Antimicrobial use in agriculture – resistance from both society and microbes

FarmSmart Agricultural Conference
University of Guelph, Guelph, Ontario

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Lethbridge Research Centre
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
May 2016: UK commissioned a review on AMR by Jim O’Neill

In nearer term, expect GDP to be reduced by 0.5% by 2020, and 1.4% by 2030.
THE RESISTANCE MOVEMENT
Carbapenem-resistant Enterobacteriaceae have been on the move since at least 1996.


2. 2003: KPC-positive bacteria are found spreading rapidly through hospitals across New York City. By 2007, 21% of Klebsiella in the city carry the resistance gene.

3. 2005: KPC-positive bacteria make their way from New York to several other countries, including Israel. From Israel, the bacteria travel to Italy, Colombia, the United Kingdom and Sweden.

4. 2008: Doctors in Sweden find a new carbapenem-resistance gene, NDM. Traced back to India, NDM-positive bacteria have moved quickly.

Nature: doi:10.1038/nature.2014.15135
Holmes et al., 2015
Figure 3: Role of modifiable drivers for antimicrobial resistance: a conceptual framework

Holmes et al., 2015
Global trends in antimicrobial use in food animals

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Log_{10} [(mg/pixel)+1]

- 0 - 1
- 0 - 4
- 4 - 5
- 5 - 6
- 6 - 7
- 7 - 8
- 8 - 9
- 9 - 10
- 10 - 11

Global consumption in livestock in 228 countries (mg/10 km\textsuperscript{2} pixel)
Global trends in antimicrobial use in food animals

- **63,151 tons** in 2010
- Increase by 67% in 2030

→ Increased demand for livestock products in middle-income countries
→ Resulting shift to large-scale farms

Van Boeckl et al., 2015
Posterior distributions for estimates of antimicrobial consumption in cattle, chickens, and pigs in OECD countries

Cattle
45 mg kg⁻¹

Chickens
148 mg kg⁻¹

Pigs
172 mg kg⁻¹
Resistance genes are ubiquitous and ancient

Lechuguilla Cave, New Mexico
Region isolated for 4M years

Bhuller et al., 2012

D’Costa et al., 2011
Microbial war
Antibiotic use heightens resistance

Chait et al., 2012

Schmieder and Edwards, 2012
Void in antibiotic development pipeline

Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.
Figure: Cost to develop a new drug. Cost in billions is represented according to the contemporary values of the period. Graph data collected from published CSDD Tufts studies [1-4].
Use of antibiotics

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
**Transduction**
Bacteriophages (viruses that infect bacteria) mediate transfer of DNA between bacteria via transduction, whereby DNA from a donor bacterium is packaged into a virus particle and transferred into a recipient bacterium during infection.

**Conjugation**
The mechanism of gene transfer responsible for the most concerning aspects of antimicrobial resistance. A sex pilus (small tube) forms between two bacterial cells through which a plasmid is transferred from one to the other.

**Transformation**
Some bacteria are able to take up free DNA from the environment and incorporate it into their chromosome.
Antibiotic classes (cellular target)

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

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

**Cytoplasmic membrane**
- polymyxins

**DNA replication**
- nalidixic acid
- quinolones

**DNA synthesis**
- metronidizole

**DNA transcription**
- rifampicin

**RNA synthesis**
- mRNA

**Folic acid metabolism**
- trimethoprim
- sulfonamide
Mechanisms of antibiotic resistance

Adapted from Levy & Marshall, 2004
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,

**IV**
Not a preferred option, not used in human medicine
Antibiotics approved for animal feed, ranked by importance to humans

### SWINE FEED

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginiamycin</td>
<td>II</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>II</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>II</td>
</tr>
<tr>
<td>Tylosin phosphate</td>
<td>II</td>
</tr>
<tr>
<td>Chlortetracycline, sulfamethazine and procaine</td>
<td>II/III</td>
</tr>
<tr>
<td>penicillin</td>
<td></td>
</tr>
<tr>
<td>Lincomycin and Spectinomycin</td>
<td>II/III</td>
</tr>
<tr>
<td>Tylosin phosphate and Sulfamethazine</td>
<td>II/III</td>
</tr>
<tr>
<td>Zinc bacitracin and procaine penicillin</td>
<td>II/III</td>
</tr>
<tr>
<td>Bacitracin methylene disalicylate</td>
<td>III</td>
</tr>
<tr>
<td>Bacitracins</td>
<td>III</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>III</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>III</td>
</tr>
<tr>
<td>Ionophores</td>
<td>IV</td>
</tr>
</tbody>
</table>

### POULTRY FEED

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginiamycin</td>
<td>II</td>
</tr>
<tr>
<td>Erythromycin thiocyanate</td>
<td>II</td>
</tr>
<tr>
<td>Hygromycin B</td>
<td>II</td>
</tr>
<tr>
<td>Penicillin from Procaine</td>
<td>II</td>
</tr>
<tr>
<td>penicillin</td>
<td></td>
</tr>
<tr>
<td>Zinc bacitracin and Procaine Penicillin</td>
<td>II</td>
</tr>
<tr>
<td>Bacitracins</td>
<td>III</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>III</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>III</td>
</tr>
<tr>
<td>Bambermycins</td>
<td>IV</td>
</tr>
<tr>
<td>Ionophores</td>
<td>IV</td>
</tr>
</tbody>
</table>

### CATTLE FEED

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylosin phosphate</td>
<td>II</td>
</tr>
<tr>
<td>Oxytetracycline hydrochloride and Neomycin sulphate</td>
<td>II/III</td>
</tr>
<tr>
<td>Bacitracins</td>
<td>III</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>III</td>
</tr>
<tr>
<td>Chlortetracycline and Sulfamethazine</td>
<td>III</td>
</tr>
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<td>Oxytetracycline</td>
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<td>Ionophores</td>
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</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
Antimicrobial resistance in bacteria from diseased animals

Most reported

Normalized to maximum = 1.0

no data
not detected
not relevant

Human use / analogue

Agriculture only

Respiratory diseases
Mannheimia haemolytica
Pasteurella multocida
Histophilus somni
Mycoplasma bovis

Abortive diseases
Trueperella pyogenes
*Campylobacter sp.

Other diseases
Fusobacterium necrophorum
Listeria monocytogenes
Dichelobacter nodosus
Moraxella bovis

Enteric diseases
*Salmonella sp.
Bacillus anthracis

Mastitis pathogens
Staphylococcus aureus
*Staphylococcus epidermidis
*Streptococcus sp.
*Escherichia coli

Source: Cameron and McAllister, 2016
E. coli, enterococci, Salmonella, Campylobacter, metagenomic DNA

E. coli, enterococci, Pasteurellaceae, metagenomic DNA

McAllister et al., unpublished
Enterococci diversity is niche-specific

- **LIVESTOCK**
  - Beef production
  - Fecal composite

- **ENVIRONMENT**
  - Catch basins
  - Surface Water
  - Wetlands & Creeks
  - Waste Water Treatment
  - Influent
  - Effluent

- **HUMAN HEALTH**
  - Alberta Health Region
  - Clinical Bacterial Isolates
  - Common antibiotics
  - Meat distribution
  - Drinking water
  - Crops

**ANTIMICROBIAL RESISTANCE CONTINUUM**

- Enterococcus casseliflavus
- Enterococcus durans
- Enterococcus faecalis
- Enterococcus faecium
- Enterococcus gallinarum
- Enterococcus hirae
- Enterococcus malodoratus
- Enterococcus mundtii
- Enterococcus villorum
- Enterococcus columbae

**SAMPLES**
- n=2,192
- n=113
- n=209
- n=429
- n=141
Antimicrobial resistance determinant (ARD) sequences were sourced from 3 databases:

- **Resfinder**
  - Center for Genomic Epidemiology
  - 2,202 ARDs

- **ARG-ANNOT**
  - Université Aix-Marseille, Marseille, France
  - 1,686 ARDs

- **CARD**
  - McMaster University
  - 2,696 ARDs

Master, non-redundant database
- 3,111 ARDs

Databases exist, but are they:
- comprehensive?
- up-to-date?
- accurate?
- complete?
AMR Prevalence

(McAllister - Morley lab unpublished)
AMR Class Abundance in Natural vs. Conventional Operations

Catch Basin

Fecal Composite

Abundance

Status

Conventional

Natural

Conventional

Natural

Class

Aminoglycosides

Beta-lactams

MLS

Multi-biocide resistance

Multi-drug and biocide resistance

Multi-drug biocide and metal resistance

Multi-drug resistance

Phenicol

Sulfonamides

Tetracyclines

(McAllister – Morley lab unpublished data)
Bacterial Abundance by Matrix Type and Conventional Status

(McAllister – Morley lab unpublished data)
What are the next steps?

- Optimize antimicrobial use through reduction in misuse.
- Benchmark actual antimicrobial use.
- More rapid and accurate diagnostics (next generation sequencing).
- Better understanding of transmission, dissemination through enhanced surveillance.
- Multiple linkages with other antimicrobial resistant genes
- Linkages with virulence factors
- Phylogenetic profile, density and distribution of human pathogens.
Dar et al., 2015

Diagram depicting the concept of One Health, focusing on surveillance and monitoring, infection prevention, responsible use, universal access, and innovation and R&D (knowledge base).
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*
Dr. Rahat Zaheer
Dr. Ed Topp
Dr. Trevor Alexander
Dr. Sheryl Gow
Dr. Patrick Boerlin
Dr. Frank Larney
Dr. Srinivas Sura
Shaun Cook
Dr. Cassidy Klima
Alicia Beukers
Ruth Barbeiri
Animal handling staff
Dr. Ron Read
Dr. Deirdre Church
Dr. Sylvia Checkly
Dr. Calvin Booker
Dr. Sherry Hannon
Dr. Paul Morley
Dr. Kim Stanford
THANK-YOU

Questions?