

***The Use of Genomics in One Health
Resistance Surveillance:
The Experience of the U.S. National Antimicrobial
Resistance Monitoring System***

Patrick McDermott, MS, PhD

Director, The U.S. National Antimicrobial Resistance Monitoring System (NARMS)

U.S. Food and Drug Administration

GOAL 2: EMPLOY ADVANCED TECHNOLOGIES TO BETTER UNDERSTAND THE EVOLUTION AND SPREAD OF RESISTANCE AMONG FOODBORNE PATHOGENS



THE NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM

STRATEGIC PLAN 2021-2025

Objective 2.1: Apply predictive resistance analytics, machine learning, and other bioinformatics tools to NARMS-related data to better understand the mechanisms, sources, and spread of resistance.

Objective 2.2: Optimize *in vitro* antimicrobial susceptibility testing to identify new resistance mechanisms.

Objective 2.3: Develop metagenomic approaches to characterize the resistome of animals, humans and environmental samples and to link resistance genes to their microbial source.

Objective 2.4: Employ long-read DNA sequencing methods to establish a reference database of fully characterized strains and their plasmids.

Objective 2.5: Conduct research to understand concomitant adaptive microbial features that might contribute to the persistence and spread of resistance (*e.g.*, colonization, stress tolerance) under different selection pressures (*e.g.*, heavy metals, antiseptics, *etc.*).



Structure of NARMS, 2020

Zoonotic Foodborne Pathogens

Animal Pathogens

WGS Data Repository

	Humans	Retail Meats	Food-Producing Animals	Food-Producing and Companion Animals	All WGS Data
Who is involved in NARMS?	Centers for Disease Control & Prevention (CDC) Health departments in 50 states	Food and Drug Administration (FDA) Health departments in 15 states Institutions of higher education in 7 states	United States Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) Agricultural Research Service (ARS) Animal Plant Health Inspection Service (APHIS)	FDA and USDA Veterinary Laboratory Investigation and Response Network (Vet-LIRN) USDA National Animal Health Laboratory Network (NAHLN) Veterinary Diagnostic Labs in 36 States	National Institutes of Health (NIH) National Center for Biotechnology Information (NCBI)
Where do the samples that are tested come from?	Ill persons	Retail meats from grocery stores Chicken Ground Turkey Ground Beef Pork Shrimp Tilapia Salmon	Ceca and regulatory samples: Chickens Turkeys Cattle Swine Veal Lamb Goat Catfish	Clinical diagnostic samples All animal species	Submitted genomic sequences
What bacteria does NARMS test for resistance?	<i>Salmonella</i> <i>Campylobacter</i> <i>Escherichia coli</i> 0157 <i>Vibrio</i> <i>Shigella</i>	<i>Salmonella</i> <i>Campylobacter</i> <i>Escherichia coli</i> <i>Enterococcus</i> <i>Vibrio</i> <i>Aeromonas</i>	<i>Salmonella</i> <i>Campylobacter</i> <i>Escherichia coli</i> <i>Enterococcus</i>	<i>Salmonella</i> <i>Staph pseudintermedius</i> <i>Escherichia coli</i> Other	



Genomes with Phenotype Data in NARMS

Bacterium	Human	FP Animals	Retail Meats	DV Labs	Total
<i>Salmonella</i>	8,629	7,206	9,041	827	25,703
<i>Campy</i>	1,041	9,571	4,770		15,382
<i>E. coli</i>	617 (STEC)	3,079	3,160	842	7,698
<i>Enterococcus</i>		1,772	325		2,097
<i>S. pseudintermedius</i>				855	855
TOTAL	10,287	21,628	17,296	2,524	51,735



NARMS Genotype-Phenotype Correlations

Bacterium	Reference	Correlation
<i>E. coli</i>	Tyson et al, JAC, 2015	98.5%
<i>Campylobacter</i>	Zhao et al, AEM, 2016	99.2%
<i>Salmonella</i>	McDermott et al, AAC, 2016	99.0%
<i>Enterococcus</i>	Tyson et al, FEMS-PD, 2018	96.5%



Interpretive Criteria for *in vitro* Antimicrobial Susceptibility Testing

- CLSI: Clinical breakpoints are based on the likelihood of **treatment success**, with S, I, R categories.
- EUCAST: Epidemiological cutoff MICs used to differentiate wild-type from **non-wild-type** isolates based on MIC distributions (I+R)
- GCV: Genotypic cutoff value is defined as the highest MIC of the population of bacteria lacking resistance determinants to a given drug. A majority of isolates above this MIC should possess resistance mechanisms.

The gene as the hazard.

*The "resistant" category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules, and/or that demonstrate zone diameters that fall in the range **where specific microbial resistance mechanisms are likely**, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies (CLSI).*



Reporting Genomic Resistance: Genotypic Cutoff Values

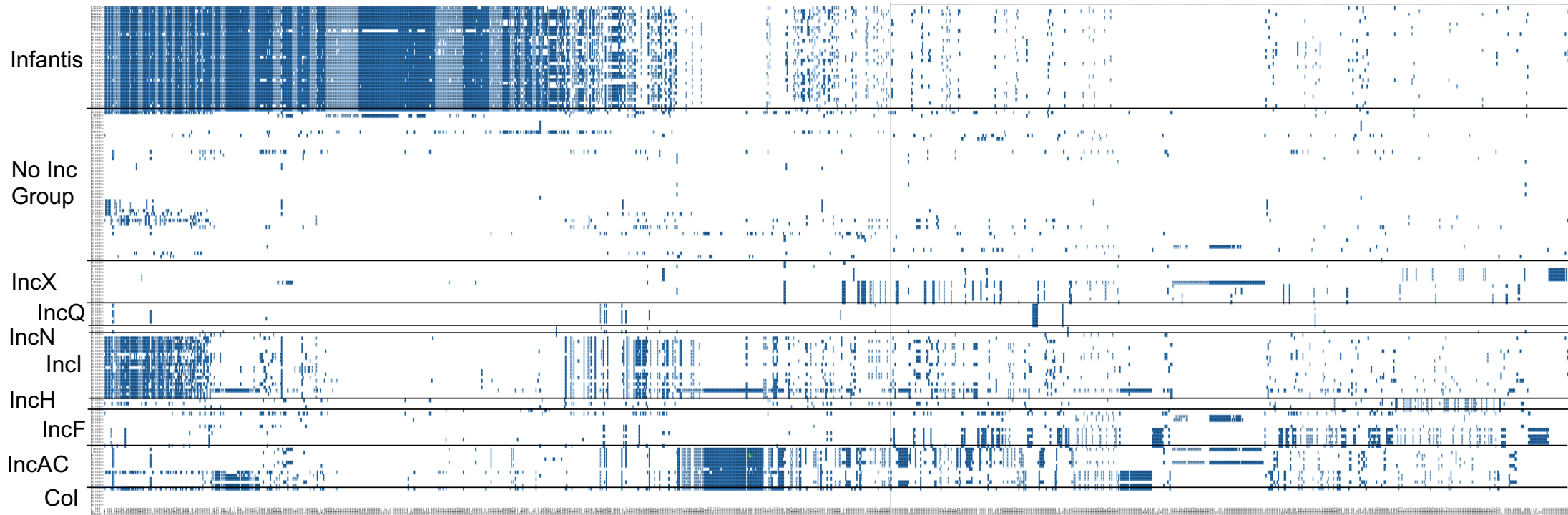
Antimicrobials	CLSI susceptible (S): treatment success likely	EUCAST ECV: wild-type (WT)	GCV: no resistance mechanism (NRM)
Ampicillin	≤ 8	≤ 4	≤ 8
Amoxicillin-clavulanate	≤ 8	None	≤ 2
Cefoxitin	≤ 8	≤ 8	≤ 8
Ceftriaxone	≤ 1	None	≤ 1
Ceftiofur	≤ 2	≤ 2	≤ 2
Gentamicin	≤ 4	≤ 1	≤ 2
Tetracycline	≤ 4	≤ 4	≤ 4
Chloramphenicol	≤ 8	≤ 16	≤ 16
Ciprofloxacin	≤ 0.06	≤ 0.06	≤ 0.06
Nalidixic acid	≤ 16	≤ 16	≤ 8
Azithromycin	None	None	≤ 16
Sulfisoxazole	≤ 256	None	≤ 256
Trimethoprim-sulfamethoxazole	≤ 2	≤ 1	≤ 0.05

Tyson GH, Zhao S, Li C, Ayers S, Sabo JL, Lam C, Miller RA, McDermott PF. Establishing genotypic cutoff values to measure antimicrobial resistance in *Salmonella*. Antimicrob Agents Chemother. 2017 Feb 23;61(3).



Plasmid Pan-genome

Pan-genomic analysis of 151 closed plasmids from *Salmonella* NARMS
ID subsets of plasmid loci clusters within plasmid groups



Resistance by source and place

[Back to Table of Contents](#)

Hover over the icon for more information about this dashboard



1. Select a bacterium (optional- select a Species or Serotype- only the most common serotypes are shown):

Salmonella

2. Select source(s) and an antimicrobial agent:

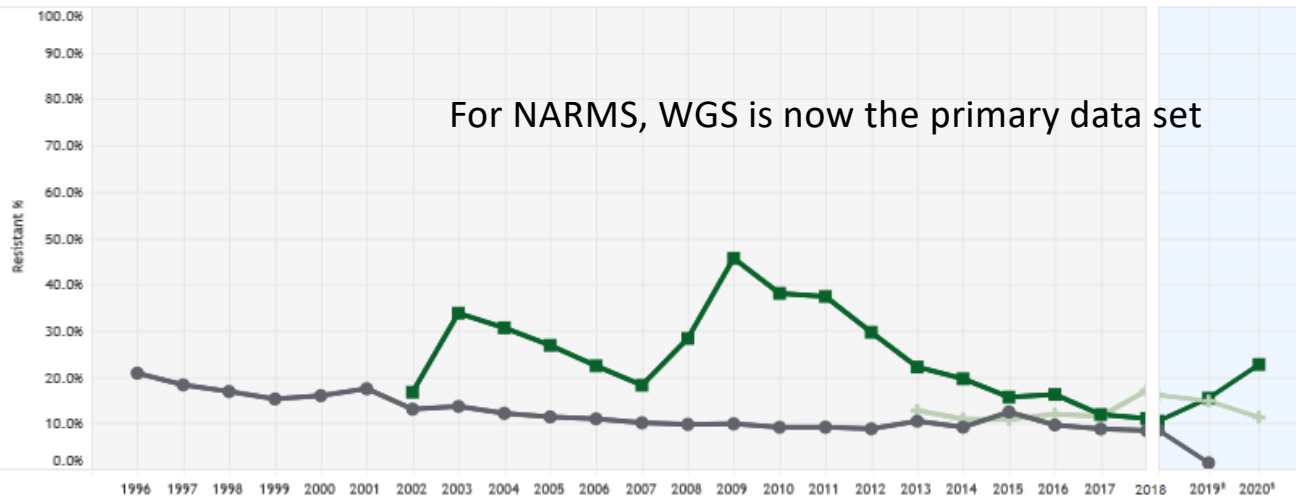
(Multiple values)

Ampicillin

Anatum Derby Enterit... Hadar Heidelberg... 14,[5],... Infantis Johan... Kentuc... Monte... Newport Reading Typhi... other

Percentage of *Salmonella* (all nontyphoidal serotypes) Isolates Resistant to Ampicillin

For NARMS, WGS is now the primary data set



Humans Retail Chickens Chickens (Cecal) Phenotypic Resistance Genotypic Resistance

Distribution of Ampicillin Resistance Genes in 2017

Distribution does not appear for *Campylobacter* for years before 2015, *E.coli* for years before 2017, *Enterococcus* from Humans or Retail sources, or HACCP sources



RESISTOME TRACKER

Salmonella

Select an icon or alert below to get started.



CUSTOMIZE



COMPARE



DISCOVER



EXPLORE

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

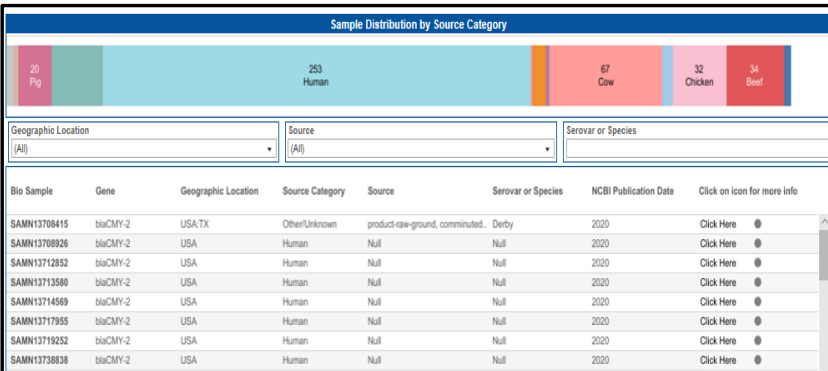
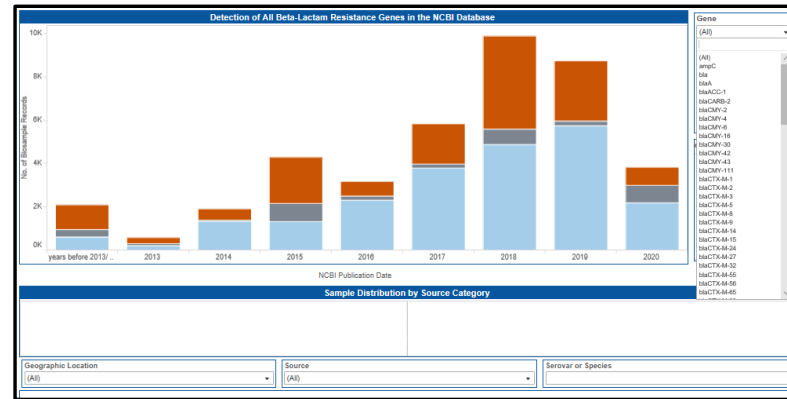
Page 1 of 5 | Records per Page 5 | Choose columns | Download | Expand all

#	Organism Group	Strain	Serovar	Isolate	Create date	Location	Isolation Source	Isolation type	Host	Min-same	Min-diff
1	Salmonella enterica	FS1520215...	Salmonella...	PDT000840557.1	2020-09-20	USA:NC	raw intact chick...	environmental/other		23	29
2	Salmonella enterica	PNUSAS152...		PDT000785738.1	2020-07-10	USA	clinical			12	12
3	Salmonella enterica	FS1512031...	Kentucky	PDT000781252.1	2020-07-03	USA:MO	raw intact chick...	environmental/other		13	32
4	Salmonella enterica	FS1512030...	Kentucky	PDT000745211.1	2020-05-22	USA:IL	raw intact chick...	environmental/other		10	33
5	Salmonella enterica	FS1520217...	Kentucky	PDT000724155.1	2020-04-20	USA:WA	comminuted chl...	environmental/other		14	33

Share | Hide Table | Labels | Load Labels | Neighbors | Common subtree | Watch | Watched isolates

5 10 15 environmental/other, 2019-09-28, USA:IA, Chicken Thighs, CVM N1950378, PDT000594083.1
 environmental/other, 2019-09-28, USA:IA, Chicken Thighs, CVM N1950379, PDT000594082.1
 environmental/other, 2019-09-28, USA:KS, Chicken Wings, CVM N1950558, PDT000592461.1
 environmental/other, 2019-12-14, USA:TX, Chicken Wings, CVM N1950559, PDT000544817.1
 environmental/other, 2019-10-08, USA:State, chicken, 19MD0362912.5, PDT000903761.1
 environmental/other, 2018-07-27, USA:MN, comminuted chicken, FS151923099, PDT000550154.1
 environmental/other, 2020-07-03, USA:MO, raw intact chicken, FS151203184, PDT000781252.1
 environmental/other, 2020-04-30, USA:WA, comminuted chicken, FS152021705, PDT000724155.1
 environmental/other, 2020-05-22, USA:IL, raw intact chicken, FS1512030784, PDT000745211.1
 environmental/other, 2020-01-14, USA:State, chicken, 19MD102810.5, PDT00061929.1
 environmental/other, 2019-06-09, USA:GA, comminuted beef, FS1511021440, PDT000518218.1
 environmental/other, 2018-10-03, USA:WI, comminuted chicken, FS1511814963, PDT000365078.1
 environmental/other, 2018-06-14, USA:WI, comminuted chicken, FS1521821919, PDT000302973.1
 environmental/other, 2018-03-08, USA:WI, comminuted chicken, FS151800799, PDT000380023.1
 environmental/other, 2018-03-19, USA:NC, comminuted chicken, FS1511918508, PDT000479068.2
 environmental/other, 2020-09-20, USA:NC, raw intact chicken, FS15202029285, PDT000840557.1
 clinical, 2020-07-10, USA, PNUSAS152408, PDT000785738.1
 environmental/other, 2018-10-07, USA:MO, Chicken Wings, CVM N1952081, PDT000602048.1
 environmental/other, 2018-06-24, USA:DE, raw intact chicken, FS151900209, PDT00050237.2
 environmental/other, 2018-12-03, USA:DE, raw intact chicken, FS151801311, PDT000413890.1
 environmental/other, 2019-04-30, USA:NC, raw intact chicken, FS151924178, PDT000498000.2

Pathogen Detection **BETA**



Gene: blaCMY-2

Geographic Location: (All) | Enter search text

Non USA: amph-1, blaACC-1, blaACC-3, blaACT-4, blaACT-5, blaACT-6, blaACT-7, blaACT-12, blaACT-14, blaCARB-1, blaCARB-2, blaCARB-3, blaCARB-5, blaCARB-6, blaCARB-11, blaCEPH-A, blaCKO-1, blaCMG

USA: blaCMY-2, blaCMY-3, blaCMY-4, blaCMY-4.1, blaCMY-4.2, blaCMY-5, blaCMY-6, blaCMY-7, blaCMY-15, blaCMY-16-1, blaCMY-17



Genomics in Food Safety

GEN-FS (2015)

- (1) Thermal tolerance
- (2) Desiccation resistance
- (3) Osmotic/Ionic tolerance
- (4) QAC resistance
- (5) Chlorine resistance
- (6) Biofilm persistence
- (7) Surface adherence
- (8) Antibiotic resistance**
- (9) Biocide resistance**
- (10) Ecological fitness
- (11) Heavy metal resistance
- (12) Metabolic persistence
- (13) Enhanced hydrophobic fitness
- (14) Produce invasiveness
- (15) Flower invasiveness
- (16) Root system invasiveness
- (17) Acid resistance
- (18) Surface water fitness
- (19) In vivo plant migratory fitness
- (20) Soil fitness
- (21) Capsaicin resistance
- (22) Swarming
- (23) Trans-ovarian poultry colonization
- (24) Fecal persistence (poultry)
- (25) Yolk content invasion
- (26) Multidrug resistance
- (27) External amoeba harborage
- (28) Internal amoeba harborage
- (29) Acyl-homoserine lactone (AHL)
- (30) KatE stationary-phase catalase
- (31) In vivo migratory fitness
- (32) RDAR phenotype
- (33) Persistence within the tomato
- (34) Virulence**

Multiple US Federal Agencies

- Food and Drug Administration (FDA)
- Centers for Disease Control and Prevention (CDC)
- National Institutes of Health (NIH)
- Food Safety and Inspection Service (FSIS)
- Agricultural Research Service (ARS)
- Animal and Plant Health Inspection Service (APHIS)

Gen-FS: Targets for development coordination and harmonization

System tools,
data pipelines,
and methods

Analytic procedures,
protocols, and
standards

Data sharing and
availability

Harmonized
proficiency testing
and training

Use is surveillance,
investigation and
research

External
communication and
partnerships

Pathogen Detection BETA



To assist the National Database of Antibiotic Resistant Organisms (NDARO), NCBI Pathogen Detection identifies the antimicrobial resistance, stress response, and virulence genes found in bacterial genomic sequences. This enables scientists to track the spread of resistance genes and to understand the relationships between antimicrobial resistance and virulence.

NCBI Pathogen Detection integrates bacterial pathogen genomic sequences originating in food, environmental sources, and patients. It quickly clusters and identifies related sequences to uncover potential food contamination sources, helping public health scientists investigate foodborne disease outbreaks.

[Find isolates now!](#)

Examples:

1. Search for isolates encoding a mobile colistin resistance gene and a KPC beta-lactamase search: [AMR_genotypes:mcr* AND AMR_genotypes:blaKPC*](#)
2. Search for Salmonella isolates from the USA search: [geo_loc_name:USA AND taxgroup_name:"Salmonella enterica"](#)

Explore the Data

Species	New Isolates	Total Isolates
Salmonella enterica	72	301,814
E.coli and Shigella	28	127,740
Campylobacter jejuni	29	55,931
Listeria monocytogenes	2	38,255
See more organisms...		

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NEW [Microbial Browser for Identification of Genetic and Genomic Elements \(MicroBIGG-E\)](#)

[Reference Gene Catalog](#)

[Isolates with antibiotic resistant phenotypes](#)

[Download analysis results \(FTP\)](#)

Submit

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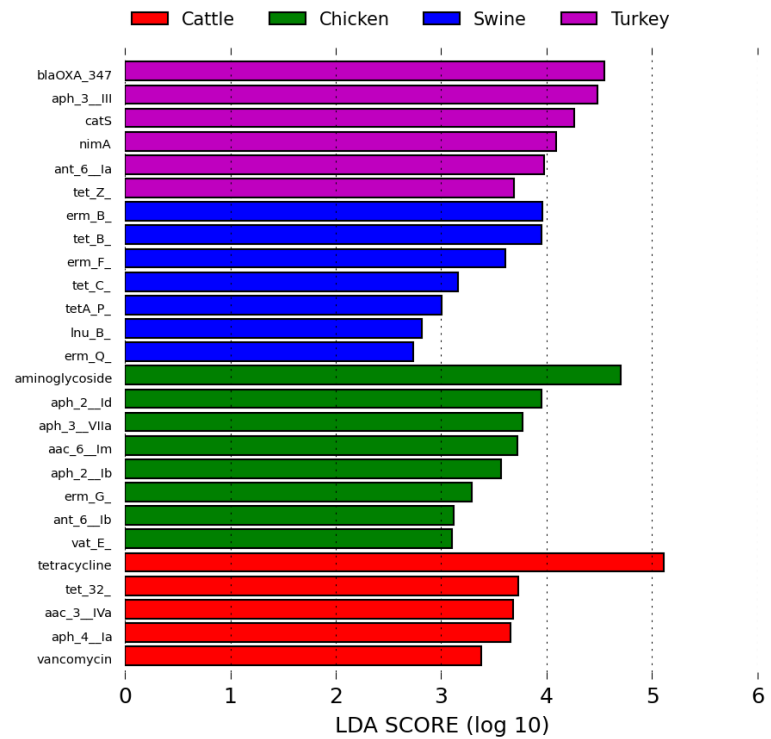
[How to submit antibiotic resistance phenotypes](#)

[How to submit beta-lactamases](#)

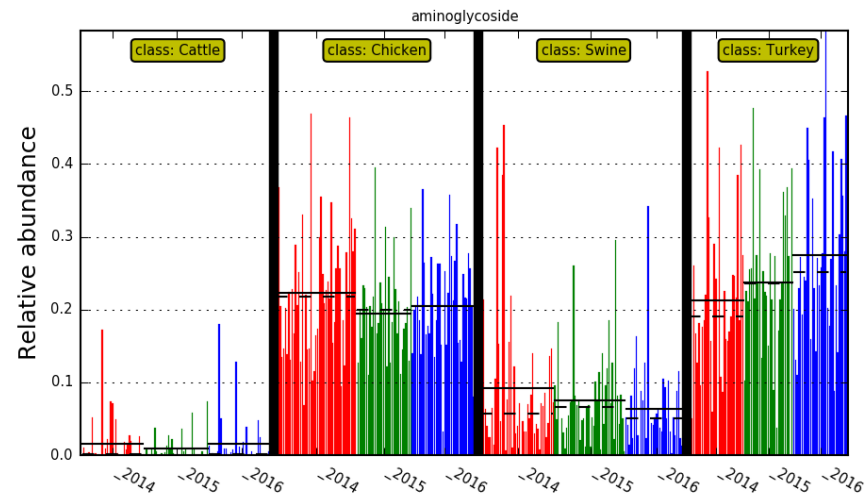
[NCBI Submission Portal](#)



Metagenomic Surveillance: Resistance Genes by Animal Origin

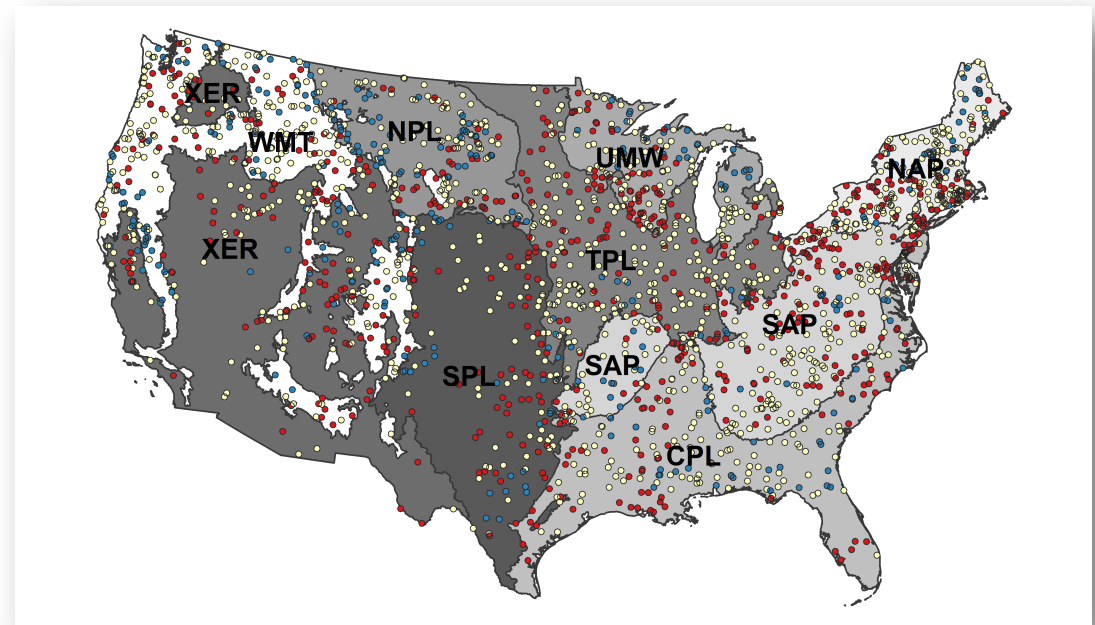


- Total cecal samples received = 25,000
- Total cecal samples DNA extracted = 23,800
- Total with completed analysis = 1,600



The Environment and 1H AMR Monitoring

- The National Aquatic Resource Surveys (NARS) are collaborative programs between the EPA, states, and tribes to assess the quality of the nation's waters using a statistical survey design
 - National Rivers and Streams Assessment (NRSA)
 - National Coastal Condition Assessment (NCCA)
 - National Lakes Assessment (NLA)
 - National Wetland Condition Assessment (NWCA)
- Surveys are staggered annually
- Impact is assessed using
 - Biological indicators (benthic macroinvertebrates, algae, fish)
 - Chemical indicators (phosphorus, nitrogen, salinity, acidity)
 - Physical indicators (sediments, fish, vegetation, riparian disturbance)
 - Human health indicators (Enterococci (fecal indicator), mercury in fish tissue)



(ECO9 Regions Shown; blue is reference; yellow is intermediate; red is Agri impacted)

Metagenomics Water Study

Goal

- Characterize the microbiome and resistome of water
- Compare less disturbed and more disturbed systems
- Documents shared and unique features with food animals

Testing Design

- Targeted the North Appalachian Ecoregion
- 91 samples (65 impacted, 26 reference; also 4 mock assays) from 2013-2014.
- Compared 219 cecal samples from cattle (73), chicken (23), turkey (58) and swine (65) between 2014 and 2016.

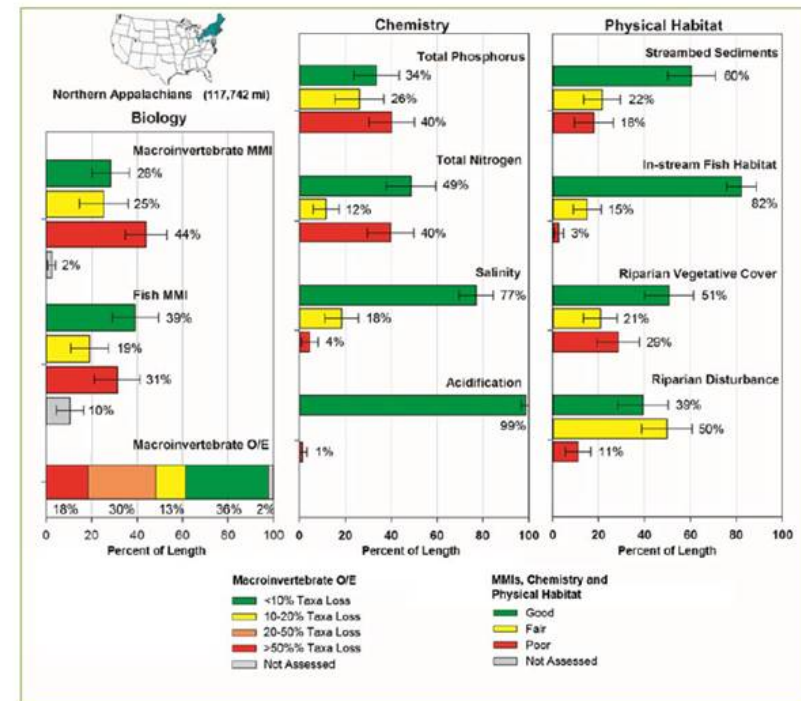
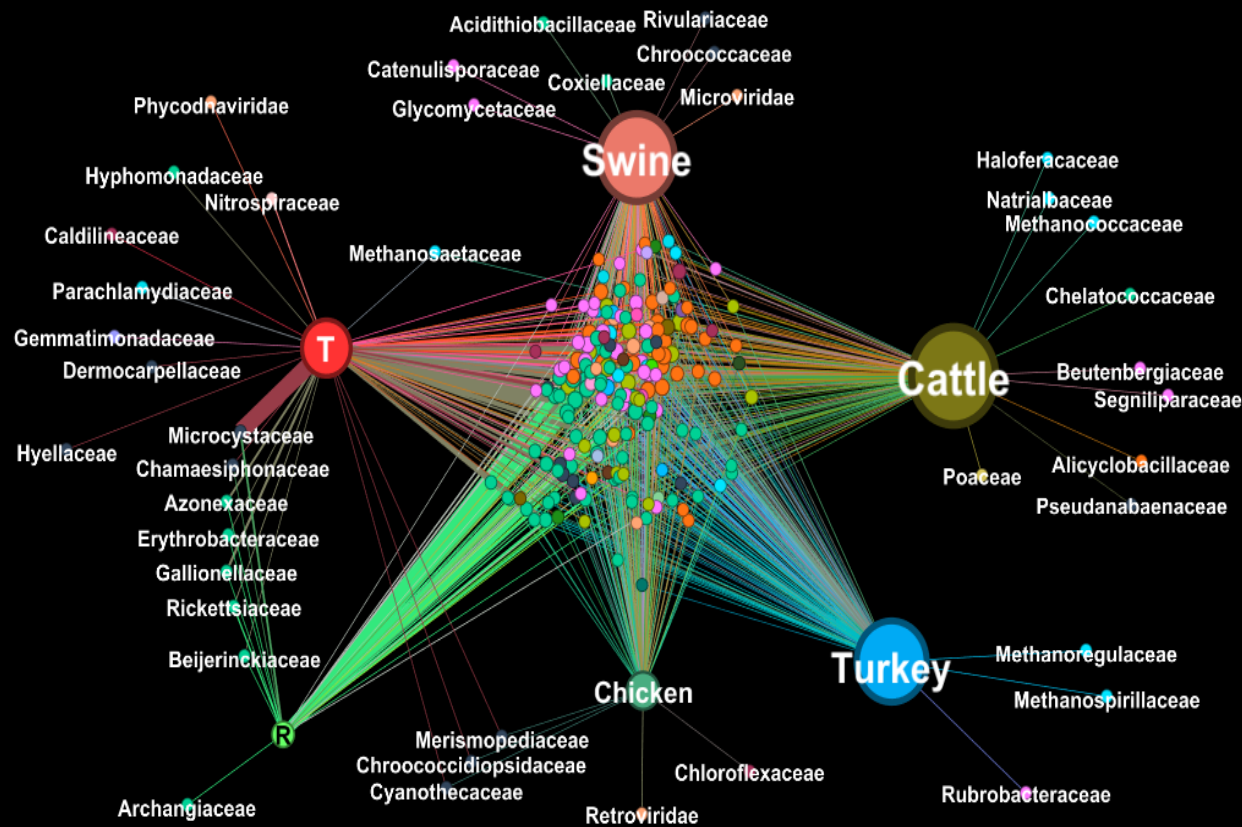


Figure 38. NRSA survey results for the Northern Appalachians ecoregion (EPA/NRSA). Bars show the percentage of river and stream length within a condition class for a given indicator. Percentages may not add up to 100% due to rounding.

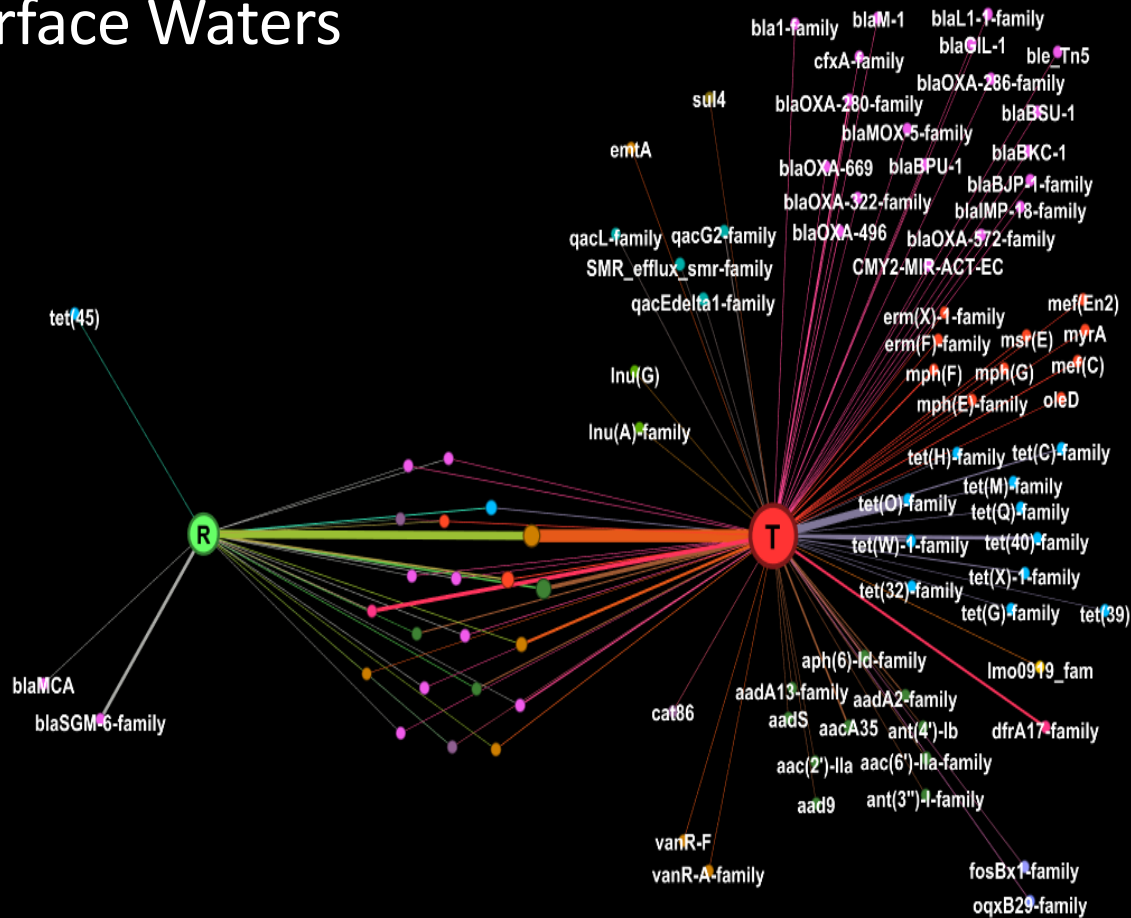
Taxonomic Differences between Less (R) and More (T) Impacted Surface Water



Taxonomic Features of the Water and Food Animal Microbiomes



The Water Resistome: Comparison of Less (R) and More Impacted (T) Surface Waters



Antimicrobial Resistance Surveillance

One Health - One Method

- Highest practical resolution of structural traits in microbial members of an ecosystem
- Accurate prediction of clinical resistance, and perhaps MIC, in NARMS bacteria
- Resistance to compounds not tested such as disinfectants and heavy metals, and other potential drivers of resistance
- Deep surveillance into previously hidden associations (*e.g.*, co-resistance with plasmid type, virulence)
- Source attribution for more precise (AMR) intervention
- Retrospective resistance surveillance
- Metagenomics to escape limitations of classical microbiology
- Look farther with few resources: domestic and wild animal populations, animal feed, environmental transmission, exposure pathways ...
- Global resistance emergence and spread
- Greater confidence in (global) public health decision making



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Non-federal partners

- Public health laboratories in all 50 states
- Universities
- Research collaborators