Some Thoughts about Antibiotic Stewardship and Choices of Antibiotic Use in Beef Cattle

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Definition of Antibiotic Stewardship

‘the careful and responsible management of ANTIBIOTICS entrusted to one’s care’

» Merriam-Webster Online Dictionary [m-w.com]
“What antibiotics won’t do!”

- Reverse existing lung damage
- Kill off resistant bugs
- All act the same – respiratory drugs are designed differently
- Kill off viruses
- Cure management issues
Societal Pressure Points

- Increasing incidence of Antibiotic resistance in Cattle
- Increasing number of human bacterial infections with resistant strains of bacteria
- Any exposure to antibiotics selects for some resistance strains
- Livestock and their bacteria are exposed to antibiotics
- Assume a connected risk between Human health and Animal health
Reality Check

- FDA 2013 report on all “antibiotics sold or distributed for use in food-producing animals”:
  - Ionophores 30% (not used in human medicine at all) are antiparasitics
  - Not Individually Reported (NIR) 8.0% (Almost none used in human medicine)
  - Tetracyclines 44% (71% of Medically Important antibiotics used in animal ag)
Introduction: The concern

- Treatment of specific bacterial infections in both human and veterinary medicine may become more complicated due to increased resistance.

- The basic question for food animal production sector is:
  - Can transfer of antibiotic resistance to humans or other animals increase the risk for failure of antibiotic therapy in both human and animal medicine?

  The answer is complicated.
Determination of the amount of pulmonary lesions when cattle are challenged with *Mannheimia haemolytica* 10 days after administration of either tildipirosin (Zuprevo) or tulathromycin (Draxxin).

- David Amrine¹, Brad J. White¹, Robert Larson¹, Derek Mosier²
Lung Lesions

- Zuprevo 8.7%
- Draxxin 13.1%
- Saline 25.5%
- \((p<0.05)\) ZUP < Draxxin & Saline
**Mannheimia haemolytica % Resistant 2005-2009**

<table>
<thead>
<tr>
<th></th>
<th>Ceftiofur (CEF)</th>
<th>Enrofloxacin (ENRO)</th>
<th>Florfenicol (FFC)</th>
<th>Tetracycline (TET)</th>
<th>Tilmicosin (TILM)</th>
<th>Tulathromycin (TUL)</th>
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</thead>
<tbody>
<tr>
<td>2009</td>
<td>0%</td>
<td>6.6%</td>
<td>8.6%</td>
<td>43.8%</td>
<td>27.3%</td>
<td>8.9%</td>
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<tr>
<td>2008</td>
<td>0%</td>
<td>5.2%</td>
<td>9.5%</td>
<td>45.0%</td>
<td>23.0%</td>
<td>9.5%</td>
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<tr>
<td>2007</td>
<td>0%</td>
<td>Not tested</td>
<td>8.7%</td>
<td>42.7%</td>
<td>23.3%</td>
<td>10.7%</td>
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<tr>
<td>2006</td>
<td>0%</td>
<td>Not tested</td>
<td>6.8%</td>
<td>31.5%</td>
<td>13.9%</td>
<td>7.1%</td>
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<tr>
<td>2005</td>
<td>0%</td>
<td>Not tested</td>
<td>4.5%</td>
<td>31.8%</td>
<td>6.9%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

• Adapted from Portis et al., 2012 J. Vet Diag Invest 24(5):932-944

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Mannheimia haemolytica isolates

Percent of Isolates

Number of "R" Interpretations per Panel

<table>
<thead>
<tr>
<th>Year</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>2009</td>
<td>(55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td>(155)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td>(179)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

MERCK Animal Health
Retail and Consumers

The competitive business of food sales and the pressure to differentiate is aligning with societal, governmental and political pressures to preserve and protect Antibiotic effectiveness.
Some Facts about Antibiotic Resistance (AR)

NOT antibiotic residues
Bacteria want to survive
AR occurs through a variety of mechanisms
  – With or without antibiotic exposure
Not a new phenomenon
Some Facts (cont.)

Foodborne illnesses down 26% from 2002-2011
Foodborne outbreaks down 42% from 2002-2011
Media hits for foodborne illnesses up 150% in same period
Media hits for recalls of food up 250% in same period
(e.g. Peanut Corporation of America)
• Macrolide resistance in *Campylobacter* remained low at 0.5% for *C. jejuni* but rose to 12% for *C. coli*. **Macrolides are the drugs of choice to treat Campylobacter for severe cases.**

• Tetracycline resistance was the most common at 50%. They have been used for over 50 years.

• Multi-drug resistance (MDR) increased in *Salmonella* while remaining very rare in *Campylobacter* but exposure was the same.

• Reality: we don’t know why.
Reality of constant media attention of Human Health MDR issues and the possible interaction with the Food Supply as adding perceived risk to the MDR issues in Human Health
Global Influence

World Health Organization and related overarching health organizations focusing and advising on a world Human Health crisis with increasing MDR bugs impacting global human health
Continuous Improvement

Animal Agriculture, increasing world food demands (especially protein), transparency in food purchases, Social Media and journalism needing a strong villain.
• Comparing DNP from healthy cattle and those diagnosed with BRD, it was found that Mh resistance to at least one antibiotic was 37% in post-treated cattle compared to 2% in healthy cattle (p<0.001) and that the transmission and spread of antibiotic resistant Mh does occur.
The consolidating meat industry, the global business of seeking new markets and increasingly connected export opportunities.
Meat protein industries and associated retail outlets (from high end restaurants to grocery stores) all seeking market advantage and customer influence
Production efficiency and effective commodity management used to be enough to be a successful enterprise. Now, differentiation rules the meat case, especially reduced to no use of Antibiotics.
Have we reached the crossroad in management of BRD?
What if the metaphylactic drugs we are using do everything we ask them to do? Lower bacterial counts in the nasopharynx, decrease BRD incidence, decrease mortalities?

What if these drugs remove all the commensal organisms in the nasopharynx leaving only the 5% of MDR pathogens?

What if we then continue to apply stressors to these animals? Concurrent viral infection, suppression of the immune system (BVDV, Mycoplasma bovis), environmental, ration changes, pro-inflammatory processing products, repeated handling, mixing groups of cattle?
Labeling Confusion

The marketplace indulges in labeling magic and confusion to exploit the consumer. Now, some protein is inferior by labeling omission!

Constant education is needed throughout the chain of animal production, all the way to the plate.
Commodity is not Good

Retail Food products must be raised better, cared for better, have improved qualities, have fewer ingredients and have labels encouraging buyer enthusiasm for crafting a **higher quality of life**.
Antibiotics-Looking Ahead

- VFD rules and regulations
  - Preventive use will be challenged
- Oversight by Veterinarians will increase
  - (VCPR will be increasingly necessary)
- Total use in each operation will be managed for reduced footprint
- Only VCPR Therapeutic use will be justified
VCPR (Veterinary Client Patient Relationship)

- Fast becoming the new expectation by regulators and consumers
- Demands of Veterinary Medical Oversight for use of all Antibiotics
- Feed grade antibiotics are the first step to more oversight to all antibiotics
- Medically important vs veterinary only
- Huge opportunity for Food Animal Veterinary Medicine
  - Societal and Business opportunity
  - Will demand increased Veterinary understanding and assessment for justification of use
Antibiotics-Looking Ahead (cont.)

- Expect increased vaccine use to reduce need for Antibiotics
- Alternatives to Antibiotics will be explored
- Expect additional regulations and compliance processes
- More funded research trying to link Human concerns/iss...
Summary

• New world of cattle management demands
• Increased push for changing the way cattle are weaned and shuttled into commerce
• Increasing veterinary interface with all phases of cattle production (VCPR/scripts)
Thank you
Conclusion

Human Health issues too big to legislate, so Ag will continue to be asked to manage reduction of total use of Antibiotics
Thank you
Antibiotic Footprint

A. Must reduce (VFD)

B. Must justify (Scripts & VCPR)

C. Must record (FDA)

D. Must report (next?)
Veterinary Feed Directive (VFD)

- http://www.fda.gov/animalveterinary/developmentapprovalprocess/ucm071807.htm

- Guidance #209 – Outlines Anti-Microbial Resistance (AMR) Policy
- Guidance #213 – Implementation of VFD
- Guidance #120 – Q & A about VFD
• Outline – Questions to Be Addressed

• What changes are being made and why?
• What drugs are affected, which ones are not?
• What is a veterinary feed directive?
• What are key elements of VFD regulation?
• When will this go into effect?
FDA’s Judicious Use Strategy

Two key principles outlined in Guidance #209:
1. Limit medically important antimicrobial drugs to therapeutic purposes (i.e., those uses considered necessary for ensuring animal health)
2. Require veterinary oversight or consultation for such therapeutic uses in food-producing animals
Guidance #213: Overview

December 2016 - Target for drug sponsors to implement changes to use conditions of medically important antibiotics in food and water to: Withdraw approved production uses such as “increased rate of weight gain” or “improved feed efficiency”

Such production uses will no longer be legal
Guidance #213: Removing Production Uses

However, therapeutic uses are to be retained treatment, control, and prevention indications

Require veterinary oversight
**Affected feed-use antibiotics**

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Specific drugs approved for use in feed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Apramycin, Hygromycin B, Neomycin, Streptomycin</td>
</tr>
<tr>
<td>Diaminopyrimidines</td>
<td>Ormetoprim</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Lincomycin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin, Oleandomycin, Tylosin</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Virginiamycin</td>
</tr>
<tr>
<td>Sulfas</td>
<td>Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfafloxinol</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Chlortetracycline, Oxytetracycline</td>
</tr>
</tbody>
</table>
Veterinary Client Patient Relationship (VCPR)

Veterinarian issuing a VFD is required to be licensed to practice veterinary medicine and operate in compliance with either: **State-defined VCPR** – if VCPR defined by such State includes the key elements of a valid VCPR defined in § 530.3(i); or

• **Federally-defined VCPR** - where no applicable or appropriate State VCPR requirements exist
Veterinary Client Patient Relationship (VCPR)

The State-defined VCPR must at least address the concepts that the veterinarian:
1) engage with the client to assume responsibility for making clinical judgments about patient health;
2) have sufficient knowledge of the patient by virtue of patient examination and/or visits to the facility where patient is managed; and
3) provide for any necessary follow-up evaluation or care.
Implementation Timeline Summary

October 1, 2015 – VFD Final Rule goes into effect
  Applies to current VFD drugs

January 1, 2017 – Target for all medically important antimicrobials for use in or on feed to require a VFD

December 2016 – Target for drug sponsors to implement changes to use conditions of products affected by GFI #213
Thank you