AMR surveillance in the US

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Director, NARMS

US FDA

Today's Approach

We asked a subcommittee of the FDA Science Board to review NARMS and make recommend-dations on future directions.

Here are the most important answers they gave.

Name	Institution	SGE Role
Lisa Nolan - Chair	Iowa State University	FDA Science Board member
Barbara Kowalcyk	Research Triangle Institute	FDA Science Board member
Lonnie King	Ohio State University	PAC CARB- vice chair
Lee Riley	UC Berkeley	CDC Board of Scientific Counselors
Tom Shryock	Consultant	PAC CARB member
Michael Apley	Kansas State University	PAC CARB member

General Comments

- Because of the past successes of NARMS and the positive working relationship it has built across the [three] federal agencies the NRC believes that NARMS has a unique opportunity to offer even more at a critical time in the long-standing challenge of AMR.
- A new commitment and momentum have recently emerged to address the … challenge of AMR. We now have new technological advances in genomics, data analytics and bioinformatics and new data sources that have laid the groundwork to add new partnerships and collaboration.
- NARMS may be reaching a point where it can improve both incrementally and transformatively.

Could changes to sampling strategies improve our understanding of resistance dynamics within a One Health paradigm?

Add other commodities: Expand monitoring to seafood and additional products such as lamb or veal.

- Expanded plant testing at slaughter up to 1,680 samples of veal (up to 480), siluriformes fish (up to 300), and cattle lymph nodes (up to 600).
- Include a Carbapenemase screen
- Pick multiple colony types off EMB agar plates to more broadly assess AMR diversity in Gram negative bacterial populations.
- Pilot seafood monitoring

What is the best way to report relationships between antimicrobial sales data and antimicrobial resistance in our national surveillance

Additional resources should be invested in investigating potential associations in actual use and resistance at the user level rather than to modify the extent or methods of evaluation for the existing [annual sales by class] systems.

- There are many challenges to establishing on-farm longitudinal studies examining use and resistance in production environments.
- FDA-CVM has funded two institutions to assess antimicrobial use by animal type before and after implementation of GFI #209/#213.
- FDA-CVM has enhanced sales and distribution data reporting online

What is the best way to report WGS data and trends in the resistome?

Report AMR trends by specific lineages (e.g., wgMLST type) that incorporates genotype and geographic data. Develop visualization tools to display the information.

CDC and NIH are working to establish wgMLST typing tools for foodborne pathogens. SNP pipelines are in place and have defined parameters for regulatory use. Other genetic characteristics will also be used for reporting AMR trends in strain subtypes.

Large WGS data must be converted into simple formats that are easily interpretable, exportable, and exchangeable within and across laboratories.

NARMS has made progress in this area through our NARMS reports and Resistome Tracker, and will continue efforts to simplify the genetic findings further.

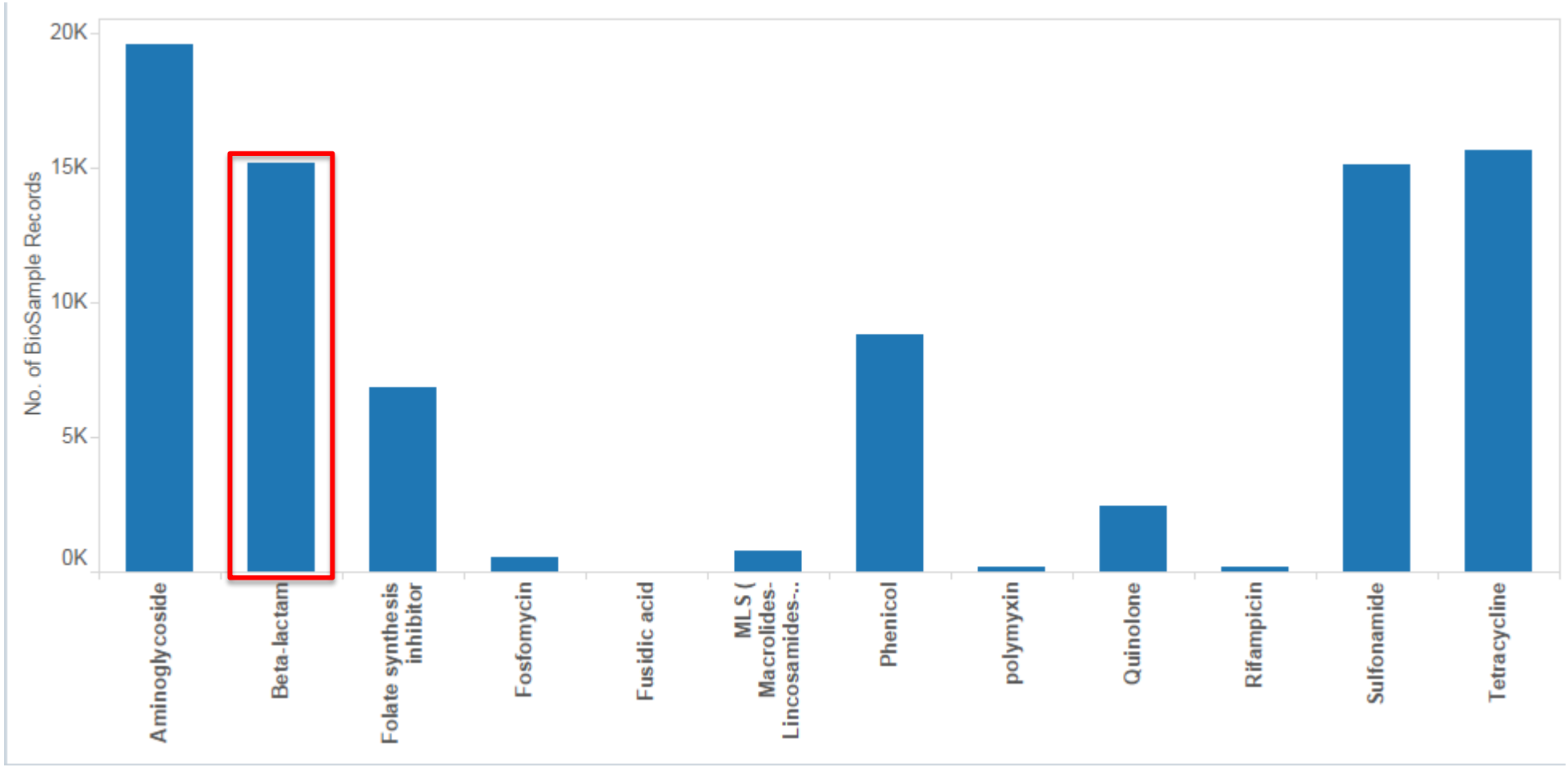
NARMS Sequencing Strategy

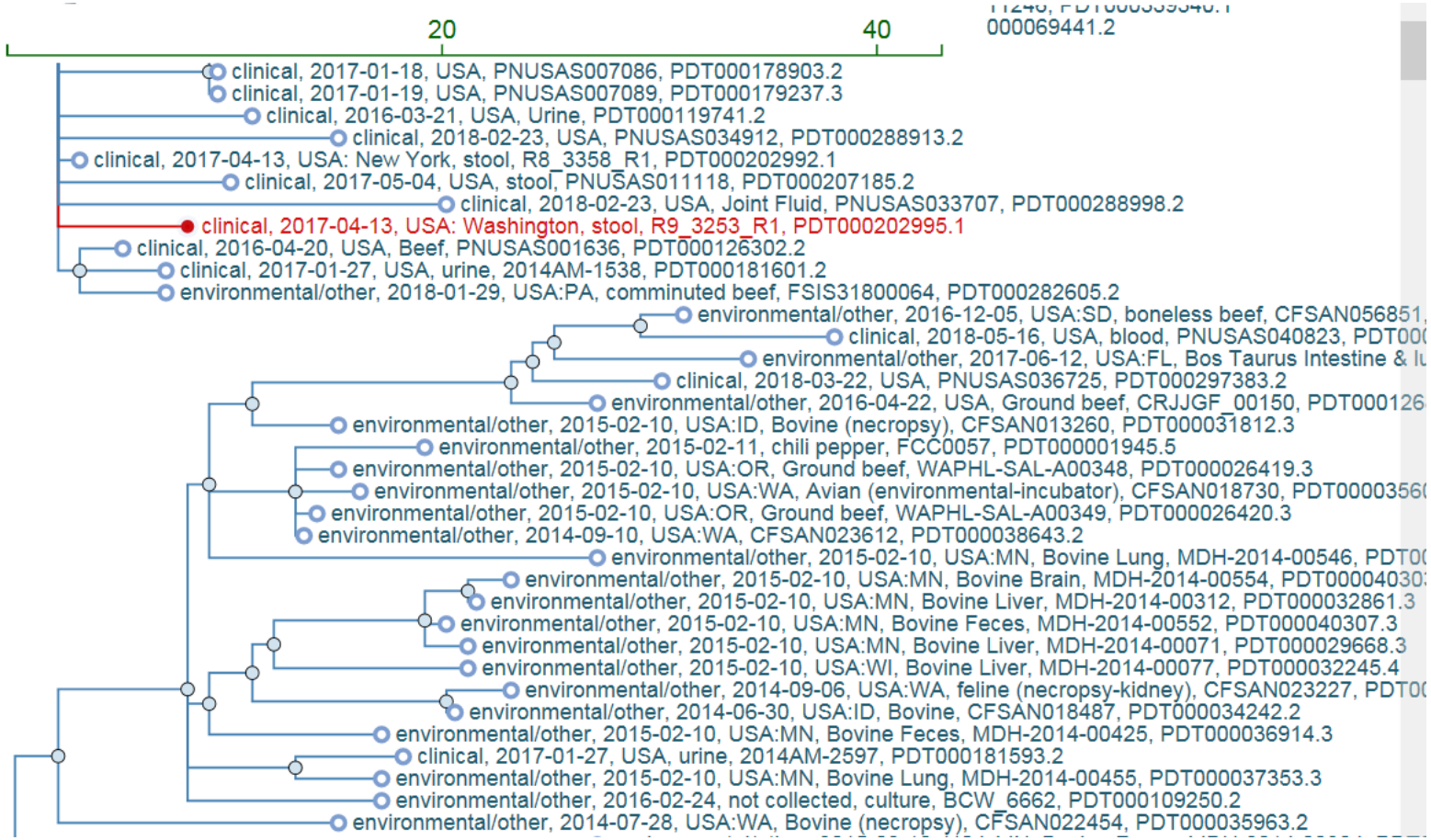
- All *Salmonella*
- All *Campylobacter*
- All *E. coli*
- Select *Enterococcus*
- Do repeat AST/sequencing when mismatches occur

	FDA-CVM	USDA-FSIS	CDC*
Salmonella	5633	5351	70444
Campylobacter	2927	6555	9666
E. coli	713	1957	24324

*not all these genomes are from NARMS sampling

RESISTOME TRACKER
Salmonella

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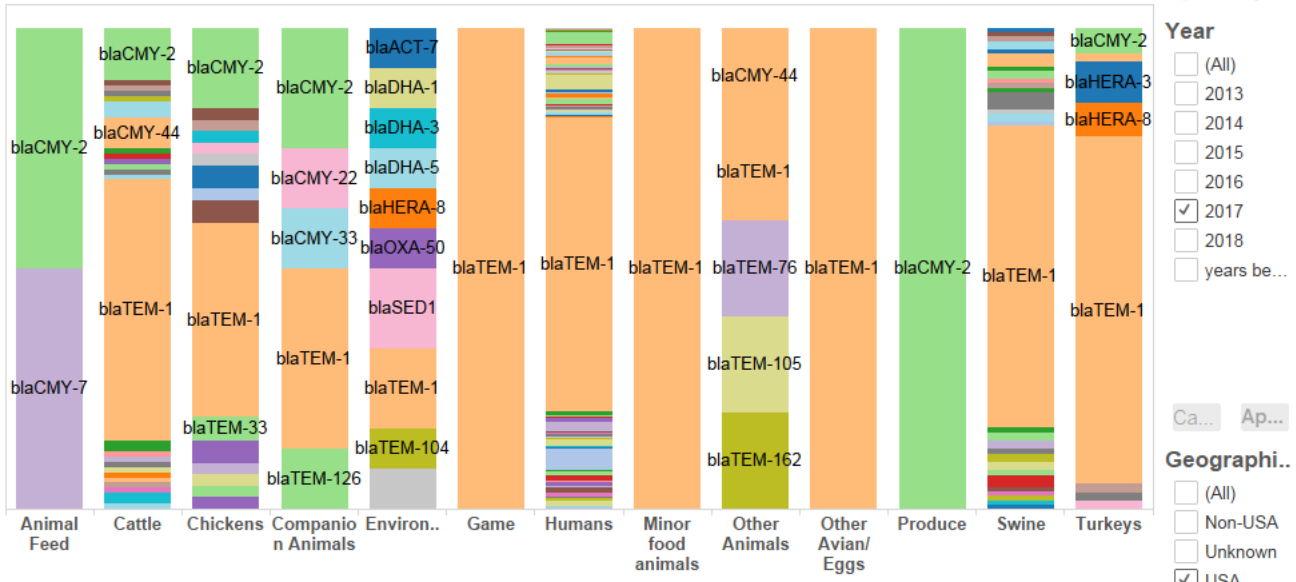
RESISTOME TRACKER

Salmonella



Year
(All)
2013
2014
2015
2016
2017
2018
years be...

Ca... Ap...

Geographi..
(All)
Non-USA
Unknown
USA

Ca... Ap...

Number of BioSample records with Beta-lactam resistance genes published in 2017 from USA regions

Animal Feed	Cattle	Chickens	Companion Animals	Environmental	Game	Humans	Minor food animals	Other Animals	Other Avian/Eggs	Produce	Swine	Turkeys
2	83	42	7	12	1	591	1	5	4	1	103	57

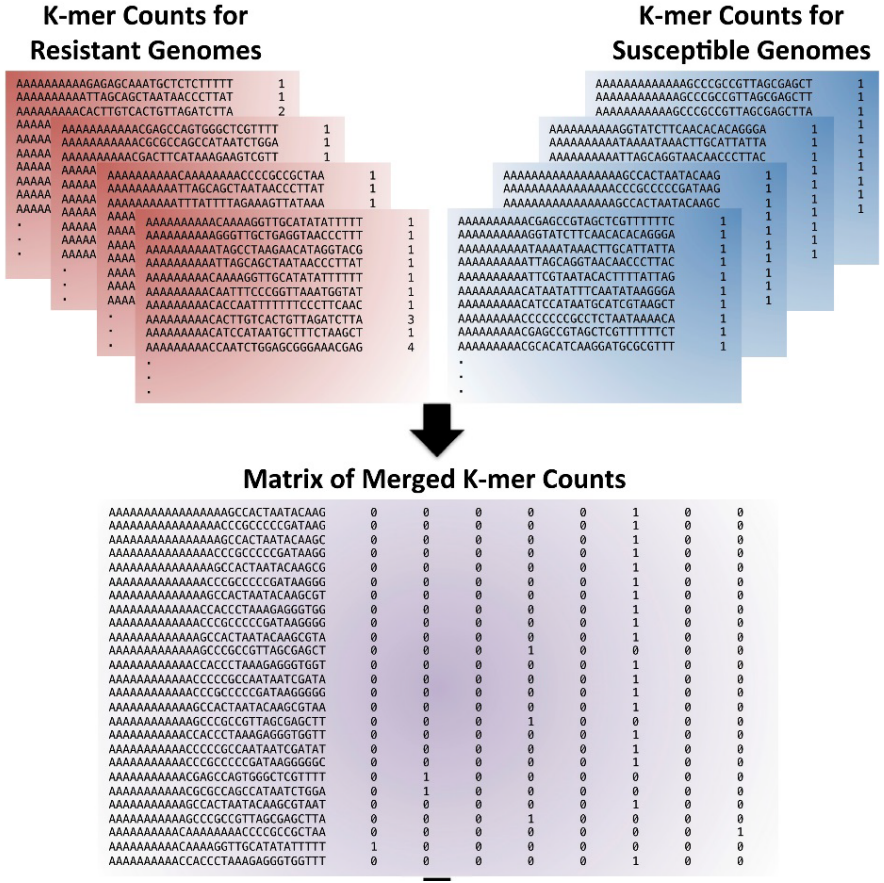
Total number of distinct Biosample records published in 2017 from USA regions

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
200	1,456	10	3,942	110	1,806	7	18,816	10	105	61	80	186	54	20	35	1,704	522

Using Machine Learning To Predict Antimicrobial MICs and Associated Genomic Features for Nontyphoidal *Salmonella*

Marcus Nguyen,[a,b*] S. Wesley Long,[c,d] Patrick F. McDermott,[e] Randall J. Olsen,[c,d] Robert Olson,[a,b*] Rick L. Stevens,[b,f*] Gregory H. Tyson,[e] Shaohua Zhao,[e] James J. Davis[a,b*]

- Used 5,278 NARMS isolates with phenotype/genotype data
- Susceptibility to 16 antibiotics
- Find non redundant k-mers
- Merge R and S to form a matrix
- Generated XGBoost-based machine learning models to predict MIC ± 1 two-fold dilution



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- The MIC prediction models have average accuracies between 95-96% within ± 1 two-fold dilution factor.
- The models are capable of predicting susceptible and resistant MICs with no *a priori* information about the underlying gene content of the genomes.
- By using diverse genomes for training sets, MIC prediction models with accuracies >90% can be generated with fewer than 500 genomes.
- Despite annual fluctuations in AMR gene content in the sampled genomes, this approach for predicting MICs is stable year after year.

	Accuracy	95% CI	Samples
Ampicillin	0.97	[0.96-0.97]	4501
Amoxy-Clav	0.97	[0.97-0.98]	4502
Ceftriaxone	0.97	[0.97-0.98]	4502
Azithromycin	0.99	[0.99-1.00]	1641
Chloramphenicol	0.99	[0.99-0.99]	4502
Ciprofloxacin	0.98	[0.98-0.99]	4502
Trimethoprim-Sulfa	0.99	[0.99-0.99]	4501
Sulfisoxazole	0.96	[0.95-0.97]	4154
Cefoxitin	0.96	[0.95-0.97]	4502
Gentamicin	0.93	[0.92-0.94]	4502
Kanamycin	0.98	[0.97-0.99]	924
Nalidixic Acid	0.98	[0.97-0.98]	4502
Streptomycin	0.91	[0.91-0.92]	4502
Tetracycline	0.98	[0.98-0.98]	4502
Ceftiofur	0.99	[0.99-0.99]	4502
Total	0.97	[0.97-0.97]	60741

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).

Summary of GCVs

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

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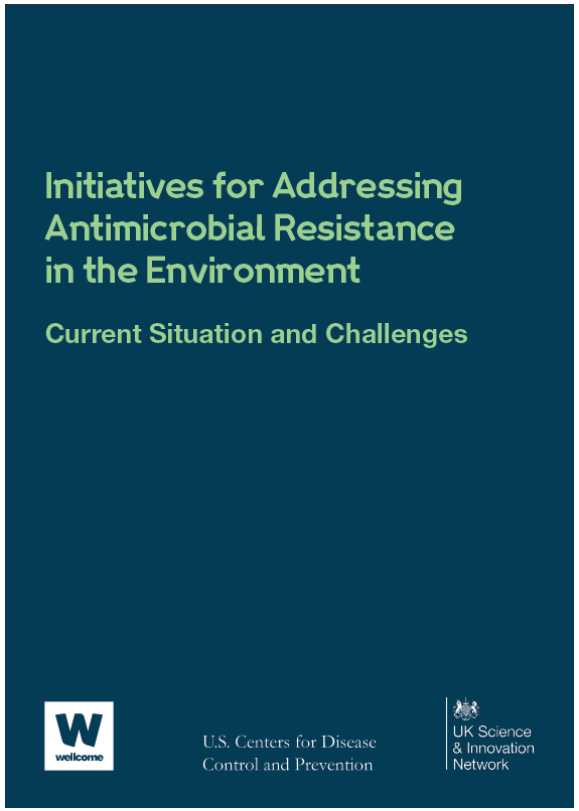
Tracking by Food Safety Traits

(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) Genetic elements (plasmids, genomic islands, etc)

General Recommendations to Advance a One Health NARMS Platform

1. More in-depth and integrated collaboration with global organizations and other countries that have also increased their commitment to AMR. With the increasing use of WGS techniques, comparisons will be easier and more meaningful.
2. The addition of an environmental surveillance component to truly complete the One Health platform
3. Envision how NARMS might integrate microbiome studies.
4. Examine other commodities and pathogens where antibiotics are used in production such as seafood.
5. Consider expanding the trend analysis to include (food) animal pathogens.
6. 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.

International Environmental AMR Forum



Hosted by the U.S. Centers for Disease Control and Prevention, the UK Science & Innovation Network, and the Wellcome Trust (April 2018).

Main Areas of Risk Mitigation

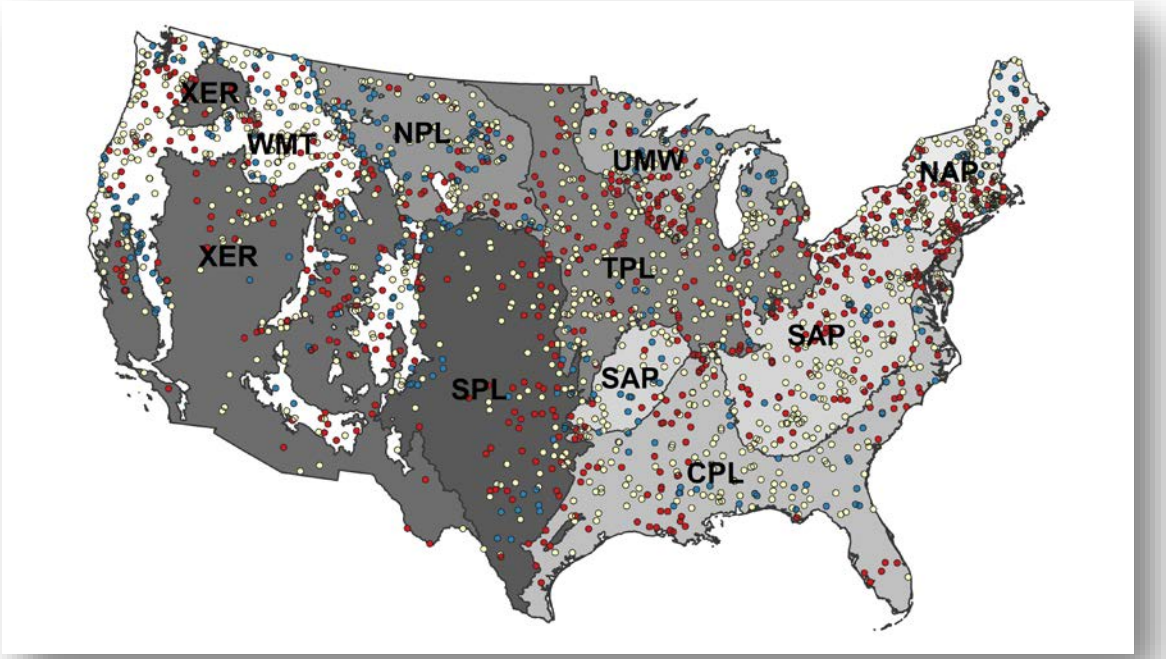
Human and animal waste (i.e. feces): Waste from people and animals can carry un-metabolized traces of consumed antimicrobials and antimicrobial-resistant microbes with transmissible resistance.

Pharmaceutical manufacturing waste: Release of active pharmaceutical ingredients into the environment can occur when antimicrobials are manufactured.

Antimicrobial pesticides for crops: Some medically important antimicrobials are used on crops to prevent or treat plant diseases. The type and amount of antimicrobials used on crops varies by country.

Partnering with the Environmental Protection Agency (EPA)

- 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 conducted annually; 5 year survey cycle

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

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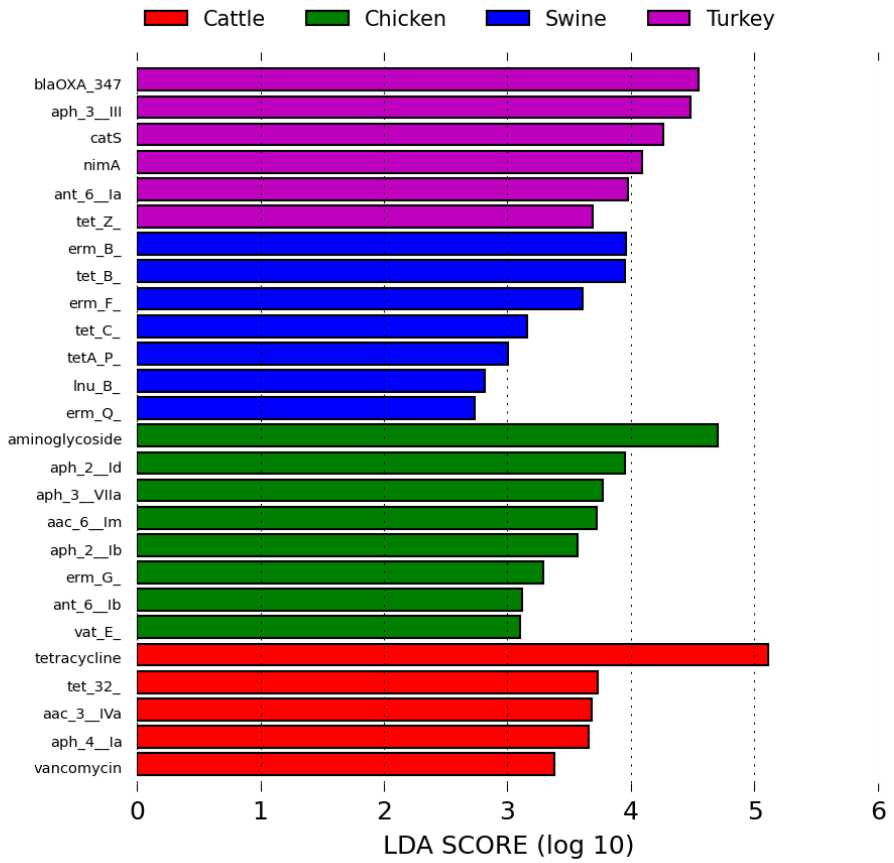
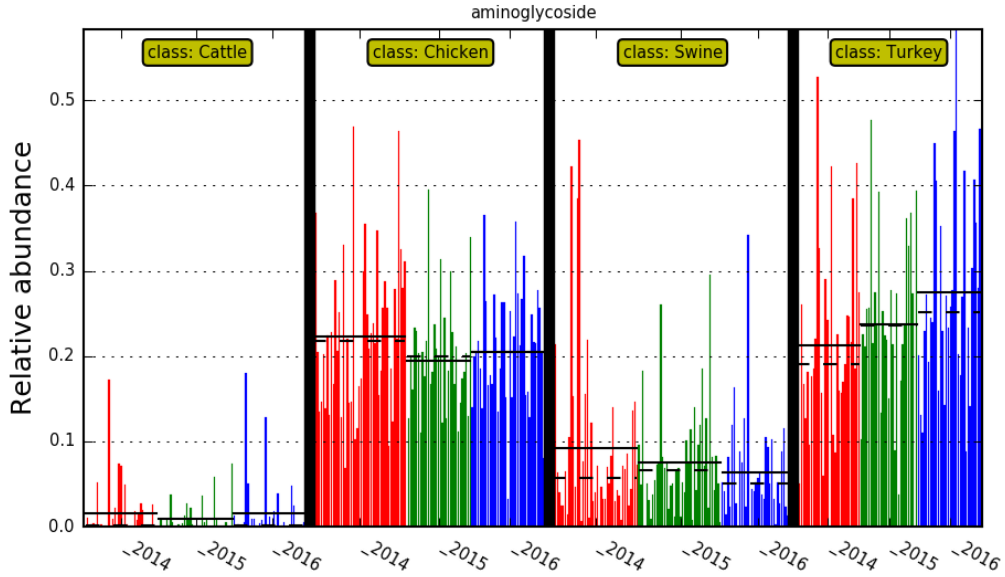
Metagenomic Surveillance Resistance Genes by Animal Origin



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



Metagenomic Surveillance of the Resistome

- In addition to the animal slaughter samples, NARMS is using MGS to evaluate the animal feeds and raw retail meats in NARMS surveillance (including seafood samples in the pilot studies), and comparing the results with our other data sets:
  - Resistance and MIC data for 15 drugs in 7 classes
  - WGS of *Salmonella, Campylobacter* and *E. coli*.
- MGS is being used to circumvent the loss of isolates from CIDT
- Surface water samples from EPA rivers and streams survey
- In the future, WGS will be used for other EPA water surveys (e.g, wastewaters), irrigation waters for crops, pet foods, etc.

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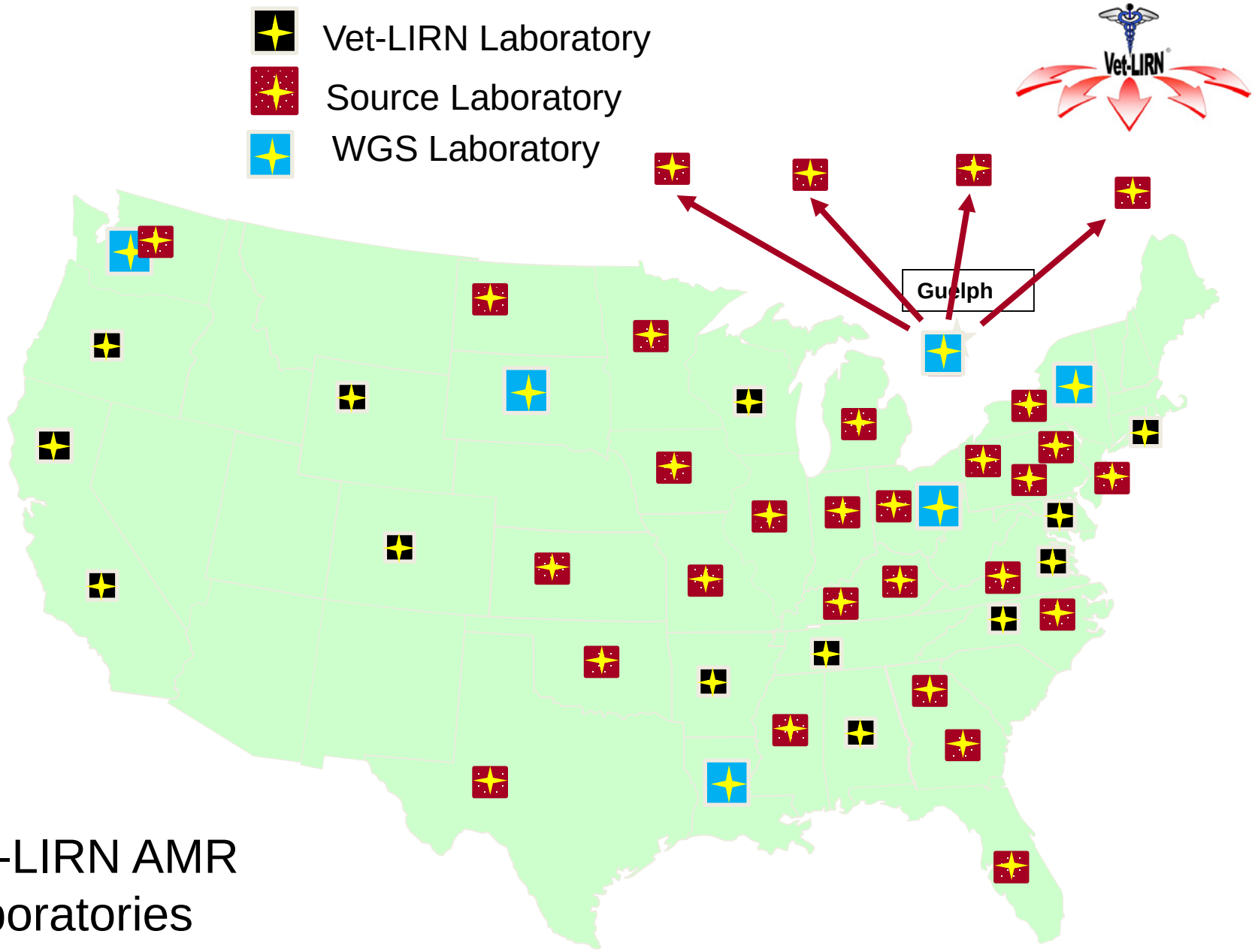

Vet-LIRN AMR Laboratories 2018

Isolates - 2017

Isolates:	AST	WGS
SAL (all hosts)	583	71
SPSE (dog)	688	61
ECOL (dog)	691	68
Total:	**1692**	**200**
2018-	**~ 3000**	**~ 1000**

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NARMS Looking Forward: From Integrated to One Health Surveillance

1. Exploit genomics fully
2. Add food animal pathogens.
3. Add food commodities
4. Test more bacterial species
5. Add appropriate on-farm testing
6. Incorporate companion animal surveillance.
7. Develop an environmental surveillance piece
8. Develop methods of microbiome surveillance.
9. Broaden collaboration with other U.S. programs
10. Continue to work toward international harmonization and cooperation


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