

Antimicrobial Selection: Considerations for Veterinarians

**California Department of Food
and Agriculture**
Antimicrobial Use and
Stewardship

UC Davis
California Animal Health and
Food Safety Laboratory



CALIFORNIA DEPARTMENT OF
FOOD & AGRICULTURE



ANTIMICROBIAL USE
AND STEWARDSHIP



UC DAVIS
VETERINARY MEDICINE

California Animal Health
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*Note: This document provides a brief overview of concepts for consideration when using antimicrobial susceptibility test data to guide clinical decisions. This information should not supersede clinical judgment or other, more detailed resources. For further information on this topic, please reference VET09 from the Clinical and Laboratory Standards Institute (CLSI).¹ VET09 can be found by **clicking here** or by pasting this URL into your web browser:
<https://clsi.org/standards/products/veterinary-medicine/documents/vet09/>*

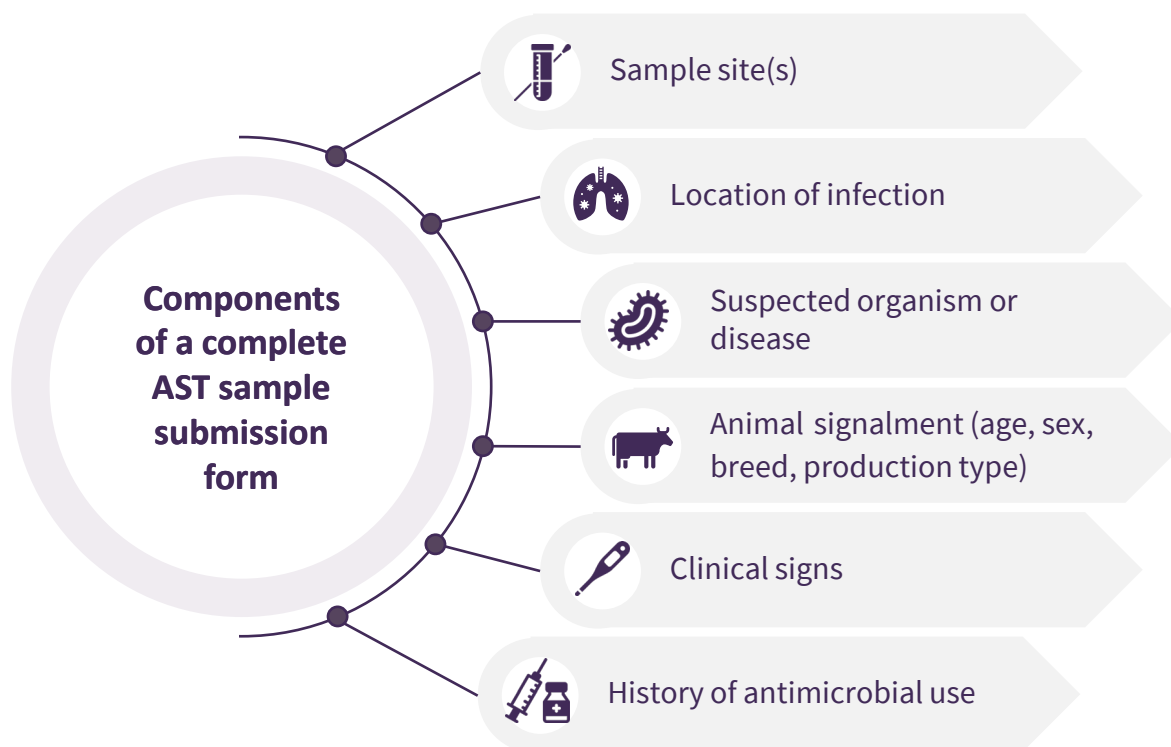
Sample collection & submission



Laboratory assessment of clinical specimens requires **appropriate sample collection, labeling, and transport**. A sample that is contaminated or compromised during collection or transport could lead to incorrect test results and, therefore, affect clinical decisions. Clinicians should abide by their laboratory's instructions for supplies, labeling, and packaging materials for transport.

Choosing the most appropriate sample type and diagnostic test is essential for gathering clinically relevant data to inform therapeutic decisions. For example, consider the suspected organism to determine whether aerobic or anaerobic culture is most suitable. If unsure about what type of sample to submit or which test to select, clinicians may provide information about suspected cause of illness or known herd health history (e.g. history of bovine respiratory disease in herd) so the laboratorian can advise on sampling methods or select the most relevant test.

Laboratorians rely on **complete submission information for antimicrobial susceptibility testing (AST)** to assess the significance of bacteria in clinical samples, determine which tests are most suitable for the case, and interpret the results.



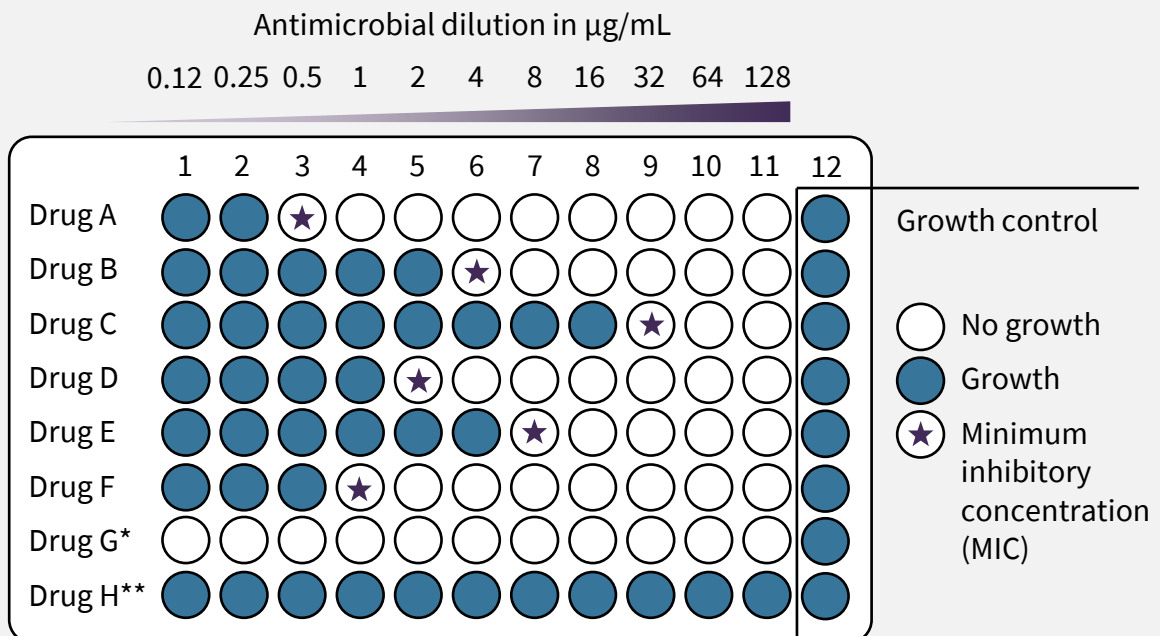
Antimicrobial susceptibility testing



Once isolated from a sample, the susceptibility of an organism to an antimicrobial drug can be determined by exposing the bacterial isolate to known concentrations of the drug. This is commonly achieved through **broth microdilution**, a process in which microbial growth or inhibition is observed, as depicted in Figure 1. This determines the **minimum inhibitory concentration (MIC)**.

In general, the broth microdilution process starts with the preparation of a bacterial suspension that contains a known amount of bacteria. This is then inoculated into the wells of a 96-well plate that contains 2-fold serial dilutions of drugs in each well. Concentrations are chosen based on clinically relevant levels achievable in plasma or serum. Plates are then incubated and assessed for growth. The minimum inhibitory concentration (MIC) is determined as the lowest concentration of drug tested for which there is no bacterial growth.

Figure 1. Broth microdilution plate



* Drug G had no growth at any concentration tested, therefore the MIC must be less than or equal to (\leq) the lowest concentration tested.

** Drug H had growth at all concentrations tested, therefore the MIC must be greater than ($>$) the highest concentration tested.

Understanding breakpoints



Breakpoint for clinical prediction: Breakpoints can be used to interpret MIC values. A breakpoint is the concentration of antibiotic used to categorize the bacteria as susceptible, intermediate, or resistant, which helps predict the likelihood of clinical success. **Bacteria that grow at concentrations above the breakpoint are considered resistant, as the effective drug concentration is not thought to be achievable at the target tissue site.**

To establish breakpoints, information about the pharmacokinetics/pharmacodynamics of the drug in the animal, characteristics of the microbial organism, and clinical outcome data associated with treatment may be utilized. Breakpoints may change as more data become available.

Breakpoints are established based on a specific dose, frequency, duration, and route of administration. Except for mastitis breakpoints, which apply to intramammary application, **breakpoints approved by the Clinical & Laboratory Standards Institute (CLSI) apply only to systemic administration of antimicrobials.** If using a dosage regimen other than what was used to determine the breakpoint (e.g. topical applications), susceptibility test results cannot be reliably interpreted.

Q: What happens when there is no breakpoint for a host species or organism?

A: Breakpoints may be extrapolated from similar bacterial species, host species, indications, or infection sites, although this process results in lower confidence in the prediction of clinical success. Some drugs have established breakpoints in animal species, while other drugs used in veterinary medicine require extrapolation from human data. Recommended extrapolations are listed in CLSI VET09.¹



Breakpoints that were determined using systemic administration of the drug cannot be applied to the feed formulation, since administration through feed may result in different, and possibly much lower, drug concentrations in the animal.

Using the breakpoint to interpret the MIC

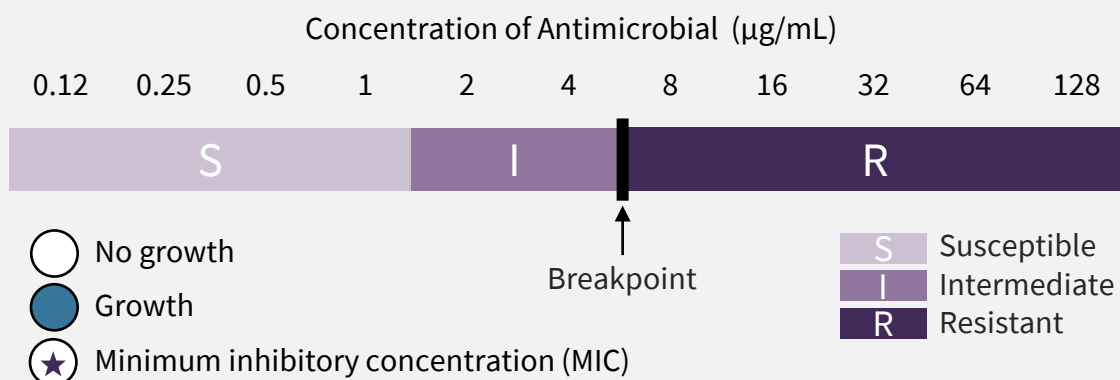


Minimum inhibitory concentration (MIC): An MIC is the lowest drug concentration that inhibits growth of the cultured organism. This value must be compared to the breakpoint to determine clinical significance.

It is important to note that the laboratory may omit susceptibility results on an MIC report for antimicrobials to which the organism is intrinsically resistant or for antimicrobials that are illegal to use in the animal species or production class.

Intrinsic resistance refers to innate (not acquired) resistance to an antimicrobial in all or almost all isolates of a bacterial species.

Figure 2. Interpretation of the minimum inhibitory concentration (MIC) as susceptible, intermediate, or resistant based on the breakpoint.



Drug A: The MIC is below the breakpoint, so the organism is **susceptible** to this drug.



Drug B: The MIC is within the **intermediate** range, and, therefore, this drug may be effective with a modified dosage regimen (i.e. higher dose or increased frequency of administration) or if the drug is known to concentrate at the site of infection.



Drug C: The MIC is above the breakpoint, so the organism is **resistant** to this drug.

Choosing an antimicrobial



Clinicians should consider the following when choosing an antimicrobial drug:



The antimicrobial susceptibility test report.

Different drugs have therapeutic activity at different concentrations; therefore, a drug should not be selected based on the lowest MIC value across a panel of drugs. In other words, **a low MIC value does not necessarily indicate the best therapeutic choice.**



The risk of antimicrobial resistance development and the resulting implications for human medicine.

The CLSI Subcommittee on Veterinary Antimicrobial Resistance Testing has deemed certain antimicrobials “drugs of last resort” to avoid selection of resistance in veterinary patients.² The U.S. Food and Drug Administration’s Guidance for Industry #152, Appendix A classifies drugs used in large animal medicine as Critically Important, Highly Important, or Important.³ Consideration of such lists when selecting an antimicrobial helps to ensure that essential antimicrobials are used only when necessary and have the best opportunity to remain effective.



Host factors and client considerations to ensure the treatment regimen will be both effective and feasible.

This may include the age and health of the animal, adverse effects, contraindications, price, and practicality of the route and frequency of drug administration.



Extra-label drug use (ELDU) regulations or other legal restrictions.

Antimicrobial susceptibility test reports may include antimicrobials that are not approved for the desired indication or species. A useful resource for ELDU decision-making is the Food Animal Residue Avoidance Databank (FARAD.org).

References

1. CLSI. *Understanding Susceptibility Test Data as a Component of Antimicrobial Stewardship in Veterinary Settings*. 1st ed. CLSI report VET09. Wayne, PA: Clinical and Laboratory Standards Institute; 2019.
2. CLSI. *Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals*. 5th ed. CLSI supplement VET01S. Clinical and Laboratory Standards Institute; 2020.
3. Food and Drug Administration Center for Veterinary Medicine. 2003. Evaluating the safety of antimicrobial new drugs with regard to their microbiological effects on bacteria of human health concern. *Guidance for Industry #152*. <https://www.fda.gov/media/69949/download>

Additional Resources

California livestock antibiograms:

https://www.surveymonkey.com/r/antibiogram_sign_up

CAHFS Antibiogram Development Process

<https://www.cdfa.ca.gov/AHFSS/AUS/docs/AntibiogramDevelopment.pdf>

California Livestock Antibiograms: A User Guide

<https://www.cdfa.ca.gov/AHFSS/AUS/docs/AntibiogramUserGuide.pdf>

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