Antibiotic Usage and Resistance on Dairy Farms

Core Concepts 1
Antibiotic Basics

- Antibiotics & Antimicrobials
  - Natural or synthetic substances that are able to destroy micro-organisms
- Mechanism
  - Disrupt cell processes
  - Bind with and burst cell walls
- Spectrum of activity
  - Types of organisms that can be destroyed
    - Narrow spectrum
      - Can kill only a few specific organisms
    - Wide spectrum
      - Can kill a wide variety of organisms

Core Concepts 1
Antibiotic Basics – DAIRY COWS

- Almost all treatments given to dairy cows are given individually
  - Intramammary infusion into teat
  - Injection under skin or in muscle
- Antibiotics in adult cows
  - are NOT administered for growth promotion
  - Are NOT given in feed and water
    - Limited usage in baby calves on milk

Core Concepts 1
What Happens to Antibiotics in the Cow?

- They are absorbed into the blood stream and metabolized
- Clearance can be
  - Through kidneys
  - Through liver
- Metabolites are excreted in urine & feces
  - Measured in PPB
- What happens to the metabolites?
  - Most are rapidly degraded by bacteria present in manure
  - Heavily diluted in manure storage
  - If present in manure applied to soils
    - Most are degraded by bacteria in soils

Antibiotics on Dairy Farms and in Milk

- Concerns about antibiotics in milk originated with concern about inhibition of cheese starters (Cogan, 1972)
- Issue of public health is relatively new and began in 1980’s
  - Initial concern was about potential of allergic reactions to penicillin type drug residues in dairy products
  - No reports of this occurring for at least 40 years
- Recent concern is about use of antibiotic on dairy farms contributing to spread of resistant organisms

US Regulation for Antibiotic Usage on Dairy Farms

- FDA regulates allowable antibiotic usage
- When antibiotics are given to dairy cows
  - Milk must be discarded during use and for a legally mandated withholding period
    - To allow the drug residues to clear the system
    - 1 antibiotic has no milk withholding period because it is not excreted in milk
  - Dairy cows may not be sold for beef until a legally mandated withholding period has passed

Use of Antibiotics in Dairy Cows Results in Reduced Income and Increased Expenses

US Regulations for Milk Residues

- Grade A Milk that moves between states is regulated by the Pasteurized Milk Ordinance
  - Minimum standard that states must adopt as the state regulation
  - Administered by the FDA
- Appendix N of the PMO requires
  - Every tanker of milk must be screened for β-lactam residues before unloading
  - Individual farm milk samples must be tested once monthly 4 times per 6-month period
  - Additional random testing is performed

Prevalence of Positive Antibiotic Test Results by Year, 2003 to 2012

Core Concept 2: Types of Antimicrobial Usage on Dairy Farms

- Therapeutic use
  - Treatment of disease
    - Use of cefotiofur for treatment of uterine infections
- Prophylactic use
  - Use of antibiotics for prevention of disease
    - Use of medicated milk replacer for calves
- Metaphylactic use
  - Use of antibiotics to minimize effects of an expected outbreak
    - Use of dry cow treatment at the end of lactation

Allowable Drug Usage

- Over the Counter
  - Can be purchased without a veterinary prescription
  - Must be used exactly as the label indicates
  - Just a couple of drugs are allowed in this category
- Prescription
  - Requires a veterinary prescription and must be used exactly as the label indicates
- Extralabel
  - Any administration of an FDA approved drug that isn't as described by the label
  - Requires veterinary oversight

Antibiotic Usage on Dairy Farms in Wisconsin

- Most dairy farms occasionally use antibiotics
- Survey of 584 WI dairy farms in Fall 2004 (Hoe & Ruegg, J Dairy Science 2005)
  - 9% of respondents reported no use of antibiotics
  - Usage of antibiotics was strongly linked to herd size
    - 88% of herds with <50 cows
    - 94% of herds with 50 - 100 cows
    - 97% of herds with 51 - 200 cows
    - 100% of herds with >200 cows

Survey of 51 Large Dairy Farms

- 800 cows/farm
- Total of antimicrobial treatments in adult cows in one-year = 14,478 treatments
  (of about 33,000 cows in the herds)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of farms reporting disease (%)</th>
<th>Proportion treated</th>
<th>Range treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical mastitis</td>
<td>51 (100%)</td>
<td>40</td>
<td>6.0 - 91</td>
</tr>
<tr>
<td>Metritis &amp; RP</td>
<td>51 (100%)</td>
<td>13</td>
<td>0.0 - 71</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>46 (90%)</td>
<td>4</td>
<td>0.2 - 12</td>
</tr>
<tr>
<td>Foot problems</td>
<td>42 (82%)</td>
<td>5</td>
<td>0.8 - 25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (32%)</td>
<td>2</td>
<td>0.6 - 19</td>
</tr>
</tbody>
</table>
Most Dairy Cows Are NOT Treated with Antibiotics on Most Days

- 14,478 treatments @ 5 d per treatment = 72,390 treatment days
- 33,000 cows @ 365 day = 12,045,000 cow days
- 0.006 of days treated per year  
  (not including DCT)  
  About 2 days per cow per year

We need to balance ensuring animal welfare with responsible antimicrobial usage

Antibiotic Usage and Resistance

- Must properly define the question
  - Issue of exposure to resistant bacteria found in milk?
    - Milk is pasteurized and bacteria are killed
  - Theoretically could be an issue if raw milk is consumed
  - Issue of chronic exposure to low levels of antibiotic residues in milk causing development of antibiotic resistance?
    - Would have to be residues below FDA thresholds
  - Issue of environmental contamination due to excreted residues
    - Do metabolites of antibiotics in urine and feces contribute to increased resistance in environment
      - Increasing concerns about human drug usage

Core Concept 3
Antibiotic Resistance

- Defined based on the failure of a defined concentration of antibiotic to inhibit growth of a specific bacteria
  - Or presence and activity of a specific gene

Core Concept 3: Resistance Terms

- **Intrinsic Resistance**
  - Usually occurs at Genus or species level
  - Target organism lacks binding site etc.
- **Acquired Resistance**
  - Previously susceptible strain of bacteria becomes resistant
  - Mutation or acquires DNA
  - Potential for spread to humans

Antibiotic Resistance Over Time

- Primary usage of antibiotics on dairy farms is for treatment of mastitis
- Mastitis pathogens in the US do not appear to be developing more resistance by year
  - Makovec & Ruegg, 2003
  - Erskine et al., 2002


In Many Instances Resistance to Commonly Used IMM Drugs is not Observed

- These 2 IMM drugs were the most frequent treatments given
- This IMM product has been used for dry cow therapy for decades
- Ruegg et al., 2015, JDS
Ingestion of Antibiotic Residues & Development of Resistance

- Ingestion of antibiotic residues in waste milk have increased antibiotic resistance of calf gut flora (Langford, et al., 2003)
- Fed calves milk spiked with PPG @ 4 concentrations
  - 0, 6.25, 12.5, 25, 50 μl/kg milk
  - 0.05 μl/ml
  - Delvo detects 0.002 μl/ml
- Tested resistance of bacteria obtained from feces

Zones of Inhibition
- Control = 2.89 +/- 0.14
- 50 μl/kg = 0.70 +/- 0.10

Resistance Genes in Dairy Environments

- Recent series of papers looking at identification of resistance genes from the microbiome of soil fertilized with dairy manure
  - Handelsman lab (formerly of UW Madison)
- 1st paper identified penicillin type resistance genes in soil microbiome
- 2nd paper determined that fertilization using manure from cows that had never received antibiotics had same effect

Prevalence & Trends in Antimicrobial Resistance of Mastitis Pathogens

- Studies usually demonstrate resistance by some organisms to some drugs
  - BUT... most studies demonstrate limited resistance and no increasing trends
- Recent review article concluded:
  - "scientific evidence does not support widespread, emerging resistance among mastitis pathogens..."

Overall Summary

- Most dairy cows are not treated with antibiotics on most days
- Most common usage is for treatment of mastitis
- When treatments are administered the milk and meat are discarded
- There is no evidence of widespread development of resistant organisms on US dairy farms
- But...
  - Drugs should only be used for treatments on dairy farms when necessary
  - Drug usage on dairy farms of all sizes should be monitored and supervised by qualified veterinarians