



Animal Health and Antibiotic Research, Development, Stewardship and Perspective

One Health Approach to Antimicrobial Use and Resistance - 2012

Dr. Rick Sibbel, Director, US Cattle

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Ecological Populations of Bacteria Act as Socially Cohesive Units of Antibiotic Production and Resistance

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In animals and plants, social structure can reduce conflict within populations and bias aggression toward competing populations; however, for bacteria in the wild it remains unknown whether such population-level organization exists. Here, we show that environmental bacteria are organized into socially cohesive units in which antagonism occurs between rather than within ecologically defined populations. By screening approximately 35,000 possible mutual interactions among Vibrionaceae isolates from the ocean, we show that genotypic clusters known to have cohesive habitat association also act as units in terms of antibiotic production and resistance. Genetic analyses show that within populations, broad-range antibiotics are produced by few genotypes, whereas all others are resistant, suggesting cooperation between conspecifics. Natural antibiotics may thus mediate competition between populations rather than solely increase the success of individuals.

World food situation redefined by new driving forces

Food consumption and production are influenced by global changes in: standards of living, **climate**, **energy prices**, **urbanization** and **population** (IFPRI, 2007).

Production is moving to regions offering the best natural resources.

With specialized and large-scale production, animals are moved within and between countries.

Animal products are shipped around the world to meet increased food demand and requests for affordable prices.

Consumer demand for higher food quality is increasing



FAO, 2007

Increasing challenges for animal health in a globalizing and ever intensifying agricultural sector

Introduction to the debate

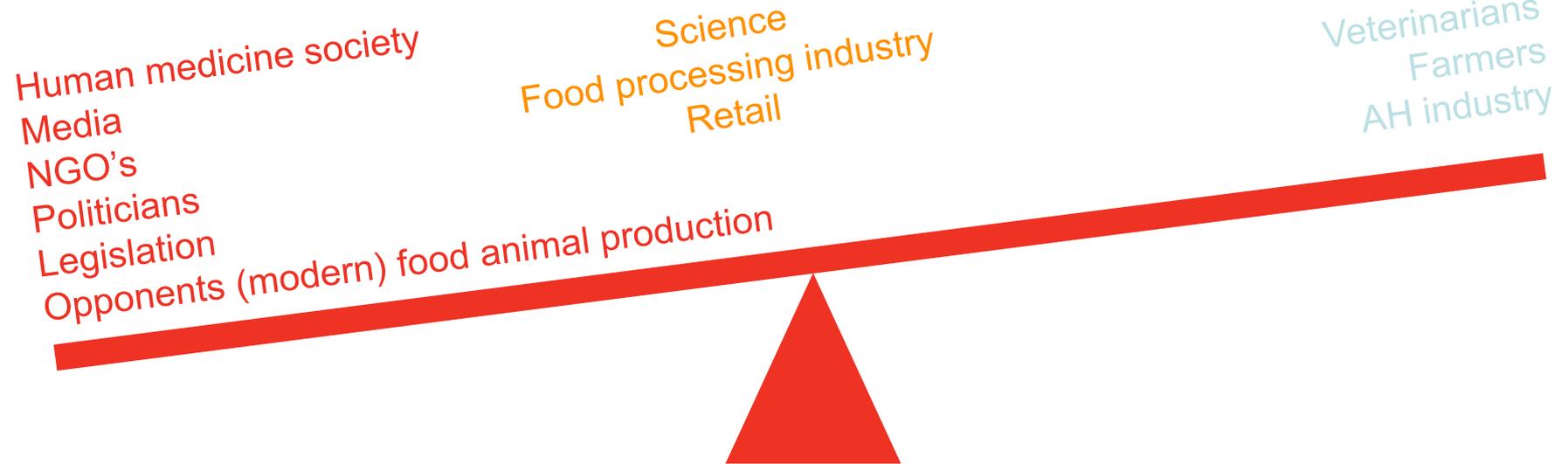
Drivers

Expected versus unexpected

Founded versus unfounded motives

Stakeholders

Very diverse and with frequent conflicting agenda's



Veterinary drug development

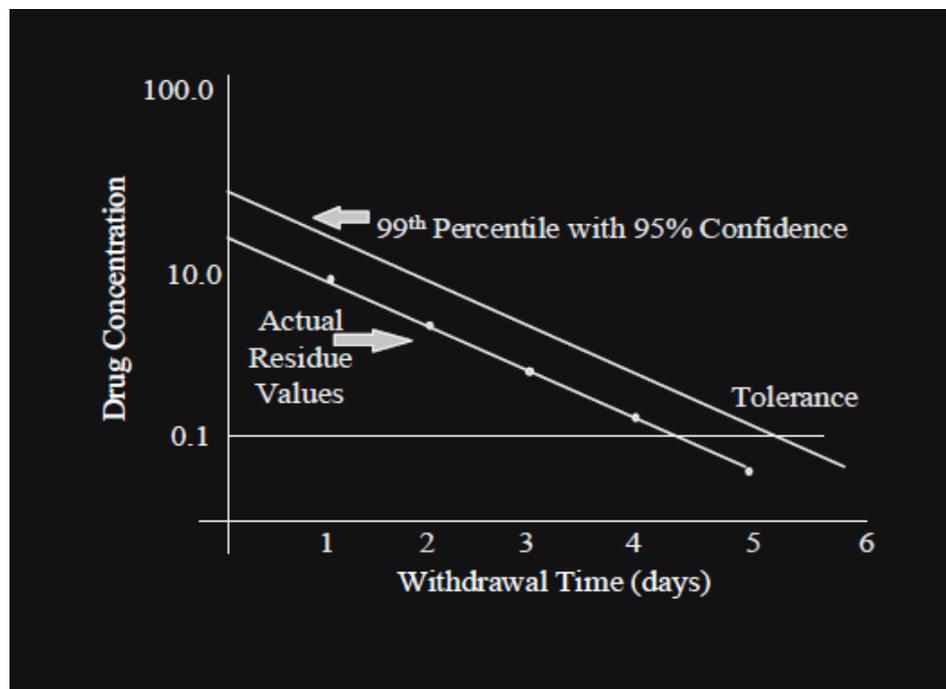
More is known about the fate of a food animal drug than a human drug.

A human food safety dossier can take 7 or more years to generate at a cost of many millions of dollars

Residue depletion studies are a major aspect of this dossier

Definition of a residue:

- any compound present in the edible tissues after treatment with the drug
- includes parent drug, metabolites, and any substance formed in or on food
- the definition is broad enough to include resistant bacteria



Veterinary drug development

Extensive safety testing of residues

- Repeat-dose toxicity testing (VICH GL31 and VICH GL37)
- Reproduction toxicity testing (VICH GL22)
- Developmental toxicity testing (VICH GL32)
- Genotoxicity testing (VICH GL23)
- Carcinogenicity testing (VICH GL28)
- Environmental testing
- Compound-specific testing
 - immunotoxicity testing
 - neurotoxicity testing
 - pharmacological effects testing

Veterinary Drug Development : What's New?

Testing for effects on the human intestinal flora (VICH GL36)

- Ingested antimicrobial drugs can potentially alter the ecology of the human intestinal flora
- purpose of the studies governed by VICH GL36 is to establish the no-observable adverse effect concentration/level of potential drug (or residue) on human gut microflora and incorporate this into the withdrawal time.
- studies include:
 - MIC determination of antibiotic on relevant genera of human intestinal bacteria
 - A variety of studies to determine the percentage of the ingested residue that may enter the colon of a human
 - determination of the degree of microbiological inactivation when the drug is incubated with feces

Stewardship

The careful and responsible management of something entrusted to one's care

» Merriam-Webster Online Dictionary [m-w.com]

Implication is that we (as stewards):

- Do not own the “something”
- Answer to whomever does
- Can have our management responsibilities revoked / restricted / altered

AABP / AASV Guidelines – Common Points (with some literary license)

The emphasis of disease control should be on preventative measures

- Genetics
- Nutrition
- Husbandry / Housing / Management
- Immunization

Are antimicrobials necessary?

- Will antimicrobials be helpful?
- Will antimicrobials be harmful?



Likely or Known Pathogens

Does an etiology need to be confirmed through culture in every case / disease outbreak?

Which calf has *Mannheimia haemolytica*?

A



B

C



Clinical presentation is not diagnostic for etiology

Maximizing Efficacy Response to therapy

“Drug X seems to be working”

Our treatment response rate is X%

owner says our work is so good, treatment is not as effective as owner normally observes

“So and so said that drug X is working really well for them this year”

Therapeutic success / failure can be attributed to:

The class of animals

- Heavy pre-conditioned calves
- The personnel / case definition
- Humans are poor at detecting acute stage disease
- The pathogens
- Resistance elements are present

Antimicrobials should be selected to minimize resistance

What does that mean?

We do not have antimicrobial resistance “figured out”

- “If you think you understand antimicrobial resistance, it hasn’t been explained to you properly”

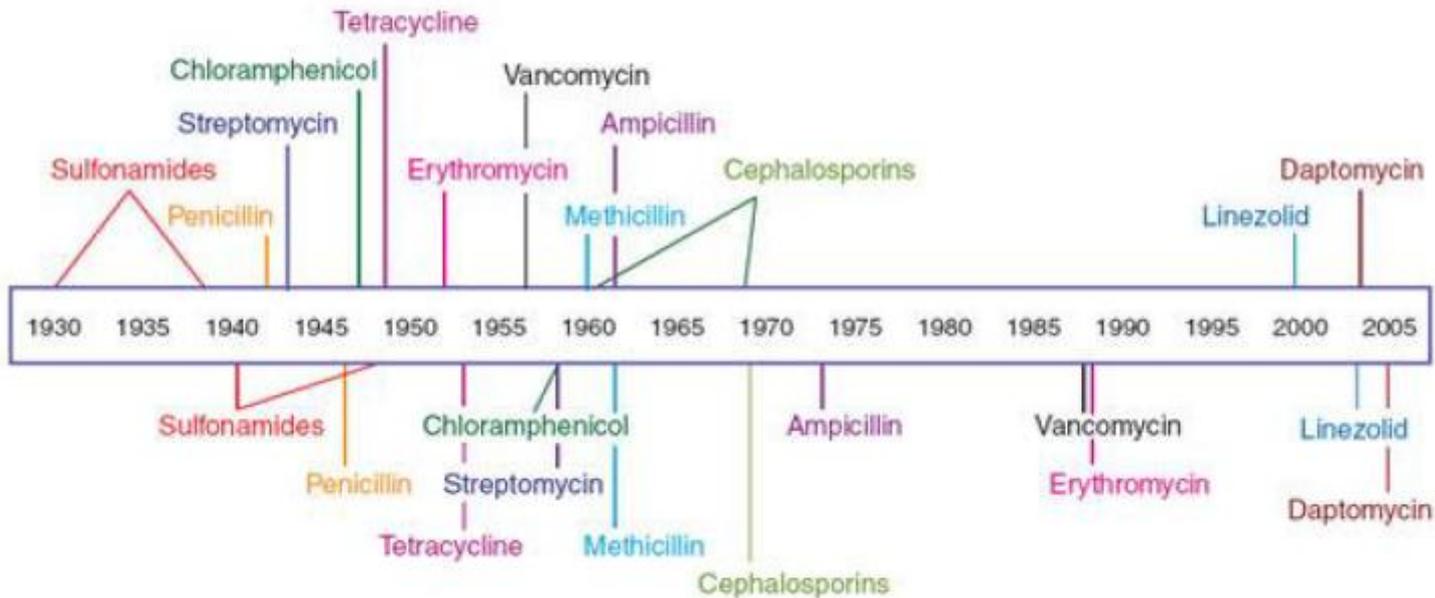
What we think we know about antimicrobial resistance:

- It is unequivocally, real and here
- Antimicrobial resistance is a natural adaptive phenomenon to a selective pressure
 - We don’t create it, but we can certainly promote it
- In most cases, development of antimicrobial resistance is a function of exposure (Are all exposures equal?)

Antimicrobials should be selected to minimize resistance: What does that mean?

- Antimicrobial resistance is a natural adaptive phenomenon to a selective pressure

Antibiotic deployment



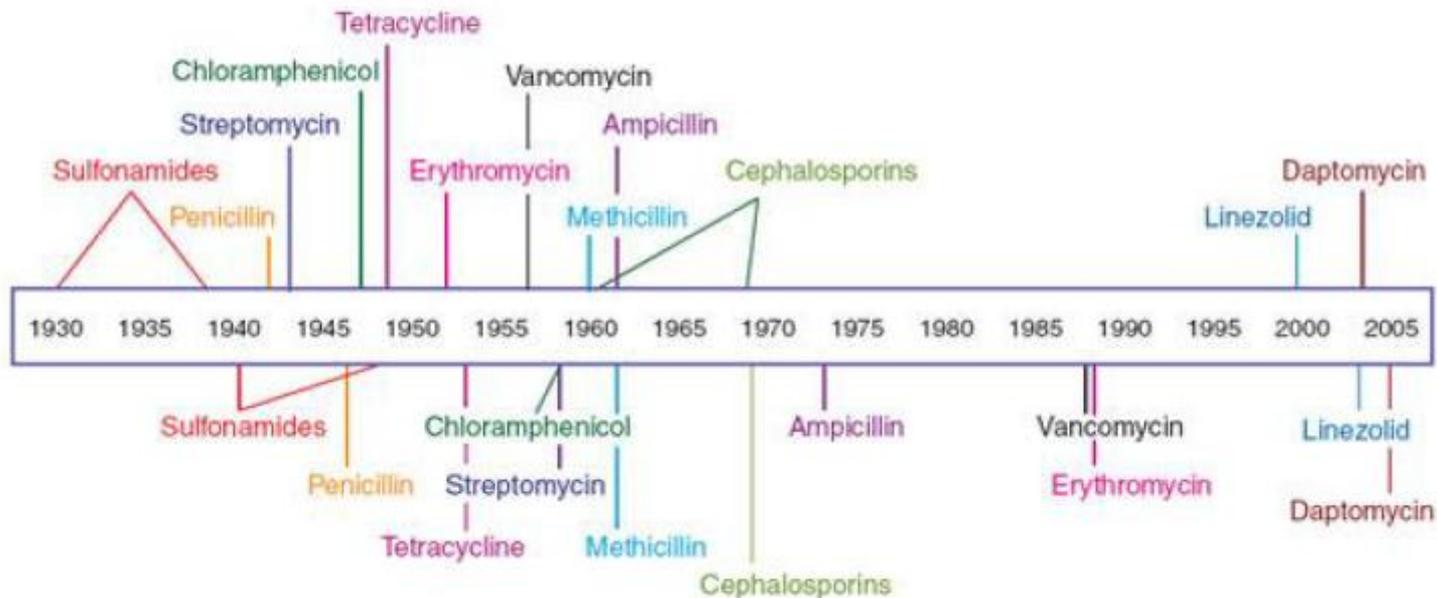
Antibiotic resistance observed

Antimicrobials should be selected to minimize resistance

What does that mean?

- Antimicrobial resistance is a natural adaptive phenomenon to a selective pressure

Antibiotic deployment



Antibiotic resistance observed

Linezolid is entirely synthetic – at the time of its introduction there were no “natural” pools of resistance.....

Veterinary Drug Development

What's New?

Microbial Food Safety Risk Assessment (Guidance 152)

- a critical risk assessment of how approval of a veterinary antibiotic may affect human/public health
- net result is that antibiotic classes that are critically important to human medicine, e.g., 4th generation cephalosporins, will likely not get approved for veterinary use.
 - may see more newer classes of antibiotics that are not critically important in human medicine, e.g., phenicols
 - may see non-antibiotic antibacterial substances, e.g., bacteriocins, or biologicals, or virulence factor inhibitors.

Fight Infection While Minimizing Resistance

develop new modalities of fighting infection

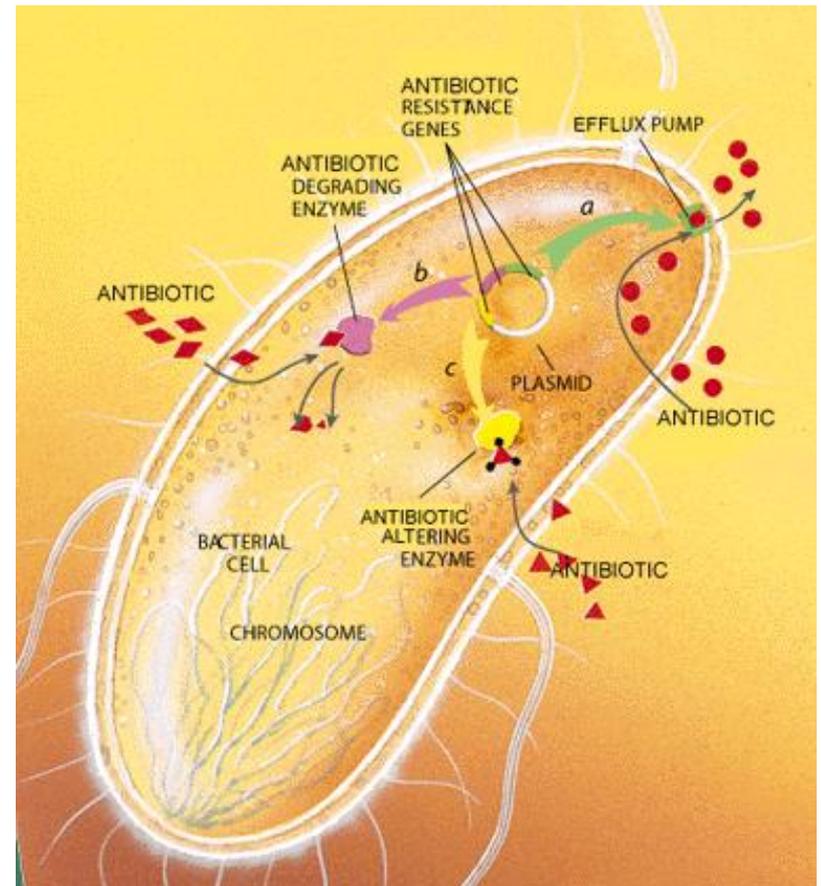
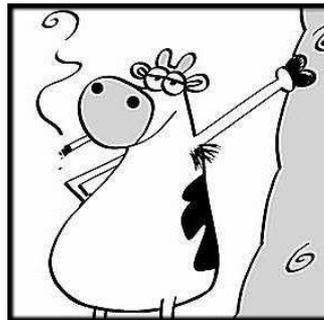
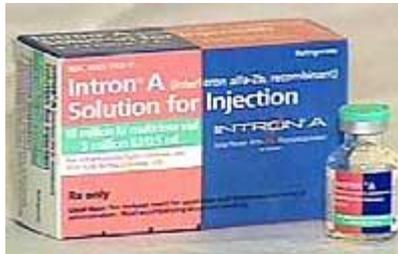
Immunostimulation

Decrease stress

- delivery systems
- anxiolytics

Address resistance factors

- e.g. antibiotic efflux pump inhibitors

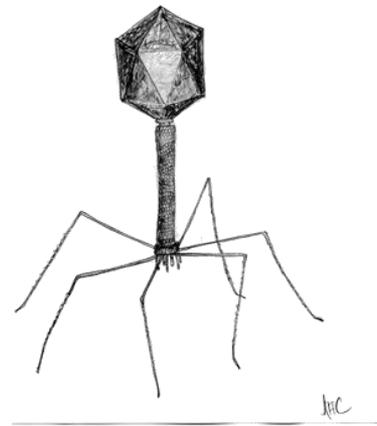


Fight Infection While Minimizing Resistance

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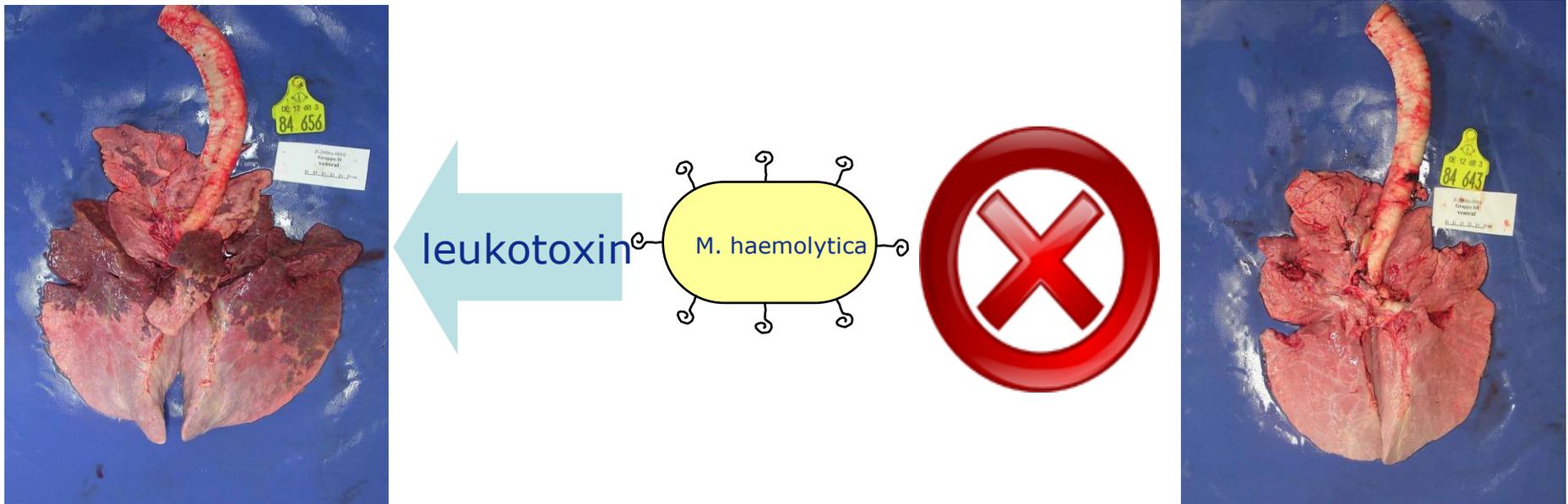
Non-antibiotic antimicrobial therapies

- biofilm disruption
- virulence factor inhibition (next slide)
- phage technology



Fight Infection While Minimizing Resistance

Virulence Factor Inhibition - Example



Exciting new molecular targets -- so-called "virulence factors" that bacteria use to thrive once they are in the host -- present an alternative, potent means of combating bacterial infection

Antimicrobials of greater importance in human medicine should be used after careful consideration

What does that mean?

Factors in considering importance to human medicine:

- World Health Organization – Critically Important Antimicrobials
- Criterion 1: Sole therapy / limited available therapies
- Criterion 2: Used to treat diseases transmitted from non-human sources or diseases that acquire resistance genes from non-human sources

- Critically important – Criteria 1 + Criteria 2
- Highly Important – Criteria 1 or Criteria 2
- Important – Neither criteria is met

Critically Important	Highly Important	Important
Aminoglycosides (most)	Spectinomycin, kanamycin, neomycin	
Carbapenems / Penems	Monobactams	
Cephalosporins (3 rd /4 th gen)	Cephalosporins (1 st / 2 nd gen) Cephamycins	
Glycylcyclines		
Lipopeptides		
Macrolides / Ketolides		Lincosamides
Oxazolidinones		
Penicillins (most)	Amdinopenicillins, Antistaphylococcal penicillins	
Quinolones		
Streptogramins		
Tetracyclines		
	Phenicol	
	Polymixins	
	Sulfonamides	
		Bacitracin

Valid VCPR

What does that mean?

(n) "Veterinary-client-patient relationship" means:

(1) The veterinarian has assumed the responsibility for making medical judgments regarding the health of the animal or animals and the need for medical treatment, and the client, owner or other caretaker has agreed to follow the instruction of the veterinarian;

(2) there is sufficient knowledge of the animal or animals by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal or animals. This means that the veterinarian has recently seen or is personally acquainted with the keeping and care of the animal or animals by virtue of an examination of the animal or animals, or by medically appropriate and timely visits to the premises where the animal or animals are kept, or both; and

(3) the practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy.

Animal Medicinal Drug Use Clarification Act

Kansas Veterinary Practice Act: 47-816

Nebraska Veterinary Drug Distribution Licensing Act: 71-8908

Iowa Administrative Code (Standards of Practice): 811-12.1(3)



This IS law



Valid VCPR

What does that mean?

Principles of Veterinary Medical Ethics of the AVMA

- Includes previous language PLUS
 1. When a VCPR exists, veterinarians must maintain medical records
 2. Dispensing or prescribing a prescription product requires a VCPR
 3. Veterinarians may terminate a VCPR under certain conditions, and they have an ethical obligation to use courtesy and tact in doing so
 - A. Inform the client
 - B. Provide continuing care until a referral can be made
 4. Clients may terminate the VCPR at any time

**This is
NOT law**



HHS to Test Live Food Animals for Antimicrobial Resistance
Veterinary Practice News
May 25, 2012

The U.S. Department of Health and Human Services plans to conduct pilot studies on farms to determine the feasibility of collecting pre-harvest samples from food animals as part of the National Antimicrobial Resistance Monitoring System, according to the NARMS 2012-2016 Strategic Plan, released today by HHS.

[For the full FDA press release, see:

<http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm305710.htm>]

Full text: <http://tinyurl.com/c6nra9v>

Summary: Human versus Animal Health Industry

AH markets are much smaller yet the regulatory burden for development of a medicine for food animal use is high

Estimated changes over the past 15 years:

- **Regulatory requirements drove up costs by 150%**
- **Development time increased by 4.5 years on average**
- **Defensive R&D absorbs 20-35% of resources**

Antibiotic Conference -2012

Summary

NY Times, Sept, 04, 2012

1. Antibiotics are considered the crown jewels of modern medicine. They have transformed health by stopping infections since they went into broad use after World War II. But many scientists say that their effectiveness is being eroded by indiscriminate use, both to treat infections in people and to encourage growth in chickens, turkeys, cows and pigs.
2. Antibiotic use in people can be closely monitored through the vast infrastructure of the nation's health care system, but there is no equivalent for animals, making it harder to track use on farms and ranches.
3. "The single biggest problem we face in infectious disease today is the rapid growth of resistance to antibiotics".

Antibiotic Conference -2012

Summary

R Sibbel 2012

4. Animal Agriculture and Veterinary Medicine will continue to advocate responsible and scientific investigation of antibiotics, through advancements in licensing discipline and stewardship of use of existing and discovered antimicrobials.
5. While development of effective disease prevention is important, veterinarians also need innovative treatments for a wide variety of diseases and pests.
6. The R&D provided by the research-based pharmaceutical industry is critical to respond to these changing conditions.
7. Balancing natural resources, husbandry practices, performance enhancement and health management with the global regulatory environment and consumer acceptance will be essential for facilitating innovation.



Thank-you