Challenges to an Integrated Antimicrobial Resistance Surveillance Program:

Experience from the U.S. National Antimicrobial Resistance Monitoring System

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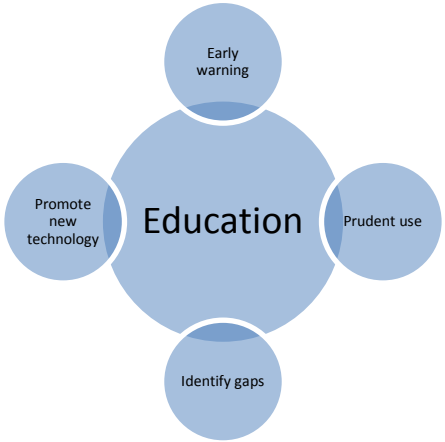
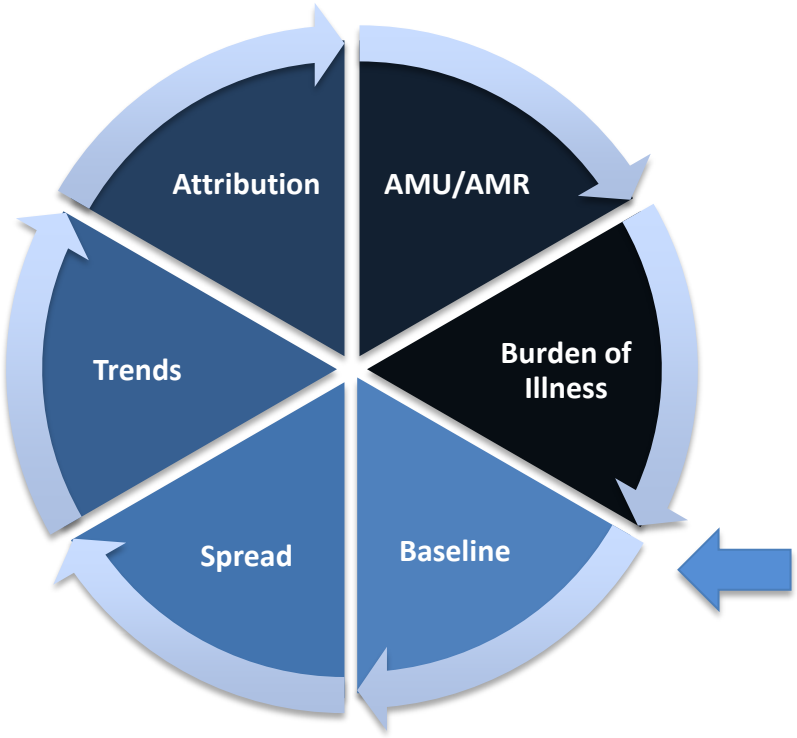
What is integrated surveillance of antimicrobial resistance in foodborne bacteria?

The coordinated sampling and testing of bacteria from food animals, foods, (the environment) 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

What is the purpose of integrated surveillance of antimicrobial resistance in foodborne bacteria?





Intervention

Regulation	Pre /Post Binding
Policy	Guidance

NARMS Integration

State Laboratories

Local Laboratories

General Practice

Centers for Disease Control & Prevention

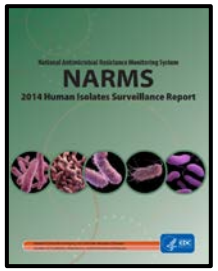
Random sampling of national production at slaughter

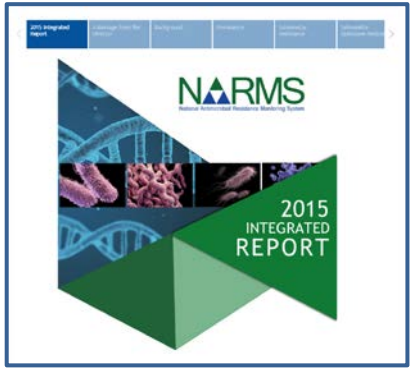
US Department of Agriculture

Random stratified sampling of chicken, turkey, beef and pork in 21 States

Food & Drug Administration

Annual Drug Sales & Distribution Data





History of NARMS Sampling - CDC

Pathogen	1996	1997	1998	1999	2000	2001	2002	2003[§]	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Nontyphoidal *Salmonella**	Every 10th*							Every 20th*					Every 20th[†]										
Salmonella Paratyphi A and C[†]													All[†]										
Salmonella Typhi				All																			
E. coli O157	Every 5th							Every 20th															
Shigella				Every 10th				Every 20th															
Vibrio (species other than *V. cholerae*)													All										
Campylobacter[‡] (FoodNet sites only)		1st received weekly							All, or every 2nd, 3rd, 5th[‡]														

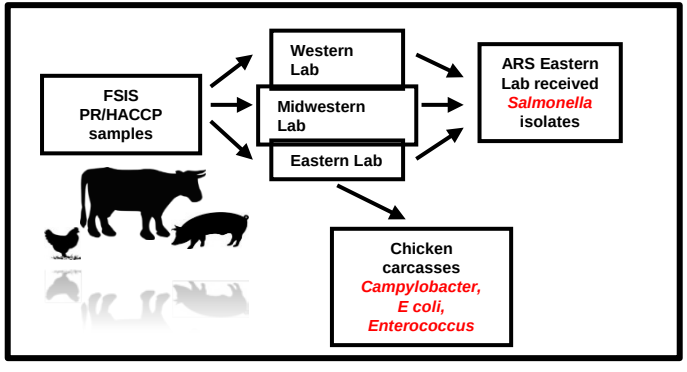
* During 1996–2007, Paratyphi A, B, and C isolates were included in the 1:10 or 1:20 sampling for nontyphoidal *Salmonella.*

[†] Since January 2008, sites have submitted all Paratyphi A and C isolates. Paratyphi B isolates have remained in the nontyphoidal *Salmonella* 1:20 sampling.

[‡] Frequency-based sampling involving a convenience sample of clinical labs was initiated in 2005. Current scheme includes all isolates (CA, CT, OR, TN), every 2nd isolate (CO, GA, MD, NY), every 3rd (NM) and every 5th (MN).

[§] Since 2003, all 50 states have participated in surveillance for *Salmonella, E. coli* O157, and *Shigella,* and all 10 FoodNet sites have participated in *Campylobacter* surveillance (*Vibrio* surveillance began in all 50 states in 2009).

History of NARMS Sampling - USDA



- Led by USDA-Food Safety Inspection Service
- Cecal samples better reflect animal status and less confounded by plant events
- A randomized, nationally representative testing of slaughterhouses
- Ability to distinguish production classes
- Complete microbiology for all animal species

Old System (HACCP)

Pathogen	Swine	Cattle	Chicken	Turkeys
Campylobacter			x	
Salmonella	x	x	x	x
E. coli			x	
Enterococcus			x	

New System (Cecal)

Pathogen	Swine hogs, sows	Cattle dairy, beef steers, heifers	Chicken	Turkeys
Campylobacter	x	x	x	x
Salmonella	x	x	x	x
E. coli	x	x	x	x
Enterococcus	x	x	x	x

History of NARMS Sampling - FDA

Sampling Scheme:

Sampling: 80 pkgs/mo.

- 40 retail chicken
- 20 ground turkey
- 10 ground beef
- 10 pork chops

Sample size increase from 6,720 in 2016 to 19,200 in 2018

Bacteria tested by State – 2018

Salmonella and *Campylobacter*

All 20 states

E. coli

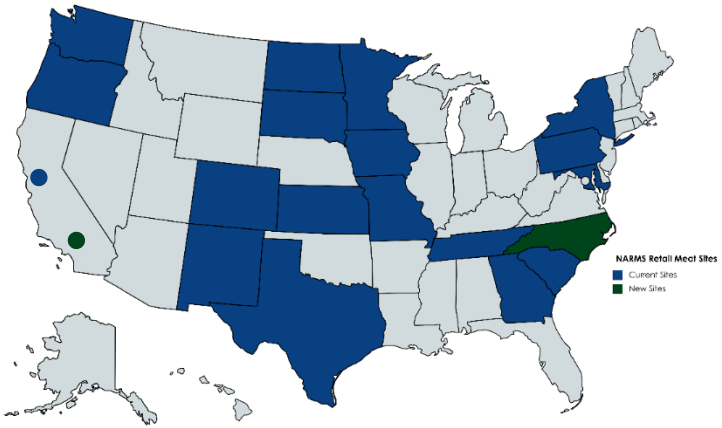
15 states (CO, GA, IA, KS, MD, OR, PA, SC, SD/ND, TN, TX/OKC, UCD, NC)

Enterococcus

10 sites (GA, IA, KS, MD, OR, SC, SD/ND, TN, TX, UCD, NC)

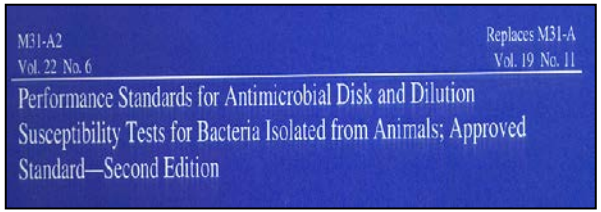
Partnership with States

- CT, GA, MD, MN, TN, OR — 2002
- CT, GA, MD, MN, TN, OR, NY, CA — 2003
- CT, GA, MD, MN, TN, OR, NY, CA, CO, NM — 2004
- CT, GA, MD, MN, TN, OR, NY, CA, CO, NM, PA — 2008
- CT, GA, MD, MN, TN, OR, NY, CA, CO, NM, PA, WA, LA, MO — 2013
- GA, MD, MN, TN , OR, NY, CA, CO, NM, PA, WA, LA, MO — 2017
  LA, MO, IA KS, SC, SD (ND), TX (OKC)
- GA, MD, MN, TN , OR, NY, CA, CO, NM, PA, WA, LA, MO — 2018
  LA, MO, IA KS, SC, SD (ND), TX (OKC) NC, CA-Davis



Harmonized Methods

- Animal, human, retail lab testing comparable
  - Same antimicrobial susceptibility testing methods
    - Broth microdilution methods
      - Sensititre System – *Salmonella, E. coli, Enterococcus*
      - 2005, *Campylobacter* following MLVS
  - Same antimicrobial plate formats
  - Same isolate handling procedures
- Quality Assurance
  - Internal and external programs
  - CLSI standards
  - Since 2003 - WHO EQAS
- PFGE: PulseNet certification and protocols

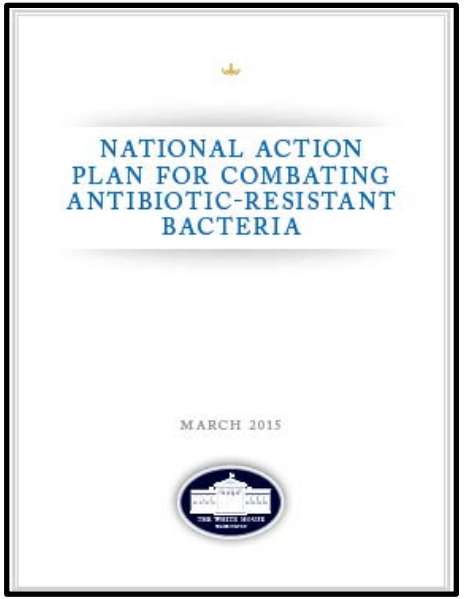


The U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB)

Vision: The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic-resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic-resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.

Five major goals

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections.
2. Strengthen national one-health surveillance efforts to combat resistance.
3. Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.
4. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.
5. Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control, and antibiotic research and development.



Goal 2: Strengthen national one-health surveillance efforts to combat resistance

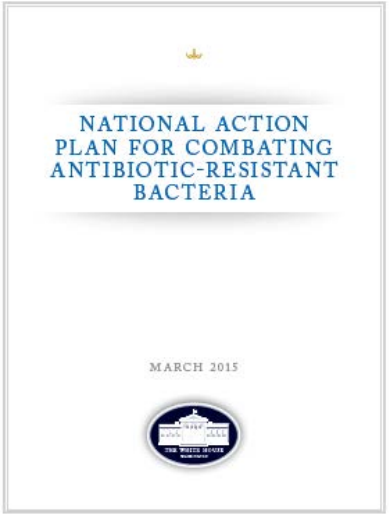
2.4. Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain from food-animals on-farm, through processing, and retail meat.

i. Enhance surveillance of antibiotic resistance in animal and zoonotic pathogens and commensal organisms by strengthening the National Antimicrobial Resistance Monitoring System (NARMS) and leveraging other field- and laboratory-based surveillance systems.

ii. Enhance collection and reporting of data regarding antibiotic drugs sold and distributed for use in food-producing animals.

iii. Implement voluntary monitoring of antibiotic use and resistance in pre-harvest settings to provide nationally-representative data while maintaining producer confidentiality.

iv. Collect quantitative data on antibiotic resistance and management practices along various points at pre-harvest, harvest, and processing, in collaboration with producers and other stakeholders and disseminate information as appropriate.



Challenges of Integrated Surveillance for Antimicrobial Resistance

- Gathering and integrating information is expensive and laborious
- Sound sampling scheme along the food chain is critical
- Burden of illness and food consumption data are needed for design and prioritization of pathogens and commodities
- Cooperation and good communication among agriculture and public health sectors
- Collaboration and information sharing between laboratorians, epidemiologists and public health officials within and across sectors and disciplines *and internationally*.

Challenges of Integrated Surveillance for Antimicrobial Resistance

- Political/financial support - recognition of the public health issues and the need for ongoing risk assessments
- Understanding the implications of the data and the role of research
- Publishing findings to different audiences in a timely manner
- Using the data to formulate sound public health policy
- Remain flexible in order to stay current
- Establish a process for review and enhancement
- International harmonization and cooperation

Previous FDA Science Board Review of NARMS-2007

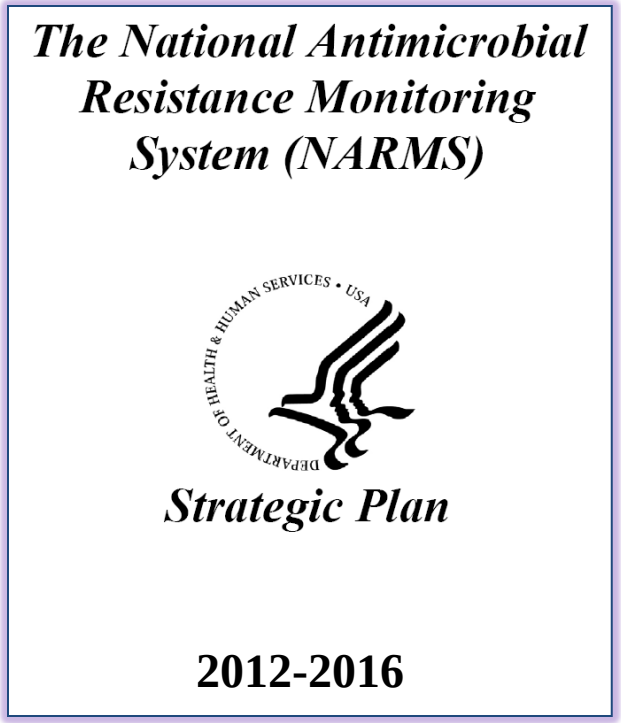
1. Are there inherit biases in the **sampling** strategies employed in NARMS? If so, how can they be improved to ensure that the data and interpretation are scientifically sound given current resources?

2. Are there epidemiological and/or microbiological **research** studies that would better serve the goals of NARMS and the regulatory work of FDA?

3. Are current plans for **data harmonization and reporting** appropriate? If not, what are the top priorities for advancing harmonized reporting?

4. Are the current NARMS **international** activities adequate to address the worldwide spread of antimicrobial-resistant food-borne bacteria?

NARMS Strategic Plan



Goal 1: To develop, implement and optimize a shared database, with advanced data acquisition and reporting tools

Goal 2: To make sampling more representative and more applicable to trend analysis

Goal 3: To strengthen collaborative research projects to address high risk food safety issues

Goal 4: To support international activities which promote food safety, and mitigate the spread of antimicrobial resistance

A new external review was conducted by a subcommittee of the FDA Science Board in 2017

1. NARMS is focused on specific commodities and sampling intervals. Could changes to **sampling** strategies improve our understanding of resistance dynamics within a One Health paradigm?

2. FDA publishes annual antimicrobial sales and resistance data. Is our analysis and presentation of these data adequate? What is the best way to report **relationships between antimicrobial sales data and antimicrobial resistance** in our national surveillance?

3. NARMS now does whole genome sequencing as a routine part of surveillance. What is the best way to report whole genome **sequence data** and trends in the resistome?

General Recommendations to Advance a One Health NARMS Platform

The NARMS mission can be accelerated and much more might be accomplished if NARMS considers the following:

1. The addition of an environmental surveillance component to truly complete the One Health platform

2. Consider expanding the trend analysis to include food animal pathogens

3. Better integrate and coordinate across the various programs and components within the NARMS' activities.

1. There are several discussions underway involving NARMS partner agencies to assess the relative value of different environmental sampling points and other elements that constitute best practices for this type of testing.
2. Efforts to collect AMR data in food animal pathogens is in need of dedicated financial support. FDA's Vet-LIRN program and USDA's NAHLN are collaborating to build capacity for this work.
3. Better coordination is a continuous goal. NARMS main federal collaborators now include CDC, CFSAN, USDA-APHIS, USDFA-FSIS, USDA-ARS, and NCBI.

General Recommendations to Advance a One Health NARMS Platform

4. Evaluate a possible on-farm component with NAHMS implemented by USDA APHIS. Consider a "sentinel farm" approach and longitudinal studies with the support of APHIS and/or strategic partnerships with universities.

4. NARMS supported pilot studies to explore the logistical and practical challenges associated with on-farm surveillance. FDA has partnered with NAHMS on this objective to facilitate a sustainable system that provides relevant information.

5. Increase efforts to broaden collaboration with other (new) AMR programs that have been started or expanded across government agencies (e.g., FoodNet, diagnostic labs, other CARB activities).

5. NARMS is currently working closely with GenomeTrakr, NCBI, Argonne National Labs and will explore new partnerships to help better achieve the goals of the National Strategy. CDC linked to PulseNet, FoodNet and other case-based surveillance systems. WGS rollout to all 50 states will result in WGS on 100% of human *Salmonella* in 2019

6. Consider a more in-depth and integrated collaboration with global organizations and other countries that have also increased their interest and commitment to AMR. With the increasing use of WGS techniques, comparisons will be easier and more meaningful.

6. NARMS is leading the world in methods to monitor resistance using genomics, and developing innovative tools to track resistance in bacteria from different sources based on WGS data. NARMS provided the foundation and expertise to NCBI to build automated resistance gene calling into their online bacteria database. Member organizations play leading roles in WHO, OIE, FAO and CLSI.

General Recommendations to Advance a One Health NARMS Platform

7. Consider collecting more metadata in such a way to be useful for purposes beyond the current NARMS objectives such as risk assessment, attribution studies and detecting newly emerging resistant bacteria in the food supply.

7. See Question 10 & 11 below

8. Envision how NARMS might integrate with some microbiome studies.

8. NARMS Scientists are working actively to explore the use of metagenomics for characterizing the microbiome, with an emphasis on the “resistome”.

9. Facilitate the research opportunity presented by the recent approval of avilamycin for use in chickens and pigs to study the mechanisms of AMR dissemination.

9. This work has begun and avilamycin has been incorporated into one of the NARMS drug testing panels

General Recommendations to Advance a One Health NARMS Platform

10. Better exploit the use of WGS surveillance data to identify hidden outbreaks, design case-control studies to identify sources, to quantify the proportion of sporadic cases to an vehicle, and identify clusters of AMR subclones within a genotype to identify the source of newly emerging resistances.

11. Expand the uses of AMR phenotypic and genotypic data based on WGS surveillance data to:

a. Facilitate epidemiologic studies to identify risk factors for sporadic drug-resistant infections caused by dominant genotypes before any outbreaks become recognized;

b. Attribute sporadic infections to a set of genotypes; and,

c. Determine the proportion of sporadic illnesses in a community attributable to a single product during a time period. Risk factors for infection with such genotypes can be sought and removed if found.

Questions 10 and 11 are closely related and address making the best of the data set, including the new data from WGS. This work is ongoing and consists mainly in bioinformatics and machine learning processes that fully mine microbial genomic data to address all these goals.

NARMS is conducting comprehensive analysis of WGS data using advance bioinformatics to fully exploit these data. NARMS is working with NCBI to develop databases of gene categories by which to analyze trends, identify sources, and to refine resistance reporting. NARMS will adopt the CDC wgMLST typing scheme to identify and track subclones, and will incorporate tools to show mobile DNA elements that carry resistance genes. (See also Question 3).

NARMS Looking Forward: From Integrated to One Health Surveillance

A subcommittee of the FDA Science Board reviewed NARMS in June 2017 and recommended:

1. Add food animal pathogens.
2. Add appropriate on-farm testing.
3. Incorporate companion animal surveillance.
4. Develop an environmental surveillance piece to advance a One Health approach.
5. Develop methods of microbiome surveillance.
6. Broaden collaboration with other U.S. programs
7. Continue to work toward international harmonization and cooperation

Summary

- 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
  - Adopting new technologies

- Because AMR is a global problem, let us continue to work better together to:
  - Harmonize our methods to ensure data comparability
  - Cooperation and data sharing to limit global spread

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Review Article

National Antimicrobial Resistance Monitoring System: Two Decades of Advancing Public Health Through Integrated Surveillance of Antimicrobial Resistance

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Thank you …

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.