Antibiotic resistance and the human-animal interface: Public health concerns

Antibiotic Use and Resistance
Moving forward through shared stewardship
National Institute for Animal Agriculture
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Centers for Disease Control and Prevention
Antibiotic treatments have been critical in human and veterinary medicine for 60+ years

- Resistance a challenge for almost as long
- Emerges in settings where antimicrobials are used
- In a variety of bacteria, viruses, fungi, parasites
- Sometimes spreads from one bacterial strain to another
- Stewardship central to managing infections
One Health: The Way Forward

A multidisciplinary collaborative effort that focuses on the interconnectedness of a large ecosystem to achieve optimal health of humans, animals, and environments across the world.

The health of animals, humans and the environment are connected and influence each other. One Health is

A multidisciplinary collaborative effort that focuses on the interconnectedness of a large ecosystem to achieve optimal health of humans, animals, and environments across the world.
CDC report released September 17, 2013

18 pathogens

Burden
• 2,049,000 illnesses
• 23,000 deaths

Foodborne pathogens
• 4 of the 18 often transmitted through foods
• 2 with animal reservoirs
• 2 with human reservoirs

http://www.cdc.gov/drugresistance/threat-report-2013
Annual burden of illness and death caused by resistant foodborne infections

- Resistant to important drugs used for treatment

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percent Resistant</th>
<th># illnesses/year</th>
<th># deaths/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>24%</td>
<td>310,000</td>
<td>28</td>
</tr>
<tr>
<td>Non-typhoidal Salmonella</td>
<td>8%</td>
<td>100,000</td>
<td>38</td>
</tr>
<tr>
<td><em>Salmonella</em> Typhi</td>
<td>67%</td>
<td>3,800</td>
<td>&lt;5</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>6%</td>
<td>27,000</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>441,000</td>
<td>66-70</td>
</tr>
</tbody>
</table>

CDC 2013 Antibiotic Resistance Threats
Tracking the public health challenge of foodborne antimicrobial resistance

- 1970’s: Periodic surveys of *Salmonella* and *Shigella*

- 1980’s: Outbreaks of resistant infections

- 1996: National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS), a collaborative effort
  - USDA - animals
  - FDA Center for Veterinary Medicine – retail meats
  - CDC – human clinical cases
  - Human, animal strains from all 50 states
  - Retail food isolates from 14 states
  - Standard panels of antimicrobial agents

(See [cdc.gov/NARMS](http://cdc.gov/NARMS) for 2012 Annual Report, testing details)
Emergence of drug resistant strains of concern: *Salmonella* and *Campylobacter*

<table>
<thead>
<tr>
<th>Decade</th>
<th>Species</th>
<th>Source</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980’s</td>
<td>S. Newport</td>
<td>Dairy &amp; Beef</td>
<td>ACKT</td>
</tr>
<tr>
<td>1990’s</td>
<td>S. Typhimurium DT104</td>
<td>Dairy &amp; Beef</td>
<td>ACSSuT</td>
</tr>
<tr>
<td>late 1990’s</td>
<td>S. Newport</td>
<td>Dairy &amp; Beef</td>
<td>ACSSuTAuCx</td>
</tr>
<tr>
<td>late 1990’s</td>
<td><em>Campylobacter jejuni</em></td>
<td>Poultry</td>
<td>Fluoroquinolone</td>
</tr>
<tr>
<td>2000’s</td>
<td>S. Heidelberg</td>
<td>Poultry</td>
<td>AAuCx (CMY2 gene)</td>
</tr>
</tbody>
</table>
Antibiotic use in animals is connected with human health

- Use of antibiotics in food-producing animals can select for antibiotic-resistant bacteria (including ones pathogenic to humans)

- Resistant bacteria can be transmitted from food-producing animals to humans through the food supply

- Resistant bacterial pathogens can cause illness in humans

- Infections caused by resistant bacteria can result in adverse health consequences for humans
Resistant strains are of particular concern

- When treatment is needed, early empiric treatment may fail, and treatment choices will be limited

- Increased morbidity and mortality
  - Longer illnesses
  - More invasive infections
  - More likely to be hospitalized
  - More deaths

- Resistant strains have an advantage in individuals who are taking antimicrobial for other reasons

- When resistance is located on a mobile genetic element like a plasmid, it may be transferred to other bacteria (jumping genes)

Mølbak 2005 Clin Infect Dis 41:1613-20
Barza 2002 Clin Infect Dis 34:S123-125, S126-130
Non-typhoidal *Salmonella*

- Causes ~ 1.2 million illnesses per year
- NARMS surveillance shows improvements
- Multi-drug resistance (3 or more classes)
  - All *Salmonella*: 12% in 2003-7 → 9% in 2012
  - In Typhimurium: 33% → 24%
  - In Newport: 16% → 7%

- NARMS surveillance also shows trends of concern
- Resistance to ceftriaxone (2012)
  - All *Salmonella*: 2.9%
  - In Heidelberg: 22%

- Decreased susceptibility to ciprofloxacin (2012)
  - All *Salmonella*: 2.5%
  - In Enteritidis: 7.7%
  - Most associated with foreign travel

2012 NARMS report

Figure 24. Percentage of non-typhoidal *Salmonella* isolates resistant to 3 or more antimicrobial classes, by year, 1996–2012

2012 NARMS report
Multidrug-resistant *Salmonella* Newport (S. Newport MDR CMY2)

- First appeared in 1999
- Disease in cattle as well as humans
- Resistant to 7 agents, sometimes more
- Including ceftriaxone
- CMY2 gene carried on one large plasmid
- Only on North American Continent

State and CDC investigators on a New England dairy farm where 6 cattle had died, and children in a day care had become infected

Salmonella Newport, human isolates ACSSuTACx resistance, 1996-2012

2012 NARMS report
## Recent multistate outbreaks of resistant *Salmonella* infections

<table>
<thead>
<tr>
<th>Year</th>
<th>Serotype</th>
<th>vehicle</th>
<th>cases</th>
<th>states</th>
<th>% hosp</th>
<th>resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Typhimurium</td>
<td>Ground beef</td>
<td>20</td>
<td>7</td>
<td>47</td>
<td>AKSSuFoxCx</td>
</tr>
<tr>
<td>2011</td>
<td>Heidelberg</td>
<td>Ground turkey</td>
<td>136</td>
<td>34</td>
<td>39</td>
<td>ASSuT</td>
</tr>
<tr>
<td>2012</td>
<td>Heidelberg</td>
<td>Chicken</td>
<td>134</td>
<td>13</td>
<td>31</td>
<td>Variable*</td>
</tr>
<tr>
<td>2013-2014</td>
<td>Heidelberg</td>
<td>Chicken</td>
<td>362</td>
<td>21</td>
<td>38</td>
<td>Variable*</td>
</tr>
</tbody>
</table>

* Polyclonal outbreak, varied patterns, Some strains had no resistance at all Some strains resistant to clinically important drugs
Non-typhoidal *Salmonella*

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  - Most associated with foreign travel

2012 NARMS report
Salmonella Heidelberg, human isolates, ceftriaxone resistance 1996-2012

Figure 20. Percentage of *Salmonella* ser. Heidelberg isolates resistant to ceftriaxone, by year, 1996–2012

2012 NARMS report
Resistant *Salmonella* Heidelberg infections of concern even if susceptible to ceftriaxone

- Prolonged outbreak traced to one poultry producer in 2013-4

- Complex challenge:
  - 7 different PFGE patterns (in patients, poultry meat and processors)
  - Multiple resistance patterns, including pan-susceptible
  - One sub-cluster from broilers cooked at a retail outlet
  - Traceback led to three different slaughter facilities

- Controlled after major efforts to reduce contamination of chicken parts in plants, and to reduce contamination on farms

- Source before processing (production? breeding pyramid?)
## Antimicrobial susceptibility testing, *Salmonella* Heidelberg poultry-associated outbreak, 2013-4

<table>
<thead>
<tr>
<th></th>
<th>Number of isolates tested</th>
<th>Resistant to ≥1 antimicrobial</th>
<th>Multidrug resistant</th>
<th>Resistant to combinations of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Heidelberg isolated from humans</td>
<td>68</td>
<td>65% (44/68)</td>
<td>35% (24/61)</td>
<td>ampicillin, chloramphenicol, gentamicin, kanamycin, streptomycin, sulfisoxazole, and tetracycline</td>
</tr>
<tr>
<td>S. Heidelberg isolated from Company A chicken leftovers</td>
<td>5</td>
<td>80% (4/5)</td>
<td>20% (1/5)</td>
<td>kanamycin, streptomycin, sulfisoxazole, and tetracycline</td>
</tr>
<tr>
<td>S. Heidelberg isolated from Company A chicken sampled at retail locations in California</td>
<td>8</td>
<td>100% (8/8)</td>
<td>50% (4/8)</td>
<td>ampicillin, chloramphenicol, gentamicin, kanamycin, streptomycin, sulfisoxazole, and tetracycline</td>
</tr>
</tbody>
</table>
Persons infected with outbreak strains of *Salmonella* Heidelberg, by date of illness onset, 2013 - 2014

- N = 634
- Median age 18 years
- 50% female
- 38% hospitalized
- 15% blood infections
- No deaths
Salmonella Heidelberg and poultry, 2013-4

Lessons learned

- Not an isolated processing issue at one point in one plant
  - Many different products (breasts, wings, whole birds)
  - Traced back to three different Company A facilities
  - At least four of the outbreak strains found at all three facilities

- Control measures at several levels
  - “Live bird side” - in breeding and production flocks
  - Processing plants – parts as well as carcasses
  - Retail safety and consumer education
Salmonella can spread vertically through the poultry breeding pyramid

Grandparent flock

Breeder flock

Grow-out flock

Slaughter & further processing

Retail

Vertical transmission

S. Pullorum
S. Gallinarum
S. Enteritidis
S. Typhimurium
S. Heidelberg

Carcasses

Parts

Ground product etc.
What is the importance of vertical (transovarial) transmission in *Salmonella* resistance?

- At what points in the breeding pyramid (production, parents, grandparents, etc.) does selection for drug-resistant *Salmonella* occur?

- Could more attention to production as well as slaughter hygiene help control serotypes with a large human health impact?
  - Enteritidis (Most common serotype in US)
  - Typhimurium (Second most common serotype in US)
  - Heidelberg (7th most common serotype in US)
**Campylobacter**

% Resistance by species, human isolates, 2012

<table>
<thead>
<tr>
<th>Agent</th>
<th>C. jejuni (1191)</th>
<th>C. coli (134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>25%</td>
<td>34%</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2%</td>
<td>9%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>48%</td>
<td>45%</td>
</tr>
</tbody>
</table>

2012 CDC NARMS report
Typhoid fever – almost all related to foreign travel
Resistance reflects human use patterns in developing world
CDC is addressing the challenge of resistant foodborne infections by

- Working with partners to prevent foodborne infections
- Tracking resistance through NARMS collaboration
- Making information more available more quickly
- Refining estimates of the health impact of resistance
- Refining understanding of sources and spread of
  - resistance genes and plasmids
  - resistant bacterial strains
- Making real time resistance data part of outbreak investigations
CMY resistance genes in *Salmonella* Heidelberg are on mobile genetic elements (plasmids)

- CMY gene for ceftiofur/ceftriaxone (Cft/Cx) resistance first described on a plasmid of *Salmonella* and *E. coli* (1998-9)

- 2009: 47 *S* Heidelberg strains with Cft/Cx-resistance in NARMS
  - All 47 genes were encoded on plasmids
  - 41 of the 47 plasmids were the same type (Inc type 1)
  - Same plasmid in variety of different Heidelberg strains
  - 26 of the 29 animal and meat isolates were from chicken

- The 2009 increase in Cft/Cx resistance followed spread of a resistance plasmid among various Heidelberg strains in poultry, rather than clonal expansion of one strain of Heidelberg

Winokur 2001 AAC 45:2716-2722
Folster et al 2012 FPD19:638-645
Making real time resistance data part of outbreak investigations

- Goal: reduce resistant *Salmonella* infections by 25% by 2020

- NARMS tests 1 in 20 human *Salmonella* isolates routinely. Resistance may be determined weeks after a cluster is detected.

- New proposal for 2015 – increase surveillance for resistance

- Test all human *Salmonella* isolates for resistance in real time

- When surveillance detects a cluster of similar isolates we will:
  - know the resistance patterns involved
  - prioritize resistant clusters for investigation and traceback
  - control them faster

- We will also be able to attribute resistance to specific sources
Tracking our collective progress

Outcome measures:

• Reductions in MDR resistance in general, and specific resistance to advanced cephalosporins and fluoroquinolones
• Number of resistant *Salmonella* infections: 25% by 2020

Process measures:

• End of use for growth promotion
• Increase in % use under professional veterinary supervision
• Measure changes in use

Welcome input into how best to measure these
Expertise in animal health and management is vital to address resistant foodborne zoonotic infections

- Reduce introduction of resistant strains or genes
  - Breed stock, hatcheries
  - Animal feed sources
  - Water, environment, employees, etc.

- Consider how to reduce selection of resistance and spread of resistant genes or strains
  - Uses that are necessary, and target specific diseases
  - Practices that prevent spread of illness among animals

- Implement antibiotic stewardship and prevention measures
  - Judicious antimicrobial use
  - Supervision by veterinarians
  - Ways to track antibiotic use
  - Alternate treatment and prevention steps
  - Reduce contamination of food
Antimicrobial resistance in foodborne infections in the 21st century

- Substantial and changing challenge to human and animal health
- Not necessarily irreversible
- Foodborne pathogens are resistant to drugs important in human medicine, related to both agricultural and human uses
- Improving stewardship and tracking of human and agricultural uses
- Limiting emergence of resistance, prolong utility of current antibiotics
  - Judicious use in food animals supervised by a veterinarian
  - Measures that prevent spread and food contamination
- Collective goals
  - Food to be safer
  - Those who eat it to be healthier
  - People to have more confidence in food supply
Thank you

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.
Our websites

Antimicrobial resistance:
www.cdc.gov/drugresistance/index.html

Our Programs:
NARMS: www.cdc.gov/NARMS
FoodNet: www.cdc.gov/foodnet
PulseNet: www.cdc.gov/pulsenet
FoodCORE: www.cdc.gov/ncezid/dfwed/orpb/foodcore/index.html

Specific pathogens:
E. coli: www.cdc.gov/ecoli
Salmonella: www.cdc.gov/salmonella
Listeria: www.cdc.gov/listeria

Multistate foodborne outbreaks:
www.cdc.gov/outbreaknet/outbreaks.html

General information about foodborne diseases:
www.cdc.gov/foodsafety
www.foodsafety.gov
Bacteria tracked in NARMS

Humans – CDC
- Non-Typhi *Salmonella* (1996)
- *E. coli* O157:H7 (1996)
- *Campylobacter* (1997)
- *Salmonella* Typhi (1999)
- *Shigella* (1999)
- *Vibrio* other than *V. cholerae*, (2009)

Animals - USDA
- Non-Typhi *Salmonella* (1997)
- *Campylobacter* (1998)
- *E. coli* (2000)

Retail meats – FDA (2002)
- Non-Typhi *Salmonella*
- *Campylobacter*
- *E. coli*
- *Enterococcus*