The impact of antibiotic resistance and its challenge for the Canadian meat industry

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Lethbridge Research Centre
Resistance genes are ubiquitous and ancient

Lechuguilla Cave, New Mexico
Region isolated for 4M years

Bhuller et al., 2012

D’Costa et al., 2011
Resistance genes are ubiquitous and ancient

Chait et al., 2012

Schmieder and Edwards, 2012
The report is the most comprehensive picture to date, with data provided by 114 countries.

Looking at 7 common bacteria that cause serious diseases from bloodstream infections to gonorrhoea.

High levels of resistance found in all regions of the world.

Significant gaps exist in tracking of antibiotic resistance.

Source: WHO, 2014
Void in antibiotic development pipeline

Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.
Antibiotic use in Canada

Number of superbug infections in 2012 from 57 Canadian hospitals

- **Clostridium difficile**
- Methicillin resistant Staphylococcus aureus (MRSA)
- Vancomycin resistant Enterococci
- Carbapenem-resistant Enterobacteriaceae

*Source: AMMI, 2013*
Canadian Facts and Figures

ANTIMICROBIAL USAGE
Humans prescribed/yr: 197,753 kg
Livestock dosage/yr: 1,615,571 kg

POPULATION FIGURES
Population of Canada: 34.5 million
Livestock slaughtered/year: 650.0 million

DOSE PER POPULATION UNIT
Humans: 5,730
Livestock: 2,485

Source: CIPARS report, 2008
Online resources
Therapeutic Uses

Treat
Animals diagnosed with an illness

Control
The spread of illness in a herd or flock

Prevent
Illness in healthy animals when exposure is likely

Growth
Balance good/bad bacteria for improved nutrition

Healthy animals
Animals with illness

Elanco Animal Health
FDA Guidance for Industry on Use of Medically Important Antimicrobial Drugs in Livestock, April 2012.

• The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.

• The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.
Canadian Animal Health Institute
April 11, 2014 - Agreed to phase out the usage of medically important antibiotics for growth promotion and supports increased veterinary oversight in antimicrobial use

- Announced on April 11 2014 by Canadian Animal Health Institute (CAHI) companies
- Restricts medically important antibiotic usage in food animals to specific disease challenges under veterinarian direction
- Expected to be implemented over the next three years possibly through the Regulatory Cooperation Council
Canadian Veterinary Medical Association
April 23, 2014.

• Agree in principal with position of CMA

• More holistic approach – all animal species including companion animals.

• 80% use of antimicrobials, but majority are not those of high importance to human health.

• Antimicrobial stewardship strategy for both human and veterinary use of antimicrobials.

• Own Use Importation, over the counter sales.
Chicken Farmers of Canada

- Canada’s chicken farmers ban injections of eggs that trigger superbugs, April 2014
- On-Farm Food Safety Assurance Program – reporting antimicrobial use and regulatory compliance
- Working cooperatively with the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)
- Funding research on antimicrobial resistance and alternatives.
- Working group to examine ways to reduce antibiotic use
- Educate consumers of the safe handling and cooking of chicken
Elanco Animal Health
Importance in treating serious human infections

**CATEGORY**

- **I**
  - Preferred option for serious infections and **limited** or no treatment alternatives available

- **II**
  - Preferred option for serious infections, alternatives available

- **III**
  - Not a preferred option for serious infections, **limited** or no alternatives available

- **IV**
  - Not a preferred option, nor limited alternatives (may be excluded from human medicine)
Antibiotics approved for animal feed, ranked by importance to humans

<table>
<thead>
<tr>
<th>SWINE FEED</th>
<th>Antibiotic</th>
<th>Rank</th>
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<tbody>
<tr>
<td>Virginiamycin</td>
<td>II</td>
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<tr>
<td>Lincomycin</td>
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<tr>
<td>Tilmicosin</td>
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<tr>
<td>Tylosin phosphate</td>
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<td>Chlortetracycline</td>
<td>II/III</td>
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<tr>
<td>sulfamethazine and procaine penicillin</td>
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<tr>
<td>Lincomycin and Spectinomycin</td>
<td>II/III</td>
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<tr>
<td>Tylosin phosphate and Sulfamethazine</td>
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<td>Zinc bacitracin and procaine penicillin</td>
<td>II/III</td>
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<td>Bacitracin methylene disalicylate</td>
<td>III</td>
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<tr>
<td>Chlortetracycline</td>
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<tr>
<td>Oxytetracycline</td>
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<tr>
<td>Ionophores</td>
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<th>POULTRY FEED</th>
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<td>Virginiamycin</td>
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<tr>
<td>Erythromycin thiocyanate</td>
<td>II</td>
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<tr>
<td>Hygromycin B</td>
<td>II</td>
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<tr>
<td>Penicillin from Procaine penicillin</td>
<td>II</td>
<td></td>
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<tr>
<td>Zinc bacitracin and Procaine Penicillin</td>
<td>II</td>
<td></td>
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<tr>
<td>Bacitracins</td>
<td>III</td>
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<tr>
<td>Chlortetracycline</td>
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<tr>
<td>Oxytetracycline</td>
<td>III</td>
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<tr>
<td>Bambermycins</td>
<td>IV</td>
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<tr>
<td>Oxytetracycline hydrochloride and Neomycin sulphate</td>
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<td>Bacitracins</td>
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<td>Chlortetracycline</td>
<td>III</td>
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<tr>
<td>Chlortetracycline and Sulfamethazine</td>
<td>III</td>
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<tr>
<td>Oxytetracycline</td>
<td>III</td>
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<tr>
<td>Ionophores</td>
<td>IV</td>
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</tbody>
</table>

Rankings according to Health Canada criteria
Ranked by importance to human medicine (I-IV)

I: 0.03%
II: 15.35%
II/III: 13.05%
III: 42.33%
IV: 29.24%

Source: CIPARS report, 2008
Ranked by importance to human medicine (I-IV)

I 26.26%
II 57.58%
III 16.16%

Source: CIPARS report, 2008
Antibiotic residues & contamination

• Excreted or discarded antibiotics may be a source of environmental contamination, which may directly and indirectly affect human health:
  – Toxicity
  – Effects on microbial diversity
  – Promoting antibiotic resistance in environment
EU withdrawal of nontherapeutic antibiotics in food animal production

- European ban on tet, pen & strep for growth promotion
- Sweden bans AGPs
- Denmark bans routine prophylactics
- Specific antibiotic bans in Norway, Germany, Netherlands, Denmark, Sweden & EU
- EU ban on all AGPs

POSITIVE outcomes of removing subtherapeutic antibiotics

Johnsen et al., 2009. Lancet Infect Dis 9: 357-364
NEGATIVE outcomes of removing subtherapeutic antibiotics

• increased incidence of enteric diseases in food-producing animals

• productivity and mortality losses

• increased use of antibiotics for therapeutic purposes with greater relevance to treatment of serious infection in humans (I, II).
What happened

Figure AP1.1. Consumption of antimicrobial agents and growth promoters in animal production and prescribed antibacterials in humans, Denmark

DANMAP 2010

Cattle drug sales in Denmark since 2001

% of antimicrobials sold by feedmills and pharmacies

Very High Importance  High Importance  Medium Importance

Source: BeefResearch.ca
Ban on subtherapeutic antibiotics in Europe

Positive implications

Trends in antimicrobial resistance among *Enterococcus faecium* from broilers and broiler meat and the usage of the growth promoter in Denmark

Ban on subtherapeutic antibiotics in Europe

Positive implications

Trends in antimicrobial resistance among *Enterococcus faecium* from pigs and pork and the usage of the growth promoter in Denmark

Data of production characteristics for total production of pigs raised in the Danish swine production system from August 15, 1991, through November 14, 2007

A:
- gray bars, millions of swine
- black diamonds, mean number of pigs farrowed per sow per year

B:
- gray triangles, Average daily gain (ADG)
- black squares, mortality rate in weaning pigs

C:
- white squares, ADG
- black diamonds, number of feed units
- gray triangles, percentage of dead or condemned finishing pigs

Data for total pig production were collected during the calendar year from January 1 through December 31; all other production values were collected from August 15 through November 14 of the following year and reported as the year in which the data collection period terminated. The ban on AGP use (vertical line) was instituted on April 1, 1998, and January 1, 2000, for finishing and weaning pigs, respectively. Weaning and finishing pigs weighed < 35 kg and > 35 kg, respectively.

Aarestrup et al., 2010
Consumption of antimicrobials for use as AGPs or for therapeutic administration from 1992 to 2007 by the Danish swine production system.

Notice the ban on use of avoparcin and on veterinary profits from the prescription and sale of antimicrobials, the ban on AGP use in finishing pigs and on use of virginiamycin in all pigs that was instituted in 1998, and the ban on AGP use in weaning pigs that was instituted in January 2000. Outbreaks of Porcine reproductive and respiratory syndrome (PRRS) (1996 to 2000), disease attributable to *Lawsonia intracellularis* (1998 to 2002), and Porcine multisystemic wasting syndrome (PMWS) (2001 to 2006) are indicated (arrows). Weaning and finishing pigs weighed < 35 kg and > 35 kg, respectively.

*Aarestrup et al., 2010*
Experimental timeline

DAY 1
ARRIVAL AT FEEDLOT

DAY 315
SLAUGHTER

BACKGROUNDING

FINISHING

= Feeding of subtherapeutic levels of antimicrobial agents

= Sampling date
Design

• 150 feedlot steers fed finishing diet
• 4 antimicrobial treatments (3 pens per treatment)
  – Control (no antimicrobials)
  – A44 (chlortetracycline, 44 ppm)
  – AS700 (chlortetracycline + sulfamethazine, 44 ppm each)
  – T11 (tylosin, 11 ppm)

• Within each treatment, feces from each pen were pooled and formed into duplicate artificial fecal pats
Prevalence of shedding: tetracycline resistant *E. coli*

![Graph showing the prevalence of tetracycline resistant E. coli shedding in steers treated with various antibiotics. The x-axis represents time in days, and the y-axis represents the proportion of steers shedding (%)].
Prevalence of steers shedding *ampicillin* resistant *E. coli*
Tylosin (Tylan™) in-feed 11ppm

Tulathromycin (Draxxin™) 2.5 mg/kg BW

Tilmicosin (Micotil™) 10 mg/kg BW

Control

TREATMENT

housed in individual pens in separate wings

n = 10

n = 10

n = 10

n = 10

DURATION

Systemic treatment

In-feed treatment

Barley (70% silage; 25% grain) + 5% supplement

Faecal & Nasal sample collection

Day

0

7

14

21

28

ANALYSIS

Enterococci

PFGE

Enterococci isolation on BEA & BEA+Ery

Species identification by pyrosequencing

Co-isolated species

M. haemolytica isolation on BAC & BAC+Ery

Disc diffusion

EryR genes PCR

16S rRNA PCR for species identification

EryR genes PCR
Compared to the control, the number of steers harboring *M. haemolytica* was reduced (P < 0.05) by systemic treatment with either tilmicosin (70% ↓) or tulathromycin (52% ↓) over the post treatment sampling period.
The species profiles of bovine isolates differ from clinical isolates of human origin.

Bovine isolates:
- E. hirea: 98%
- E. casseliflavus: 2%
  n = 130

Human clinical isolates:
- E. faecium: 20%
- E. faecalis: 80%
  n = 51

n: Number of isolates pyro-sequenced
Proportion of Ery-resistant bovine enterococci over the study period, with 0 samples collected prior to treatment. **Compared to the control group, treated groups were 76 times more likely (P < 0.05) to have erythromycin resistant enterococci.**
**Enumeration data**

**Average proportion of ery resistance (%)**

- **Day**
  - Control
  - Tylosin

**Average proportion of tyl resistance (%)**

- **Day**
  - Control
  - Tylosin
Distribution of enterococcus species over sampling days and between treatments

<table>
<thead>
<tr>
<th>Species prevalence (%)</th>
<th>Control</th>
<th>Tylosin</th>
<th>Control</th>
<th>Tylosin</th>
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<th>Tylosin</th>
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<th>Tylosin</th>
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<tbody>
<tr>
<td>E. hirae</td>
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<td>E. casseliflavus</td>
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<td>E. faecalis</td>
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</tr>
</tbody>
</table>

0 14 84 112 224
Distribution of enterococcus species over sampling days

Species prevalence (%)

Sampling day

0 14 84 101 224

E. hirae  E. faecium  E. casseliflavus  E. durans  E. faecalis
Design

- Two treatments (n = 100; 5 pens / 10 cattle; two treatments)
  1. Control (no antimicrobials)
  2. AS700 (44 ppm of chlortetracycline and sulfamethazine)
- *E. coli* enumerated and isolated from 3 points in processing:

  **Animal**
  - Feces
  - Hide brisket
  - Hide rump
  - Digesta (small intest.)

  **Environment**
  - Air
  - Gate
  - Saw
  - Inspection wall
  - Viscera tub
  - Rendering wall

  **Tissue**
  - Carcass brisket (pre-, 24h- chill)
  - Carcass rump (pre-, 24h- chill)
  - Ground beef brisket (1-, 8- day)
  - Ground beef rump (1-, 8- day)

- No selection (MC)
- Ampicillin (MA)
- Tetracycline (MT)
Genotypes

- Most resistant *E. coli* detected in samples from the abattoir environment, carcasses and ground beef were closely related to those originating from the hide or digesta of cattle
- Aerosols generated during hide removal may promote the transmission of resistant *E. coli* within the abattoir
- Controlling resistant *E. coli* on the hide may have greater impact on reducing the contamination of meat products than the removal of AGP from the diet of feedlot cattle
Transmission of antimicrobial resistance

Selection for mutations which confer **adaptive advantages** for susceptible populations

eg. antibiotic producers found in the environment may be a source of resistance-encoding genes

eg. runoff, leaching, compost application

eg. nosocomial infections

eg. zoonoses

**Animals**

**Humans**

**Environment**

**molecular ecology**
Antibiotic producers and pathogens are problematic for clinical medicine. Antibiotic producing strains of bacteria and fungi have genetically encoded natural defense mechanisms which prevent “antibiotic suicide.”

Precursor genes

Cryptic embedded genes

Genes which encode some non-inhibitory function targeting antibiotic molecules, but may evolve to confer resistance with selective pressures.

Resistance genes with insufficient levels of expression to confer phenotypic resistance.
The SCIENCE of antimicrobial usage in livestock production

**RESEARCH**
Study the kinds & flow of resistance (genes) and zoonotic potential of microbes

**MANAGEMENT**
Consider livestock production practices to reduce use and potential impact on human medicine

**SURVEILLANCE**
Monitor the emergence of resistance (genes) and potential for transfer between livestock – the environment – and consumer products

**DEVELOPMENT OF ALTERNATIVES**
Design/test therapeutic approaches against veterinary or zoonotic diseases
Take Home Point

• Microbes are masters of adaptation

Oct. 15, 2012 - Health Canada Recalls Antibacterial hand soap
– Pseudomonas aeruginosa
Beef AMR / AMU funding
The McAllister Team
THANK-YOU

Questions?
Design

• Fecal pats were sample over 175 d
• *E. coli* resistance:
  – Total and ampicillin- and tetracycline-resistant *E. coli* were isolated
  – Counts, encoded resistant genes, genotypes analyzed
• Metagenomic resistance
  – Resistance genes in total extracted DNA quantified
**E. coli populations (A44, AS700, Control pats)**

- All populations experienced a growth phase by d42
  - exception: Control MAC+AMP group

- No difference between total E. coli (MAC)

- A time X treatment interaction for MAC+AMP and MAC+TET populations
MANOVA of Amp\textsuperscript{r} *E. coli* PFGE profiles

- Genetic background of Amp\textsuperscript{r} *E. coli* grouped strongly according to treatments
- Genetic background of Control population changed significantly by day 175, in comparison to early time points
MANOVA of Tet$^r$ *E. coli* PFGE profiles

- Genetic background of Tet$^r$ *E. coli* more diverse compared to Amp$^r$ *E. coli*.

- Weaker effect of treatment on Tet$^r$ *E. coli*
Resistant genes encoded by Amp<sup>+</sup> *E. coli* varied between treatments

<table>
<thead>
<tr>
<th>Gene profile</th>
<th>Genes detected</th>
<th>No. isolates within treatments (%)</th>
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<tr>
<td></td>
<td>tetA</td>
<td>tetB</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>+</td>
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</table>
Resistant genes encoded by Tet’ *E. coli* varied less between treatments (few exceptions)

<table>
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<th>Gene profile</th>
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<th>No. isolates within treatments (%)</th>
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<td></td>
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<td>12</td>
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</tbody>
</table>
Conclusions

• Pats are a matrix for the growth and persistence of Tet\textsuperscript{r}, Amp\textsuperscript{r} and generic \textit{E. coli}
• The true microbial load introduced into the environment increased from initial counts
• Encoding Tet\textsuperscript{r} resistance had minimal affects on the environmental fitness of \textit{E. coli}
Tetracycline resistant genes

![Graph showing the analysis of Tetracycline resistant genes.](image-url)
Sulphonamide resistant genes

Log copies (g DM)^{-1}

Day
Erythromycin resistant genes

Log copies (g DM)^{-1} vs Day

- ermA
- ermF
- ermB
- ermX

Day
Metagenomic conclusions

- **Tetracycline:**
  - Antimicrobial treatment selected Tet$^r$ genes

- **Sulphonamide:**
  - Tetracycline alone (A44) resulted in higher levels of sul genes compared to tetracycline + sulphonamide (AS700)

- **Erythromycin:**
  - Differences dependent on the gene analyzed
  - Tetracycline alone (A44) and tylosin (T11, macrolide) resulted in greater levels of ermA and ermX, respectively

- *Fecal pats can serve as a reservoir of AMR E. coli for months after defecation*
Farm to Fork Characterization of antimicrobial-resistant *E. coli* from feedlot cattle
Genotype analyses (across treatments)

- Genotype, as represented by PFGE profiles, were classified as two or more isolates related ≥ 90% homology using Dice similarity
  - 31 genotypes detected (G1-G31)
  - 39 isolates had unique PFGE patterns (GU)
Genotype vs. antibiogram profiles
Publications


Future work

• Therapeutic vs subtherapeutic macrolid use in feedlot cattle
• Enterococci
Concluding remarks...

• Administration of known amounts at known frequency to known animals has a role in defining the etiology of AMR in livestock
• Mobility elements may be just or even more important than AMR genes in assessing risk
• High through-put genomic sequencing
  – Accelerate knowledge accumulation
  – Teach us more about complexity / fluidity of AMR and how it is linked to much more than simply the use of antibiotics in agriculture
Recap: Experimental design

- Steers – 10 per pen, 5 pens per treatment \( (n=100) \)
- Treatments:
  - Control (C) no antibiotics \( (n=50) \)
  - Tylosin phosphate (T11) [11 ppm] \( (n=50) \)
- Diet:

<table>
<thead>
<tr>
<th>Silage-based diet</th>
<th>Transition diet</th>
<th>Grain-based diet</th>
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<tbody>
<tr>
<td>(70% barley silage, 24% barley grain, 5% supplement on DM basis)</td>
<td></td>
<td>(85% barley, 10% barley silage, 5% supplement on DM basis)</td>
</tr>
<tr>
<td>80 days</td>
<td>21 days</td>
<td>124 days</td>
</tr>
</tbody>
</table>

- Antimicrobials were administered continually for 197 days starting on day 1 and were withdrawn 28 days before slaughter
- Rectal faecal samples taken
Recap: Proposed isolates to use

### Breakdown of isolates

<table>
<thead>
<tr>
<th>Date</th>
<th>Day 0 29-Nov-04</th>
<th>Day 14 13-Dec-04</th>
<th>Day 84 21-Feb-05</th>
<th>Day 112 21-Mar-05</th>
<th>Day 224 11-Jul-05</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td><strong>D-Bea</strong></td>
<td></td>
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<tr>
<td>Control</td>
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<td>42</td>
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<td>49</td>
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<tr>
<td><strong>E-BeaEry</strong></td>
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<td>Control</td>
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<tr>
<td><strong>F-BeaTyl</strong></td>
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<tr>
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<td>16</td>
<td>14</td>
<td>46</td>
<td>39</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

- These numbers represent the first isolate taken from each animal
Concerns of resistant bacteria

- Transfer of:

  1. AR pathogens
  2. AR commensal bacteria → AR gene transfer

Furuya and Lowy, 2007
Objective

- To investigate the effects of administering macrolides to beef cattle at:
  - subtherapeutic dose (daily, in-feed - tylosin)
  - therapeutic dose (single injection - tilmicosin, tulathromycin)

on the prevalence and antimicrobial resistance (AMR) of *M. haemolytica* from the nasopharynx and *Enterococcus* species from feces.
Dendrogram of PFGE Smal profiles from erythromycin resistant enterococci.

PFGE profiles were similar for enterococci isolated pre- and post-treatment.
Alignment of groES-EL spacer from Enterococcus species. Pyrosequencing was done across this region for species identification. Asterisk (*) indicates ‘variant’ spacer sequence. Stop codon of groES (TAA) and start codon of groEL (ATG) are underlined.

Zaheer et al., 2012. J. Microbiol. Meth. 89: 174
The McAllister Team

2012
Ban on subtherapeutic antibiotics in Europe

Trend in usage of antimicrobials for treatment of food animals by route of administration and usage of antimicrobial growth promoters (AGPs) 1996-2001, Denmark.

CASE STUDY: Denmark & Norway

Johnsen et al., 2009. Lancet Infect Dis 9: 357-364
Antibiotic classes (cellular target)

- **Cell wall synthesis & integrity**
  - bacitracin
  - carbapenems
  - cephalosporins
  - D-cycloserine
  - monobactams
  - penicillins
  - vancomycin

- **Cytoplasmic membrane**
  - polymyxins

- **Folic acid metabolism**
  - trimethoprim
  - sulfonamide

- **DNA replication**
  - nalidixic acid
  - quinolones

- **DNA synthesis**
  - metronidizole

- **DNA transcription**
  - rifampicin

- **Translation (protein synthesis)**
  - 50s inhibitors:
    - erythromycin
    - chloramphenicol
    - clindamycin
    - lincomycin
  - 30s inhibitors:
    - tetracycline
    - streptomycin
    - spectinomycin
    - kanamycin
    - gentamycin

- **Ribosomes**
  - 50s
  - 30s

- **mRNA**

- **DNA**
  - chromosomal
  - cytoplasmic

- **Membrane**
  - polymyxins
Public health concerns

Antibiotic-resistant bacteria transferred from animals to humans

• Antibiotic resistant *E. Coli* and *Campylobacter* strains increased in humans with increased usage of antibiotics in animals

• Antibiotic resistant *Campylobacter* and *Salmonella* strains in humans were indistinguishable from those found in animals

• Risk to human health

*GOA report, 2004*
<table>
<thead>
<tr>
<th><strong>Definitions of antimicrobial use</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapy (noun)</strong> /ˈTherəpē/</td>
</tr>
<tr>
<td>Administration of an antimicrobial to an animal, or group of animals, which exhibits frank clinical disease.</td>
</tr>
<tr>
<td><strong>Control (noun)</strong> /kənˈtrōl/</td>
</tr>
<tr>
<td>Administration of an antimicrobial to animals, usually as a herd or flock in which morbidity and/or mortality has exceeded baseline norms.</td>
</tr>
<tr>
<td><strong>Subtherapeutic (adjective)</strong> /ˌsüb’therə’pyōōtik/</td>
</tr>
<tr>
<td>Below the dosage level used to treat disease. In livestock, often includes additives in the feed or water to prevent bacterial diseases or improve growth efficiency (antibiotic growth promoters, AGP)</td>
</tr>
<tr>
<td><strong>Prophylaxis (noun)</strong> /ˌprōfaˈlaksəs/</td>
</tr>
<tr>
<td>Administration of an antimicrobial to exposed healthy animals considered to be at risk, but prior to onset of disease</td>
</tr>
<tr>
<td><strong>Metaphylaxis (noun)</strong> /ˌmetaˈfəlaksəs/</td>
</tr>
<tr>
<td>Mass medication of a cohort to mitigate an <em>anticipated</em> outbreak</td>
</tr>
</tbody>
</table>
Antimicrobial resistance - acquisition

Selection for mutations which confer **adaptive advantages** for susceptible populations.

eg. resistant determinants which develop in livestock may be detected in unrelated microbes in humans.

**MUTATION**

**HORIZONTAL GENE TRANSFER**

- Susceptible
- Resistant
- Animals
- Environment
- Humans

**intra/inter-species resistance gene acquisition**
Ban on subtherapeutic antibiotics in Europe

**Negative implications**

- increased incidence of enteric diseases in food-producing animals
- productivity and mortality losses
- increased use of antibiotics for therapeutic purposes.

**Specific Examples:**

- Sweden – increased incidence of necrotic enteritis in broiler chickens requiring antibiotic treatment
- Denmark – increased morbidity and mortality among pigs, mostly associated with enteric infections
- Denmark – 11% of ‘finishing’ herds (weighing more than 35 kg) experienced permanent problems with increased frequency of diarrhoea or reduced weight gain
- Denmark, although overall antibiotic use is lower than it was before the bans, therapeutic antibiotic use has increased.
- Denmark – the broiler industry has been “struggling with leg and skin problems” since the late 1990s
- France – the broiler industry experienced a 51% increase in use of antibiotics for treatment of necrotic enteritis after the bans
- UK – increase in sales of therapeutic antimicrobials from 383 tonnes in 1999 to 437 tonnes in 2000
- Denmark – an overall increase in therapeutic antibiotics from 48 tonnes in 19964 to 94 tonnes in 2001
- 13% increase in use of therapeutic antibiotics in food animals following the bans in Germany

Reviewed by Caswell et al., 2003 & Cervantes et al., 2006.
Recommended principles regarding judicious antimicrobial use in animals

The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health and include veterinary oversight or consultation.

Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark

Frank M. Aarestrup, DVM, PhD; Vibeke F. Jensen, DVM, PhD; Hanne-Dorthe Emborg, DVM, PhD; Erik Jacobsen, MS; Henrik C. Wegener, PhD

Objective—To evaluate changes in antimicrobial consumption and productivity by Danish swine farms during 1992 to 2008.

Sample Population—All Danish swine farms for antimicrobial consumption data and a representative sample of Danish swine herds for productivity data.

Procedures—Antimicrobial consumption by Danish swine farms from 1992 to 2008 was determined and evaluated in light of policies to regulate antimicrobial consumption, changes in disease patterns, and productivity data. Trend analyses of productivity data were conducted before and after a ban on use of antimicrobial growth promoters (AGPs).

Results—Antimicrobial consumption peaked at 100 mg/kg of swine produced in 1992, decreased to 31 mg/kg in 1999, and increased to 49 mg/kg in 2008. Key factors for changes were regulations banning subtherapeutic use of antimicrobials and veterinary profits from the prescription and sale of antimicrobials in 1994 and termination of AGP use by January 2000. Pig production increased from 18.4 to 27.1 million pigs, and the mean number of pigs per sow per year raised for slaughter increased from 21 in 1992 to 25 in 2007. Average daily gain for weaning (<35 kg) and finishing (>35 kg) pigs was higher in 2008 than in 1992, but mortality rates for weaning and finishing pigs were similar in 1992 and 2008.

Conclusions and Clinical Relevance—From 1992 to 2008, antimicrobial consumption per kilogram of pig produced in Denmark decreased by >50%. Furthermore, there was improvement in productivity, suggesting that long-term swine productivity was not negatively impacted by a ban on AGP use. (Am J Vet Res 2010;71:726-733)

Aarestrup et al., 2010. Am J Vet Res. 71:726-33
Fluoroquinolones (I) 0.03%
Aminoglycosides (II) 0.36%
Other antimicrobials 2.02%
Lincosamides (II) 2.55%
Trimethoprim and sulfonamides (II) 3.66%
β-lactams (II) 6.76%
Macrolides (II), pleuromutilins, and bacitracins (III) 13.05%
Amphenicols (III) 0.20%
Ionophores, chemical coccidiostats, arsenicals, and nitroimidazoles (IV) 29.24%
Tetracyclines (III) 42.13%

Source: CIPARS report, 2008
There is probably no chemotherapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring ‘fastness’ [resistance]

Alexander Fleming, 1946
Antimicrobial resistance - transmission

- Multi-drug resistance
- Absence of selective pressure
- Selective pressure
- Resistant population
- Spread of resistance via propagation or horizontal gene transfer

Transmission examples:
- Healthcare workers
- Manure application
- Cough/sneeze

Due to selective pressure, resistant populations can spread resistances via propagation or horizontal gene transfer.
## Antibacterial products approved for use in livestock in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antibiotic family</th>
<th>Animals used in</th>
<th>May be used in feed</th>
<th>Used in human medicine</th>
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<tbody>
<tr>
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<td>β-lactam</td>
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<td>Orthosomycin</td>
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<td>Ellamycin</td>
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<td>Sulfachlorpyridazine</td>
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<td>Virginiamycin</td>
<td>Streptogramin</td>
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</tr>
</tbody>
</table>

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⁹Adapted from CVP, 2006; Guardabassi and Courvalin, 2006; FDA, 2006b.

⁹Closely related analogs are used in and are of importance to human medicine.

B, beef cattle; D, dairy cattle; P, poultry; S, swine.
Ban on subtherapeutic antibiotics in Europe

Trend in usage of antimicrobials for treatment of food animals by route of administration and usage of antimicrobial growth promoters (AGPs) 1996-2001, Denmark.

Combinations of penicillins, including β-lactamase inhibitors (I) 4.04%

Cephalosporins (I) 10.10%

Fluoroquinolones (I) 12.12%

Trimethoprim and combinations of trimethoprim and sulfonamides (II) 5.05%

β-lactamase resistant penicillins (II) 1.01%

β-lactamase sensitive penicillins (II) 3.03%

Macrolides and lincosamides (II) 23.23%

Penicillins with extended spectrum (II) 25.25%

Tetracyclines (III) 13.13%

Nitrofuran derivatives (III) 3.03%

Source: CIPARS report, 2008

HUMANS
Principles of antimicrobial use in livestock

- Challenges unique to veterinary medicine:
  - Inability to communicate
  - Large, confined flocks and herds
- Certain diseases are predictable and preventable. Prevention is considered *economically* and *medically* justifiable
- Little known about the mechanisms of antibiotic growth promotion

“An ounce of prevention is worth a pound of cure”

Ben Franklin
Antimicrobial use by category

- Humans (retail pharmacies)^
- All animals (inc. pets)^
- Feedlot cattle^b

Legend:
- Very High
- High
- Medium
- Low

Source: BeefResearch.ca

^Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) Annual Report, 2009
^Development of a Longitudinal Antimicrobial Resistance and Antimicrobial Use Surveillance Program for the Feedlot Sector in Western Canada (BCRC 6.41)