Impact of Antibiotic Use in Animal Agriculture and Influence on Resistance Controversy

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Get Smart
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www.nourishlife.org
- Animal Care and Therapeutics
- Preventative care vs. disease treatment
- Quality concerns
- Regulatory issues & food safety concerns
  - What does that mean for producers
  - What does that mean for consumers
  - What does it mean for animal well-being
  - Impact for markets and environment
Man vs. Microbe We’re losing the battle against bacteria. Can we win the war?

BY ALICE PARK
All Animal Ag Species- Care and Well-being Initiatives

• Address injured or ill animals
  – Treatment protocols
• Painful conditions
• Chronic conditions and euthanasia
• Relative economic value animals
• Routine care procedures of caretakers (+ training)
• Care and welfare of animals during transportation

• Prevention & keep well > treat when ill
Animal use and contribution to resistance?

- Animals consume **and excrete** antibiotics (~2 trillion lbs of manure generated in USA annually)
- Animals can transmit resistant bacteria in food
  - Food of animal origin as cause of food-borne infections:
    - *Salmonella*
    - *Campylobacter*
    - *Yersinia*
    - *E Coli 0157-H7*
- Transfer to human specific organisms (esp. seen in examples from pigs and chickens when sick).
## Antibiotic by Route of Use

- **Antimicrobial Drugs Approved for Use in Food-Producing Animals**
- **Actively Marketed in 2014**
- **Domestic Sales and Distribution Data**
- **Reported by Medical Importance and Route of Administration**

<table>
<thead>
<tr>
<th>Route of Use</th>
<th>Annual Totals (kg)</th>
<th>% Subtotal</th>
<th>% Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medically Important</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feed1</td>
<td>6,977,747</td>
<td>74%</td>
<td>45%</td>
</tr>
<tr>
<td>Injection1</td>
<td>341,790</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Intramammary</td>
<td>11,450</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Oral5 or Topical1</td>
<td>104,082</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Water6</td>
<td>2,040,920</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>9,475,989</td>
<td>100%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Not Medically Important</strong></td>
<td>All Routes7</td>
<td>5,882,221</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td>15,358,210</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

NARMS 2014, p 44
Why use antibiotics in feed?

• Use at periods of higher stress: feed changes, transportation, weather changes

• Reduces shedding of food safety pathogens
  – Trade 1/53,000,000 illness due to resistance
  – Vs. 1/32, 900 illness due to greater food safety illness (additional 6,000 severe cases/yr)

• Lower carbon footprint
  – Average 13% greater gain/kg of feed
  – Saves 4-6% of input cost

Cox and Ricci, Envir Sci, 2007
Matthew, et al., Food Path Dis 2007
<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Therapeutic vs. Disease Prevention/control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acutely ill animals</td>
</tr>
<tr>
<td></td>
<td>Many fewer animals</td>
</tr>
<tr>
<td></td>
<td>Higher doses (gm vs. mg)</td>
</tr>
<tr>
<td></td>
<td>More handling</td>
</tr>
<tr>
<td></td>
<td>Tissue residue</td>
</tr>
<tr>
<td></td>
<td>New products &amp; cost R&amp;D</td>
</tr>
<tr>
<td></td>
<td>Treat pain and suffering</td>
</tr>
<tr>
<td></td>
<td>Stunted growth</td>
</tr>
<tr>
<td></td>
<td>Higher cost/animal</td>
</tr>
<tr>
<td></td>
<td>Keep healthy vs. sick</td>
</tr>
<tr>
<td></td>
<td>Entire herd or flock</td>
</tr>
<tr>
<td></td>
<td>Low dose, no residue</td>
</tr>
<tr>
<td></td>
<td>Fewer food pathogens</td>
</tr>
<tr>
<td></td>
<td>Older products, not normally for humans</td>
</tr>
<tr>
<td></td>
<td>Avoid prevent pain/suffering</td>
</tr>
<tr>
<td></td>
<td>Lowers cost of production</td>
</tr>
<tr>
<td></td>
<td>Improves efficiency (less manure, less acres)</td>
</tr>
</tbody>
</table>
TOP ANTIBIOTICS USED IN HUMANS vs. ANIMALS

The top antibiotics used for food producing animals in 2011 were rarely used in humans, and vice versa.

HUMAN ANTIBIOTICS SALES
- 44% Penicillin
- 15% Cephalosporin
  - 14% Sulfas
  - 9% Quinolones
  - 9% Other
  - 5% Macrolides
  - 4% Tetracyclines

ANIMAL ANTIBIOTICS SALES
- 41% Tetracycline
- 30% Ionophores
  - 11% Not Individually Reported
  - 6% Penicillins
  - 4% Macrolides
  - 5% Other

Ionophores are antibiotics that are never used in human medicine.

SOURCE: FDA 2011 reports

Wholly or partially funded by one or more Checkoff programs
Reduction of Residues and Resistance

• Judicious use programs
• Restrict extra label use
  – Diagnostics to inform science based protocols
  – Create written protocols for common conditions
  – Up to date and written VCPR and VFD
• Supervise use as much as possible on farms
• Extended withdrawal times
  – Physiological state of animal
  – Dose, depot and tissue location
• FARAD (www.farad.org)
Factors that can affect elimination of therapeutic product

• Dose and size of depo
  – Rate of absorption
  – IV < IM < SQ (product moves depo to plasma)
  – Pharmokenetics
    • Overall health and status of animal
    • Target plus elimination organs
    • Special characteristics of product
  – Multiple doses or different doses
  – Dose in different site than designed
Extended WDT

- WDT is the time required after dosing for tissue concentrations to be depleted to or below specific safe concentration
- More closely associated to tissue depots vs. plasma depots
- Tissue with the slowest depletion determines the WDT for the species
  - $10 \times t^{\frac{1}{2}} = 99.9\%$ depletion, days usually rounded up (no fractions of days), physiological state, different tissue
  - In US safe concentration can be defined as the tolerance limit-law is zero for not approved compounds
- In Europe usually termed Maximum residue level
Normal Dose
Normal Kidney/Liver ~ Predictable Withdrawal

- Same dose but repeated
- Withdrawal (slightly extended)
  - (e.g., few d plus new dose)
- Milk withholding
  - Pretty predictable even if 1 ppb

MIC

Safe withdrawal

Re-treat ~ 1 days  Single dose ~10 wd
Multiple doses - safe ~ + few d
Extended Treatment or Compromised Kidney/Liver
Very Long Withdrawal

- Same dose but repeated
- Withdrawal (can be greatly extended)
  - (e.g., not just 3 d plus new dose)
- Milk withholding
  - Very long if target is 1 ppb

Re-treat ~ 3 days
Safe ~ 30 d  Safe ~ 50 + d
Malaria Resistance and Lessons Learned

- Read and Huijben, Evol. App., 2009

Fallacies

- Drugs with long half lives are preferable
- De novo resistance mutations are main enemy
  - (vs. transportation around globe)
- Genetic trade offs alone determine costs of resistance to pathogen
  - (vs. in host ecology)
- Fixation of resistance is inevitable if drug pressure is maintained
Staphylococcus aureus

- Samples submitted to ADL for mastitis or bulk tank milk culture (2008, 2013, 2014, 2015) examined for *S. aureus*
  
  - *S. aureus* isolates
    
    - 163 isolates (n=115 QMS; n=48 BTM) from 77 farms
      
      - **Small cell variant phenotype analysis**
      - **Antibiotic resistance**
        
        - Amoxicillin + Clavulanic acid, Cefoxitin, Ciprofloxacin, Clindamycin, Erythromycin, Gentamicin, Oxacillin, Tetracycline, Vancomycin, Penicillin.
      - **Enterotoxin genes:** A, B, C, D, E, F, G, H, I, J, K, L, M, O, P, Q, R, TSST-1
      - **Leukocidin genes:** LukAB, LukED, LukMF
      - **DNA Fingerprinting:** Multi Locus Sequence Typing

Jayarao, unpublished 2015
## Antimicrobial Resistance

- 130/163 = 80% of isolates sensitive to all ten antimicrobials examined.
- BTM: 37/48 = 77%
- QMS: 93/115 = 81% NO MRSA strain isolated from Pennsylvania dairy herds

<table>
<thead>
<tr>
<th>Antibiotic Resistance Profile</th>
<th>No of Isolates</th>
<th>No. of Farms</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>130</td>
<td>74</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1</td>
<td>1 (QMS)</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>3</td>
<td>2 (BTM), 1 (QMS)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>7</td>
<td>1 (BTM), 6 (QMS)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>5</td>
<td>5 (QMS)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>11</td>
<td>3 (QMS), 2 (BTM)</td>
</tr>
<tr>
<td>Amoxicillin, Penicillin</td>
<td>1</td>
<td>1 (BTM)</td>
</tr>
<tr>
<td>Clindamycin, Erythromycin</td>
<td>2</td>
<td>1 (QMS)</td>
</tr>
<tr>
<td>Oxacillin, Penicillin</td>
<td>1</td>
<td>1 (QMS)</td>
</tr>
<tr>
<td>Clindamycin, Erythromycin, Tetracycline, Penicillin</td>
<td>2</td>
<td>2 (BTM, QMS)</td>
</tr>
</tbody>
</table>
# Prevalence of Antibiotic Resistance %

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Salmonella n=202</th>
<th>E coli ‘07 n=525</th>
<th>Salmonella n=232</th>
<th>E coli ‘08 n=500</th>
<th>Salmonella n=117</th>
<th>E coli ‘09 n=510</th>
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</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Amoxi/clav.</td>
<td>1.0</td>
<td>1.5</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1.5</td>
<td>2.1</td>
<td>0</td>
<td>2.2</td>
<td>0</td>
<td>1.6</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>1.0</td>
<td>1.5</td>
<td>0</td>
<td>1.3</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>1.0</td>
<td>0.8</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1.0</td>
<td>0.2</td>
<td>0</td>
<td>0.9</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>0</td>
<td>3.8</td>
<td>0</td>
<td>4.8</td>
<td>1.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1.0</td>
<td>5.1</td>
<td>0.4</td>
<td>6.5</td>
<td>1.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Sulfizoxazole</td>
<td>1.0</td>
<td>3.8</td>
<td>0</td>
<td>4.8</td>
<td>1.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1.0</td>
<td>13.1</td>
<td>0</td>
<td>9.8</td>
<td>1.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Trim. /sulfa</td>
<td>0</td>
<td>1.0</td>
<td>0</td>
<td>1.5</td>
<td>0</td>
<td>1.2</td>
</tr>
</tbody>
</table>
### Resistant *E. coli* isolates from Various Cattle Groups in PA

<table>
<thead>
<tr>
<th>Antimicrobial Agents</th>
<th>Farm Prevalence (%)</th>
<th>Pre-weaned calves (n=77)</th>
<th>Post-weaned calves (n=75)</th>
<th>Dry cows (n=72)</th>
<th>Lact. cow (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUG</td>
<td>40.3 (31)</td>
<td>14.7 (11)</td>
<td>0.0 (0)</td>
<td>5.0 (4)</td>
<td></td>
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<tr>
<td>AMP</td>
<td>57.1 (44)</td>
<td>33.3 (25)</td>
<td>1.4 (1)</td>
<td>12.5 (10)</td>
<td></td>
</tr>
<tr>
<td>AZI</td>
<td>2.6 (2)</td>
<td>1.3 (1)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td></td>
</tr>
<tr>
<td>FOX</td>
<td>37.7 (29)</td>
<td>13.3 (10)</td>
<td>0.0 (0)</td>
<td>5.0 (4)</td>
<td></td>
</tr>
<tr>
<td>TIO</td>
<td>31.2 (24)</td>
<td>12.0 (9)</td>
<td>0.0 (0)</td>
<td>5.0 (4)</td>
<td></td>
</tr>
<tr>
<td>AXO</td>
<td>36.4 (28)</td>
<td>13.3 (10)</td>
<td>0.0 (0)</td>
<td>6.3 (5)</td>
<td></td>
</tr>
<tr>
<td>CHL</td>
<td>29.9 (23)</td>
<td>18.7 (14)</td>
<td>1.4 (1)</td>
<td>1.3 (1)</td>
<td></td>
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<tr>
<td>CIP</td>
<td>1.3 (1)</td>
<td>1.3 (1)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td></td>
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<tr>
<td>GEN</td>
<td>13.0 (10)</td>
<td>5.3 (4)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td></td>
</tr>
<tr>
<td>NAL</td>
<td>7.8 (6)</td>
<td>4.0 (3)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td></td>
</tr>
<tr>
<td>STR</td>
<td>70.1 (54)</td>
<td>38.7 (29)</td>
<td>6.9 (5)</td>
<td>21.3 (17)</td>
<td></td>
</tr>
<tr>
<td>FIS</td>
<td>67.5 (52)</td>
<td>44.0 (33)</td>
<td>11.1 (8)</td>
<td>22.5 (18)</td>
<td></td>
</tr>
<tr>
<td>TET</td>
<td>81.8 (63)</td>
<td>69.3 (52)</td>
<td>26.4 (19)</td>
<td>40.0 (32)</td>
<td></td>
</tr>
</tbody>
</table>
No resistance detected

Sal. Heideberg
Sal. Newport
Sal. Typhimurium
Sal. Non Typhi
Sal. Typhi

NARMS ‘14
Malaria Resistance and Lessons Learned

• *White, et. al., Malaria Journal, 2009*

Resistance

• Greater: fast parasite growth and high burdens
• Recrudescence and multiple recrudescence are required for de novo selection of resistance
• Inadvertent treatment of asymptomatic parasitemia is unlikely source of resistance
• Strive for therapeutic levels in all patients
• Ill patients with hyperparasitemia very risky
Antibiotic use the only cause or solution for AMR?

• Genes in environment
  – Co selection against metals
  – Allows for plasmids and integrons +cassettes to DNA
  – Co-resistance to heavy metals allows for maintenance of resistance (polluted countries)
  – Increased use of trace minerals to improve performance

• Heavy industrial impact = greater resistance

Berendonk, et.al, Nat Rev Micro, 2015
McAurther, et.al, Micro Ecol, 2015
Example: Imported Shrimp

- ~ One hundred percent of Vietnamese shrimp farms use ciprofloxacin.
- Fluoroquinolone concentrations in sediments and surface waters may reach >4,000 μg/kg.
- All kinds of bacteria inhabit these ponds, including those present in the manure of terrestrial animals (such as chickens) that is fed to the shrimp

- “Where does this lead?”
Systems Approach
Advantages of US Food Supply vs. Production Forced Out of Country

INTEGRATOR DRIVEN BMP/HACCP PROGRAMS

- Environmental Stewardship
- Market Incentives
- Diet Options
- Antimicrobial Usage
- Well being-Welfare
- Food Safety and Security
- Rearing Practices & Housing
Penn State is committed to affirmative action, equal opportunity and diversity of its workforce.