A One Health Perspective on Antimicrobial Resistance

Laura H Kahn, MD, MPH, MPP, FACP
NIAAA Antibiotic Symposium
November 2, 2017
The One Health Concept

• One Health: human, animal, and environmental health are linked.

• Because they are linked, complex issues such as antibiotic resistance must be analyzed using an interdisciplinary One Health approach.

• The One Health Initiative: http://www.onehealthinitiative.com
A One Health Analysis

- United Kingdom
- Sweden
- Denmark
- European Union
- United States

- Antibiotic Use
- Antimicrobial Resistance (AMR)
- History of Ban of Low Dose Antibiotics
- Livestock Production
- Healthcare Costs
- Global AMR
- Environmental AMR
- Antibiotic R & D Issues

Disclaimer: I do not represent any of these country’s governments!
All analyses and conclusions from government data are my own work.
Disclaimer

• Disclaimer: “The views and opinions of the authors expressed herein do not necessarily state or reflect those of the ECDC. The accuracy of the authors’ statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data”.
Evolution of Medicine and Agriculture in the 20\textsuperscript{th} century

**Medicine**
- Increasingly specialized
- Technology driven
- Dependent on antibiotics
- Price of medical care increased

**Agriculture**
- Increasingly specialized
- Technology driven
- Dependent on antibiotics
- Price of food decreased
USDA: Percent of consumer expenditures spent on food, alcoholic beverages, and tobacco that were consumed at home by selected countries, 2014

Our entire consumer economy depends on relatively inexpensive food

Why is food security so important?

• Agriculture and food security (a.k.a. preventing hunger) are 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.
# Time of Complex Life on Earth

## Paleozoic Era

- Cambrian Explosion: Thriving life in seas but barren land
- Permian-Triassic Extinction

<table>
<thead>
<tr>
<th>Time</th>
<th>Temperature of Planet Earth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambrian</td>
<td>Pliocene, Pleistocene, Holocene</td>
</tr>
</tbody>
</table>

## Cenozoic Era

- Early hominids

## Earth is 4.5 Billion Years Old

https://commons.wikimedia.org/wiki/File:All_palaeotemps.png
http://gergs.net/2015/06/updating-the-geological-temperature-plot/all_palaeotemps/
Resistant *Enterococcus faecium* drove policy in the European Union

**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*)
**Relationship 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></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th><em>Enterococcus faecium</em></th>
<th><em>Enterococcus faecalis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin/Gentamicin of Ampicillin/Cephtriaxone</td>
<td>+ increasing resistance</td>
<td>+</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*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.

Figure 4.1. Prescribed antimicrobial agents for humans, and for animals compared with the number of pigs produced, Denmark
Denmark: Ban Decreases VRE in Farm Animals! But not in hospitals

VRE declined on farms

VRE in hospitals increased

Vancomycin resistant E. faecium (%)

DANMAP 1997 to 2008

European Union

- 2003, European Parliament passed regulations prohibiting all antibiotics as growth promoters.
- 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 across the EU countries.
Antibiotic sales for food animals mostly corresponded with size of livestock production.

**Antibiotic Sales in Tons 2011**

<table>
<thead>
<tr>
<th>Country</th>
<th>Tons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
</tr>
</tbody>
</table>

**EU Pig and Poultry Production % of country contribution 2011**

- **DK**: 18%
- **SE**: 16%
- **UK**: 12%

**Antimicrobial Classes**

- Tetracyclines
- Penicillins
- Sulfonamides
- Macrolides
- Fluoroquinolones

**Sources**

- European Surveillance of Veterinary Antimicrobial Consumption (ESVAC).
EU countries vary widely in human antibiotic use

Cephalosporin Use 2011

Vancomycin Use 2011

Data provided by ECDC extracted from The European Surveillance System – TESSy
Names of countries removed at request of ECDC

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

FAO Data: EU and U.S. Pig Meat Production (yield/carcass weight) (Hg/Animal) 1996–2013


Note: Hg = heclogram (100 grams).
Relative Pig Meat Yield
(EU/United States) 1995–2015

Note: There was an approximately 3 percent decrease in relative yield after the ban.
Source: UN Food and Agriculture Organization, FAOSTAT, Production, Livestock Primary,
Cost of 3 percent decrease in yield?

• Approximately $1.1 billion per year (in 2012 dollars) in lost revenue to pork producers.
• Cost to consumers is unknown.
• However, according to LABORSTA, the International Labor Organization, the retail price of pork in some European countries is generally higher than the price of pork in the U.S.
Global Chicken Meat Production (yield/carcass weight) (0.1 grams/animals) 1996–2012

Recall that the EU ban did NOT include coccidiostats.

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.*

---

World’s Largest Consumers of Antibiotics in Humans

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Units</th>
<th>Units per Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>$12.9 \times 10^9$</td>
<td>10.7</td>
</tr>
<tr>
<td>China</td>
<td>$10.0 \times 10^9$</td>
<td>7.5</td>
</tr>
<tr>
<td>USA</td>
<td>$6.8 \times 10^9$</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Countries with high antibiotic consumption rates per person in 2010: Australia 87 and New Zealand 70. Also, Asia, Hong Kong, Malaysia, Singapore, and South Korea.

But not all high-income countries had high consumption rates: The Netherlands 7.89 compared to France 23.12.

Food-producing Animals Receive Primarily Tetracyclines and Ionophores (Coccidiostats) in U.S.

Kilograms

2009 2010 2011 2012

FDA Summary Reports on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. Page 40, Table 10. NIR (Not Independently Reported)

http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm042896.htm
## National Antibiotic Resistance Monitoring System (NARMS): *Enterococcus faecium*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Chickens*</th>
<th>Chicken Meat**</th>
<th>Pork Chops</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
<td>2006</td>
<td>%Δ</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quinupristin/dalf opristin</td>
<td>36.9</td>
<td>65.8</td>
<td>+28.9</td>
</tr>
</tbody>
</table>

NARMS does not collect *Enterococcus faecium* data on humans!

Unspecified Enterococcus in Chickens; ***Enterococcus faecium* and *Enterococcus faecalis* in Chicken Meat and Pork Chops

^ Enterococcus faecium resistance

USDA NARMS:

Page 16, 52, Table 4D

FDA NARMS Report 2011 Pages 50 and 51, Table 22.1 and Table 22.2


( ) =Total number of isolates tested.
# National Animal Health Monitoring System (NAHMS): Resistant Enterococcus in Pigs

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>2006 (857)*</th>
<th>%</th>
<th>2012 (563)*</th>
<th>%</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</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>
</tr>
</tbody>
</table>

*( )= total number isolates tested.


Enterococcus species included: *E. hirae* (29.6%), *E. faecalis* (27.4%), *E. species not identified* (16%), *E. faecium* (7.9%), *E. mundtii* (7.7%), *E. casseliflavus* (3%) and others.


Susceptibility against quinupristin/dalfopristin was not done.
Comparing the EU and USA

EU
• Europe approved avoparcin in the early 1970’s.
• PP: banned avoparcin after rise of VRE in food animals.
• Banned all antibiotic growth promoting agents.
• No evidence that avoparcin ban decreased VRE in hospitalized humans.

USA
• PP: Never approved avoparcin because of cancer concerns.
• Very high vancomycin use in hospitals
• VRE appeared in hospitalized patients about a decade before widespread in Europe.
• No evidence that VRE came from US livestock.
• Implemented voluntary measures to stop using growth promoting antibiotics.

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.

![Diagram showing horizontal and vertical gene transmission]

- **Horizontal Transmission**: Exchange of genetic material between microbial contemporaries.
  - Resistance genes spread among VRE through horizontal transmission.

- **Vertical Transmission**: Parent to offspring transfer of genetic material.
  - Genomic data revealed surprising findings in vertical transmission scenarios.

![Diagram illustrating horizontal and vertical transmission pathways]

- **Bacterial DNA** and **Plasmids** are key players in the transmission of resistance genes.

**Diagram Explanation**:
- The diagram on the right illustrates the pathways of horizontal (left) and vertical (right) transmission.
- **Horizontal Transmission** involves exchange of genetic material directly between individuals.
- **Vertical Transmission** involves the transfer of genetic material from parent to offspring.

**Key Points**:
- Until 2008, analysis focused on resistance genes on plasmids.
- Horizontal transmission facilitated by the exchange of genetic material among bacteria.
- Vertical transmission involves transmission from parent to offspring.
- Genomic sequencing costs significantly reduced, enabling comprehensive microbial genome analysis.
- Genomic data reveal unexpected findings in both transmission modes.

**Visual Elements**:
- The diagram uses arrows to depict the flow of genetic material, distinguishing between horizontal and vertical transmission.
- Bacterial DNA and plasmids are highlighted to emphasize genetic material exchange.

**Conclusion**:
- The epidemiology of resistant bacteria is complex, involving both horizontal and vertical gene transmission pathways.
- Advances in sequencing technology have drastically reduced costs, enabling deeper insights into microbial genetic dynamics.
VRE genomic data reveals surprising findings

• 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...

VRE precursors (AREF CC17) genetically related to VRE CC17 in hospitals have been isolated in dogs.
Conclusions

• No evidence that EU ban in 2006 decreased VRE in hospitals.

• Antibiotic use varies widely between states and countries showing large variations in how medicine is practiced.

• Antibiotic resistance surveillance must include whole genome sequencing.

• Antibiotic resistance in pets is potentially an important hidden source of antimicrobial resistance in humans.
Where do we go from here?
Can we have our pork chops and antibiotics too?

http://1888steak.com/
Discoveries in the microbiome (i.e. gut microbes) are making us rethink how we approach health and disease.

http://hmpdacc.org/
Human microbiome project has shown that our bodies harbor *many* microbes.

http://fullspectrumbiology.blogspot.com/2013/06/a-healthy-microbiome-is-healthy-you.html
Animals have microbiomes too

Food Animal Microbiomes

• Some microbes are positively correlated with growth while others are negatively correlated.
• Need more studies to improve our understanding of these relationships.
• Low dose antibiotics somehow altered animals’ microbiomes.
• Bacteriophages could theoretically target the unwanted microbes.
• Probiotics could supplement desired microbes.
Bacteriophages ("Phages")

- Bacteria’s natural foes
- Resistance is not an issue
- Phages evolve along with the bacteria
- Most prevalent bioform on the planet.
- They might be an antibiotic alternative.
Electron Microscope Image of Bacteriophages Attacking a Bacteria

https://en.wikipedia.org/wiki/Bacteriophage
Bacteriophages have been approved for food safety use

- FDA approved a bacteriophage cocktail as a food additive in 2006 that targeted *Listeria monocytogenes* on ready-to-eat meals containing meat and poultry products.

http://www.fda.gov/food/ingredientspackaginglabeling/ucm083572.htm
Informal survey of NIH grant funding for bacteriophage research, FY 2016

- NIH Research Portfolio Online Reporting Tool (RePORT):
- In FY 2016, $10.66 billion awarded to 23,664 projects.
- 21 projects investigated phages’ structure and function relating to bacterial or viral diseases. Total $8.1 million awarded (approx .076 percent of total R01 grant awards)
- Of 21 projects, only 2 specifically studied phages’ potential as antibiotic substitutes. Total $968,200 (approx .009 percent of total R01 grant awards)
Informal survey of NIFA grant funding for bacteriophage research, FY 2016

- USDA’s NIFA research grant awards search showed 10 awards over a 10 year period (2006-2016).
- Four project related to food safety.
- Two involved aquaculture safety and security.
- Four addressed water quality.
- Total cost over 10 years: $1.8 million.
- USDA spent $10.4 billion on research grant awards from 2008 to 2015.
- Approx .018 percent was spent on research involving bacteriophages.
• One Health Initiative *pro bono* team:
  
  – Bruce Kaplan, DVM
  
  – Tom Monath, MD
  
  – Lisa Conti, DVM, MPH

http://www.onehealthinitiative.com