Physicians, Farmers and the Politics of Antimicrobial Resistance

Laura H. Kahn, MD, MPH, MPP
Virginia Veterinary Medical Association Conference
Roanoke, VA
February 17, 2017

The One Health Concept

• One Health: a concept that recognizes the links between human, animal, and environmental health.
• Because they are linked, issues such as antibiotic resistance must be analyzed using a holistic One Health approach.
• The One Health Initiative: http://www.onehealthinitiative.com

A One Health Analysis

• United Kingdom
• Sweden
• Denmark
• European Union
• United States
• History of Ban of Low Dose Antibiotics
• Antibiotic Use
• Antimicrobial Resistance (AMR)
• Livestock Production
• Healthcare Costs
• Global AMR
• Environmental AMR
• Antibiotic R & D Issues

Evolution of Medicine and Agriculture in the 20th century

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Agriculture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasingly specialized</td>
<td>Increasingly specialized</td>
</tr>
<tr>
<td>Technology driven</td>
<td>Technology driven</td>
</tr>
<tr>
<td>Dependent on antibiotics</td>
<td>Dependent on antibiotics</td>
</tr>
<tr>
<td>Price of medical care increased</td>
<td>Price of food decreased</td>
</tr>
</tbody>
</table>

Uses of Antibiotics

• Livestock
  – Growth
  – Prevention
  – Treatment

• Humans
  – Prevention
  – Treatment

All uses lead to antibiotic resistance

Defining Terms

• Low dose
• Sub-therapeutic
• Non-therapeutic
• Growth promoting
  All mean essentially the same thing.
• Typically mean levels as low as 1-2 parts per million in feed.
• Higher doses, up to 100 parts per million or higher used to treat sick animals.
Resistant Enterococcus faecium drove European Union policy

Zoonotic Bacteria
• Cause illness in both livestock and people. Major cause of food-borne illness.
• Salmonella enterica (subspecies: Salmonella typhimurium)
• Campylobacter species.

Indicator Bacteria
• Part of normal intestinal microbiome in both animals and people. Can cause life-threatening illnesses.
• Escherichia coli (E. coli)
• Enterococcus (Enterococcus faecium and Enterococcus faecalis)

Accidental Discovery of Antibiotics as Growth Promoting Agents in 1940’s

Work at Lederle Labs, Division of American Cyanamid Company
• Fed vitamin B12 to chicks and piglets
• Growth rates increased
• Residues from chlortetracycline
• Increased efficiency in agriculture.
• Adopted in many countries

Effect of Aureomycin (chlortetracycline) on Chick Growth

Average weight (Gms)

<table>
<thead>
<tr>
<th>Day</th>
<th>Control 1</th>
<th>Control 2</th>
<th>Aureomycin 100 ml</th>
<th>Aureomycin 300 ml</th>
<th>Autoclaved liver extract, 0.5 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>25</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>21</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>25</td>
<td>350</td>
<td>350</td>
<td>350</td>
<td>350</td>
<td>350</td>
</tr>
</tbody>
</table>

Since WWII, Cost of Food in U.S. Has Decreased

USDA: Percent of consumer expenditures spent on food, alcoholic beverages, and tobacco that were consumed at home by selected countries, 2014

<table>
<thead>
<tr>
<th>Country</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>47.3</td>
</tr>
<tr>
<td>Canada</td>
<td>21.9</td>
</tr>
<tr>
<td>Sweden</td>
<td>17.5</td>
</tr>
<tr>
<td>Brazil</td>
<td>11.8</td>
</tr>
<tr>
<td>Poland</td>
<td>9.2</td>
</tr>
<tr>
<td>Malaysia</td>
<td>6.3</td>
</tr>
<tr>
<td>China</td>
<td>5.3</td>
</tr>
<tr>
<td>India</td>
<td>4.1</td>
</tr>
<tr>
<td>Egypt</td>
<td>3.6</td>
</tr>
<tr>
<td>Nigeria</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Why were antibiotics used as growth promoting agents?
Price of Beef and Pork in U.S., 1900-1969

Why were antibiotics used as growth promoting agents?

- Before WWII, U.S. raised on traditional and feed/animal oil for growth
- Drove growth in livestock
- Consumers began to expect fresh meat
- Non-susceptible bacteria increased
- Sensitivity to antibiotics decreased
- Antibiotic consumption increased

Accidental Discovery of Antibiotics as Growth Promoting Agents in 1940’s

Work at Lederle Labs, Division of American Cyanamid Company
• Fed vitamin B12 to chicks and piglets
• Growth rates increased
• Residues from chlortetracycline
• Increased efficiency in agriculture.
• Adopted in many countries
Why is food security so important?

- Agriculture and food security (a.k.a. preventing hunger) form the foundation of civilization.
- Food security is inextricably linked with global health, global sustainability, and international security.
- There is no global health without global food security.
- Many diseases (i.e. Ebola, Zika, Chikungunya, SARS, Nipah, etc.) are emerging and spreading because of widespread deforestation, environmental degradation, and bushmeat consumption—linked to food security.
- Global climate change affects food security.

Can we have pork chops and antibiotics too?

The Rise of Vancomycin-Resistant Enterococcus faecium (VRE)

- In 1988, first case reports of VRE reported in seriously ill patients in Paris (acute leukemia) and London (End Stage Kidney Failure).
- Three months before the London VRE cases, a new policy was implemented: administer vancomycin and ceftazidime to all chronically ill (i.e. end stage kidney failure) patients with fever and undiagnosed infections.
- A few years later, VRE was isolated from food animals in England and Germany.
- Avoparcin, a growth promoting agent in livestock, chemically related to vancomycin and used in Europe since the early 1970’s, was implicated as the probable source of VRE in hospitals.

Relation between Avoparcin and Vancomycin; Vancomycin is effective against both *E. faecium* and *E. faecalis*

<table>
<thead>
<tr>
<th>Growth Promoting Antibiotic in Livestock</th>
<th>Related Antibiotic in Human Medicine</th>
<th>Antibiotic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoparcin</td>
<td>Vancomycin</td>
<td>Glycopeptide</td>
</tr>
<tr>
<td>Ampicillin/Gentamicin of Ampicillin/Cephrinaxone</td>
<td><em>Increasing resistance</em></td>
<td>*</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Vancomycin used to treat gram positive bacteria.

*New Antibiotics: Quinupristin-Dalfopristin, approved by FDA Sept. 1999, only treats *E. faecium* Linezolid, approved by FDA April 2000, only treats *E. faecium*

Denmark

- Danish scientists concerned about emergence of VRE and general use of antibiotics in livestock.
- Denmark relied heavily on avoparcin and other growth promoting antibiotics.
- In January 1995, VRE identified in fecal samples from healthy chickens and pigs in Denmark.
- Danish farmers concluded that they had to change their practices and stop using antibiotics as growth promoting agents.
Danish Growth Promoter Ban

- Farmers voluntarily stopped using avoparcin in May 1995.
- In 1997, the EU banned avoparcin.
- 1998, Denmark banned virginiamycin, another growth promoting antibiotic, related to quinupristin/dalfopristin, an antibiotic used to treat VRE.
- 1999, Danish farmers stopped using all antibiotic growth promoting agents in response to consumer concerns.

Danish pork exports and imports do not appear adversely affected by ban

Pork exports increased

- Frozen non-domestic meat
- Frozen with bone domestic meat
- Frozen boneless domestic meat
- Fresh/chilled non-domestic meat

Pork imports minimally decreased

- Frozen non-domestic meat
- Frozen with bone domestic meat
- Frozen boneless domestic meat
- Fresh/chilled non-domestic meat

Denmark No Longer World’s Top Exporter of Pig Meat

- Denmark
- Netherlands
- USA
- Belgium
- France
- Germany
- Spain

Pig meat yield (mill. kg/1000 heads), Denmark, 1990-2013

- VRE declined on farms
- VRE in hospitals increased

Vancomycin resistant E. faecium (%)

- Broilers
- Hog
- Pigs
- Pork
- Healthy Humans

Sources: Human therapeutics: The Danish Medicines Agency. Veterinary consumption: Until 2001, data are based on annual reports from the Ministry of Food, Agriculture and Fisheries, the Danish Veterinary and Food Administration and the Danish Medicines Agency. Data from reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996–2000). Data from reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996–2000). Data from reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996–2000). Data from reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996–2000). Data from reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996–2000). Data from reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996–2000).
European Union

- 2003, European Parliament passed regulations prohibiting all antibiotics as growth promoters.
- Used Precautionary Principle to set policy.
- Ban took effect January 1, 2006.
- European Union established a number of surveillance systems to assess antibiotic use and resistance.
- Reporting was voluntary for enterococcus in livestock, not possible to assess VRE rates in livestock before or after ban.

Evidence that 2006 ban adversely affected pig meat yield, 1996-2013

Human vancomycin use and VRE in hospitals are highly correlated

EU countries vary widely in human antibiotic use

Relative Pig Meat Yield (EU/USA)

No consistent trend in VRE isolates from hospitalized humans after 1997 EU avoparcin ban
**United States**

- US never approved avoparcin because of concerns about its carcinogenicity, so epidemiology of VRE has been different compared to Europe.
- Congress has spent decades debating the risks of growth promoting antibiotics.
- Consistently concluded that more data was needed, but never appropriated resources to get more data.
- Bureaucratic leaders at CDC, FDA, USDA scrounged together funds for NARMS and NAHMS.

---

**VRE in U.S.**

- VRE in US emerged in 1990’s in hospitals.
- Preceded spread in European hospitals by about a decade even though first few cases reported in Europe.
- CDC estimates that 77% of US healthcare-associated infections due to *Enterococcus faecium* are resistant to vancomycin.*
- CDC estimates approximately 10,000 VRE infections and 650 deaths per year.*
- Healthcare costs specifically for VRE not available.
- CDC estimates that >2 million people fall ill with resistant infections, 23,000 die, healthcare costs between $20 to $35 billion per year.*


---

**Outpatient antibiotic consumption, by state in the US in 2010**

- The Center for Disease Dynamics, Economics & Policy. "Outpatient Antibiotic Use". Available online at: http://cddep.org/node/4933

---

**Food-Producing Animals Primarily Use Tetracyclines and Ionophores (Coccidiostats) in U.S.**

- The Center for Disease Dynamics, Economics & Policy. "Outpatient Antibiotic Use". Available online at: http://cddep.org/node/4933

---

**Americans Used Much More Vancomycin than the Europeans: Human vancomycin use (in kg) per capita per year**

- The Center for Disease Dynamics, Economics & Policy. "Outpatient Antibiotic Use". Available online at: http://cddep.org/node/4933
Almost all VRE

NARMS does not collect Entrobacter faciium data on humans!

Unspecified Entrobacter faciium in chickens, Entrobacter faecium in chickens, and unspecified in other animal species.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Chicken</th>
<th>2013</th>
<th>2014</th>
<th>Δ</th>
<th>Chicken Meat</th>
<th>2013</th>
<th>2014</th>
<th>Δ</th>
<th>Pork Chops</th>
<th>2013</th>
<th>2014</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NARMS: Percent Resistance in non-typhoidal Salmonella

U.S. Exports of Pork and Broiler Chickens Have Skyrocketed

Americans eat a lot of chicken

Comparing the EU and USA

EU
- Unclear why Europe approved avoparcin in the early 1970's.
- Banned avoparcin after rise of VRE in food animals.
- Almost all VRE vonA*
- Banned all antibiotic growth promoting agents using Precautionary Principle.
- Evidence that total ban adversely affected pig meat production.
- No evidence that avoparcin ban decreased VRE in hospitalized humans.

USA
- Never approved avoparcin because of cancer concerns. (Precautionary Principle)
- Very high vancomycin use in hospitals
- VRE appeared in hospitalized patients about a decade before widespread in Europe.
- 70% vonA and 25% vonB*
- No evidence that VRE came from US feedlot.
- Needed better data to do proper risk analysis before making any decisions.

Confusing epidemiology of resistant bacteria: horizontal versus vertical gene transmission

- Until 2008, analysis of resistant microbes focused on resistance genes on plasmids.
- Horizontal transmission: exchange of genetic material between microbial contemporaries.
- vanA, vanB, vanD acquired resistance genes spread among VRE.
- Cost of genome sequencing cost $10 million per genome.
- After 2008, cost plummeted.
- Allowed sequencing of microbial genomes.
- Vertical transmission (parent to offspring) of genetic material.
- Genomic data revealed surprising findings.

VRE genomic data suggests a surprising culprit

- One or two VRE clones caused initial outbreaks, proliferating into multiple clones, and becoming endemic in hospitals. VRE CC17
- Hospital associated VRE appears to be genetically distinct from VRE in livestock and from healthy people in the community.
- Genetic analysis suggests that VRE precursor came from an animal, just not the livestock that everyone assumed...

Two Danish studies

1. First Danish study analyzed fecal specimens from 127 healthy dogs and found 20 *E. faecium* isolates resistant to ampicillin. One isolate was related to VRE CC17. Only 14 dogs had been treated with antibiotics within 6 months of the study.
2. Second Danish/UK study found ampicillin resistant *E. faecium* in 61/208 dogs. Only 1 person out of 18 tested positive—a 10 year old boy. 1 in every 4 dogs tested had AREF CC17, precursor to VRE CC17.

Conclusions

- Denmark’s ban of avoparcin decreased VRE in pigs and poultry.
- No evidence that EU ban decreased VRE in hospitals.
- Evidence that EU ban adversely affected pig meat yield in Europe compared to the US.
- Antibiotic use varies widely between states and countries showing large variations in how medicine is practiced.
- Surveillance must include microbial genomes.
- Antibiotic resistance in pets is potentially an important hidden source of resistance in humans.
- Antibiotic resistance surveillance should include pets.
• One Health Initiative pro bono team:
  – Bruce Kaplan, DVM
  – Tom Monath, MD
  – Lisa Conti, DVM, MPH

http://www.onehealthinitiative.com