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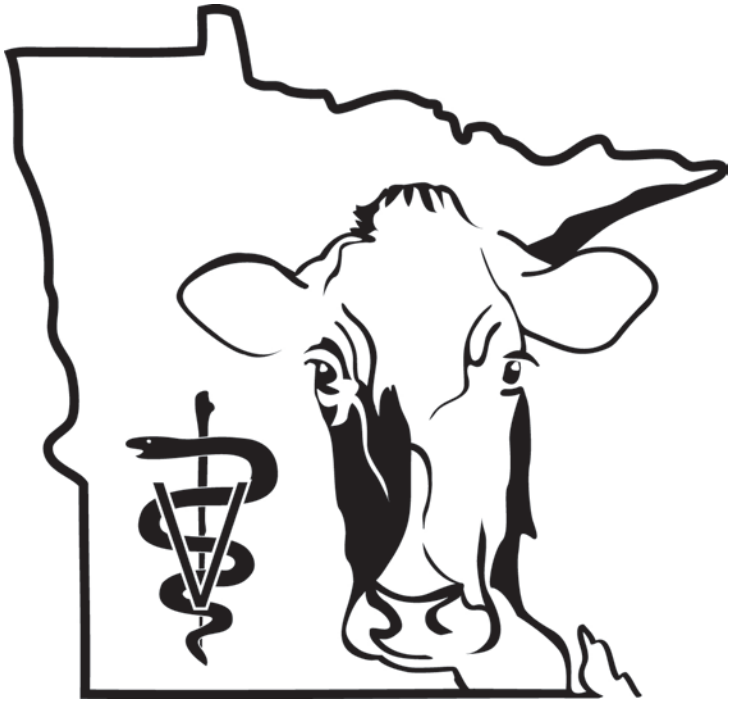

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Veterinary Antimicrobial Decision Support System

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Your main reference for this presentation is the VADS System website. These proceedings contain some of the subjects from the frequently-asked-question section of the site.

The VADS System is the result of a collaboration between Drs. Mike Apley, Virginia Fajt, Cory Langston, and Jeff Wilcke. There have been approximately 15 other people involved in the development as administrative assistants, technicians, and student workers.

What is the purpose of the VADS System?

The VADS System collaborators recognize that randomized clinical trials with negative controls are the best evidence for designing antimicrobial regimens. However, extralabel antimicrobial use is often necessary for applications where there is limited, or no clinical trial data available to guide regimen design. It is doubtful that the pot of money to conduct clinical trials for many food animal diseases, especially in minor species, will ever materialize. Even when clinical trial data is available, other cases may be encountered with a pathogen that has significantly different antimicrobial susceptibility characteristics.

The VADS System is intended to assist food animal veterinarians in designing antimicrobial regimens in the following situations.

- There are no labeled products for the application.
- There are labeled products for the application but guidance is needed in...
    - interpreting susceptibility testing results to help in evaluating the need for a regimen adjustment in response to a lack of clinical efficacy, or
    - when the labeled products do not have Clinical and Laboratory Standards Institute Veterinary Antimicrobial Susceptibility Testing Subcommittee (CLSI/VAST) approved breakpoints for the label application. This would include cases where the CLSI/VAST breakpoints have been adapted from human medicine without direct consideration of the disease being treated in veterinary medicine.
- The veterinarian wishes to review published and diagnostic laboratory susceptibility summaries and published clinical trial data for labeled antimicrobials.

The VADS System is designed to be completely transparent related to the data used, the methods used to collate, model, and interpret these data, and the assumptions necessary in these steps. Feedback from users on the data used as well as modeling and interpretation methods is both welcome and encouraged.

The VADS System collaborators hope that this website serves as a central location for discussion and debate that advances the judicious use of antimicrobials in food animal veterinary medicine.

How was the VADS System built and were there any assumptions that had to be made during the process?

The VADS System combines the following data to develop suggested antimicrobial regimens.

- Pharmacokinetics of the antimicrobial
  - Drug concentration profiles related to multiple dose regimens
- Pharmacodynamics of the antimicrobial
  - The optimum concentration profile for exposure of the pathogen to the antimicrobial
- Susceptibility profile of the pathogen
  - Minimal inhibitory concentration (MIC) for the specific isolate, or
  - Consideration of the MIC distribution of multiple isolates of this pathogen from available datasets

It is not reasonable to conclude that combining these factors will allow precise regimen calculations for a specific pathogen MIC. However, the above data categories may be combined to give reasonable regimen targets and to eliminate unreasonable regimens.

During system development, many decisions have been necessary where clear direction is not available. For example:

- Use of free, unbound drug concentrations in serum or plasma as opposed to total drug concentrations (protein-bound and unbound fractions combined)
- Methods for extrapolation of pharmacokinetic trials with small numbers of animals (4-6 animals) to populations of animals
- Determination of pharmacodynamic targets with minimal available data
  - Available data is often derived from in-vitro or animal-model studies in other animal species
  - Available data is often based on pathogens, diseases, and animal species other than the situation for which the model is being developed
  - Pharmacodynamic data is often developed using single or multiple dose strategies that do not reflect the serum or plasma profiles of extended release drugs used in veterinary medicine
  - Conflicting evidence and/or opinion as to the best pharmacodynamic target (e.g., 50% vs. 100% of the dosing interval above the MIC for β-lactam antibiotics in the therapy of Gram negative organisms)
- Proportion of the animal population for which the suggested regimen is adequate
  - Pharmacokinetic data is typically reported as mean ± variance.
  - The VADS System is constructed such that suggested regimens are modeled to address 95% of the animal population.
  - Extrapolating from one or several pharmacokinetic studies with 5-10 healthy animals apiece to an entire population of diseased animals is a concern. The reality is that these are the data available to work with. Population pharmacokinetic studies are needed in diseased animals to advance our understanding of the relationship between pharmacokinetic parameters, pathogen MICs, and clinical efficacy. These relationships may then be used to guide decisions in other diseases until clinical trial data is available.

To address these decisions in the absence of clear guidance, the VADS System collaborators have based decisions on the best evidence available. The methods for developing the suggested regimens and the data sources are completely transparent with provisions made for feedback on methods and regimens. Using this approach, it is hoped that the VADS System will function as a central point for

discussion of modeling approaches and for identification of research needed to move forward in this area.

What antimicrobials are addressed in the VADS System?

The following antimicrobials have been researched and considered in the VADS System development process for bovine and swine applications.

Penicillins: Penicillin V, Procaine penicillin G, Sodium and potassium penicillin G, Benzathine/procaine penicillin G

Aminopenicillins: Amoxicillin trihydrate, Amoxicillin sodium, Ampicillin, trihydrate, Ampicillin sodium

Cephalosporins: Ceftiofur sodium, Ceftiofur hydrochloride, Ceftiofur crystalline free acid

Phenicols: Florfenicol

Lincosamides: Lincomycin

Tetracyclines: Oxytetracycline, Chlortetracycline, Tetracycline, Doxycycline

Macrolides: Tilmicosin, Erythromycin, Tylosin

Sulfas and diaminopyrimidines: Trimethoprim, Trimethoprim/sulfadiazine, Trimethoprim/sulphamethoxazole, Sulfadimethoxine, Sulfamethazine, Sulfachlorpyridazine

Aminoglycosides: Gentamicin, Neomycin, Amikacin, Aminocyclitols, Spectinomycin, Apramycin

Diterpines: Tiamulin

What pathogens are addressed in the VADS System and what sources of antimicrobial susceptibility data are available to evaluate these pathogens?

The diseases and pathogens for which susceptibility and clinical trial data have been researched include the following. Pathogens for which diagnostic laboratory extended-range dilution susceptibility testing data are available are included in separate tables from those where literature data only is utilized in the VADS System.

Bovine – Extended range susceptibility data available	
Disease	**Pathogen(s)**
Arthritis	*Histophilus somni (Haemophilus somnus)*
Bovine Respiratory Disease Complex (BRDC)	*Mannheimia (Pasteurella) haemolytica* *Pasteurella multocida* *Histophilus somni (Haemophilus somnus)*
Mastitis - Coagulase-negative Staphylococci (CNS)	*Staphylococcus hyicus* *Staphylococcus epidermis* *Staphylococcus xylosis* *Staphylococcus warneri* *Staphylococcus intermedius*
Mastitis - Coliform	*Escherichia coli* *Klebsiella pneumoniae* *Enterobacter aerogenes*
Mastitis - Contagious Streptococci	*Streptococcus agalactiae*
Mastitis - Environmental Streptococci	*Streptococcus dysgalactiae* *Streptococcus uberis*
Mastitis - Other Gram-negative	*Pseudomonas aeruginosa* *Pasteurella multocida* *Serratia marcesens* *Proteus vulgarius*
Mastitis - Other Gram-positive	*Archanobacterium pyogenes*
Mastitis - Staph.	*Staphylococcus aureus*
Metritis	*Streptococcus* spp. *Staphylococcus spp* *Arcanobacterium pyogenes*
Neonatal enteric disease and septicemia associated with neonatal enteric disease	*Escherichia coli* *Salmonella spp*
Thrombolic Meningo-encephalitis	*Histophilus somni (Haemophilus somnus)*

Bovine – Literature data only	
Disease	**Pathogen(s)**
Anaplasmosis	*Anaplasma marginale*
Arthritis	*Mycoplasma bovis*
Bacillary Hemoglobinuria	*Clostridium haemolyticum*
Bovine Respiratory Disease Complex (BRDC)	*Mycoplasma bovis*
Blackleg	*Clostridium chauvoei*
Blacks Disease	*Clostridium novyi*
Coccidiosis	*Eimeria bovis* *Eimeria zurnii*
Cryptosporidiosis	*Cryptosporidium parvum*
Diphtheria	*Fusobacterium necrophorum*
Enterotoxemia	*Clostridium perfringens* Type C
Footrot (Infectious pododermatitis)	*Fusobacterium necrophorum* *Bacteroides melaninogenicus* *Dichelobacter (Bacteroides) nodosus*
Giardiasis	*Giardia spp.*
Hemorrhagic bowel disease	*Clostridium perfringens* Type A
Leptospirosis	*bratislava* *canicola* *grippotyphosa* *hardjo type hardjo-bovis* *icterohaemorrhagiae* *pomona*
Listeriosis	*Listeria monocytogenes*
Lumpy Jaw (Actinomycosis)	*Actinomyces bovis*
Malignant edema	*Clostridium sordellii* *Clostridium septicum*
Mastitis - Mycoplasma	*Mycoplasma bovis*
Metritis	*Streptococcus* spp. *Staphylococcus spp* *Arcanobacterium pyogenes*
Pinkeye (Infectious kerato-conjunctivitis)	*Moraxella bovis*
Tetanus	*Clostridium tetani*
Woody tongue (Actinobacillosis)	*Actinobacillus lignieresii*

Porcine – Extended range susceptibility data available	
Disease	**Pathogen(s)**
Erysipelas	*Erysipelothrix rhusiopathiae*
Greasy pig disease (Exudative epidermitis)	*Staphylococcus hyicus*
Infectious arthritis	*Streptococcus suis* *Erysipelothrix rhusiopathiae* *Haemophilus parasuis* *Staphylococcus aureus*
Mastitis (Gram-negative)	*Escherichia coli*
Mastitis (Gram-positive)	*Staphylococcus aureus*
Neonatal bacterial enteric disease	*Escherichia coli* *Salmonella spp*
Porcine respiratory disease complex (PRDC)	*Streptococcus suis* *Actinobacillus suis* *Actinobacillus pleuropneumoniae* *Haemophilus parasuis* *Pasteurella multocida* *Bordetella bronchiseptica* *Salmonella cholerasuis*

Porcine – Literature data only	
Disease	**Pathogen(s)**
Cervical lymphadenitis	Group E *streptococci*
Cystitis/Pyelonephritis	*Actinobaculum (Eubacterium) suis*
Infectious arthritis	*Mycoplasma hyosynoviae*
Leptospirosis (serovars)	*pomona* *bratislava* *muenchen* *copenhageni* *icterohaemorrhagiae* *grippotyphosa*
Mastitis (Gram-positive)	*Arcanobacterium pyogenes*
Neonatal bacterial enteric disease	*Clostridium perfringens*
Porcine Proliferative Enteropathy (Ileitis)	*Lawsonia intracellularis*
Porcine respiratory disease complex (PRDC)	*Mycoplasma hyopneumoniae*
Swine Dysentery	*Brachyspira (Serpulina) hyodysenteriae*

Are there concerns with the use of diagnostic laboratory susceptibility testing data to characterize populations of food animal pathogens?

Yes. Concerns with diagnostic laboratory data include the following.

- There are no indications as to whether the sample was from an acute, untreated case or from an animal which had received extensive therapy.
- There are no records concerning what antimicrobial regimens may have been used for therapy prior to sample submission. Evaluation of data from pathogens surviving therapy with a specific antimicrobial may bias the data towards higher MICs while in fact the majority of the isolates in the acute phases of the disease may have had lower MICs.
- Population distributions may be biased by multiple samples from some production sites experiencing a challenge with a resistant organism.

However, there are benefits in examining and monitoring diagnostic laboratory data.

- The population of pathogens in diagnostic laboratory data represent cases where a veterinarian is seeking guidance in antimicrobial selection. This population is very similar to the population of veterinarians which will be accessing the VADS System.
- In many cases, the population distributions of pathogens in diagnostic laboratory data are monophasic, indicating that whatever previous exposure to antimicrobials has occurred and whatever phase of disease the animal was experiencing likely had little effect on the MIC of the pathogen. As examples of monophasic populations, look at the susceptibility profiles of ceftiofur and enrofloxacin against the bovine respiratory *pathogens Manheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*. In cases where the pathogen populations are distinctly biphasic (e.g., oxytetracycline against the same pathogens) the questions of previous exposure and disease chronicity may be raised. In these cases, the veterinary practitioner is advised to determine antimicrobial susceptibility of pathogen isolates in the production system in question rather than relying on empiric selection of oxytetracycline based on the susceptibility summary data. Or, if the veterinarian selects an oxytetracycline regimen sufficient to address the lower MIC population without knowledge of the specific pathogen involved in their current situation, then they should be closely monitoring the treated animals for clinical response in case a pathogen representative of the higher MIC population is involved.

Wouldn't clinical trial data be better than comparing pharmacokinetic and pharmacodynamic data to pathogen MICs?

Yes. Clinical trial confirmation of the suggested regimens in the VADS System is the ultimate goal. However, in absence of clear clinical data related to a combination of a regimen, a disease, and a pathogen with a defined MIC, the use of pharmacokinetic and pharmacodynamic data to rule out unreasonable regimens is the next best thing.

Clinical trial data have been researched and are documented on the VADS System website. In the future, available clinical trial data will be evaluated according to the principles of evidence-based medicine with results available in the VADS System.