

Antibiotic Usage and Resistance on Dairy Farms

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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



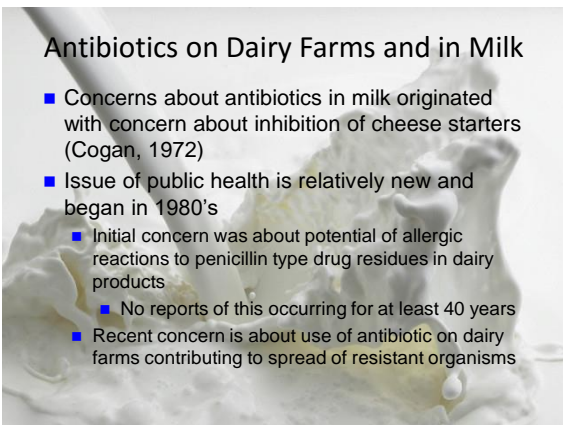
Core Concepts 1 What Happens to Antibiotics in the Cow?

- 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



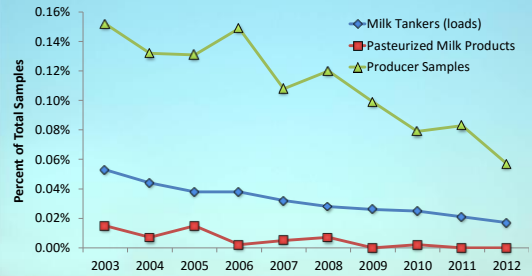
Use of Antibiotics in Dairy Cows Results in Reduced Income and Increased Expenses

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 ceftiofur 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

Dairy Cows are not given antibiotics in feed or water as that would require discarding milk



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
 - Older products
 - Example: Penicillin
- **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 responders 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

Oliveira and Ruegg, 2014

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

| Disease | Number of farms reporting disease (%) | Per 100 cows per year | |
|----------------------------|---------------------------------------|-----------------------|---------------|
| | | Proportion treated | Range treated |
| Clinical mastitis | 51 (100%) | 40 | 6.0 - 91 |
| Metritis & RP | 51 (100%) | 13 | 0.0 - 71 |
| Respiratory disease | 46(90%) | 4 | 0.2 - 12 |
| Foot problems | 42(82%) | 5 | 0.8 - 25 |
| Diarrhea | 16(32%) | 2 | 0.6 - 19 |

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



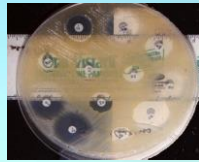
Antibiotic Usage and Resistance

- 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



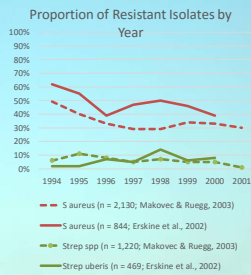
Core Concept 3: Resistance Terms

- **Intrinsic Resistance**
 - Usually occurs at Genus or species level
 - Target organism lacks binding site etc.
 - Gram neg. bacteria that is impermeable to the antibiotic (pirlimycin)
- **Acquired Resistance**
 - Previously susceptible strain of bacteria becomes resistant
 - Mutation or acquires DNA
 - Potential for spread to humans
- Ability to acquire resistance varies among antimicrobials
 - Example
 - A greater proportion of Gram + mastitis organisms are usually resistant to pirlimycin as compared to 1st and 3rd generation cephalosporins
 - Acquired resistance through known mechanism



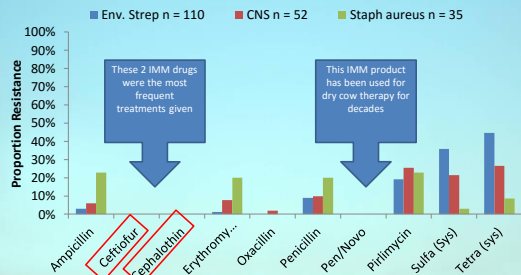
Antibiotic Resistance Over Time US Situation 1994 to 2001

- 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

Resistance on 50 WI Dairy Farms 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

Source of Genes was Simply Growth of Particular soil Bacteria that naturally harbor those genes

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

- Handelsman lab (formerly of UW Madison)
- Udikovic-Kolic et al., Proc. Natl Acad Sci 2014 111:15202



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..."



Oliver and Murinda, 2012. Vet Clin Food Anim. 28:165-185.



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

