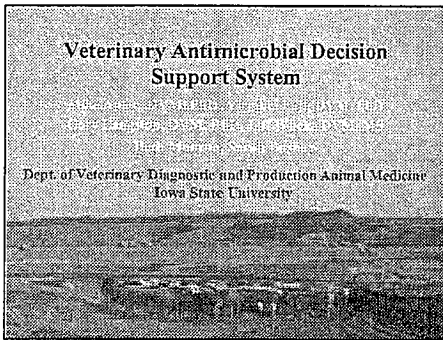
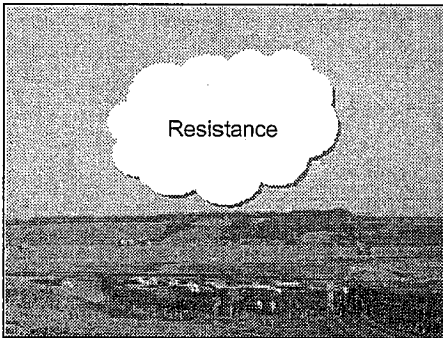


VETERINARY ANTIMICROBIAL DECISION SUPPORT SYSTEM

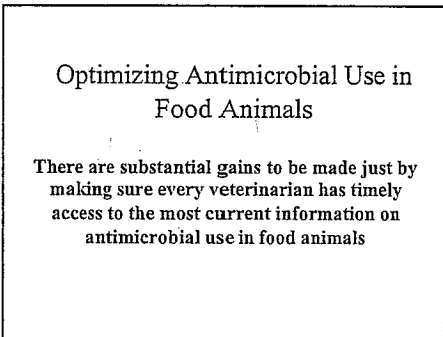
Mike Apley, DVM, PhD, Virginia Fajt, DVM, PhD, Cory Langston, DVM, PhD, Jeff Wilcke, DVM, MS, Beth Monroe, Sarah Bashaw



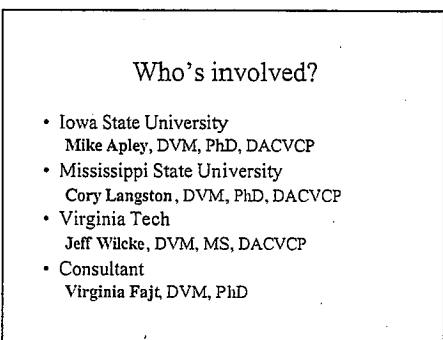
You will get to see myself, Virginia Fajt, and Cory Langston up front during this presentation. I'd like to introduce the fourth member of our team to you, Jeff Wilcke. Jeff, raise your hand over there. Jeff is holder of the Metcalf Endowed Chair for Informatics and is a professor of informatics at Virginia-Maryland regional School of Veterinary Medicine. Jeff was a very fortunate find for us in that he has provided his expertise in actually putting this in a format where veterinarians can use it. The way this all got started was after a meeting back in 1998, Virginia and I sat down to draft a proposal and we talked with Jeff (Wilcke) and Cory (Langston), and pretty soon it became one of those deals where if Virginia and Cory and Jeff, and of course Beth had not come on, it would have still been an Excel spreadsheet concept, instead of going where I think it's going to go now.



The issue of resistance has been hanging over food animal medicine for several years now. The concerns of antimicrobial resistance and the need to educate veterinarians on the optimal use of antimicrobials has led to funding of the VADS project.



Among food animal practitioners, I would propose to you that the number one thing to do is to make sure that every practitioner has the most current information available at his or her fingertips. So that is the goal of this project, to provide timely access to the most current information on antimicrobial use in food animals to veterinary practitioners.



And here again are the people involved, myself (Mike Apley), and Drs. Cory Langston, Jeff Wilcke and Virginia Fajt.

Founding Characters

Veterinary Antimicrobial Decision System



Here is a picture of us so that you can pick us out in the hall; the lady in the blue dress is Beth Monroe, she is our project secretary, who is responsible for actually keeping track of the money flow in and keeping everything else going.

Objectives

- To bring antimicrobial decision support to the food animal practitioner in a format that is
 - Easy to access
 - Easy to use
 - Rapid

So, our objective is to bring antimicrobial decision support to the food animal practitioner in a format that is easy to use, easy to access, and rapid.

Objectives

- Centered on therapeutic applications.
- **Will Not** be a cookbook, or an attempt to dictate clinical practice.
- **Will** be a vehicle for the publication of consensus on reasonable antimicrobial use in cattle and swine.
- **Will** be an attempt to provide the most current information to the practicing veterinarian.

This is not going to be a cookbook or an attempt to dictate clinical practice. The final decision in the selection of the antimicrobial is in the hands of the attending veterinarian. We have no illusion that we can sit in an office for example, in Ames, Iowa and actively give the exact regimen that should be used out of all the regimens for an outbreak in Washington state. There will be some consensus, there will be a lot of review, and we are going to try to continually update the site. In contrast to FARAD, this is not a phone call system where you make a phone call, and we provide the information you need. We intend to have it up there for you to use, and if we do not have the correct information there, there will be a mechanism to contact us and tell us, so that we can strive to do that.

Current funding sources

Founding Supporters:

Academy of Veterinary Consultants
American Association of Bovine Practitioners
National Cattlemen's Beef Association
American Association of Swine Practitioners
American Veterinary Medical Association

To start with, the system is aimed towards swine and cattle. This reflects the interests of the founding supporters; The Academy of Veterinary Consultants, The American Association of Bovine Practitioners, The National Cattlemen's Beef Association, The American Association of Swine Veterinarians, and American Veterinary Medical Association.

Funding Sources (cont.)

Additional support now provided by:

National Pork Producers Council

Funding also provided by:

US Pharmacopeia

Iowa Beef Center

Total startup funding: \$ 197,000

We received, over three years back, about two hundred thousand dollars in start up funding. We also received support from the National Pork Producers Council, Iowa Beef Center, and the USP funded a research fellowship for one year for Dr. Fajt, supporting some of her activities while she was at Iowa State.

Funding Sources (cont.)

- FDA/CVM funding
 - \$1,244,914
 - April 30, 2001 through April 29, 2006
 - Adds small ruminants and poultry to the project

Just recently as of April 30th, we started five years of FDA/Center for Veterinary Medicine funding- for which we are very thankful for their support. This is at the level of one million, two hundred forty-five thousand dollars over five years. It supports partial salaries for myself and Drs. Wilcke and Langston. It provides technical support to three institutions. It also provides for secretarial support and some operating expenses. The last year startup funding we are using to support Dr. Fajt for the next couple of years while she works with the system part-time.

Pieces of the puzzle

- What concentration of the antimicrobial does it take to inhibit bacterial growth?
- How is the antimicrobial best presented to the bacteria (pharmacodynamics)?
- What are the pharmacokinetics in the animal?
- Do our predictions hold true in clinical trials or in practice situations?

Here are the pieces of the puzzle the system is built around. (1) What concentrations does it take to inhibit bacterial growth? If you attended last hour here, we talked about susceptibility testing, and some of the considerations in applying that. Then, (2) how is the antimicrobial best presented to the bacteria? And that is pharmacodynamics. (3) What are the pharmacokinetics of the animal. Then, (4) do our predictions hold true in clinical trials or in practice situations? These are basically the core of what we are doing. Now, when there are drugs approved for specific situations that are effective, we are not going to go in and second-guess doses on them, but we may be able to provide dose regimen adjustment advice if they are found to be ineffective, or an intermediate or a resistant

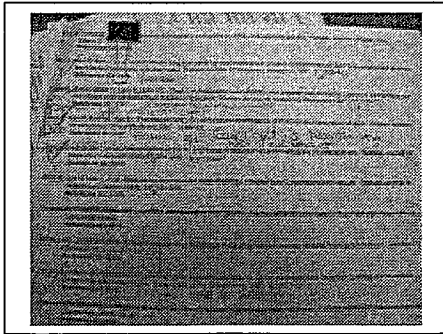
isolate is found.

Format and implementation

- Final form
 - Web-based, possible CD ROM, palm pilot
 - Subscription -- commitment to continual updating
- Review panels
 - Review and approve the content
- Board of directors
 - "Big picture" guidance and liaisons with their organizations

It is web based, I still have possible CD-ROM up there, but that just isn't going to work. That was one of the initial proposals. PDA type application or download could be in the future. Right now with our starting funding, we will be releasing it hopefully without a subscription, where if you are a veterinarian, you are able to demonstrate so and get access to the system. We need to be very clear that this is designed for veterinary use only, to aid your clients. We are not going to provide access to lay people. We feel that the training a veterinarian has is absolutely necessary to implement what is contained in the system. There will be review panels. Also, veterinary practitioners and everyone who uses the system will serve as a reviewer, giving input on the usability,

and if we missed something. We want the system to be completely transparent where the user will be able to see the techniques used to provide the suggested regimens.

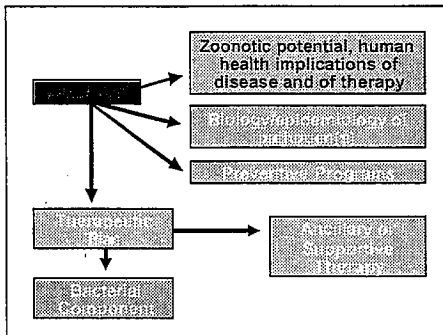


This is how we started out. This is a list of literature citations that Dr. Fajt was very instrumental in working on along with Sarah Bashaw, who is a senior now, and has been a very big help to the system. Going through, they may get a thousand hits on a topic, but distill it down to three hundred that we really seriously look at. We might get a hundred of those and then pull the articles to look over.

For cattle, hundreds down to 345 down to:

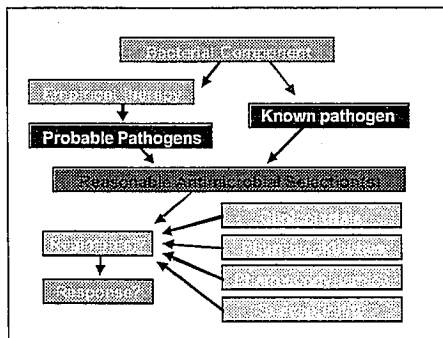
| Drug | No. of Articles | Information Tabulated into File - No. of Pages |
|---------------------------|-----------------|--|
| Amoxicillin | 6 | 6 |
| Ampicillin | 12 | 12 |
| Ceftiofur | 14 | 10 |
| Florfenicol | 5 | 5 |
| Doxycycline (in progress) | 4 | 1 |
| Oxytetracycline | 26* | 22 |
| Penicillin | 24 | 17 |
| Sulfonamides | 8 | 17 |
| Tilmicosin | 3 | 3 |

I've got a table that shows how that works. For cattle, we initially had a few hundred hits that we got down to 345 that we actually considered for the article. And then the number of articles we actually considered for pharmacokinetic input into the system are listed in the table. We found six for amoxycillin, twelve for ampicillin, fourteen for ceftiofur, five for chloramphenicol, four for doxycycline. Oxytetracycline has quite a few. Now we are really wrestling with the drugs on an individual basis. We find a lot of these articles aren't exactly solid enough to support what we want to do, or the modeling isn't there for us.



So, how is the system designed? The practitioner will come in with a disease idea (it's therapeutically based; it is not drug based). So you come in knowing you want to treat neonatal diarrhea. We are going to have information readily available on things such as zoonotic potential, human health implications if there are any, references where you can go find out more about it. The biology and epidemiology of the pathogens will also be included. This isn't going to be a textbook, but this is designed to serve a big cross-section of the veterinary profession, including students. We hope to provide this to the veterinary schools for student use, and it is a way that they can go in and weigh some of the factors that might contribute to the need for therapy. Also included will

be a summary of there are preventive programs available.



Of course, the reason a practitioner will be here will be for help in deriving a therapeutic plan, and in some instances, ancillary therapy is probably more important than the antimicrobial therapy. One case would be neonatal diarrhea in calves, which we are wrestling with for our first application. If it is septic, then we are fairly comfortable with many drugs approaching the regimen by a pharmacokinetic/pharmacodynamic method. But if it is enteric and confined to an enteric application, that is probably going to be one of the holes in the big piece of Swiss cheese that the system is going to be. Dehydration management and acid-base status are obviously very important things to cover. And then of course we are here to address the bacterial component. There can be an

empirical therapy route where we identify probable pathogens and come up with reasonable antimicrobial selections. Dr. Fajt is going to talk about how we are trying to incorporate this into a population model. And if there is a known pathogen, that's when we'll take susceptibility data and help you build the pharmacokinetic/dynamic based regimen off of that susceptibility data. So the regimens are being created from clinical trials, kinetics, the dynamics and susceptibility, and of course the ultimate thing is you as the veterinarian coming up with what the clinical response is.

Challenges Ahead

- Developing a prototype that is applicable to all therapeutic applications
- Make the system easy to use by practicing veterinarians, since they are the primary audience
- Provide decision support while maintaining the practitioner's role as the final interpreter of the clinical situation
- Maintaining funding support

So, we are still working with a prototype that is applicable to all therapeutic applications, and Dr. Wilcke has been the person in the group for that because as we develop ways of presenting things, he is always thinking about how the final stage is going to be when we are putting stuff together now. So we are trying to build so that we don't have to rebuild any parts of something that needs changed or updated. We want to be easy to use. It is very critical that we provide decision support, but we have no desire to be a formulary- this drug first, this drug second, this drug third- we just can't predict all of these things. And then, of course, maintaining funding support for the long run, to keep it going.

What is the goal?

- To provide veterinarians with ready and rapid access to the information discussed in this presentation.
- This information will be compiled by clinical pharmacologists, and then the information will be reviewed by clinicians, microbiologists, and other experts.

And here is the ultimate goals of the system;

What is the goal?

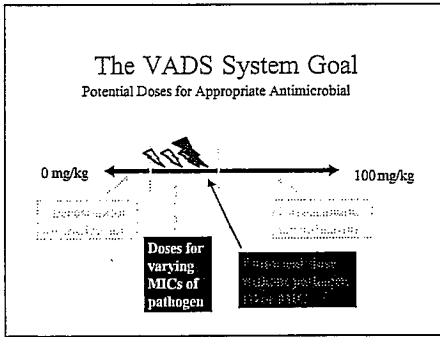
- A veterinarian can be in and out of the program with the information they need in 5-10 minutes maximum.

That a veterinarian can be in and out of the program with the information needed in ten minutes. If you are interested in how the clock was built rather than just the time, you can go in deeper.

Issues we must resolve

- Evidence levels?
 - Peer-reviewed literature
 - Proceedings
 - Trial data

We have some issues we are still working on resolving, for example, which literature we will include or will not include. What about proceedings, what about proprietary trial data? We're working on evidence level systems to work on that.



So the VADS system goal, and you will recognize this slide from my last presentation if you were here, is to rule out unreasonable regimens, and then for varying MIC's of the pathogen, have reasonable dose regimen selection. And if you don't have susceptibility data, we'll model the population to try to give you a reasonable empirical dose. The goal of the presentation format is to give you an idea what percentage of the population you would be actively treating with a certain regimen versus a certain pathogen and disease syndrome. So we don't really want to impress you with model pharmacokinetics, we want to make it a population application approach. So with that, we will set up Dr. Langston next to talk about some modeling approaches.