

# WGS data sharing in the NARMS experience

Heather Tate, PhD MS

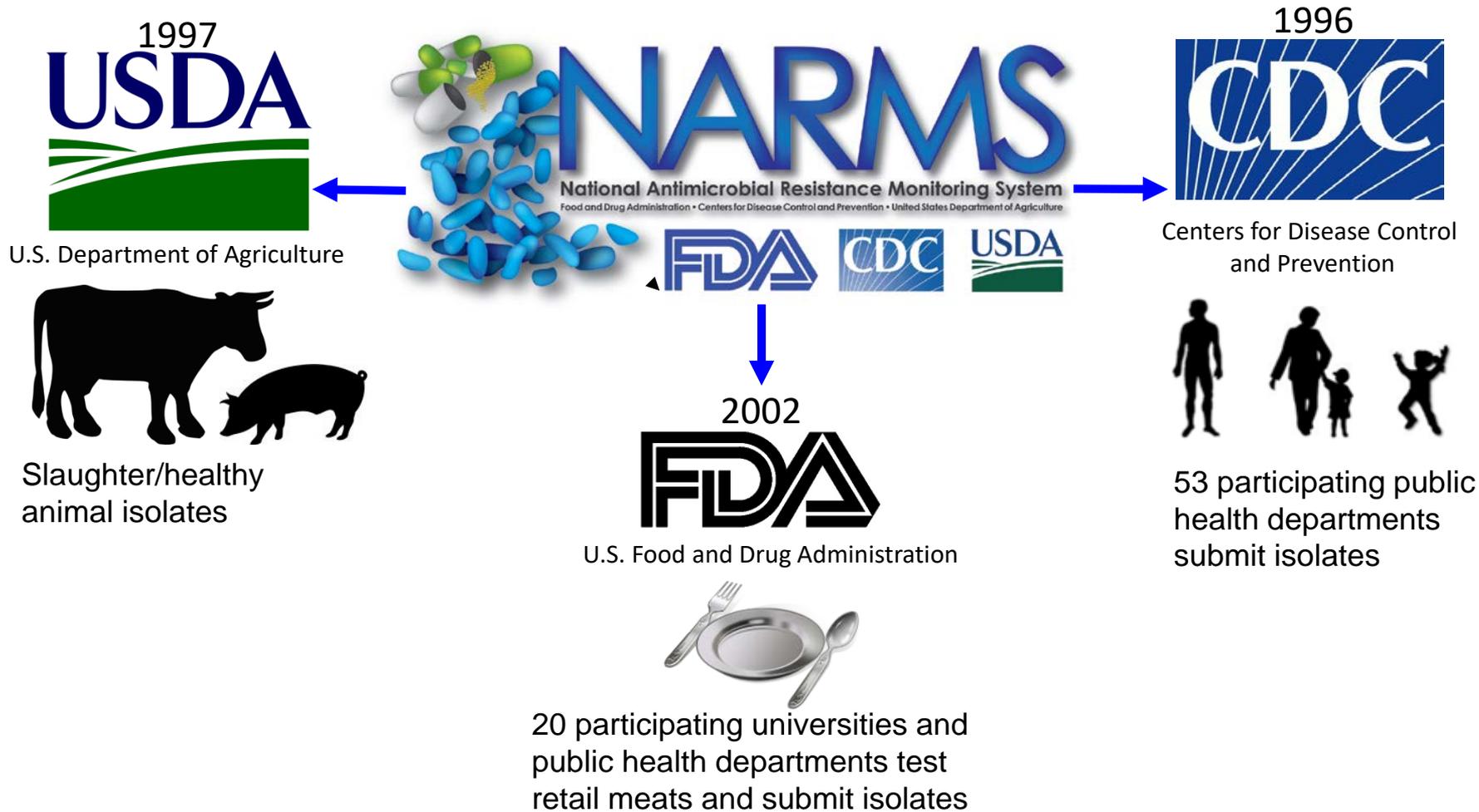
Epidemiologist

U.S. Food and Drug Administration

Center for Veterinary Medicine

EURL-AR Training Course

September 25, 2019

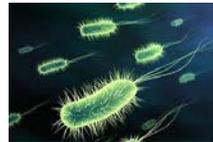


# Earlier Lab Methods Used at FDA

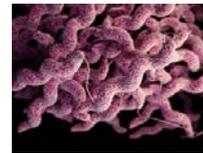
Salmonella



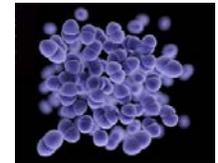
E. coli



Campylobacter



Enterococcus



## Sensitouch



### Antimicrobial Susceptibility Testing (AST)

- ID susceptibility phenotype
- “gold-standard”

## Vitek



### Biochemical Methods

- ID all organisms
- Speciate *Enterococcus*

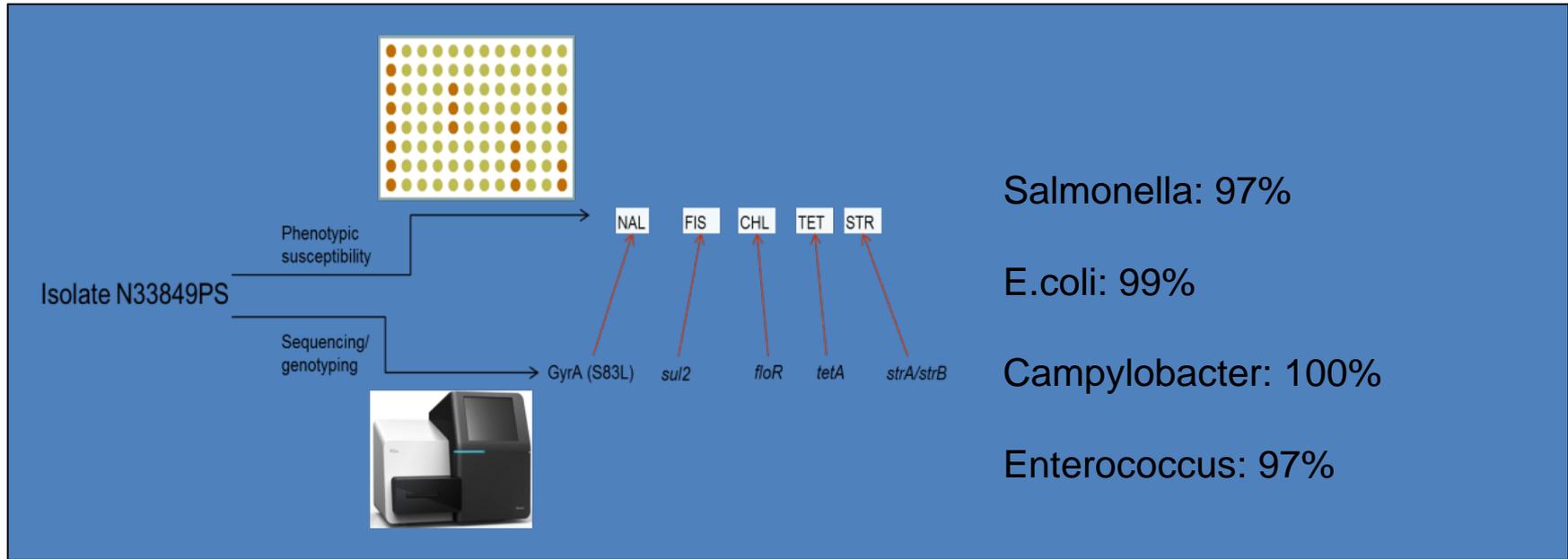
## Chef Mapper



### Pulsed Field Gel Electrophoresis

- *Salmonella* and *Campylobacter*
- Some *Salmonella* serotyping
- Mostly done by SPHD; performed as needed at FDA
- Assist with outbreak investigations (until WGS fully implemented by PulseNet- completed April 2019)

# Phenotype-Genotype Concordance



Whole-genome sequencing based characterization of antimicrobial resistance in *Enterococcus*

Pathogens and Diseases, 76, 2018, fy018

doi: 10.1093/pid/fgy018

Advance Access Publication Date: 12 March 2018

Research Article

Downloaded from <https://academic.oup.com/pid/article-abstract/18/3/181/2888888>

RESEARCH ARTICLE

**Whole-genome sequencing based characterization of antimicrobial resistance in *Enterococcus***

Gregory H. Tyson<sup>a</sup>, Jonathan L. Sabo, Crystal Rice-Trujillo, Jacqueline Hernandez and Patrick F. McDermott

U.S. Food and Drug Administration, Center for Veterinary Medicine, Office of Research, 8401 Muirkirk Rd, Laurel, MD 20708, USA

\*Corresponding author: U.S. Food and Drug Administration, Center for Veterinary Medicine, Office of Research, 8401 Muirkirk Rd, Laurel, MD 20708, USA. Tel: +1 (204) 402-5440; Fax: +1 (201) 210-6485; E-mail: [Gregory.Tyson@fda.hhs.gov](mailto:Gregory.Tyson@fda.hhs.gov)

One sentence summary: The authors used sequencing technologies to improve the understanding of antibiotic resistance in *Enterococcus*.

Using assembled WGS sequences through DIASX analysis, eighteen resistance genes, including *tet(O)*, *bla<sub>TEM</sub>*, *catA*, *lnu(C)*.

... Detecting Antimicrobial Resistance in ...

... ra,<sup>a</sup> Yuansha Chen,<sup>a</sup> Cong Li,<sup>a</sup> Jason P. Folster,<sup>b</sup> Sherry L. Ayers,<sup>a</sup>

<sup>a</sup> Veterinary Medicine, U.S. Food and Drug Administration, Laurel, Maryland, USA<sup>a</sup>; Division of ... Control and Prevention, Atlanta, Georgia, USA<sup>b</sup>

... testing is the foundation for guiding anti-infective therapy and monitor-  
ome sequencing (WGS) technology to identify known antimicrobial re-  
*Salmonella* and correlated these with susceptibility phenotypes to evaluate  
ance. Six hundred forty *Salmonella* of 43 different serotypes were selected  
at were tested for susceptibility to 14 antimicrobials using broth microdilution  
-nd resistance genotypes were identified

... Predicts Antimicrobial

... i. Whichard,<sup>b</sup> P. F. McDermott<sup>a</sup>

... ministration, Laurel, Maryland, USA<sup>a</sup>; Division of  
USA<sup>b</sup>

... ylobacter and to evaluate the correla-  
-ility testing and whole-genome se-  
-i) obtained from 2000 to 2013 from hu-  
-as part of the National Antimicrobial  
-ined using broth microdilution of  
-nd resistance genotypes were identified

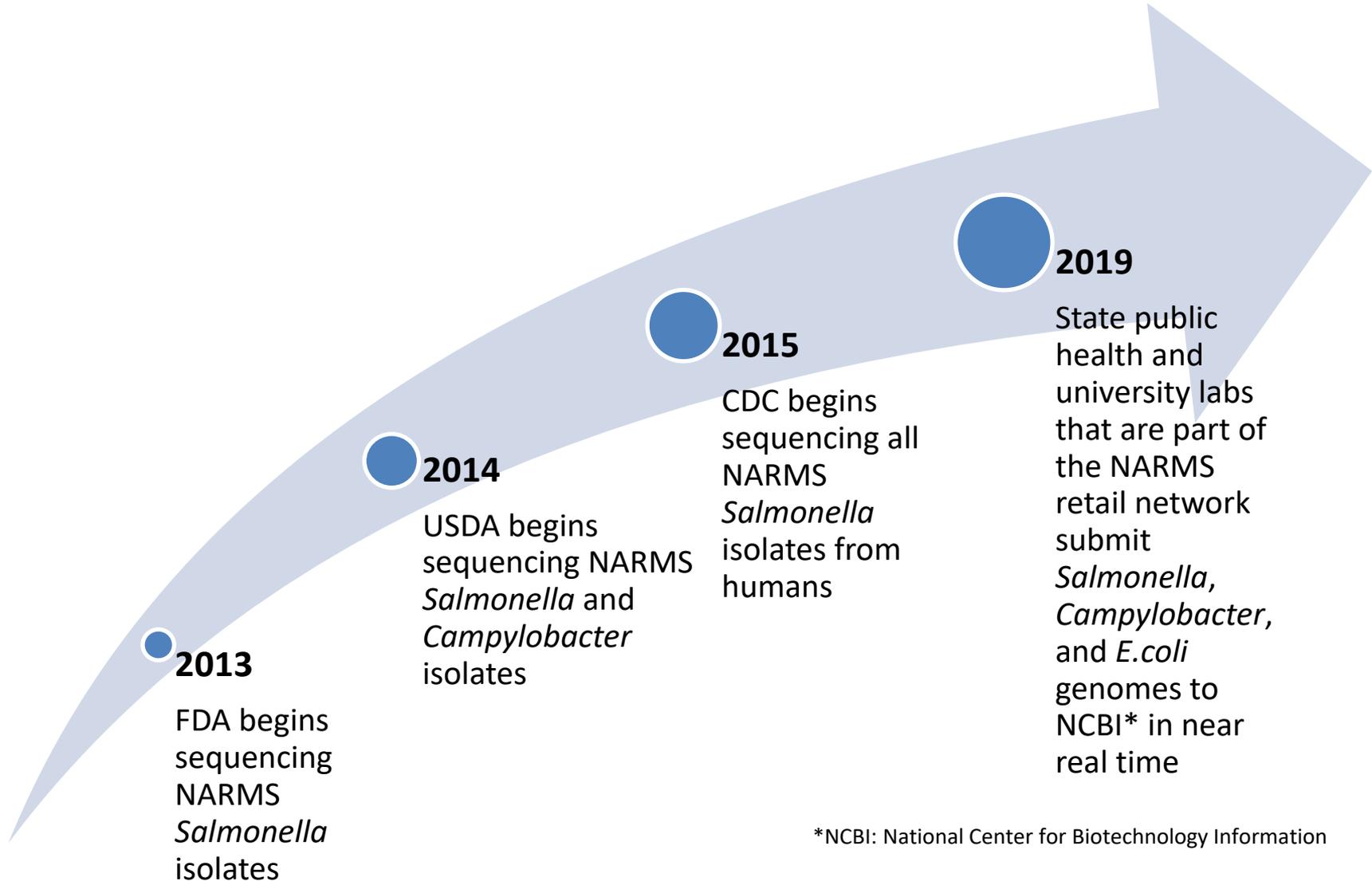
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... Mukherjee<sup>1</sup>,  
rington<sup>1</sup>,

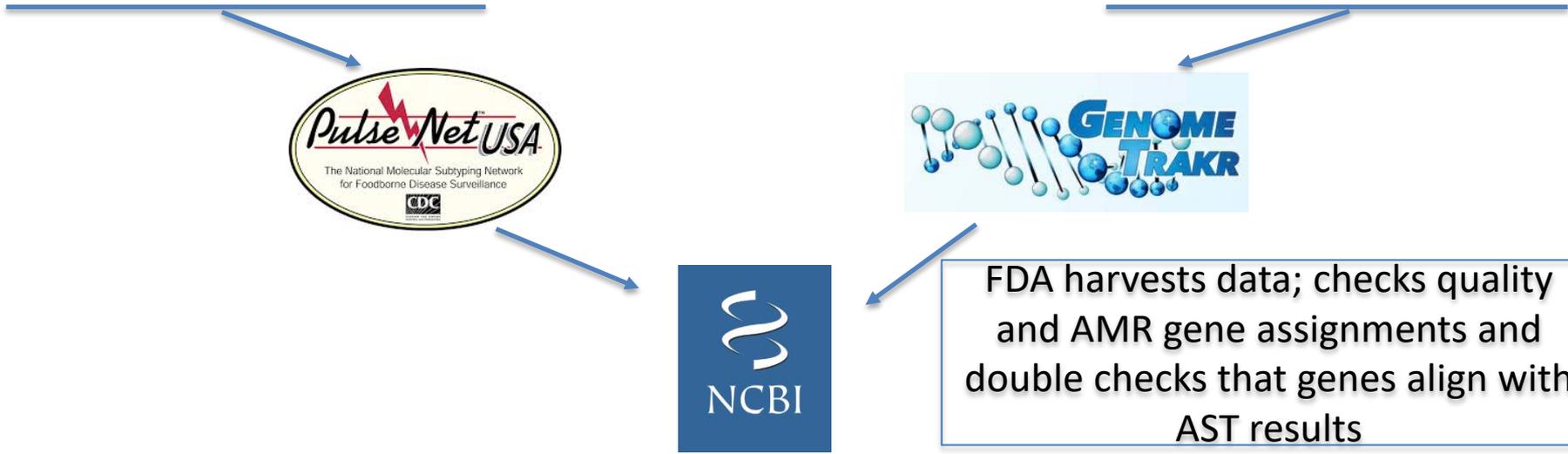
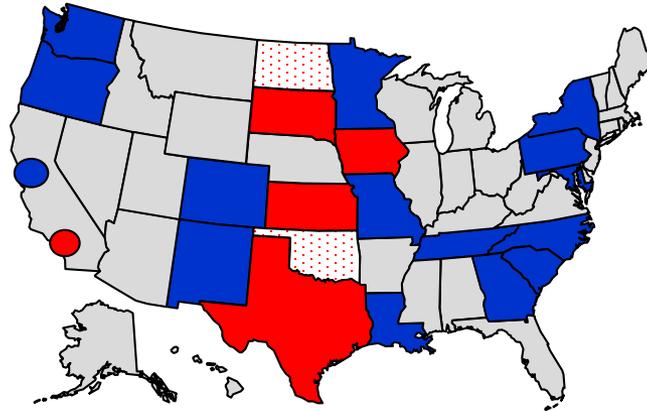
... nistration, Laurel, MD,  
ity, Lubbock, TX, USA;  
TX, USA<sup>2</sup>; <sup>3</sup>Center for  
h Center, Agricultural

# NARMS Transition to WGS

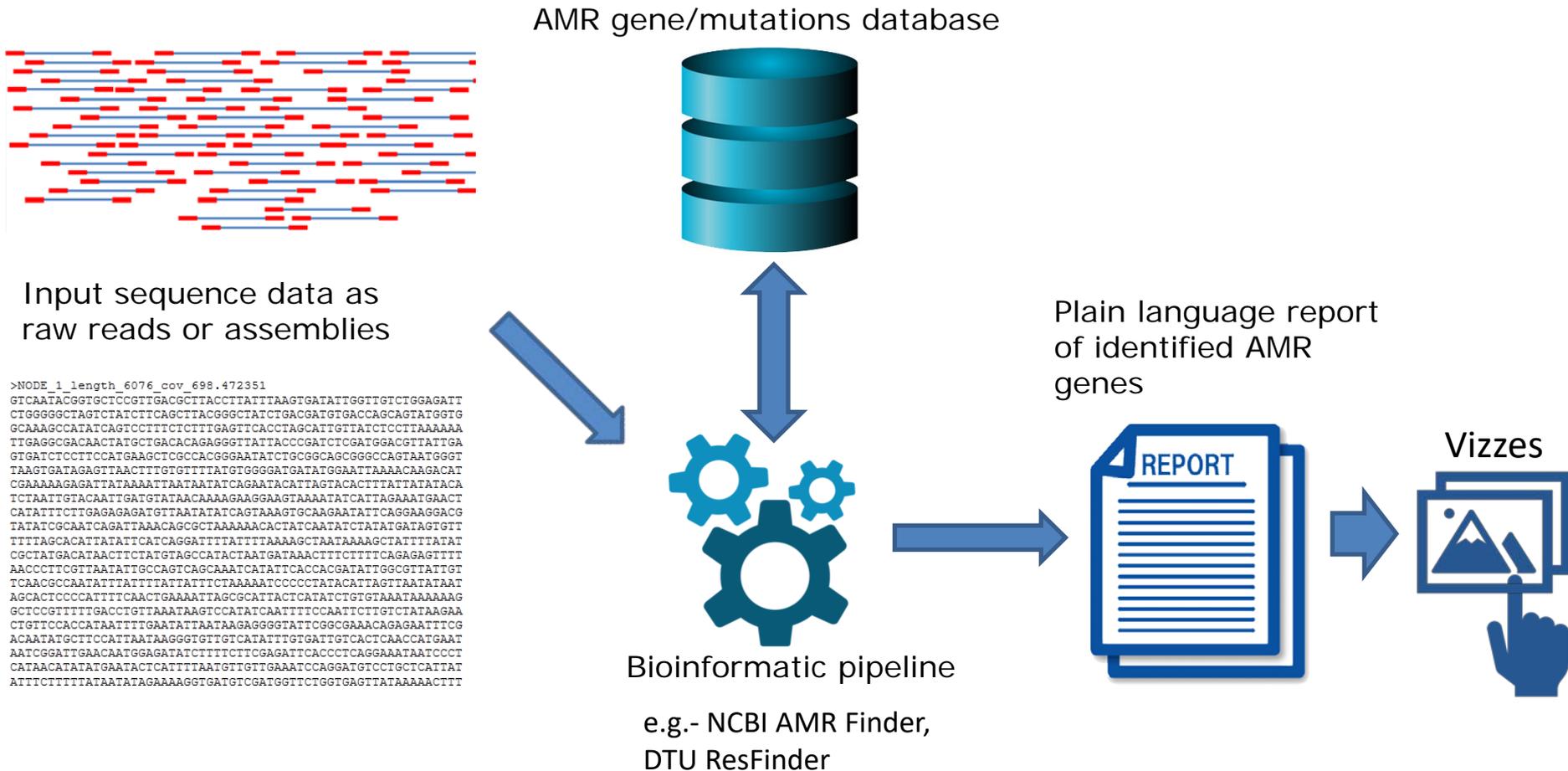


\*NCBI: National Center for Biotechnology Information

# NARMS Retail Meat Network



# Converting Genome Sequences to Useful Data





## RESISTOME TRACKER

### Salmonella

Select an icon or alert below to get started.

CUSTOMIZE

COMPARE

DISCOVER

EXPLORE

**ALERTS**

There are **138** records with **16** flagged genes uploaded in the last 60 days

Last update: 6/17/2019 5:20:49 PM

Resistome Tracker is a tool that can be used to explore antibiotic resistance alleles present in the genomes of Salmonella submitted to the NCBI. The isolates represented here are collected from around the world for various reasons. Because most are not from programs with an ongoing systematic collection of samples, please use caution when making inferences about associations between resistance determinants and sources or time-periods. You can refer to the NARMS website for access to antibiotic resistance surveillance data in the United States.

Data are pulled from the NCBI Pathogen Detection website, which uses AMR Finder to name resistance genes. Data are updated to the visualization tool on a regular basis. Typhoidal Salmonella isolates (if known) were removed from the analysis.

## NARMS Now: Integrated Data

Click on the icons below

**The Big Picture: Resistance by Species and Serotype**

**Resistance by Sample Source and Place**

**Resistance Genes in Salmonella**

**Compare multidrug resistance for any combination of antimicrobial agents**

**View multidrug resistance by the number of antimicrobial classes**

**References**

!!!INTERACTIVE!!!

## NARMS Salmonella Whole Genome Sequencing Data

Whole genome sequencing (WGS) has ushered in a new age in infectious disease science, with the power to greatly enhance diagnostic surveillance and treatment. WGS can be used to predict antimicrobial resistance for a number of bacteria, including the Foodborne pathogen, Salmonella.

Since its inception, NARMS has strived to understand how resistant enteric bacteria isolated from retail meat and food animals compare to resistant infections identified in humans. WGS has made it possible for such comparisons to be conducted at the genetic level.

A variety of interactive displays were designed to help understand this relationship between retail meat, food animals, and humans. Below is a list of the interactive displays listed in the images for a brief description. [To go from display, click on the link #125385.](#)

**Changes in resistance genes by year**  
Explore the changes in the resistance genes over time among isolates from retail meat.

**Changes in resistance genes over time**  
Explore distribution of salmonella serotype for a given gene

**Resistance genes by serotype**  
Compare serotype distribution by a given antimicrobial and gene between two sources over time.

**Comparison of resistance genes by source**  
Explore the distribution of genes associated with a particular resistance phenotype for a single source over time.

**References**  
For those interested in other NARMS resources, including the isolate level data, go to the reference page.

# NARMS Visualization Tools for AMR Genes

Click on the icons below

The Big Picture: Resistance by Species and Serotype



Resistance by Sample Source and Place



Resistance Genes in Salmonella



Compare multidrug resistance for any combination of antimicrobial agents



View multidrug resistance by the number of antimicrobial classes



References



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Changes in resistance genes over time

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Comparison of resistance genes by source

Explore the distribution of genes associated with a particular resistance phenotype for a single source over time.



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Pull from a highly curated in-house database of NARMS data

Combine genomic and phenotypic data

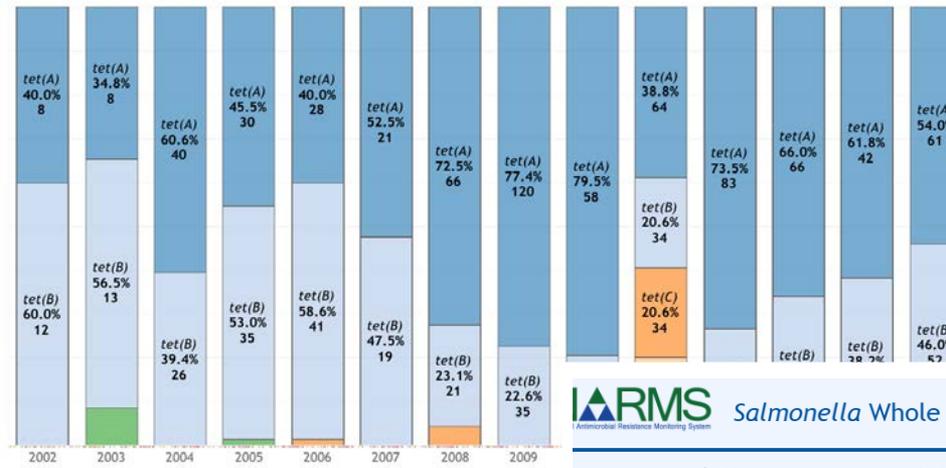
Currently updated on an annual basis

To get started select a **source**, then an **antimicrobial agent**

Source: Retail Chickens  
Antimicrobial Agent: Tetracycline

## Tetracycline resistance genes in *Salmonella* from Retail Chickens

(Click on a gene for more information)



Note: The years shown vary by the source selected because whole genome sequencing was

## Antimicrobial resistance genes in NARMS Isolates

[Back to Table of Contents](#)

Whole genome sequencing (WGS) has ushered in a new age in infectious disease science, with the power to greatly enhance diagnosis, surveillance and treatment. WGS can be used to predict antimicrobial resistance for a number of bacteria, including the foodborne pathogen, *Salmonella*. In addition, WGS data reveal the range of genes causing resistance to a particular antimicrobial.

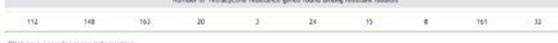
Please note: Not all resistant isolates were sequenced and of those sequenced, some did not carry genes known to confer resistance to a certain antimicrobial or classes of antimicrobials. As a result, the resistance information does not always align with the genetic information.

This dashboard allows users to explore how resistance varies in the most common serotypes of *Salmonella*. To get started, select an **antimicrobial**.

Select Genus: *Salmonella*  
Select an Antimicrobial agent: Tetracycline  
Select Year: 2017

Select from the most common serotypes found in human and animal *Salmonella* infections:

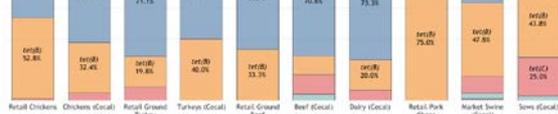
Serotype: All



Number of Tetracycline resistance genes found among resistant isolates



Click on a gene for more information



All isolates with tetA variant also have a sul gene to account for resistance to both Trimethoprim and Sulfamethoxazole

This display only features isolates that are resistant and had at least one corresponding resistance gene. Genes were identified using ResFinder

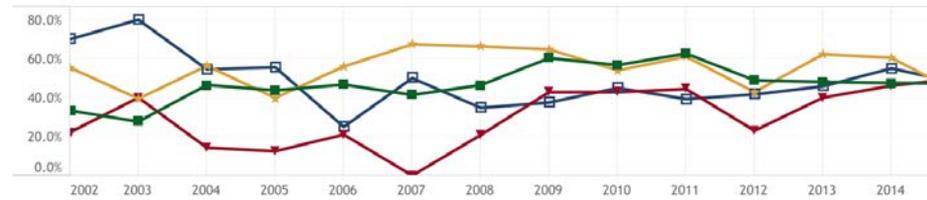
[https://github.com/jdmccomb/resfinder](#)

begin, select an **antimicrobial**. To view a specific retail meat source, use the **source** filter. Move the cursor from left to right to view the changes in distribution of the resistance genes.

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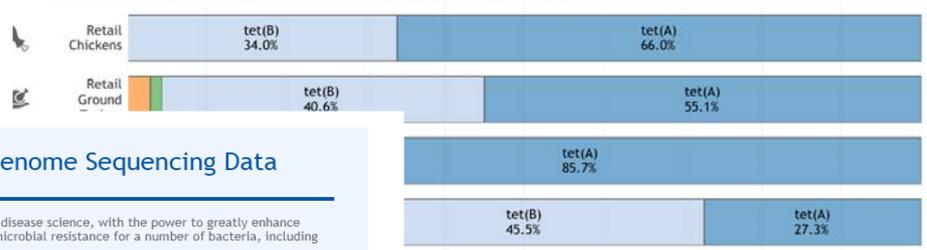
Select an Antimicrobial: Tetracycline  
Source: All  
Retail Chickens: [Green Square]  
Retail Ground Turkey: [Yellow Star]  
Retail Ground Beef: [Red Triangle]  
Retail Pork Chops: [White Square]

## Tetracycline resistance in *Salmonella* from retail meat



## Distribution of resistance genes in 2013

(click on a gene for more information)



## NARMS Salmonella Whole Genome Sequencing Data

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Interactive displays were designed to help understand this relationship between retail meat, food animals, and humans. Below is a list of the interactive displays; hover in the images for a brief description. [To go to the displays, click on the link below.](#)

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## NARMS Now: Integrated Data

National Antimicrobial Resistance Monitoring System

- [The Big Picture: Resistance by Species and Serotype](#)
- [Resistance by Sample Source and Place](#)
- [Resistance Genes in \*Salmonella\*](#)
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- [View multidrug resistance by the number of antimicrobial classes](#)

# Resistome Tracker



**RESISTOME TRACKER**  
*Salmonella*

Select an icon or alert below to get started.

			
CUSTOMIZE	COMPARE	DISCOVER	EXPLORE

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## Pathogen Detection BETA



View the recent webinar: '[Introducing the Pathogen Detection Isolates Browser](#)'.

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
<a href="#">Salmonella enterica</a>	<a href="#">93</a>	<a href="#">204,595</a>

### Learn More

[About](#)

[FAQ](#)

[Browser Factsheet](#)

[Antimicrobial Resistance](#)

[Antimicrobial Resistance](#)

[Contributors](#)

[Help](#)

### Data Resources

[Isolates Browser](#)

[Pathogen Detection Refe](#)

[Isolates with antibiotic re  
phenotypes](#)

[Download analysis result](#)

[Submit](#)

Data come from the curated NCBI Pathogen Detection database. Because this database includes global genomic sequences originating in food, animal, human, and environmental sources it is inherently One Health. A portion of these sequences are from GenomeTrakr sites.

Several US public health agencies contribute- 65% of sequences come from the US; 22% from Public Health England.

# Resistome Tracker- data source

# Fields pulled into Resistome Tracker



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

drhgreen

Health > Pathogen Detection > Isolates Browser

Find one or more isolates ...   [Saved searches](#)

Select an organism group

#	Organism Group	Serovar	Create Date	Location	Isolation Source	Isolation type	BioSample	AMR genotypes	BioProject	Collection Date
1	Salmonella enterica	enterica / Newport	2013-10-18		with plasmid tomato isolate	environmental/other	<a href="#">SAMN01816172</a>		<a href="#">PRJNA78363</a>	
2	Salmonella enterica	enterica / Newport	2013-10-18	USA:VA	Pond	environmental/other	<a href="#">SAMN01816171</a>		<a href="#">PRJNA78361</a>	
3	Salmonella enterica	enterica / Newport	2013-10-18	USA:VA	Pond	environmental/other	<a href="#">SAMN01816170</a>		<a href="#">PRJNA78359</a>	
4	Serratia marcescens		2011-12-20			environmental/other	<a href="#">SAMN02604291</a>		<a href="#">PRJNA32211</a>	
5	Enterobacter		2019-07-03	France	feces	clinical	<a href="#">SAMN11638198</a>	aac(6')-Ib' aadA1 aph(3'')-Ib <a href="#">Show all 15 genes</a>	<a href="#">PRJNA542787</a>	2017
6	E.coli and Shigella		2019-08-06	USA: New York	water	environmental/other	<a href="#">SAMN12438500</a>	blaEC	<a href="#">PRJNA357722</a>	2000
7	E.coli and Shigella		2019-08-06	USA: Texas		environmental/other	<a href="#">SAMN12438501</a>	blaEC blaTEM-1 sul2 <a href="#">Show all 4 genes</a>	<a href="#">PRJNA357722</a>	2000
8	E.coli and Shigella		2019-08-06	USA: New York		environmental/other	<a href="#">SAMN12438502</a>	blaEC	<a href="#">PRJNA357722</a>	2000
9	E.coli and Shigella		2015-10-19			environmental/other	<a href="#">SAMN00808719</a>	blaEC	<a href="#">PRJNA65697</a>	

**RESISTOME TRACKER**  
*Salmonella*

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Data are pulled from the NCBI Pathogen Detection website, which uses AMR Finder to name resistance genes. Data are uploaded to the visualization tool on a regular basis. Typhoidal *Salmonella* isolates (if known) were removed from the analysis.

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Pulls from an external dataset containing sequences from NARMS and non-NARMS isolates. Data are downloaded from NCBI, restructured, and manually linked to the tool.

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Does not pair with phenotypic data...yet

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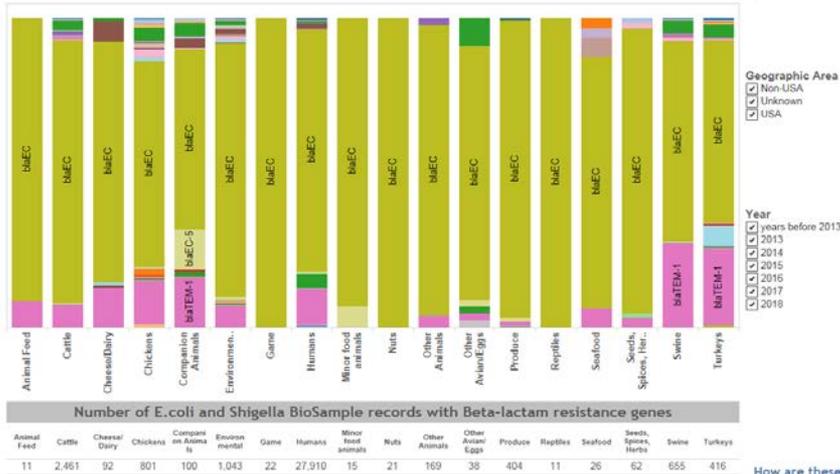
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Currently updated at least once per quarter

Note: This display does not include 'Unknown' or 'Other' sources. If data do not appear it means no data were reported for the selected Class, Year, Geographic Area combination or isolate sources are categorized as 'Unknown' or 'Other'. Please use caution when making inferences about associations between resistance genes and sources. Most data are not from a systematic collection of samples.

- Folate synthesis inhibitor
- Fosfomycin
- MLS (Macrolides-Lincosamide)
- Phenicol
- Polymyxin
- QAC (Quaternary Ammonium)
- Quinolone
- Rifampicin
- Streptoficin
- Sulfonamide
- Tetracycline

Isolate Source  
All

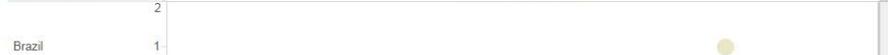


How are these sources grouped?

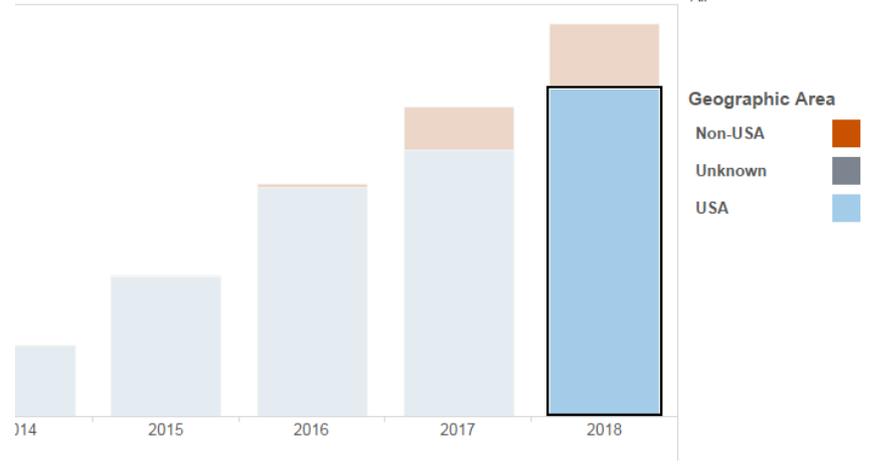
### Global Distribution of E.coli and Shigella Isolates With mcr-1 Genes by Collection Year-2017



### Running Sum of Number of Isolates by Source, Year, and Country



### Beta-lactam Resistance Genes in E.coli and Shigella



### NCBI Publication Date

Class	Gene	Geographic Location	Sources	Species/Serotype	Year of NCBI Release Date	Click Buttons for Links to NCBI
Beta-lactam	blaEC	USA:IA	animal-cattle-heifer	Null	2018	<a href="#">Click Here</a> <span style="color: green;">■</span>
Beta-lactam	blaEC	USA:TX	animal-cattle-heifer	Null	2018	<a href="#">Click Here</a> <span style="color: green;">■</span>
Beta-lactam	blaEC	USA:AR	animal-chicken-young chicken	Null	2018	<a href="#">Click Here</a> <span style="color: green;">■</span>
Beta-lactam	blaEC	USA:DE	animal-chicken-young chicken	Null	2018	<a href="#">Click Here</a> <span style="color: green;">■</span>
Beta-lactam	blaEC	USA:TX	canine bite wound (canis lupus)	Null	2018	<a href="#">Click Here</a> <span style="color: red;">◆</span>
Beta-lactam	blaEC	USA:PA	feces-bovine (bos taurus)	O36	2018	<a href="#">Click Here</a> <span style="color: grey;">●</span>
Beta-lactam	blaEC	USA:PA	bovine, cow-udder	O53:H10	2018	<a href="#">Click Here</a> <span style="color: grey;">●</span>
Beta-lactam	blaEC	USA:PA	intestine-bovine (bos taurus)	O171	2018	<a href="#">Click Here</a> <span style="color: grey;">●</span>
Beta-lactam	blaEC	USA:CO	feces-chicken (gallus gallus)	O49:H9	2018	<a href="#">Click Here</a> <span style="color: grey;">●</span>
Beta-lactam	blaEC	USA:CO	feces-chicken (gallus gallus)	O128:H42	2018	<a href="#">Click Here</a> <span style="color: grey;">●</span>

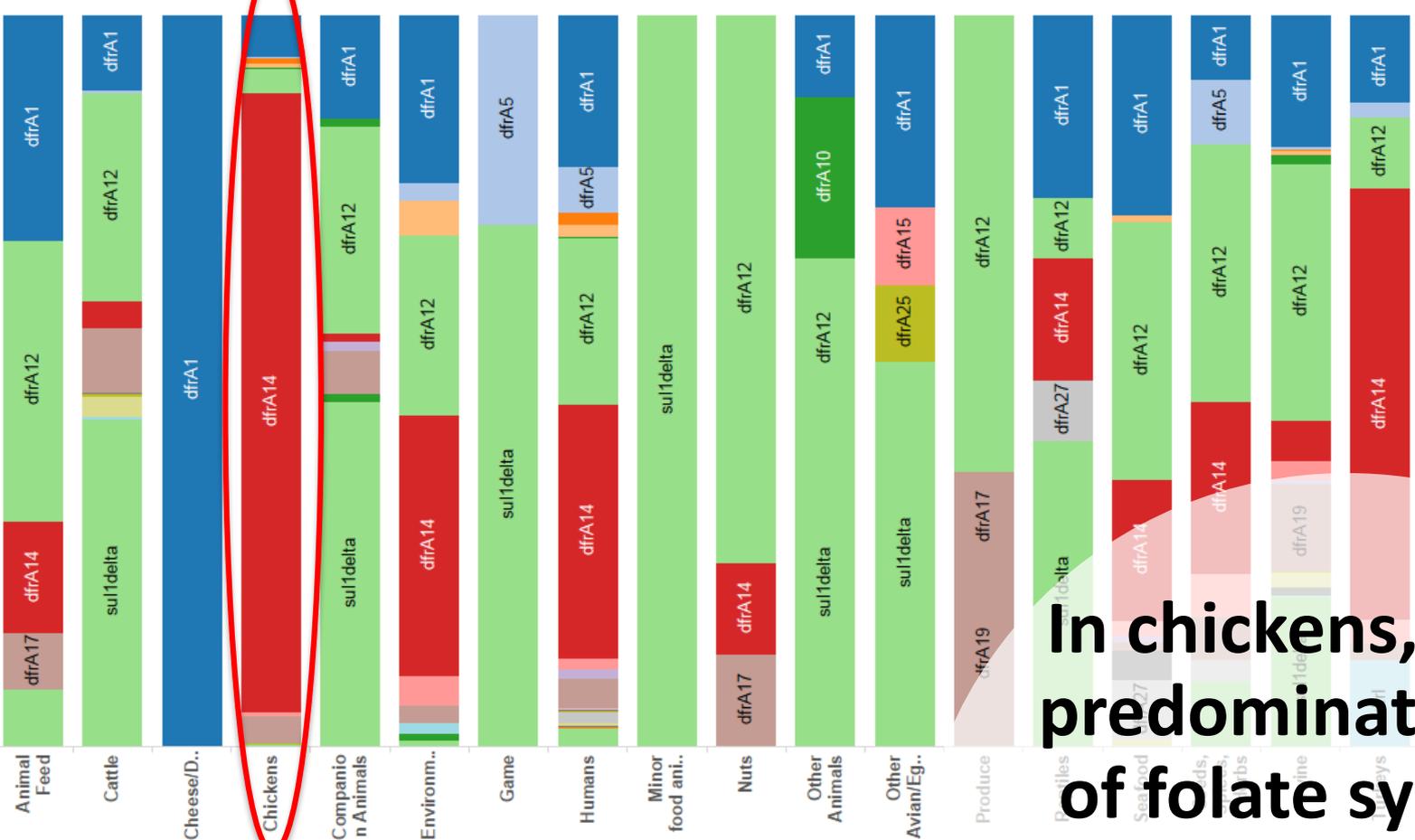
entry if there is more than one SRA number per Biosample. Green squares indicate NARMS isolates. Red diamonds indicate Vet-LIRN isolates.

Back



- Class**
- Aminoglycoside
  - Bacitracin
  - Beta-lactam
  - Bleomycin
  - Folate synthesis inhibitor
  - Fosfomicin
  - MLS (Macrolides-Lincosamides..
  - Phenicol
  - Polymyxin
  - QAC (Quaternary Ammonium C..
  - Quinolone
  - Rifamycin
  - Streptothricin
  - Sulfonamide
  - Tetracycline

- Year**
- 2013
  - 2014
  - 2015
  - 2016
  - 2017
  - 2018
  - 2019
  - 2020
  - 2021
  - 2022
  - years before 2013/ no year reco..



**In chickens, dfrA14 predominates (85% of folate synthesis inhibitor genes)**

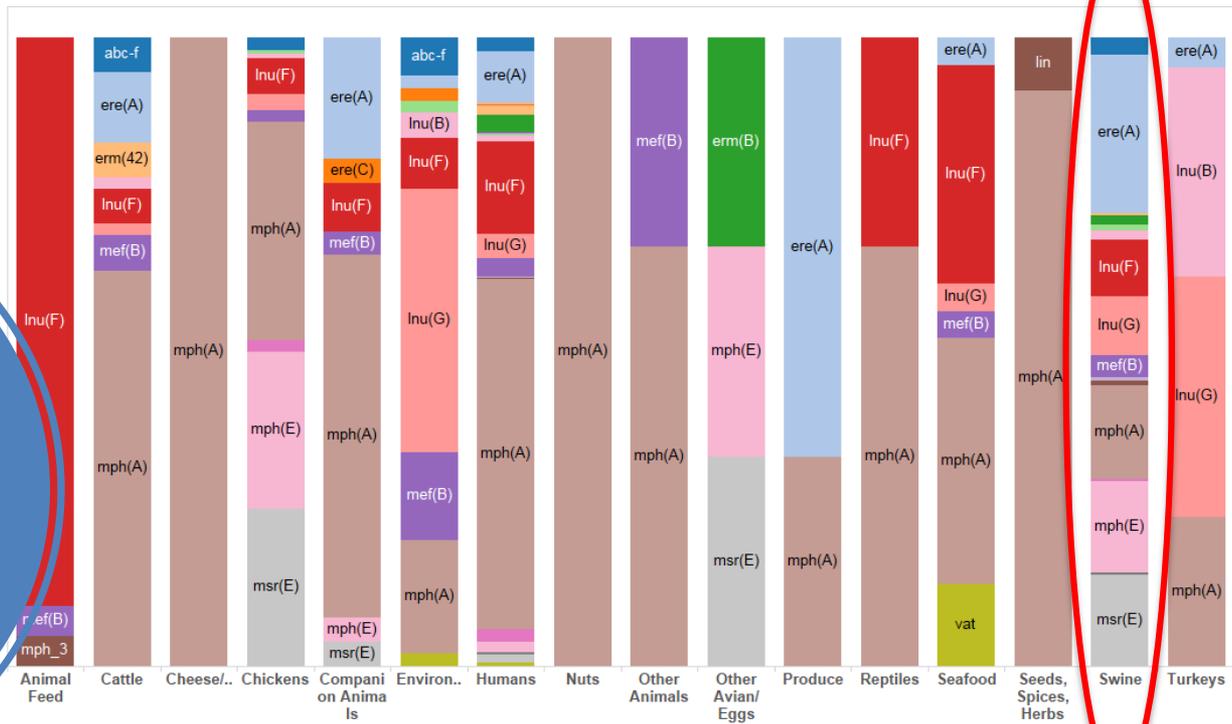
Number of BioSample records with Folate synthesis inhibitor resistance genes published in 2013-2022

Animal Feed	Cattle	Cheese/Dairy	Chickens	Companion Animals	Environmental	Game	Humans	Minor food animals	Nuts	Other Animals	Other Avian/Eggs	Produce	Reptiles	Seafood	Seeds, Spices, Herbs	Swine	Turkeys
12	317	1	1,200	84	126	7	4,858	4	8	9	19	8	11	99	34	404	92

Total number of distinct Biosample records published in All from All regions

Animal Feed	Cattle	Cheese/Dairy	Chickens	Companion Animals	Environmental	Game	Humans	Minor food animals	Nuts	Other Animals	Other Avian/Eggs	Produce	Reptiles	Seafood	Seeds, Spices, Herbs	Swine	Turkeys
893	7,192	182	16,844	571	9,861	61	113,556	182	950	154	848	2,036	315	2,026	2,412	6,668	4,838

MLS genes are highly varied among isolates from swine



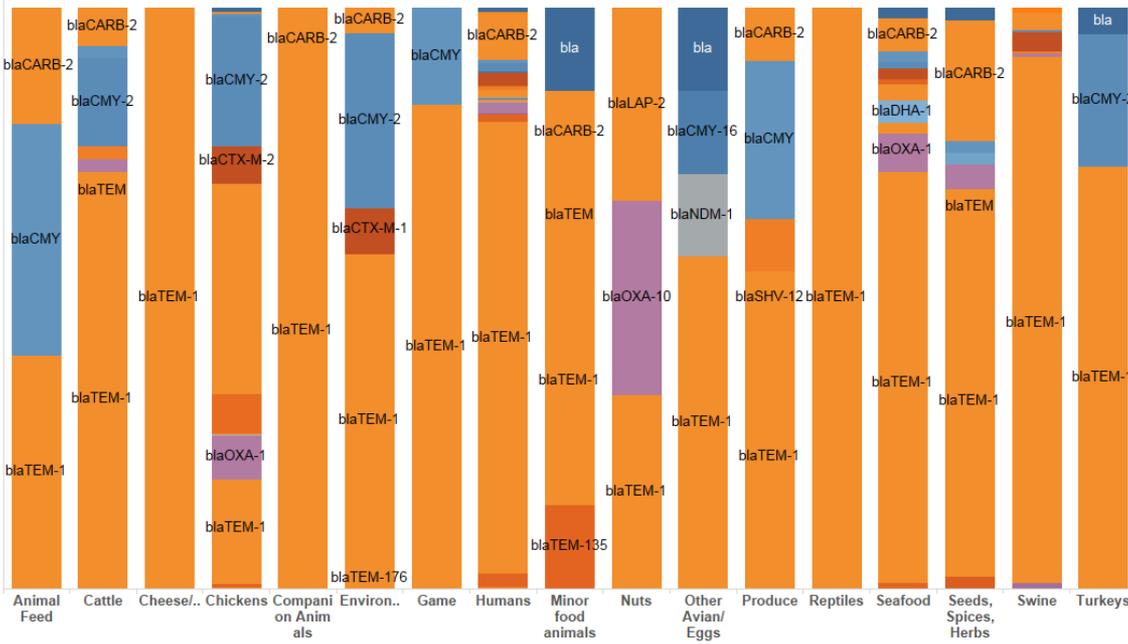
Number of BioSample records with MLS (Macrolides-Lincosamides-StreptograminB) resistance genes published in All from All regions

Animal Feed	Cattle	Cheese/Dairy	Chickens	Companion Animals	Environmental	Humans	Nuts	Other Animals	Other Avian/Eggs	Produce	Reptiles	Seafood	Seeds, Spices, Herbs	Swine	Turkeys
21	53	1	77	24	42	1,180	1	3	1	3	3	22	12	194	21

Total number of distinct Biosample records published in All from All regions

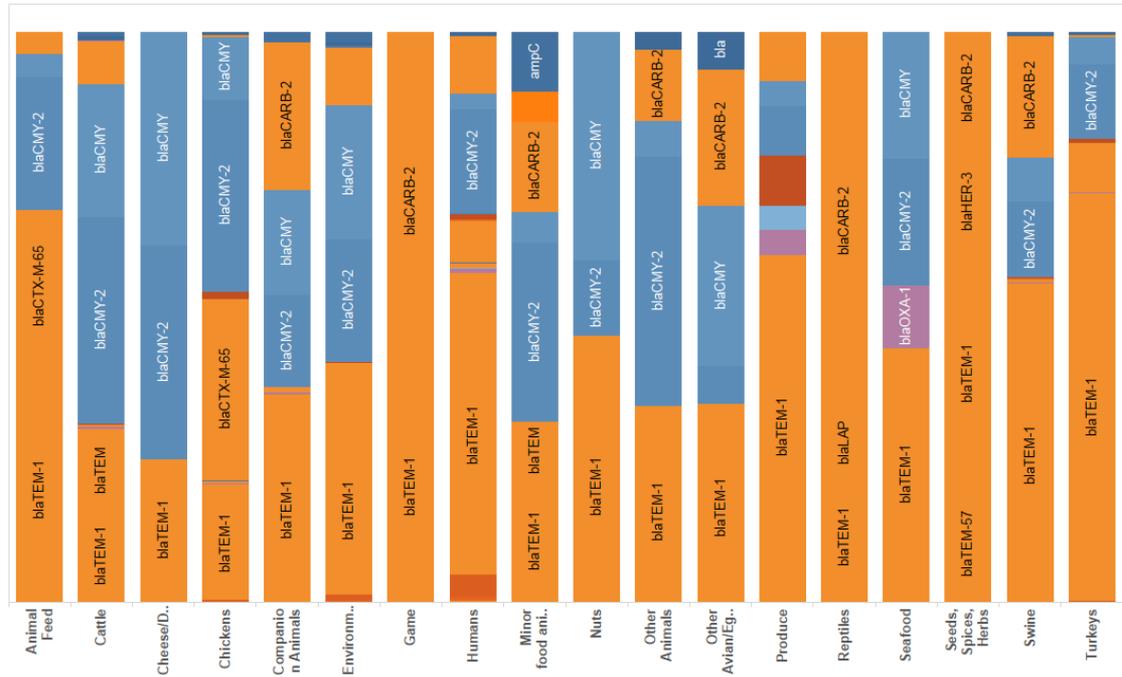
Animal Feed	Cattle	Cheese/Dairy	Chickens	Companion Animals	Environmental	Game	Humans	Minor food animals	Nuts	Other Animals	Other Avian/Eggs	Produce	Reptiles	Seafood	Seeds, Spices, Herbs	Swine	Turkeys
893	7,192	182	16,844	571	9,861	61	113,556	182	950	154	848	2,036	315	2,026	2,412	6,868	4,838





More Class A beta-lactamases in non-USA regions

More Class B beta-lactamases in USA



# Benefits of WGS data sharing

- Global access is important as food trade and travel increases
- Can look for specific genes in other sources not collected for your surveillance program
- Better understanding of where resistance genes originate and how they spread
- Data can be used to construct QMRA and attribution models

# Limitations of WGS data sharing

- Analysis is only as good as the data
  - Much of the data represent isolates from various research, clinical, and other studies and therefore cannot be used to determine true resistance gene prevalence for certain sources.
  - For some sources (dairy, game, reptiles) very few isolates make it difficult to assess the population of resistance genes in that source
  - Most genomes are from North America and Europe, so regional comparisons cannot be made
  - Missing metadata make the tool less useful
- Others can misinterpret the data/or publish your studies

## Future Enhancements to NARMS Visualization Tools

Predicted resistance

Use ontological tools (LexMapr) to standardize and categorize source fields

Add new organisms (*E. coli*, *Campylobacter*, etc)

Add virulence and other biocide resistance genes

Improve timeliness

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