PANEL:
State of Science –
What Do We Know?
What Don't We Know?
State of Science –
What Do We Know?
What Don't We Know?

Mark G. Papich
North Carolina State University
College of Veterinary Medicine
Raleigh, North Carolina
mark_papich@ncsu.edu
The Role of CLSI
• Publish standard methods
• Establish Interpretive Categories for susceptibility testing
• Educate health care professionals
• Subcommittee on Veterinary Antimicrobial Susceptibility Testing (VAST) continuously updates existing standards
• Veterinary Antimicrobial Susceptibility Testing subcommittee (VAST)

• Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; approved standards.
  - 3rd edition (M31-A3), 2008
  - 4th edition (M31-A4, now called VET01), 2013
  - VET01-S3 (third supplement), 2015
  - VET01-S4 and VET08 due in 2017
Veterinary-Specific Interpretation: Large Animals

- Fluoroquinolones
  - Danofloxacin (cattle)
  - Enrofloxacin (horses, cattle, pigs)
- Tulathromycin (cattle)
- Ceftiofur (horses, cattle, pigs)
- Florfenicol (cattle, pigs)
- Spectinomycin (cattle)
- Tilmicosin (cattle, pigs)
- Ampicillin (horses, pigs; cattle pending)
- Tetracycline (cattle, pigs)
- Enrofloxacin (pigs)
- Penicillin G (horses, cattle, pigs)
- Tildipirosin (cattle, pigs)
- Gamithromycin (cattle)
What we know.
What we know

- Administration of antimicrobial agents selects for resistant strains
- Resistant strains in the intestine of animals has potential to be transmitted to people
- Some drugs (and drug regimens) may be more likely to select for resistance than others
Examples of How Antibiotic Resistance Spreads

1. Animals get antibiotics and develop resistant bacteria in their guts.
2. Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.
3. Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.
4. Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.
5. George gets antibiotics and develops resistant bacteria in his gut.
6. George stays at home and in the general community. Spreads resistant bacteria.
7. George gets care at a hospital, nursing home or other inpatient care facility.
8. Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.
9. Resistant bacteria spread to other patients from surfaces within the healthcare facility.
10. Patients go home.

Healthcare Facility
2015

SUMMARY REPORT

On

Antimicrobials Sold or Distributed for Use in Food-Producing Animals

Center for Veterinary Medicine
Protecting Human and Animal Health

FDA

Food and Drug Administration
Department of Health and Human Services
December, 2016
ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS actively marketed in 2015
SALES AND DISTRIBUTION DATA REPORTED BY DRUG CLASS

[Bar chart showing annual totals (kg) for various drug classes, with specific data points for each class.]

- Aminoglycosides
- Amphenicols
- Cephalosporins
- Fluoroquinolones
- Ionophores
- Lincomycin
- Macrolides
- Penicillins
- Sulfa
- Tetracyclines
- N1
- NRE

Legend:
- Domestic
- Export
ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS ACTIVELY MARKETED IN 2015
DOMESTIC SALES AND DISTRIBUTION DATA REPORTED BY MEDICAL IMPORTANCE AND DRUG CLASS

![Graph showing annual totals (kg) for different drug classes.](image-url)
ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS
ACTIVELY MARKETED IN 2015
DOMESTIC SALES AND DISTRIBUTION DATA
REPORTED BY MEDICAL IMPORTANCE AND ROUTE OF ADMINISTRATION
ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS\textsuperscript{1} ACTIVELY MARKETED IN 2015
DOMESTIC SALES AND DISTRIBUTION DATA REPORTED BY MEDICAL IMPORTANCE AND DISPENSING STATUS

![Bar Chart]

- OTC\textsuperscript{1,5}: 9,500,000 kg
- RX\textsuperscript{1,6}: 100,000 kg
- RX\textsuperscript{6}/OTC\textsuperscript{1,5,7}: 500,000 kg
- VFD\textsuperscript{8}: 0 kg
- OTC\textsuperscript{5}: 5,000,000 kg

Medically Important\textsuperscript{3}

Not Currently Medically Important\textsuperscript{4}
Efforts to reduce use of antibiotics in food animals
Reducing Antibiotic Use in Food Animals

• Eliminate production uses of antibiotics (growth promotion)
• Antibiotics administered in feed and water require veterinary oversight – *no over-the-counter availability*
• Veterinary Feed Directive rules (VFD) (January 1, 2017)
• Reduce frequency of administration of antibiotics (single-shot)
What we don’t know?
What we don’t know?

• The impact of new initiatives on emergence of drug-resistant bacteria in food animals

• The impact of the other agents used for treatment (by injection) on antimicrobial drug resistance
Antibiotic Distribution Studies in Cattle

Mark G. Papich & Derek Foster
North Carolina State University
College of Veterinary Medicine
Raleigh, North Carolina
Antibiotics Studied

Enrofloxacin

Ceftiofur Crystalline Free Acid

Ceftiofur Sodium

Fluoroquinilone

Cephalosporin

Cephalosporin
**In vivo ultrafiltration device**

- 3 semi-permeable loops
- Inserted with a guide needle into tissue.
- Vacutainer for collection
- Collects fluid and unbound compounds in ISF
Questions

• For antibiotics administered by injection to cattle for treatment of BRD:

1. Do they diffuse into intestine?
2. Are they degraded in intestinal fluids?
3. Are they present in an active form?
4. Are concentrations high enough to affect intestinal bacteria (eg, *E. coli*)
Metabolism

Enrofloxacin → Ciprofloxacin

F
6 5 4 3

N
7 8

C

H₃CH₂

N

F
6 5 4 3

N
7 8

C

HN
Intestinal Studies

Enrofloxacin (and Ciprofloxacin)
Enrofloxacin + Ciprofloxacin Concentrations (High Dose)
12.5 mg/kg SC single dose

- Plasma
- Interstitial Fluid
- Ileum Fluid
- Colon Fluid

E. coli MIC 0.06 µg/mL
Fecal *E. coli* Concentration after Treatment with Enrofloxacin

![Graph showing Fecal E. coli Concentration](graph.png)

- * indicates significantly different from Time 0 for high dose (p<0.05)
- # indicates significantly different from Time 0 for low dose (p<0.05)
The “inverted U” concept of antibacterial resistance
Resistant Bacteria

Low number of resistant organisms at baseline.

Resistance suppressed at high exposure.

Antibiotic Exposure
Future Development

• To reduce the risk of drug-resistant intestinal bacteria, future efforts should focus on identifying the impact of antimicrobial agents in intestinal fluids.
  1. Optimize exposure with short-course, high concentrations.
  2. Develop agents with low distribution to the intestine
  3. Develop agents that are inactivated in the intestine
Thank you!

Any questions?
Contact Information

Mark G. Papich
College of Veterinary Medicine
North Carolina State University
1060 William Moore Drive
Raleigh, North Carolina, USA
Phone: 919-513-6221
E-mail: mark_papich@ncsu.edu