Emerging Antimicrobial Resistance Issues

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Antibiotic Resistance

- WHO
- CDC
- CARC
- AMA
- PAHO
- OIE
- FAO
- USDA-FSIS
- FDA-CVM
- AVMA

Pan American Health Organization
World Health Organization

American Medical Association
Physicians dedicated to the health of America

U.S. Food and Drug Administration

Department of Health and Human Services
ANTIBIOTICS IN ANIMAL AGRICULTURE
Poultry

100% of chickens and turkeys have antibiotics included in their diet during some part of their lives.

Swine

• Antibiotics are used in:
  – 90% starter feeds
  – 75% grower feeds
  – 50% finisher feeds
  – 20% sow feeds

• Benefits include reduced morbidity and mortality in growing pigs, improve farrowing rate, litter size, birth weight, pigs weaned/litter in breeding animals.

National Research Council, 1999
Feedlots

- 60% of beef cattle receive diets containing antibiotics during some part of their lives.
  - Low concentrations are fed at stressful times when they are most apt to get sick.

Milk Replacers

- Nearly 53 percent of producers (1,811 operations in 28 states) fed medicated milk replacer.
  - Medicated mixtures fed to 60 percent of the time to calves from birth to 3 weeks.

Heinrichs et al., 1995.
Antibiotics

- **Tetracyclines**
  - Used in livestock and poultry feeds represent almost 50% of the total antibiotics used in feeds

- **Beta-Lactams**
  - 50% of global antibiotic consumption. Used for treating infectious diseases in food animals. Popularity attributed to, low toxicity and strong bactericidal activity
Beef, Dairy, Sheep, Swine, & Poultry Contribute More than $87 Billion to the Nation’s Economy

• 18 million lbs. of antibiotics were used with 90% used for subtherapeutic use.
Introduction of antibiotics, reduced mortality in food animals, added 10 years to the average life expectancy of humans but ……………..What is the concern about antibiotics?

Bacterial resistance to antibiotics

Drug Residues in animal origin food
Antimicrobial resistance is defined as “a property of bacteria that confers the capacity to inactivate or exclude antibiotics, or a mechanism that blocks the inhibitory or killing effects of antibiotics, leading to survival despite exposure to antimicrobials” (IOM, 1998).
Selective Pressure

- Use of antimicrobials selects for resistant organisms, leaving them to multiply more freely after the susceptible bacteria have been eliminated.
- This phenomenon is called **selective pressure**. *The classic example of continuous selective pressure in the animal industry is use of antibiotics in feed at subtherapeutic concentrations.*
Resistance to antimicrobials

- **1940s**: growth enhancement properties of antimicrobials identified

- **1950s**: widespread use of antimicrobials as feed additives
  - Usage without veterinary prescription

- **1960s**: Resistance in *Salmonella* from calves lead to ban in penicillin and tetracycline as feed additive
Resistance to antimicrobials

- **1970s**: reports of multidrug resistant bacteria

- **1978**: WHO defines rules for monitoring bacterial resistance in veterinary and human origin organisms

- **1980-90s**: Emergence of antimicrobial resistance
  - Vancomycin resistance *Enterococci*
  - Multidrug resistance *S. Typhimurium* DT104
  - Floroquinolone resistance *Campylobacter*
Resistance to antimicrobials

• Beta-Lactams
  – 1998: Extended spectrum beta-lactamases (ESBLs)
    • Point mutations develop resistance to cephalosporins
  – 2000: ESBLs from food producing animals in Canada
  – 2001: Resistance extended to cephamycins (cefoxitin, ceftriaxone)
  – 2001: Beta-lactam resistant *Salmonella* found in retail ground meat
  – 2002: Nosocomial outbreaks of ESBLs reported in America, Asia, and Europe
## Milk replacers v/s OXY-GNB bacteria

<table>
<thead>
<tr>
<th>Feed Milk replacers</th>
<th>Oxytetracycline resistant bacteria on farms</th>
<th>Test of significance: $\chi^2 (P &lt; 0.05) = 4.58 (0.0322844)$</th>
<th>Odds ratio (confidence interval): 12.00 (1.17-170.32)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Detected</td>
<td>Non-detected</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>10</td>
<td>22</td>
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</tbody>
</table>
Withdrawal of tetracycline

FARM A

Tet
Linear (Tet)
Effect of precipitation on tet counts

FARM A: Precipitation and Tet counts
Extended Spectrum Beta-Lactamases (ESBLs)

- Ampicillin resistant enteric *E. coli* (n=94 isolates) from healthy lactating cattle
  - susceptibility to other antibiotics
  - genetic determinants that encode for beta-lactam resistance.
- *E. coli* isolates were resistant to
  - tetracycline (88.3%)
  - chloramphenicol (29.8%)
  - spectinomycin (35.1%)
  - ticarcillin (33.0%)
  - ceftiofur (26.6%)
- Multidrug resistance (≥3 to 8 antimicrobial agents) was observed in 44 of 94 (46.8%) isolates)
Emerging Resistance

• Resistance to 1st, 2nd, and 3rd generation of cephalosporins was observed only in isolates that were resistant to ceftiofur.
• Interestingly twenty three of 25 (92%) ceftiofur resistant *E. coli* were also resistant to chloramphenicol.
• All *E. coli* isolates were susceptible to 4th generation of cephalosporin cefepime.
Emerging Resistance

- All ceftiofur resistant isolates encoded for cephamycinase (blaCMY) gene
- On sequence analysis of blaCMY gene from *E. coli* showed 99% to 100% match with blaCMY-2 gene from *Salmonella* spp.
Emerging Resistance

• The findings of our study suggest
  • Multidrug resistance was not uncommon but was more pronounced in isolates that were resistance to ceftiofur.
  • Ceftiofur resistant isolates were able to confer resistance to 1st, 2nd, and 3rd generation cephalosporins.
  • The widespread prevalence of beta-lactam resistance in the dairy environment could pose considerable public health risk if these organisms gain access to the food chain.
Why should be concerned about antimicrobial resistant bacteria in companion animals?
Why should we be concerned about antimicrobial resistant bacteria in companion animals?

- Antimicrobial resistance in companion animals is potentially important because pets are present in the home and in close contact with humans.

- Widespread inappropriate use could reduce the overall efficacy and create problems with infections that are more difficult and expensive to treat.
Multidrug Resistant Salmonella Typhimurium

- Idaho - Small animal veterinary clinic with 20 employees
- Sept-October 1999
  - 10 employees had bloody diarrhea
  - Index case
    - Employee caring for several kittens with diarrhea 1-2 days before onset of diarrhea
  - All 10 employees ate meals at the clinic and had no common exposure outside the clinic
  - Salmonella Typhimurium from 5 patients
    - Isolates with similar DNA fingerprint type
    - Resistant to ampicillin, ceftriaxone, cephalothin, chloramphenicol, amoxicillin/clavulenic acid, gentamicin, kanamycin, streptomycin, sulfamethoxazole and tetracycline
Multidrug Resistant Salmonella Typhimurium

- Minnesota – Animal Shelter
- 4 cats and seven human patients
  - 4 cats purchased from shelter during August-October 1999
  - A child who owned two of the cats and two other children from the same day care became seriously ill
  - The owner of the other 2 cats became ill with Salmonella 77 days after purchase
- Salmonella Typhimurium
  - Isolates with similar DNA fingerprint type
  - Resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole and tetracycline
Multidrug Resistant Salmonella Typhimurium

- Washington State
  - Small animal clinic
  - 1999- three individuals with Salmonellosis
    - One employee
    - Two owners who brought cats to the clinic
    - The cats developed diarrhea after their discharge from the clinic and the owners became subsequently ill
    - Clinic was the only common exposure for the 3 ill persons
  - Salmonella Typhimurium
    - Isolates with similar DNA fingerprint type
    - Resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole and tetracycline
What are some of the types of antibiotic resistance we should be concerned with?

- MRSA?
- VRE?
Staphylococci from skin surface of clinically normal cats*

- 148 adults cats
  - Staph. felis
  - Staph. simulans
  - Staph. epidermidis
  - Staph. saprophyticus
  - Staph. intermedius
  - Staph. aureus

- 50% isolates resistant to Penicillin G, amoxycillin, and ampicillin
- 22% resistant to oxacillin
- 12% rifampin
- 21.4% of Staph. aureus resistant to methicillin
- 19 methcillin resistant isolates included Staph. intermedius, Staph. simulans, Staph. felis

MRSA in dogs

• 2003, first case of MRSA in dog reported from Netherlands. The dog had undergone surgery abroad

• 2003, Asymptomatic nasal carriage of MRSA in dog was associated with infection from a household contact
• Methicillin resistant *S. aureus* can be spread among people having close contact with infected people.

• MRSA spread by direct physical contact.
• Spread may also occur through indirect contact by touching objects (e.g., towels, sheets, wound dressings, clothes, workout areas, or sports equipment) contaminated by the infected skin of a person

• MRSA infections are usually mild, superficial infections of the skin that can be treated successfully with proper skin care and antibiotics. MRSA, however, can be difficult to treat and can progress to life-threatening blood or bone infections because there are fewer effective antibiotics available for treatment
Enterococcus faecium isolated from canine UTI infection: evidence of gene exchange between human and animal Enterococci*

- Enterococcus faecium isolated from a dog with UTI. Isolate had an MIC > 32 µg/ml to vancomycin
- Canine isolate had acquired Tn 1546
- First report of vancomycin-resistant E. faecium isolated from a companion animal in the United States.