Does Antibiotic Use in Cattle Affect Human Health?

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Does Antimicrobial Drug Use in Cattle Affect Human Health?

- Commonly Held Societal Beliefs About AMD Exposures in Animals and Poultry
  - Exposures lead to residues in food and the environment.
  - Use of AMDs is an “excuse” for poor management.
  - Treatment of animals with AMDs is a strong driver for promotion of AMR.
  - Resistant bacteria from animals infect people and cause health problems.

- Some people believe AMD use in animals poses an unacceptable risk → RWA meat
We Must Increase Food Production!
And yet ...
We Must Also Address Complex Challenges

- Global Food Security
- Animal Welfare
- Increasing Affluence
- Patterns of Population Growth
- Changing (converging) Food Preferences
- Social Concerns (people, animals, environment)
- Public Health
- Increasing Competition for Limited Resources

COMPETING INTERESTS

Land
Energy
Water
Social Priorities
As a scientist, I believe it is critical to attempt refutation of hypotheses. Do We Know That All Uses of AMDs are Equally Problematic Regarding AMR?
Does Antimicrobial Drug Use in Cattle Affect Human Health?

- **Positive Impacts:**
  - Animal health and welfare → Societal wellbeing
  - Promotion of efficient, abundant production of safe and wholesome food supply.
  - Control of zoonotic diseases?

- **Negative Impacts:**
  - Residues in food and the environment.
  - Covering for poor management.
  - Treatment of animals with AMDs is a strong driver for promotion of AMR.
  - Resistant bacteria from animals infect people and cause health problems.
Does AMD Use In Animals Harm People?

Anthropogenic Hypothesis for Antimicrobial Resistance

- Antimicrobial Drug Use in Food Animals
- Antimicrobial Resistance in Bacteria Found in Animals (or their environment)
- Infection/Colonization in Humans
- Adverse Health Events in Humans
What Do Metagenomic Resistomes Look Like?
(Target-Enriched Metatgenomic Sequences Aligning to AMR Genes, by Source of Sample and Drug Class)

- Tetracycline
- Macrolide
- Lincosamide
- Streptogramin
- Beta-lactam
- Aminoglycoside
- MDR (eflux)
- Other
- Copper
- Iron Acquisition
- Mercury
- Sulfa

Noyes, et al. Microbiome 2017; 5:142
Ancient DNA from 30,000-year-old permafrost.

Identified a highly diverse collection of genes encoding resistance.
- beta-lactam
- tetracycline
- glycopeptide

Functionally confirmed vancomycin resistance gene with similarity to modern variants.

"Results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use."
The Resistome of Free-Ranging Elk and Bison

Grace Kuiper
Does AMD Use In Animals Harm People?

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Antimicrobial Use and Resistance in the Hospitalized Patients

- Patients with intensive care have highest risks for nosocomial infections
  - Susceptibility, invasive procedures, contact
- Nosocomial infections have higher likelihood of being resistant to commonly used drugs (and also to be MDR)
- Selection pressure
  - Patients are just as likely to run into bacteria in the environment with less use...
  - But they are more likely to run into resistant bacteria
- **THEORY:** So... the more commonly you use a drug in ICU patients, the more commonly you will see resistance in nosocomial infections
Impact of hospitalization and antimicrobial drug administration on antimicrobial susceptibility patterns of commensal *Escherichia coli* isolated from the feces of horses

Magdalena Dunowska, LW, PhD; Paul S. Morley, DVM, PhD, DACVIM; Josie L. Traub-Dargatz, DVM, MS, DACVIM; Doreene R. Hyatt, PhD; David A. Dargatz, DVM, PhD, DACT

Is resistance in *E. coli* isolated from equine patients affected by hospitalization and antimicrobial drug administration?
Is this true? Canine Patients

Resistance in NTSEC Isolated from Canine Patients

- Hospitalized Treated (n=13)
- Hospitalized Non-Treated (n=93)
- Community (n=31)

Bolte, et al
Short-term Effect of Ceftiofur CFA Exposures

- No Exposure
- Single Dose (6.6 mg/kg)
- Single 2/3 Dose (4.4 mg/kg)
- 3 Doses q7d (6.6 mg/kg)

Differences diminished over time

Lowrance et al, 2007

Figure 1—Proportion of *Escherichia coli* isolates, on the basis of the number of antimicrobials to which they were resistant, recovered from fecal samples collected from control steers (A); steers administered 6.6 mg of CFA/kg, SC, once on day 0 (B); steers administered 4.4 mg of CFA/kg, SC, once on day 0 (C); or steers administered 6.6 mg of CFA/kg, SC, on days 0, 6, and 13 (D).
Longitudinal Study of Feedlot Cattle – Adjusted Pct Resistance by Days on Feed

Higher in Hospital Pen Samples

Decreasing Resistance Over Time

Wittum and Morley
Conventional and Natural Feedlot Cattle

Despite Absence of Tetracycline Exposure, Increasing Resistance Over Time

Morley et al., 2011
Feedlot Cattle: 2007 - 2010

E. Coli Isolated from Individual Feedlot Cattle

Benedict et al., 2015

305 Pens housing 60,189 Cattle
5,849 Individual Cattle

Percent Resistance

Increasing Resistance Over Time

Weak Associations with Tetracycline Use

Arrival Sample (n=1663/4042/2379)
33-75 days on feed (n=700/1737/1037)
75-120 days on feed (n=631/1552/921)
>120 days on feed (n=533/1300/767)
Adjusted Prevalence of Resistance in *M. haemolytica* Isolated from Feedlot Cattle

Resistance NOT predicted by *E. coli*
Arrival Samples

Mannheimia haemolytica
Georgia Stocker Calves

Second Samples
(after tildipirisin metaphylaxis)

Snyder et al., 2017
Ecological Disconnect in Previous Studies?

100s to 1000s of Cattle

1g from 10-20 animals

~30 kg feces/day

10⁹-10¹² bacteria per gram

>1000 bacterial species

1 to 5 Colonies
1 or 2 Species

10-20 AMDs

Conclusions about Risks

What Does This Represent?

E. coli

Fecal Microbiome

Firmicutes
Proteobacteria
Bacteroidetes
Actinobacteria

VERO
VETERINARY EDUCATION, RESEARCH, & OUTREACH
Ceftiofur and Chlortetracycline Exposures in Feedlot Cattle

- Intervention study: 2x2 factorial treatment with ceftiofur and chlortetracycline.

- Kanwar et al 2013. tet(A), tet(B), and bla CMY-2 resistance genes in *E. coli*.  
  \[PCR\text{ of } E.\text{ coli isolates } \rightarrow \text{bla}(\text{CMY-2}), \text{tet}(\text{A}), \text{tet}(\text{B})\]

  \[PCR\text{ of metagenome } \rightarrow \text{bla}(\text{CMY-2}), \text{bla}\text{(CTX-M)}, \text{tet}(\text{A}), \text{tet}(\text{B})\]

  \[\text{metagenomic sequencing } \rightarrow \text{entire resistome}\]
Effects of Tulathromycin Metaphylaxis on the Fecal Resistome and Microbiome of Feedlot Cattle

Dr. Enrique Doster

Analysis to investigate differences
- Treatment group (Draxxin metaphylaxis vs. Control)
- Time (Arrival vs. day 11)
Greatest changes occurred over TIME, not by treatment group
Resistome diversity in cattle and the environment decreases during beef production

Noyes et al. eLife 2016;5:e13195

Dr. Noelle Noyes
Abundance of Resistance Genes Generally Declines During Feeding (Source: Noyes et al., 2016)

- More abundant at placement
- More abundant at shipping

- soil
- water
- feces

Class of Resistance Genes:
- spectinomycin
- aminocoumarin
- aminoglycoside
- MLS
- tetracycline
- phenicol
- β-lactam
- sulfonamide
- bacitracin
- fluoroquinolone
- permeability genes
- polymyxin B
- rifampin
- modulatory genes
- efflux pumps

Log-Fold Change in Abundance
-8 -6 -4 -2 0 2
Effects of Antimicrobial Use in Beef Feedlots On the Microbiome and Resistome Dynamics in Individual Cattle

- Detailed Records of All AMD Use Throughout Feeding Period.
- Antimicrobial Use was not Associated with Significant Differences in the Resistome.
- Sampling Time Explained 2.5% of Variance in Resistome
Other Unknowns (Time Scale, etc)
Does AMD Use In Animals Harm People?

Anthropogenic Hypothesis for Antimicrobial Resistance

Antimicrobial Drug Use in Food Animals

AND

Antimicrobial Resistance in Bacteria Found in Animals (or their environment)

AND

Infection/Colonization in Humans

AND

Adverse Health Events in Humans
Characterization Of Resistome and Microbiome of Retail Ground Beef from Cattle Raised in RWA and Conventional Production Systems

NMDS for AMR by Production System: Class

NMDS for AMR by Production System: Mechanism

Kevin Thomas

Conventional Labeled Ground Beef

RWA Labeled Ground Beef
Quantitative Risk Analysis of Antimicrobial Food Safety Risks Associated with Beef Consumption
Summary of key findings

- Rates of beef-attributed *Salmonella* infections that are MDR have stayed stable over time
  - Consumption patterns varied over time.
  - Resistance is not associated with consumption of more beef meals.

- If all production changed to 100% RWA, the numbers of resistant salmonellosis in humans would not significantly change
Ongoing Research Regarding Risk to Humans

- Double-blinded, cross-over feeding trial in human subjects.

- RWA Labeled Beef vs. Conventional Labeled Beef

- Characterization of metagenomic resistome:
  - Food Rinsates
  - Fecal Samples
The Truth About Antimicrobial Resistance...

→ IT’S COMPLICATED!!
→ and we want simple!
OBJECTIVE
We hypothesized that mass distribution of a broad-spectrum antibiotic agent to preschool children would reduce mortality in areas of sub-Saharan Africa that are currently far from meeting the Sustainable Development Goals of the United Nations.

RESULTS
A total of 1533 communities underwent randomization, 190,238 children were identified in the census at baseline, and 323,302 person-years were monitored. The mean (±SD) azithromycin and placebo coverage over the four twice-yearly distributions was 90.4±10.4%. The overall annual mortality rate was 14.6 deaths per 1000 person-years in communities that received azithromycin (9.1 in Malawi, 22.5 in Niger, and 5.4 in Tanzania) and 16.5 deaths per 1000 person-years in communities that received placebo (9.6 in Malawi, 27.5 in Niger, and 5.5 in Tanzania). Mortality was 13.5% lower overall (95% confidence interval [CI], 6.7 to 19.8) in communities that received azithromycin than in communities that received placebo (P<0.001); the rate was 5.7% lower in Malawi (95% CI, −9.7 to 18.9), 18.1% lower in Niger (95% CI, 10.0 to 25.5), and 3.4% lower in Tanzania (95% CI, −21.2 to 23.0). Children in the age group of 1 to 5 months had the greatest effect from azithromycin (24.9% lower mortality than that with placebo; 95% CI, 10.6 to 37.0).
Antimicrobial Use Decisions for the Future

- Use AMDs less frequently when possible.
- The public is voting with buying decisions.
- Treating sick animals is ethically required, if ...
- Educate public about safety of meat products from treated animals.

- The role of research !!!
Concern vs. Funding for AMR Research

Attribution and Concern about AMR

Research for Funding

Use in Humans

Use in Animals

My Perception
Thank You!

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