Twenty Years of the National Antimicrobial Resistance Monitoring System (NARMS)
What Have We Learned So Far and What Is Next?

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Questions to Consider

- What are the key findings and lessons learned from 20 years of NARMS?
- What is the value of a One Health surveillance system such as NARMS?
- What actions have been taken based on the data collected?
- What have been the challenges in terms of data gaps, sharing, reporting, and quality issues, as well as collaboration with other agencies and sectors, and how have they been overcome?
- What can be learned from NARMS to inform AMR surveillance systems that aim to incorporate a One Health approach?
- What is next in enhancing NARM’s capabilities?
- Can NARMS help to measure the success of the recent FDA Guidance 209, 213 and changes to the VFD?
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.*

*Nationally representative, randomized sampling of animals at slaughter

54 participating public health departments submit 1/20 NT Salmonella

19 State partners test (17,000) retail meats annually

*WHO-AGISAR report
The Value of One Health 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 antibiotic use practices and resistance
6. BOI - Identify risk factors and clinical outcomes of infections caused by resistant bacteria
7. Education - Provide data for education on current and emerging issues
8. Policy - Guide evidence-based policies and guidelines for judicious antibiotic use
9. Regulations
   - Pre-harvest - Support risk analysis of foodborne antimicrobial resistance hazards (GFI #152)
   - Post-harvest - Identify interventions to contain resistance and evaluate their effectiveness (withdrawal of fluoroquinolones in poultry, ELU prohibition for cephalosporins)
10. Evaluate interventions – did changes have the intended effect
11. Go back to #1
Challenges of One Health Surveillance for Antimicrobial Resistance

1. Gathering accurate information and bacterial isolates is expensive and laborious
2. Sound sampling scheme along the food chain (and environment) is critical for valid trend analysis
3. Collaboration and data sharing between
   - Agriculture, industry and public health sectors
   - Microbiologists & Epidemiologists within and across sectors
4. Establishing a process for review and enhancement
5. Publishing complex findings to different audiences in a timely manner
6. Using the data to formulate sound public health policy
7. International harmonization and cooperation
What Have We Learned about Resistance to Critically-Important Antibiotics in Nontyphoidal *Salmonella* from humans in the US

MDR = Multidrug Resistant; AXO = Ceftriaxone; AZI = Azithromycin; CIP = Ciprofloxacin
Resistance to Critically-Important Antibiotics in Human Nontyphoidal *Salmonella* from Select EU Countries, Norway and the USA

*Breakpoints used for interpreting MICs were derived from the EUCAST.

†Among critically-important drugs (defined here as macrolides, fluoroquinolones, extended-spectrum cephalosporins, and carbapenems), azithromycin, meropenem and colistin resistance were very rare and not reported in most countries.

*Percentage based on reporting of either cefotaxime or ceftazidime resistance from the EU or ceftriaxone from US.
Resistance to Critically-Important Antibiotics in Broiler Nontyphoidal *Salmonella* from Select EU Countries, Norway and the USA

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Antibiotic Resistance in Human Nontyphoidal *Salmonella* from Select EU Countries, Norway and the USA

Breakpoints used for interpreting MICs were derived from the EUCAST.
Antibiotic Resistance in Broiler Nontyphoidal *Salmonella* from Select EU Countries, Norway and the USA

Breakpoints used for interpreting MICs were derived from the EUCAST.
From Phenotype to Genotype:
Advantages of a Whole Genome Sequencing in Surveillance

<table>
<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Human Animal</td>
<td>Genus, species</td>
<td>Slow and piecemeal</td>
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<tr>
<td>Food Environmental</td>
<td>Serotype</td>
<td>Low resolution typing</td>
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<tr>
<td>Pure Culture</td>
<td>Resistance pattern</td>
<td>Multiple assays and reagents</td>
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<tr>
<td>Identification</td>
<td>Genetic relationship</td>
<td>Limited drug coverage</td>
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<tr>
<td>Serotyping</td>
<td>Resistance mechanisms</td>
<td>Limited resistance mechanisms</td>
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<tr>
<td>Antibiotic Susceptibility</td>
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<td>Specialized training</td>
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<tr>
<td>PFGE</td>
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<td>Labor intensive</td>
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<tr>
<td>Molecular study</td>
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<td>Costly</td>
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<tr>
<td>Molecular study</td>
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<td>Historical continuity</td>
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<tr>
<td>Pure Culture</td>
<td>Identification</td>
<td>Rapid and comprehensive</td>
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<tr>
<td>DNA</td>
<td>Serotype</td>
<td>Highest resolution typing</td>
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<tr>
<td>WGS</td>
<td>Resistance genes</td>
<td>Single assay/instrument/output</td>
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<tr>
<td>Metagenomic Sample</td>
<td>Resistance genes</td>
<td>Extensive drug coverage</td>
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<tr>
<td>Identification</td>
<td>Genetic relationships</td>
<td>Detect all known genes</td>
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<tr>
<td></td>
<td>Virulence properties</td>
<td>Details on genetic context</td>
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<tr>
<td></td>
<td>Phage type</td>
<td>Computation intensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower costs</td>
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<tr>
<td></td>
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<td>Requires new standards</td>
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Traditional

WGS
# Resistance genotype-phenotype correlations for foodborne pathogens

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Genotype-phenotype correlation</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td><em>Salmonella enterica</em></td>
<td>99.7%</td>
<td>Zankari et al., 2013, J Antimicrob Chemother</td>
</tr>
<tr>
<td></td>
<td>99.0%</td>
<td>McDermott et al., 2016, Antimicrob Agents Chemother</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>97.1%</td>
<td>Stoesser et al., 2013, J Antimicrob Chemother</td>
</tr>
<tr>
<td></td>
<td>98.5%</td>
<td>Tyson et al 2015., J Antimicrob Chemother</td>
</tr>
<tr>
<td><em>Campylobacter spp.</em></td>
<td>99.2%</td>
<td>Zhao et al 2015., J Antimicrob Chemother</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>98.8%</td>
<td>Gordon et al 2014., J Antimicrob Chemother</td>
</tr>
</tbody>
</table>
The history of resistance is recapitulated in modern strains
NARMS Now: Interactive Data Dashboards for Real Time Reporting
FDA Announces Implementation of GFI #213, Outlines Continuing Efforts to Address Antimicrobial Resistance

Update (2/17/17): CVM has completed its audit of affected applications and revised the final number of new animal drug applications that have withdrawn production indications from 22 to 31.

January 3, 2017

Today, the U.S. Food and Drug Administration announced that it has completed the implementation of Guidance for Industry #213, a process begun in 2013 to transition antimicrobial drugs with importance in human medicine (medically important antimicrobials) that are used in the feed or drinking water of food-producing animals to veterinary oversight and eliminate the use of these products in animals for production (e.g., growth promotion) purposes.

7 Classes Affected
1. Aminoglycosides (streptomycin, spectinomycin)
2. Lincosamides (lincomycin)
3. Macrolides (tylosin, erythromycin)
4. Penicillins (penicillin G procaine)
5. Streptogramins (virginiamycin)
6. Sulfonamides (sulfamethazine)
7. Tetracyclines (chlortetracycline, oxytetracycline)
How to monitor impact?

• 2014-2017 (mid-June)
  – Total Cecal Samples received
    • ~14,782
  – Total Cecal Samples DNA extracted
    • 12,852
  – DNA extraction that may need repeat based on concentration and quality
    • 1,721 (<10ng/µl)

• Mid February 2017-2018
  – 98 weeks X ~100 cecal samples = 9800 samples
Metagenomic Surveillance of AMR Genes

![Graphs showing relative abundance of AMR genes over time for different classes: aminoglycoside, macrolide, tetracycline, and sulphonamide. Each graph is divided into segments for different classes (Cattle, Chicken, Swine, Turkey).]
Resistance Genes by Animal Origin
Gaps in One Health Surveillance

- Expand the **food component** of NARMS surveillance to enhance the statistical power of trend analysis and to evaluate other commodities derived from animals raised with antibiotics.
- Add food **animal pathogens**. The health, safety and productivity of livestock and poultry is also a public health strategy.
- Add **on-farm** testing to assess the range of husbandry practices on resistance.
- Incorporate **companion animal** surveillance.
- Develop an **environmental** surveillance piece to complete the One Health platform to better understand the movement of pathogens and resistant genes across the three One Health domains.
- Broaden **collaboration** with other U.S. programs that have been started or expanded across government agencies and programs.
- Continue to work toward **international** harmonization and cooperation with other countries and institutes (GMI) that have increased their commitment to antibiotic resistance surveillance. With whole genome sequencing, comparisons will be more informative.
- Move toward **microbiome** surveillance to better understand resistance genes and microbial profiles in healthy animals.
- Advice to growers on **appropriate actions** that can be taken to mitigate resistance
Acknowledgements

• FDA (CVM, CFSAN, ORA)
• CDC (NCZEID)
• USDA (FSIS, ARS, APHIS)
• NIH/NCBI
• State Public Health Labs, Universities

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
Temporal changes in resistance of NTS *Salmonella* from humans: 1940s-2014


[Graph showing temporal changes in resistance of NTS *Salmonella* from humans: 1940s-2014.]