilitate this, a clear understanding of what constitutes a “critically important antimicrobial” is needed. The current World Health Organization definition<sup>47</sup> is not useful in this context because it encompasses most of the antimicrobials used in veterinary medicine, including drugs whose use should be encouraged over other options. Some guidance is available from efforts such as the FDA’s “Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern”.<sup>48</sup> However, much of the difficulty revolves around a lack of evidence, so while expert opinion and regulatory guidance can be useful, those recommendations are still made with a paucity of high quality data.

Related to this is the often-discussed concept of avoiding or limiting the use of “critically important antimicrobials” because they are important from a public health standpoint. However, as mentioned above, excluding the use of drugs on the current World Health Organization list of critically important antimicrobials is not practical because it encompasses most of the antimicrobials that are used clinically, including older drugs whose use should be fostered. The Committee recommends that the concept of critically important antimicrobials be reviewed to develop categories that are practical in the context of therapeutic antimicrobial use in companion and food animals, yet maintain the principles of antimicrobial stewardship.

### *Is On-label Use Equivalent to Prudent Use?*

Prudent use of antimicrobial agents is often defined broadly as the optimal selection of drug, dose and duration of antimicrobial treatment along with reduction in inappropriate and excessive use, as a means of achieving the best clinical outcome while minimizing the emergence of antimicrobial resistance.<sup>49</sup> Because of regulations prohibiting the extra-label use of certain drugs, there is a common misconception that the use of antimicrobial agents according to the label is always consistent with the principles of prudent use of antimicrobial agents. However, the label dose, dosing interval and indications for older drugs are not always consistent with current principles of antimicrobial drug use. Some approved labels provide information that is over 30 years old and not based on solid evidence. For example, procaine penicillin is widely available in the United States and many other countries for intramuscular injection at a dose of 6,700 IU/kg q24h. This dose is much lower than current recommendations (22,000 IU/kg q12h) and the dose that forms the basis of CLSI breakpoints.<sup>50</sup> Dosage recommendations for most antimicrobial agents approved more recently are typically based on more comprehensive scientific data. Nevertheless, even use of more recently approved agents according to label is not always consistent with all principles of prudent antimicrobial drug use. Most antimicrobial agents approved in recent years were approved for a narrow indication, but these drugs, such as fluoroquinolones and later generation cephalosporins, possess activity against a wide range of bacteria and potential far-reaching effects on the microbiota. There can be increasing conflict between the use of newer drugs with label claims versus “older” options which do not necessarily have label claims consistent with modern clinical practice. Thus, while label indications must be a consideration when choosing an antimicrobial agent, particularly in food animals, this cannot be done at the exclusion of broader aspects of prudent use.

### *Compounding of Antimicrobials*

Compounding is usually performed for ease of administration to improve compliance, but has also

been done to create a lower cost alternative to an approved product. Compounding can also include the process of combining a drug with one or more active ingredients to create a final formulation in an appropriate form for dosing. Examples of appropriate compounding in veterinary practice include mixing 2 approved drugs, preparing an oral paste or suspension from crushed tablets, or adding flavoring to an approved drug. Compounded preparations are not equivalent to generic drug products, as generic products are approved by the appropriate regulatory authorities (eg, FDA) based on evidence of bioequivalence in comparison to the innovator product (approved reference formulation). Compounded preparations lack approval from regulatory authorities.

Regulatory bodies must be cognizant of the importance of compounding in veterinary practice, but also must ensure that compounded drugs do not cause harm to the treated animals, produce ineffective potency, or lead to residues in food animals. In the United States, FDA regulations permit the compounding of formulations from approved animal or human drugs (Federal code 21 CFR 530.13), but compounding from bulk drugs or unapproved drug substances is not allowed except for a few compounds that are not subject to regulatory action, none of which are antimicrobials. Yet, compounding from bulk drugs is commonly practiced by some pharmacies.

Although there are legitimate reasons to compound antimicrobials for individual animals, on an as-needed basis, there are reasons for concern. Unless specific studies have been conducted, compounded products have uncertain pharmacokinetic profiles and unknown stability, potency, and safety. Many antimicrobials are subject to instability and inactivation when mixed with incompatible excipients or exposed to light. The pH of the resulting suspension or solution might not be compatible with stability or solubility of the antimicrobial. A drug solution or suspension might be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it might degrade in minutes or days. Some studies on veterinary compounded products have found tested products to be both under- and over the mandated range of  $\pm 10\%$ .<sup>51-53</sup> There can also be inadequate bioequivalence compared to brand name products.<sup>54</sup> The beyond-use-date for aqueous (water-containing) oral formulations stored at controlled cold temperatures is 14 days, but this is frequently exceeded on labeling from compounding pharmacies. Furthering concern was a study of compounded doxycycline that identified profound decreases in drug concentration after 7 days of storage,<sup>51</sup> indicating that even this 14 day limit might be excessive for some products. Extreme potency variation can result in administration of sub-therapeutic antimicrobial doses, which has the potential to increase the selection of antimicrobial resistant bacteria, or overdosing, which might result in adverse effects.

The Committee recognizes that there are situations in selected animals for which compounding from approved animal or human drugs is necessary because no other

method or route of drug delivery is practical. This can include crushing tablets to combine the drug with syrup or another substance for palatability and ease of delivery. This must be done on a animal-by-animal basis by an individual with adequate knowledge of compounding practices, compound stability and other relevant issues. Currently, the Committee sees no legitimate reasons for the compounding of antimicrobial agents in food producing animals. The Committee strongly urges regulatory authorities to enforce existing regulations on compounding and to abolish the practice of compounding antimicrobial agents from bulk chemicals or active pharmaceutical ingredients. The Committee also discourages compounding of antimicrobials into transdermal preparations unless there are data to support the maintenance of adequate drug concentrations and efficacy, because the potential for inadequate drug concentrations raises concerns for both animal care and antimicrobial selection pressure.

### *Use of Generic Antimicrobials*

The use of generic antimicrobials is acceptable if approached with the same stewardship principles as brand-name drugs. While manufacturers of generic drugs are not required to replicate safety and efficacy studies, properly manufactured generic antimicrobials are bioequivalent to their brand name counterparts and similar efficacy is expected. However, use of a related human generic drug in lieu of a licensed veterinary drug (eg, use of ciprofloxacin in dogs as a cheaper alternative to licensed veterinary fluoroquinolones) is not recommended when efficacy or bioavailability data are lacking for the generic drug compound or where bioavailability is known to be poorer or less predictable than for the licensed veterinary drug.<sup>55</sup>

### *How should Veterinary Internal Medicine Specialists Interact with Diagnostic Laboratories to Facilitate Prudent Use of Antimicrobials?*

Veterinarians should have a relationship with their diagnostic laboratories so that they can discuss test results with the microbiologist. Veterinarians should feel comfortable asking questions about appropriate testing standards, and asking for follow-up susceptibility information (sometimes called extended-panels) and discussing unexpected results.

Veterinarians should rely on a laboratory that uses appropriate standards for testing. These include (but are not limited to the European Committee on Antimicrobial Susceptibility Testing (EUCAST, <http://www.eucast.org/organization/>) and the Clinical and Laboratory Standards Institute (CLSI, <http://clsi.org/>). Currently, only the CLSI has testing standards and methods for veterinary isolates,<sup>50,56</sup> which are prepared by the Veterinary Antimicrobial Susceptibility Testing subcommittee. It is important for laboratories to use the most current document because breakpoints are revised and added with each new edition.

### ***Should Diagnostic Laboratories Test and Withhold Culture and Susceptibility Results for Certain Antimicrobial Drugs or Isolates?***

Data reporting from diagnostic laboratories can impact whether antimicrobials are prescribed and which drugs are selected. In human medicine, laboratories do not typically report the isolation of bacteria that are deemed to be contaminants, including bacteria consistent with commensal microorganisms that are present at the sampling site. In veterinary medicine, there are no standards and the approach is variable between laboratories. The Committee encourages diagnostic laboratories to withhold reporting of isolates that are deemed clinically irrelevant based on the bacterial species identified and the site of infection. However, for this to be effective and not potentially impact animal care, it is critical that this determination be made by a microbiologist, preferably a veterinary microbiologist, with an adequate clinical background. Clear reporting guidelines are needed to facilitate this process and are currently lacking.

Similarly, in human medicine, diagnostic laboratories often do not report results for all tested antimicrobials. Rather, drugs that are typically effective against the pathogen and which are recommended for initial use are reported, while other drugs are tested but results are withheld, so that clinicians do not unnecessarily prescribe those drugs in situations where they are not required or where the drug is not appropriate, such as nitrofurantoin in isolates not from urine. Some laboratories use *cascade reporting*, which is another form of *selective reporting*. Cascade reporting of antimicrobial susceptibility test results is a strategy in which secondary agents are only automatically reported if an organism is resistant to primary agents within a particular drug class. Each laboratory typically makes decisions about which drugs to report and in what situations, ideally in consultation with relevant clinical experts. There are no standard approaches in veterinary medicine. The Committee supports the use of selective reporting as a measure to both optimize animal care and foster antimicrobial stewardship. Dialog between laboratories and clinicians is required to ensure there is adequate understanding of the laboratory's testing and reporting protocols.

### ***In-clinic Culture***

Performing bacterial culture in a veterinary clinic (in-house) can be useful because of a shorter turnaround time, less chance of loss of viability or overgrowth during storage and shipping, and potentially lower costs. Simple, in-clinic culture kits have become widely available in recent years, particularly for culture of urine and milk specimens. While potentially useful to rule out infection, limitations in specificity and accuracy of bacterial identification<sup>57</sup> have also been identified, in contrast to a study of a different assay in humans.<sup>58</sup> This highlights the need for continued species-specific validation of these assays in field studies to determine their

clinical sensitivity and specificity. Clinicians must consider whether they are using these tests to recover isolates for subsequent identification and testing by a microbiology laboratory or whether they desire (or require) identification in-house, as would be the case for in-house susceptibility testing. At least one of these assays offers a limited ability to determine antimicrobial drug susceptibility, but this component of the kit was found to generate inaccurate results in one field study.<sup>59</sup>

Another common practice in some regions is inoculation of bovine mastitis isolates onto penicillin-impregnated agar, to determine whether the isolates are penicillin susceptible. Accuracy of testing can be evaluated by routine proficiency testing, as is done in Denmark. In regions where bovine mastitis isolates are widely penicillin-susceptible, a simple and cost-effective approach like this could foster the use of this drug. However, these simple tests are in contrast with more substantive approaches to antimicrobial susceptibility testing that require rigorous testing and quality control practices, and care must be taken when performing tests and interpreting results.

Veterinarians and clinics considering in-house culture must evaluate the costs and benefits, and whether they can perform quality testing in a safe manner. If not performed properly, in-house culture can be clinically misleading, if not harmful, and pose a risk to personnel through exposure to large numbers of drug-resistant bacteria, bacterial pathogens that require enhanced laboratory biosafety practices (eg, *Brucella* spp.) or unexpected isolation of pathogenic fungi. Notably, erroneous bacterial identification and antimicrobial susceptibility testing results can contribute to antimicrobial drug misuse or treatment failure. Commercial diagnostic laboratories typically have experienced personnel, specialized facilities and equipment, structured testing practices, and comprehensive quality control and biosafety programs. While it is unrealistic to expect a veterinary clinic to replicate those practices, the general concepts must be maintained and clinics must ensure that they have adequate facilities and equipment, adequately trained staff, a proper quality control program and a biosafety program. If a clinic cannot meet standard containment level 2/biosafety level 2 protocols, they should not attempt culture. Clinics must consult with local authorities to determine legal requirements, since culture is more strictly regulated in some jurisdictions.

In-house culture might be best used a screening tool (at least for urine and milk specimens), with identification and susceptibility testing of isolates performed at an external veterinary diagnostic laboratory because of the need for added expertise. Clinics must ensure that they can fulfill pathogen shipping regulations if this approach is taken. Susceptibility testing must only be performed on bacteria that have been properly identified, and must be performed according standard guidelines. A quality control program must be in place, including the use of quality control strains. This is beyond the ability of most veterinary clinics and considering the importance of accurate susceptibility data, the Committee believes that antimicrobial susceptibility test-

ing should be performed only by appropriately equipped laboratories that comply with standard (eg, CLSI) guidelines.

### ***De-escalation of Antimicrobial Therapy***

It is preferable to commence antimicrobial therapy using an approach targeted towards the known or likely pathogen(s). However, in some situations, use of antimicrobials that are effective against a wide range of pathogens might be required or initial treatment might have been started at another facility. This is typically in animals with life-threatening disease such as sepsis, septic peritonitis or pneumonia, yet even in cases such as these, transition to more targeted treatment for longer term therapy can often be achieved based on culture and susceptibility testing results, additional diagnostic information and clinical progression. In some cases, the initial treatment is unnecessarily continued because of a failure to consider alternatives, even when a pathogen is identified and its susceptibility determined. Also, situations can arise whereby antimicrobials are added to an existing antimicrobial treatment regimen without considering whether all drugs are compatible or must be continued. Both of these scenarios can result in use of excessively broad regimens that have no clinical benefit over more narrow approaches but which can increase the risks of adverse effects, drug–drug interactions, drug cost and antimicrobial resistance selection pressure. While high level data are lacking,<sup>60</sup> in humans, de-escalation has been associated with either no negative clinical impact<sup>61,62</sup> or improved patient outcome, including for life-threatening conditions such as sepsis.<sup>63</sup>

In human medicine, considerable efforts are underway to promote de-escalation, based on both patient care and antimicrobial resistance concerns. This involves a variety of approaches including education, pharmacist intervention and restricting automatic continuation of antimicrobial prescriptions, as well as novel approaches such as automated “best practice alerts” to alert clinicians about the need to re-consider therapy (i.e., de-escalation or discontinuation).<sup>64</sup> This range of approaches should be considered in veterinary medicine.

The Committee recommends that the antimicrobial treatment regimen be assessed regularly during therapy, and that de-escalation be considered whenever possible. Before addition of antimicrobials to a animal’s regimen consideration should be given of whether the currently administered antimicrobials should be discontinued.

### ***Duration of Therapy***

There is limited evidence to guide duration of therapy for most conditions in animals. While recommendations are available in clinical guidelines,<sup>65</sup> review article or general (eg, textbook) references, these have limited scientific foundation. The Committee emphasizes the need for properly designed randomized clinical trials to provide guidance on optimal duration of therapy. That is particularly true in light of recent randomized trials in humans that have provided support for shorter treat-

ment durations in many infectious syndromes, including pneumonia, skin-soft tissue, pyelonephritis and UTIs in men.<sup>66–69</sup> In lieu of proper trials, there should be consideration of the animal’s condition, recommendations from veterinary resources and data from human medicine. While the Committee recognizes that direct comparisons with human dosage regimens should be done with care, treatment durations are typically shorter in humans compared to corresponding veterinary recommendations,<sup>65,70</sup> with little apparent justification for longer therapy in animals. Shorter durations of treatment reduce exposure of commensal bacterial populations to antimicrobial drugs<sup>71</sup> and are likely to be associated with improved client compliance, reduced cost and inconvenience to the client, and a reduced likelihood of adverse drug effects. While study has been limited in veterinary medicine, recent data have indicated lack of inferiority of short courses of antimicrobial therapy compared to typical long-term therapy for urinary tract infections in dogs.<sup>72,73</sup> Investigation of shorter durations of therapy for other species and conditions is needed.

A common misconception is the need to complete a minimum duration of an antimicrobial drug to prevent the emergence of resistance. The Committee is aware of no foundation to this and antimicrobials should never be continued once there is clinical and microbiological evidence that an infection has been eliminated or once an alternate diagnosis has been made, simply because of a perceived need for a minimum duration of administration.

### ***Use of Periodic Antimicrobial Dosing***

Some animals are periodically treated with antimicrobials to prevent disease, typically recurrent infections. Examples include single daily (usually night-time) dosing of amoxicillin for prevention of bacterial UTI, periodic short courses of cephalexin for prevention of superficial folliculitis in dogs and intermittent administration of azithromycin for prevention of *Rhodococcus equi* pneumonia. In the absence of strong evidence supporting these practices, the Committee discourages such approaches because these approaches fail to adhere to sound PK-PD concepts and the lack of evidence of efficacy or the impact on antimicrobial resistance. While clinical impression suggests that these approaches might be effective in some animals with complicated and difficult-to-control disease, this approach should not be used in lieu of comprehensive investigation of underlying causes and the use of other preventive measures, along with careful consideration of potential costs and benefits.

### ***Use of Antimicrobials for Nonantimicrobial Activity***

Antimicrobials might have properties beyond that of their antimicrobial effect, such as anti-inflammatory, immunomodulatory or prokinetic properties.<sup>74–77</sup> The clinical relevance of these is poorly understood, with compelling evidence of efficacy lacking and no data per-

taining to potential adverse effects. While not discounting potential beneficial nonantimicrobial effects, until strong evidence is available the Committee does not support the use of antimicrobials for their nonantimicrobial effects.

### *Use of Screening Cultures in Animals*

The Committee strongly supports the use of bacterial culture to guide diagnosis and treatment of disease. However, isolation of *potential* pathogens in the absence of clinical evidence of disease can lead to unnecessary antimicrobial use and might only promote colonization or infection by antimicrobial-resistant bacteria. Therefore, the Committee recommends that clinicians refrain from requesting culture when clinical signs of disease are absent (with the exception of testing done as part of structured infection control surveillance programs). While it might seem counterintuitive, the concept of “knowing less leads to doing less”<sup>78</sup> has been discussed in human medicine, “doing less” (ie, less unnecessary testing) being a positive outcome (ie, less unnecessary antimicrobial use) in many situations.

Isolation of bacteria from the urine of clinically normal individuals (“subclinical bacteriuria”) is a leading example of this. Although routine screening of selected populations for bacteriuria such as animals with diabetes mellitus or those treated with immunosuppressive drugs has been suggested,<sup>79,80</sup> evidence that these animals should be treated is lacking. As a result, it has been recommended by others that animals with subclinical bacteriuria not be routinely treated.<sup>65</sup> Human guidelines recommend against treatment of subclinical bacteriuria except in specific circumstances, such as pregnant women or before invasive urological interventions.<sup>81,82</sup> There is also evidence that treatment of subclinical bacteriuria might increase the likelihood of recurrent UTI in humans.<sup>83</sup> In addition to strong recommendations against treatment of subclinical bacteriuria in antimicrobial use guidelines and antimicrobial stewardship programs, other approaches in human medicine include discouraging routine culture submission and having laboratories withhold urine cultures reports until results are specifically requested by the physician.<sup>78,84,85</sup> Similarly, culture of sites usually colonized by commensal organisms where clinical interpretation of results is difficult or impossible, such as bacterial culture of nasal or vaginal swab specimens, is not recommended.

### **Other Issues**

There are many situations where veterinarians might be able to reduce antimicrobial use, in addition to those described above. This would include reduction in the use of antimicrobials to treat healthy animals with positive serologic tests for tick-borne pathogens or prophylactic treatment of animals after tick removal, neither of which imply the presence of infection. Veterinarians should also be discouraged from prescribing antimicrobial drugs for a recurring problem

without re-examination of the animal. In addition, when antimicrobial drug therapy is discontinued, clients should be encouraged to return unused antimicrobial drugs to their local veterinary hospital or pharmacy for disposal so that clients do not store old prescriptions that they might subsequently use (inappropriately) at their discretion.

### **Moving Forward**

Many fundamental questions remain. In this Statement, use of “narrow spectrum” and “broad spectrum” was avoided because, while they are commonly used, there are no clear and logical definitions for these terms. Indeed, some antimicrobials often referred to as “narrow spectrum” have wide-reaching effects on the bacterial microflora? Further, from the standpoint of antimicrobial resistance pressure, spectrum is only one aspect and the amount of active drug that reaches sites populated by the commensal microbiota might actually be a greater concern.

Similarly, the use of antimicrobial “tiers” was avoided. While the Committee supports the concept of assigning drugs to tiers and focusing use on “first tier” drugs, it is difficult to assign drugs to different tiers with any degree of confidence and objective data. Tiers should be assigned based on the spectrum of activity, activity of the drug at commensal microbiota sites, likelihood of resistance emergence and importance of the drug for treatment of serious infections in humans and animals, yet data required to make these determinations are typically lacking. While limiting use of classes such as the 3rd generation cephalosporins and fluoroquinolones is widely accepted and consistent with principles of antimicrobial stewardship, the relative impact of many other commonly used drugs on antimicrobial resistance is poorly understood. For example, recent data indicate that cephalexin, a drug typically assigned to the “first tier”, might contribute to the spread of extended spectrum cephalosporin resistance in Enterobacteriaceae.<sup>29</sup> These points are not raised with a goal of stopping the use of tier-based antimicrobial selection, but as an indication that more information is required to properly assign drugs to tiers.

### **Conclusions**

Antimicrobials are among the most important treatment options available in veterinary and human medicine. Yet, antimicrobial resistance has progressively compromised their efficacy. This has affected patient care (in both humans and animals) and heightened awareness and concern about the use of antimicrobials in animals. It is critical for the veterinary community to engage in discussions pertaining to prudent and effective antimicrobial use and to consider ways to improve antimicrobial use practices, to optimize animal care, reduce antimicrobial resistance selection pressure and maintain access to important antimicrobial agents. There are no simple solutions to this complex problem, yet veterinarians must consider the influence of the decisions that they make on

a daily basis and optimize antimicrobial use for the benefit of their patients and society as a whole.

### Acknowledgment

**Conflict of Interest Declaration:** The authors declare the following sources of research grants, speakers' fees, consultation fees or other funds as follows: JSW: Zoetis and Merck; SG: Bayer Animal Health, Merial, Zoetis, Merck; LG: None; PM: None; MP: Novartis, Bayer Animal Health, Zoetis, Merck, Putney, Pennfield; DR: None; JS: IDEXX, Bayer Animal Health, Zoetis.

**Off-label Antimicrobial Declaration:** Authors declare no off-label use of antimicrobials.

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