Antimicrobial Resistance and Food Safety: The Surveillance Challenge

Patrick McDermott, M.S., Ph.D.,
Director, The U.S. National Antimicrobial Resistance Monitoring System
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Laurel, MD
The Global Resistance Threat

“The rise of antimicrobial resistance is a global health crisis. Medicine is losing more and more mainstay antimicrobials as pathogens develop resistance. Second-line treatments are less effective, more costly, more toxic, and sometimes extremely difficult to administer. Many are also in short supply. Superbugs haunt hospitals and intensive care units all around the world. With few replacement products in the pipeline, the world is heading towards a post-antibiotic era in which common infections will once again kill”.

Margaret Chan, WHO Director General, Address to the G7 Health Ministers, 2015
General Principles

- The development of resistance is linked to how often antibiotics are used.
- Because many antibiotics belong to the same class of medicines, resistance to one specific antibiotic agent can lead to resistance to a whole related class.
- Resistance that develops in one organism or location can also spread rapidly and unpredictably and can affect antibiotic treatment of a wide range of infections and diseases.
- Drug-resistant bacteria can circulate in populations of human beings and animals, through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration.
- Resistant bacteria can be found in food animals and food products destined for consumption by humans.
Although antimicrobial resistance is a natural phenomenon, it is being propagated by
- misuse of antimicrobial medicines,
- inadequate or inexistent programmes for infection prevention and control,
- poor-quality medicines,
- weak laboratory capacity,
- inadequate surveillance
- insufficient regulation of the use of antimicrobial medicines.

A strong, collaborative approach will be required to combat antimicrobial resistance, involving countries in all regions and actors in many sectors.

April 2015
FDA Strategy to Limit Resistance in Animal Agriculture

Multipronged strategy designed to limit or reverse resistance arising from the use of antibiotics in food-producing animals, while continuing to ensure the availability of safe and effective antibiotics for use in animals and humans.

- The National Antimicrobial Resistance Monitoring System 1996
- Extralabel use prohibition of fluoroquinolones and glycopeptides 1997
- Revised safety assessment process (GFI #152) 2003
- Withdrawal fluoroquinolones in poultry 2005
- Cephalosporin extralabel use prohibition 2012
- Revised judicious use guidance (GFI #209) 2012
- Industry guidance on eliminating production uses (GFI #213) 2013
- Enhanced annual summary of antibiotic sales data 2014
- Update on veterinary feed directive (GFI #120) 2015
- Collaboration with international partners (WHO, OIE, Codex)
What is integrated surveillance of antimicrobial resistance in foodborne bacteria?

The coordinated sampling and testing of bacteria from food animals, foods, and clinically ill humans; and the subsequent evaluation of antimicrobial resistance trends throughout the food production and supply chain using harmonized methods.

Source: WHO-AGISAR report
Ecology of Antimicrobial Resistance

After Linton AH (1977), modified by Irwin RJ - 2012 version
Organization of NARMS

**FOOD ANIMALS**
- Intestinal Samples from Individual Animals at Processing Facility
- HACCP Samples at Processing Facility
  - Department of Agriculture Food Safety Inspection Services

**FOOD**
- Raw Meats at Retail Outlets in 14 States
- Import Isolates
  - Food & Drug Administration Center for Veterinary Medicine

**HUMANS**
- Proportion of Human Clinical Isolates from State Laboratories
  - Centers for Disease Control and Prevention

**Shared databases for outbreak investigations**
- NARMS Report (online, interactive)
  - NARMS Now (open data sharing)

**NCBI (DNA Sequences)**
NARMS Goals

1. Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats and animals

2. Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria

3. Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance

4. Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals
Public Health Value of Integrated Surveillance

1. **Baselines** - Document resistance levels in different reservoirs
2. **Spread** - Describe the spread of resistant bacterial strains and resistance genes
3. **Trends** - Identify temporal and spatial trends in resistance
4. **Attribution** - Generate hypotheses about sources and reservoirs of resistant bacteria
5. **Risk analysis** - Understand links between use practices and resistance
6. **BOI** - Identify risk factors and clinical outcomes of infections caused by AMR bacteria
7. **Education** - Provide data for education on current and emerging hazards
8. **Aid practitioners** - Guide evidence-based prescribing practices and prudent use guidelines to maintain effectiveness of resources
9. **Regulations**
   - Pre-approval: Support risk analysis of foodborne antimicrobial resistance hazards
   - Post-approval: Identify adverse events, design interventions & develop policies to contain resistance
10. **Evaluate interventions** -
11. Go back to #1
Challenges of Integrated Surveillance for Antimicrobial Resistance

1. Gathering accurate information and bacterial isolates is expensive and laborious
2. Burden of illness and food consumption data are needed for design and prioritization of pathogens and commodities
3. Sound sampling scheme along the food chain is critical for valid trend analysis
4. Combining resistance and use data is complicated
5. Cooperation, collaboration, good communication and data sharing between all stakeholders
   – agriculture, industry and public health sectors
   – microbiologists & epidemiologists within and across sectors
Challenges of Integrated Surveillance for Antimicrobial Resistance

6. Political/financial support - requires recognition of the public health issues and the need for ongoing risk assessments
7. Establish a process for review and enhancement
8. Remain flexible in order to stay current
9. Adapt to changing technologies
10. Understanding the implications of the data and the need for research
11. Publishing often very complex findings to different audiences in a timely manner
12. Using the data to formulate sound public health policy
13. International harmonization and cooperation
Factors to Consider

- Which animal types (including age) to be sampled
- Foods at retail or abattoir, and domestic vs. imported
- What proportion of human isolates
  - Need to separate outbreak isolates
- Sampling strategy - Should be nationally or regionally representative
  - Active or passive sampling
  - Random, stratified or systematically collected samples
  - Statistically based or convenience sampling
- Samples to be collected
  - Feces, carcasses, raw, processed
Factors to Consider

- Monitoring may be at regular intervals or be ongoing
- Bacterial species to be isolated
  - Most important enteric pathogens may vary by region.
  - Commensals are valuable but add expense
- Antimicrobials to be tested and reported
  - Standardized methods with appropriate QC
  - MIC vs. disk diffusion
- Database design for data mining, analysis and reporting
  - WHONET is widely used (J. Stelling).
  - Analysis and reporting should be structured to enable international comparison
  - Interactive web-based data displays
  - Will isolate-level data be made publicly available?
Research Challenges

*Susceptibility surveillance data alone are not always enough.*

- Burden of illness from AMR pathogens
- Strain relatedness and outbreak response
- The effects of different selection pressures pre- and post-harvest
- Impact of intervention
- Co-resistance and cross-resistance
- Horizontal gene transfer
- Clonal dissemination
- Environmental routes of spread (DT104)
- The role of animal feeds, etc.
Data Management & Reporting Challenges

Annual monitoring reports
– Labor-intensive to write and clear
– Often difficult to comprehend
– Not timely
– Non-interactive
– Display only select analyses
– Costly
Current Approach to Data Reporting in NARMS

• In the 2013 test year, NARMS produced 81,000 antibiotic susceptibility data points for *Salmonella*, 24,400 for *Campylobacter*, 36,000 for *E. coli* and 40,688 for *Enterococcus*.

• Isolates are recovered from samples 13 sources

<table>
<thead>
<tr>
<th>Human</th>
<th>Chickens</th>
<th>Turkeys</th>
<th>Cattle</th>
<th>Swine</th>
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<tr>
<td>Clinical illness</td>
<td>Retail Chicken</td>
<td>Retail Ground Turkey</td>
<td>Retail Ground Beef</td>
<td>Retail Pork Chops</td>
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<td>PR/HACCP</td>
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<td>PR/HACCP</td>
<td>PR/HACCP</td>
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<tr>
<td>Cecal</td>
<td>Cecal</td>
<td>Cecal (Beef &amp; Dairy)</td>
<td>Cecal (Market Hogs &amp; Sows)</td>
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</tbody>
</table>

• *Salmonella* resistance varies by serotype, and serotype by animals source in some cases.

• Stakeholders include consumer advocacy groups, farmers, pharmaceutical companies, politicians, physicians, agriculture specialists, epidemiologists, veterinarians, policy makers, consumers, etc.
**What is the best way to communicate complicated surveillance data to different audiences?**

1. Press release with three messages
2. Highlights section for the most important pathogens & drugs
3. A narrative summary
4. Dense data tables with preset analyses
5. Interactive graphs for data exploration
6. Interim data releases/reports
7. Isolate level data
NARMS Now: Integrated Data

The NARMS Isolate Level Dataset is Being Made Public

Background

On January 21, 2009, the President launched the Open Government initiative based on the principles of transparency, participation, and collaboration. The goal of this initiative is to increase government accountability, promote informed participation by the public, and create economic opportunity by expanding access to information through online publication of records. In September 2014 the White House also released the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB), which emphasizes that improved detection of resistance can be achieved through appropriate data sharing, enhancement, expansion, and coordination of existing surveillance systems.

Historically, NARMS reports have presented aggregated data in various ways, but it was not possible to examine the complete set of characteristics within individual bacterial isolates. In keeping with the CARB goals and Open Government policies of HHS and USDA, the National Antimicrobial Resistance Monitoring System (NARMS) is publishing online the bacterial isolate-level data in a new format called NARMS Now: Integrated Data. This contains the entire collection of NARMS enteric bacterial isolates collected over the past 18 years (1996-2013) for Salmonella, Campylobacter, E. coli and Enterococcus. The data are available in a spreadsheet format that can be downloaded and analyzed by commonly used software applications.

While the availability of NARMS Now: Integrated Data will allow interested parties to download and analyze the microbiological data in different ways, the CDC is also making available a powerful interactive web tool, NARMS Now: Human Data, to visualize the human isolate data. In the near future, NARMS Now: Integrated Data will be incorporated into the interactive displays associated with the NARMS Integrated Reports to allow readers to visualize the findings across the various sample sources in NARMS. Both tools will be updated on a regular basis as new NARMS data are available.

Download NARMS Isolate Level Data

- Human Clinical Cases
- Retail Meats
- Food Producing Animals
  - HACCP 1997-2005
  - HACCP 2006-2013
  - Decal
# Surveillance tomorrow

<table>
<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Characteristics</th>
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<tr>
<td>Culture</td>
<td>Serotype</td>
<td>• Historical continuity</td>
</tr>
<tr>
<td>Serotyping</td>
<td>Resistance pattern</td>
<td>• Low resolution typing</td>
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<tr>
<td>Antibiotic Susceptibility</td>
<td>Genetic relationship</td>
<td>• Multiple assays and reagents</td>
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<tr>
<td>PFGE</td>
<td>Resistance mechanisms</td>
<td>• Limited drug coverage</td>
</tr>
<tr>
<td>Molecular study</td>
<td></td>
<td>• Limited resistance mechanisms</td>
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<tr>
<td></td>
<td></td>
<td>• Specialized training</td>
</tr>
<tr>
<td></td>
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<td>• Labor intensive</td>
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<tr>
<td></td>
<td></td>
<td>• Costly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Slow and piecemeal</td>
</tr>
<tr>
<td>WGS</td>
<td>Serotype</td>
<td>• Requires new standards</td>
</tr>
<tr>
<td>Metagenomic Sample</td>
<td>Resistance pattern</td>
<td>• Higher resolution typing</td>
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<tr>
<td>Culture</td>
<td>Genetic relationship</td>
<td>• Single assay/one instrument</td>
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<td>DNA</td>
<td>Resistance mechanisms</td>
<td>• Extended drug coverage</td>
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<tr>
<td>WGS</td>
<td></td>
<td>• Detect all known mechanisms</td>
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<tr>
<td></td>
<td></td>
<td>• Details on genetic context</td>
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<tr>
<td></td>
<td></td>
<td>• Computation intensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lower costs</td>
</tr>
<tr>
<td></td>
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<td>• Rapid and comprehensive</td>
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</table>

Traditional

- Serotyping
- Antibiotic Susceptibility
- PFGE
- Molecular study

WGS

- Metagenomic Sample
- Culture
- DNA
- WGS
Correlation between Antimicrobial Resistance Phenotype and Genotype in *Salmonella*

<table>
<thead>
<tr>
<th>ANTIBIOTIC</th>
<th>Phenotype: Resistant</th>
<th>Phenotype: Susceptible</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td></td>
<td>Genotype: resistant</td>
<td>Genotype: susceptible</td>
<td></td>
<td></td>
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<tr>
<td>GENTAMICIN</td>
<td>99</td>
<td>6</td>
<td>5</td>
<td>530</td>
<td>94.3%</td>
<td>99.1%</td>
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<tr>
<td>STREPTOMYCIN</td>
<td>257</td>
<td>3</td>
<td>35</td>
<td>345</td>
<td>98.8%</td>
<td>90.8%</td>
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<tr>
<td>AMOXY/CLAV</td>
<td>114</td>
<td>2</td>
<td>0</td>
<td>524</td>
<td>98.3%</td>
<td>100.0%</td>
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<tr>
<td>CEFOXITIN</td>
<td>93</td>
<td>2</td>
<td>21</td>
<td>524</td>
<td>97.9%</td>
<td>96.1%</td>
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<tr>
<td>CEFTIOFUR</td>
<td>113</td>
<td>0</td>
<td>4</td>
<td>523</td>
<td>100.0%</td>
<td>99.2%</td>
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<tr>
<td>CEFTRAXONE</td>
<td>116</td>
<td>0</td>
<td>1</td>
<td>523</td>
<td>100.0%</td>
<td>99.8%</td>
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<tr>
<td>AMPICILLIN</td>
<td>241</td>
<td>1</td>
<td>1</td>
<td>397</td>
<td>99.6%</td>
<td>99.7%</td>
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<tr>
<td>SULFA</td>
<td>244</td>
<td>1</td>
<td>0</td>
<td>395</td>
<td>99.6%</td>
<td>100.0%</td>
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<tr>
<td>TRM/SULFA</td>
<td>19</td>
<td>3</td>
<td>0</td>
<td>618</td>
<td>86.4%</td>
<td>100.0%</td>
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<td>AZTREONAM</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>639</td>
<td>100.0%</td>
<td>100.0%</td>
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<tr>
<td>CHLORAMPHENICOL</td>
<td>44</td>
<td>0</td>
<td>1</td>
<td>595</td>
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<td>CIPROFLOXACIN</td>
<td>4</td>
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<td>0</td>
<td>636</td>
<td>100.0%</td>
<td>100.0%</td>
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<td>NALIDIXIC ACID</td>
<td>13</td>
<td>2</td>
<td>0</td>
<td>625</td>
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<td>TETRACYCLINE</td>
<td>349</td>
<td>0</td>
<td>0</td>
<td>291</td>
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<tr>
<td><strong>Totals</strong></td>
<td><strong>1707</strong></td>
<td><strong>20</strong></td>
<td><strong>68</strong></td>
<td><strong>7164</strong></td>
<td><strong>98.8%</strong></td>
<td><strong>99.1%</strong></td>
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Added Value of Integrated Surveillance

- Source attribution is useful in burden of illness estimates
- Database of strain relatedness for outbreak detection
- Phylogenetics
- Evolution of MDR
- Virulence
- Method development
- Emerging trends
- Networked of trained and dedicated laboratory personnel and epidemiologists
- Infrastructure for targeted studies

Opportunity to serve broader food safety priorities
Benefits of Integrated Surveillance

1. **Baselines** - Document resistance levels in different reservoirs
2. **Spread** - Describe the spread of resistant bacterial strains and resistance genes
3. **Trends** - Identify temporal and spatial trends in resistance
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Summary

- Integrated antimicrobial resistance monitoring of foodborne pathogens is important to ensure the safety of the food supply and for public health policy.
- Sustainable integrated resistance surveillance is expensive, laborious and has many challenges:
  - Design and prioritization
  - Collaboration across agencies
  - Gathering and integrating information
  - Understanding the implications of the data
  - Publishing findings to different audiences in a timely manner
  - Using the data to formulate sound public health policy
- Next generation DNA sequencing is changing surveillance.
- Because AMR is a global problem, there is a need for international:
  - Harmonization of surveillance methods to ensure data comparability
  - Cooperation and data sharing to limit global spread
# Acknowledgements

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Thank you …