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Genome Sequencing and Its Prospects for Improving Food Safety

Agricultural Outlook Forum
Smart Agriculture in the 21st Century

Modernizing Food Safety: February 20, 2015

David G. White, PhD
Chief Science Officer and Research Director
Office of Foods and Veterinary Medicine
Office of the Commissioner
U.S. Food and Drug Administration

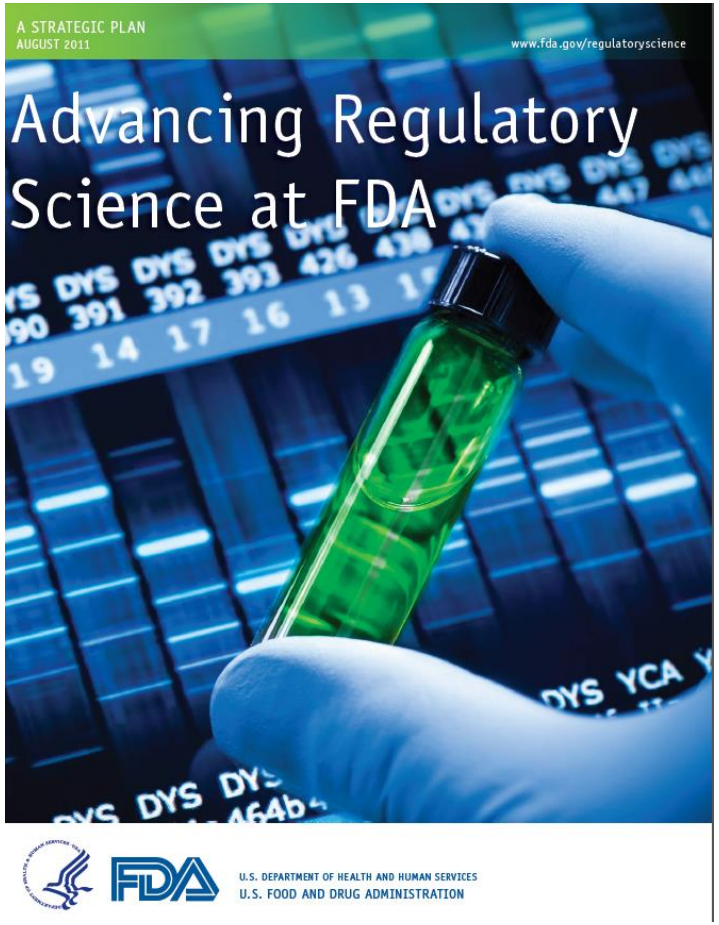
Challenges for FDA

- Recent breakthroughs in science and technology have the potential to transform our ability to prevent, diagnose and treat disease.

- However, major investments in basic and translational research are not efficiently yielding new products needed to benefit consumers
  - Product development is increasingly costly, success rates remain low, and time is $
  - Development/evaluation tools and approaches have neither kept pace with nor incorporated emerging technologies

- FDA's Advancing Regulatory Science Strategic Plan is designed to allow both to meet today's public health needs and to be fully prepared for the challenges and opportunities of tomorrow

Advancing Regulatory Science at FDA



- Regulatory science is a relatively new term but an old concept
- The application of science to the development and utilization of new tools, standards, and approaches for the assessment of product efficacy, safety, and quality
- 8 Science priority areas

Advancing Regulatory Science at FDA

Advancing Regulatory Science at FDA

EXECUTIVE SUMMARY

INTRODUCTION

VISION STATEMENT

SCIENCE PRIORITY AREAS

1. Modernize Toxicology to Enhance Product Safety
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes
3. Support New Approaches to Improve Product Manufacturing and Quality
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Product

IMPORTANCE OF A STRONG REGULATORY SCIENCE CULTURE AND INFRASTRUCTURE:
IMPLEMENTATION STRATEGIES FOR THE STRATEGIC PLAN FOR REGULATORY SCIENCE

CONCLUSION

GLOSSARY

- Two key elements in plan
  - Evaluate innovative emerging technologies
    - Enhance multidisciplinary collaboration
    - Improved external partnerships
  - Implement a new prevention-focused food safety system
    - Invest in emerging technologies to mitigate risk
    - Improve information sharing internally and externally
- http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf

Economic Burden of 15 Major Pathogens

Cost Estimates of Foodborne Illnesses

Overview
Documentation
How to Read a Worksheet
Glossary

Related Topics
Consumer Price Index (CPI)
Food Safety & International Markets
Foodborne Illness
Labeling & Information Policy
Market Incentives & Government Regulation
Response to Incidents

Overview

The Cost Estimates of Foodborne Illnesses data product provides detailed data about the costs of major foodborne illnesses in the United States, updating and extending previous ERS research. This data set includes:

1. Detailed identification of specific disease outcomes for foodborne infections caused by 15 major pathogens in the United States
2. Associated outpatient and inpatient expenditures on medical care
3. Associated lost wages
4. Estimates of individuals' willingness to pay to reduce mortality resulting from these foodborne illnesses acquired in the United States.

Disease outcomes include both acute illness and chronic disease that sometimes follow these acute illnesses. These 15 pathogens account for over 95 percent of the illnesses and deaths from foodborne illnesses acquired in the United States for which the U.S. Centers for Disease Control and Prevention (CDC) can identify a pathogen cause. These estimates build on CDC estimates of the incidence of foodborne disease; peer-reviewed synthesis of data on medical costs, and economic, medical and epidemiological literature; and publicly available data on wages.

This data product provides Federal agencies such as USDA's Food Safety and Inspection Service (FSIS) with a set of consistent, peer-reviewed estimates of the costs of foodborne illness that can be used in analyzing the impact of Federal regulation. It also provides other stakeholders and the general public with a means of understanding the relative impact of different foodborne infections in the United States. Cost estimates of foodborne illnesses have been used in the past to help inform food-safety policy discussions, and these updated cost estimates will provide a foundation for economic analysis of food safety policy.

This product consists of 15 Excel files detailing disease outcomes for each pathogen together with associated costs, technical notes and documentation, and links to associated research projects and publications.

- Campylobacter (all species)
- Clostridium perfringens
- Cryptosporidium parvum
- Cyclospora cayetanensis
- Escherichia coli O157
- Non-O157 Shiga toxin-producing Escherichia coli

Campylobacter (all species) – $1,928,787,166

Clostridium perfringens – $342,668,498

Cryptosporidium parvum – $51,813,652

Cyclospora cayetanensis – $2,301,423

Escherichia coli O157 – $271,418,690

Non-O157 Shiga toxin-producing Escherichia coli – $27,364,561

Listeria monocytogenes – $2,834,444,202

Norovirus – $2,255,827,318

Salmonella (nontyphoidal) – $3,666,600,031

Shigella (all species) – $137,965,962

Toxoplasma gondii – $3,303,984,478

Vibrio parahaemolyticus – $40,682,312

Vibrio vulnificus – $319,850,293

Vibrio (all other non-cholera species) – $142,086,209

Yersinia enterocolitica – $278,111,168

http://ers.usda.gov/data-products/cost-estimates-of-foodborne-illnesses.aspx#48443

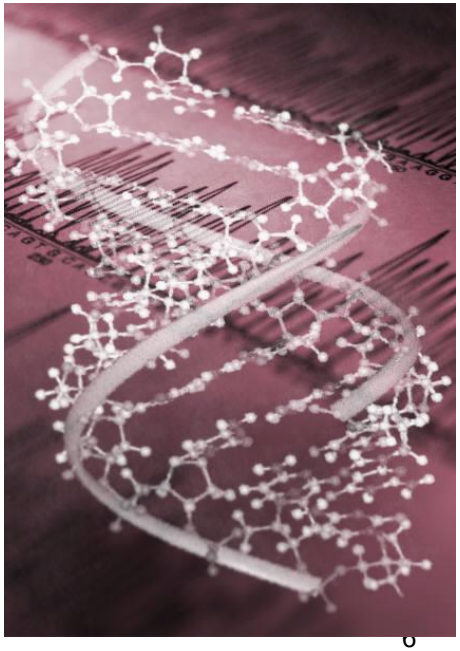
Whole genome sequencing is changing the science of

WGS has to potential to serve as the single assay for microbial surveillance/outbreak detection and supplant multiple methods

1. Classical serotyping
2. PFGE and other strain typing methods
3. *In vivo* antimicrobial susceptibility testing
4. Piecemeal PCR gene detection and plasmid typing

And to provide:

1. Genome/nucleotide surveillance
2. Virulence profiles
3. Molecular phage typing
4. Markers for source attribution
5. Better understanding of emerging trends
6. Costs savings



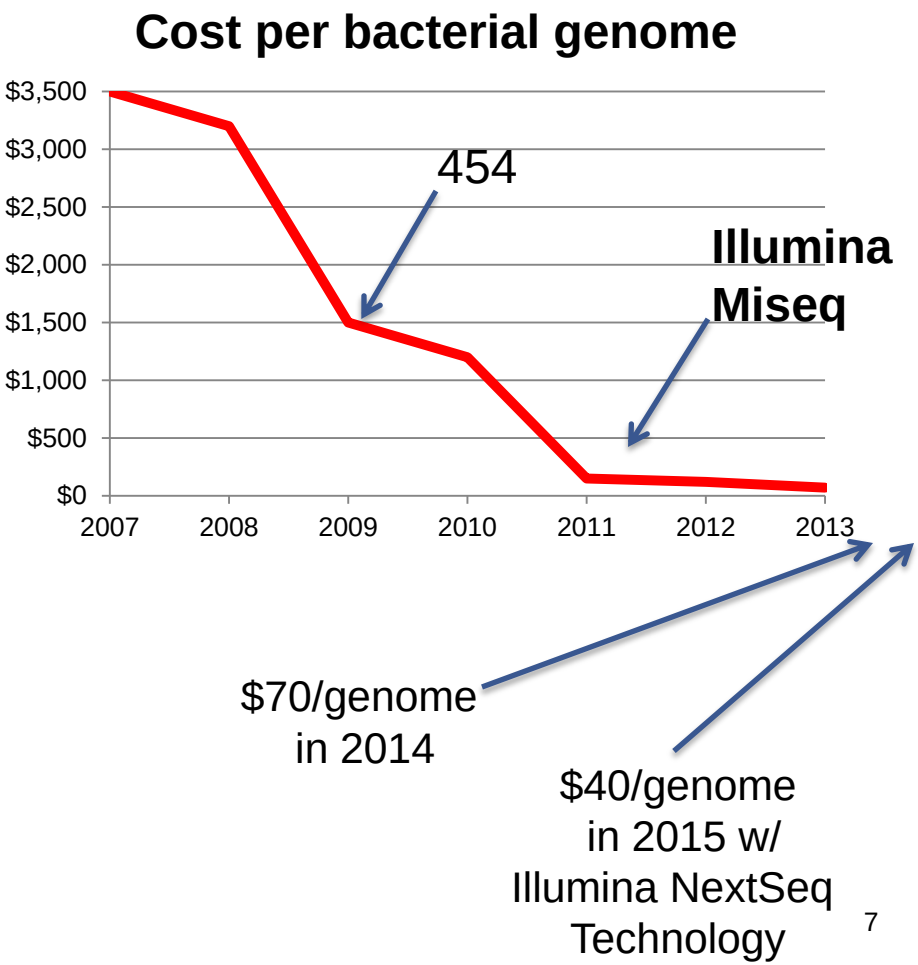
DNA Sequencing

- Bases of DNA (ATGC) are sequentially identified from a DNA template strand

- Next Generation Sequencing (NGS) extends this process across millions of reactions in a massive parallel fashion

- NGS involves rapid sequencing of large DNA stretches spanning entire genomes
  - Technology shift
  - 3-5 million data points for each isolate

- Increasing availability and affordability of NGS is rapidly changing the face of microbiology



How FDA is Using WGS

- To differentiate sources of contamination, even within the same outbreak
- To determine which ingredient in a multi-ingredient food harbored the pathogen associated with an outbreak
- To narrow the search for the source of a contaminated ingredient, even when the source may be half way around the world
- As a clue to the possible source of illness – even before a food has been associated with illness using traditional epidemiological methods
- To determine unexpected vectors for food contamination
- To develop rapid methods to identify/characterize resistant bacteria

WGS USED FOR FIRST TIME AS PART OF REGULATORY ACTION

By RYAN JASLOW / CBS NEWS / March 12, 2014, 12:07 PM /

FDA shuts down Roos Foods cheese plant over listeria outbreak

A product from Roos Foods under the Mexicana brand name is seen in this image. The Delaware company recalled cheeses after a death from the listeria infection. / HTTP://WWW.ROOSFOODS.COM/BRANDS.PHP

Comment / 7 Shares / 25 Tweets / Stumble / Email More

Cheese manufacturer Roos Foods, Inc. has been shut down by the Food and Drug Administration after an investigation linked a multistate listeria outbreak to the processor of Hispanic-style cheeses.

WGS of *Listeria monocytogenes* strains isolated from Roos Foods cheese products was performed by the FDA and Virginia's Division of Consolidated Laboratory Services.

These strains were found to be highly related by WGS to the *Listeria* strains isolated from patients in this outbreak, adding further confidence that cheese products produced by Roos Foods were a likely source of the outbreak.

WGS provided genetic information that allowed investigators to rapidly identify differences among isolates.

SECRETARY PICK!

HHS INNOVATES CELEBRATES 7TH ROUND OF INNOVATIONS!

By Steven Randazzo On July 21, 2014 ·

Today, the six finalist teams for Round 7 of HHS Innovates were celebrated by HHS Leadership and their peers for their innovative projects and their impact on the Department of Health and Human Services and services to the American people. The People's Choice Award and Secretary's Picks were announced today.

Whole Genome Sequencing: Future of Food Safety

Sometimes the food we eat can be hazardous and finding contaminated foods before consumers become ill is a major challenge. The process for identifying disease-causing organisms that can be found in food and can be a slow and cumbersome process using conventional detection testing methods. Whole genome sequencing is a new technology has the potential to speed up detection and enable faster interventions to stop an outbreak of disease in its tracks. The Centers for Disease Control and Prevention partnered with agencies across state and federal government, including the Food and Drug Administration and the National Institutes of Health National Center for Biotechnology Information to engage in a demonstration project to showcase the benefits of using Whole Genome Sequencing for food surveillance and detection purposes.

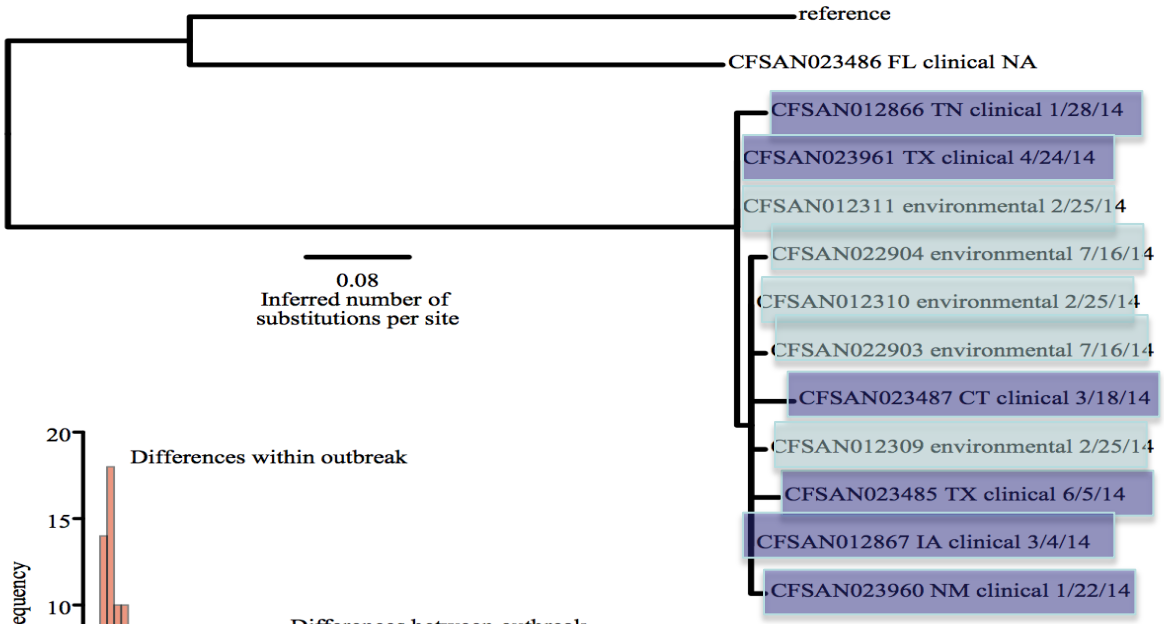
CFSAN, CDC, NIH, USDA Partnership

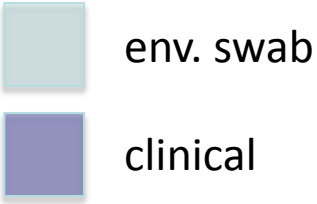
Potential biggest transformation of public health microbiology in decades

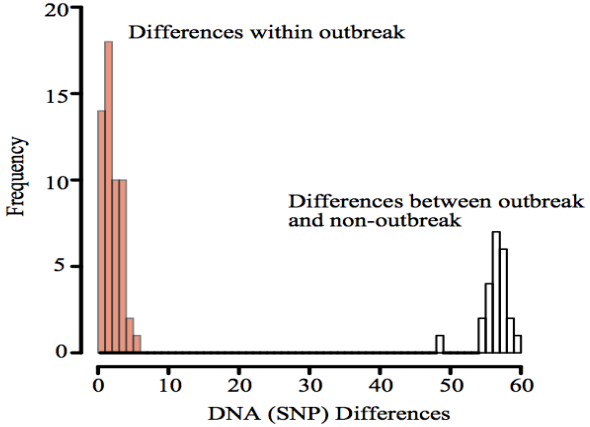
New technology has the capacity to revolutionize foodborne disease tracking by replacing current methods

A Growing Regulatory Role:

An increased degree of certainty that comes with high resolution data allowed for detection of this Salmonella contamination event in nut butter across several states with low level contamination in a widely distributed product.
In this case, WGS identified the link and preempted an outbreak even w/o availability of food - it informs the epidemiology and our inspectors actions

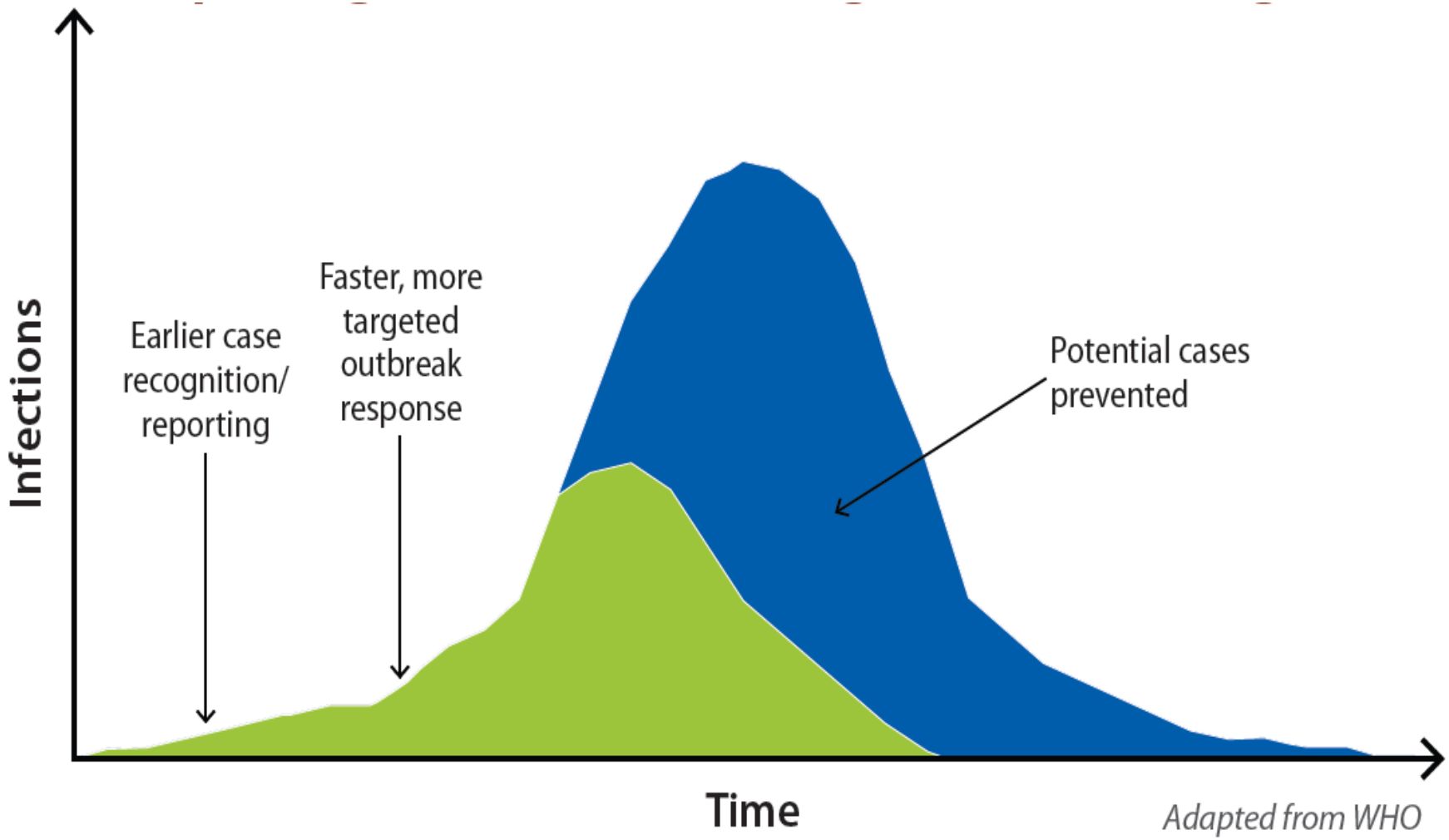






Outbreak/Pre-outbreak summer of 2014

WGS-surveillance approach to public health



FDA WGS Application to Actual Food Contamination Events

S. Montevideo black and red pepper
S. Senftenberg black and red pepper
S. Enteritidis shell/liquid eggs
S. Heidelberg ground turkey
S. Heidelberg chicken broilers
S. Heidelberg chicken livers
S. Enteritidis custard
S. Bareilly tuna scrape
S. Tennessee peanut butter/peanut butter paste
S. Typhimurium peanut butter
S. Braenderup peanut butter/nut butter
S. Tennessee cilantro
S. Agona dry cereal
S. Agona papaya
S. Newport tomatoes
S. Newport environmental
S. Kentucky - Cerro dairy/dairy farms
S. Anatum spices/pepper flakes
S. Javiana cantaloupes
S. Saintpaul hot peppers
4,5,12: i –

L. mono cantaloupes
L. mono queso cheese
L. mono potato salad
L. mono artisanal cheeses
L. mono avocados
L. mono ricotta
L. mono celery/chix salad
L. mono smoked fish
L. mono other herbs
L. mono peaches

Cronobacter infant formula

V. para oysters

EcO157:H7 lettuce

STEC beef

…Numerous other taxa

Whole Genome Sequencing Program (WGS)

U.S. Department of Health and Human Services

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Food

Home > Food > Science & Research (Food) > Whole Genome Sequencing Program (WGS)

Science & Research (Food)
- Whole Genome Sequencing Program (WGS)
- Projects
- Researchers
- Events
- Whole Genome Sequencing (WGS) Fast Facts

Whole Genome Sequencing Program (WGS)

On this page:
- Introduction
- GenomeTrakr: Using Genomics to Identify Food Contamination
- How FDA Uses Whole Genome Sequencing for Regulatory Purposes
- Proactive Applications of Whole Genome Sequencing Technology

Introduction

Whole genome sequencing reveals the complete DNA make-up of an organism, enabling us to better understand variations both within and between species. This in turn allows us to differentiate between organisms with a precision that other technologies do not allow. FDA is using this technology to perform basic foodborne pathogen identification during foodborne illness outbreaks and applying it in novel ways that have the potential to help reduce foodborne illnesses and deaths over the long term both in the U.S and abroad.

The most basic application of this technology to food safety is using it to identify pathogens isolated from food or environmental samples. These can then be compared to clinical isolates from patients. If the pathogens found in the food or food production environment match the pathogens from the sick patients, a reliable link between the two can be made, which helps define the scope of a foodborne illness outbreak. This type of testing has traditionally been done using methods such as PFGE, but there are some strains of *Salmonella spp.* that PFGE is unable to differentiate. Whole genome sequencing performs the same function as PFGE but has the power to differentiate virtually all strains of foodborne pathogens, no matter what the species. Its ability to differentiate between even closely related organisms allows outbreaks to be detected with fewer clinical cases and provides the opportunity to stop outbreaks sooner and avoid additional illnesses.

Genome Trakr

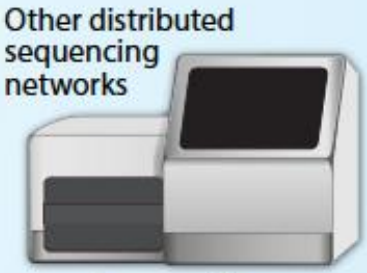
- State and Federal laboratory network collecting and sharing genomic data from foodborne pathogens
- Distributed sequencing based network
- Partner with NIH NCBI
- Open-access genomic reference database
  - http://www.ncbi.nlm.nih.gov/bioproject/183844
- Can be used to find the contamination sources of current and future outbreaks

http://www.fda.gov/Food/FoodScienceResearch/WholeGenomeSequencingProgramWGS/default.htm#trakr

Basic Data Flow for Global WGS Public Access Databases

DATA ACQUISITION

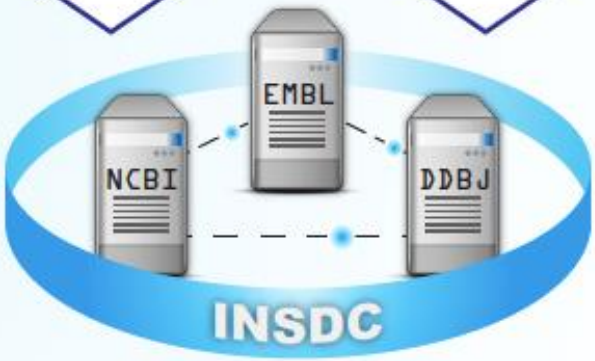
Sequence and upload genomic and geographic data



DATA ASSEMBLY, ANALYSIS, AND STORAGE

International Nucleotide Sequence Database Collaboration (INSDC)
Shared Public Access Databases

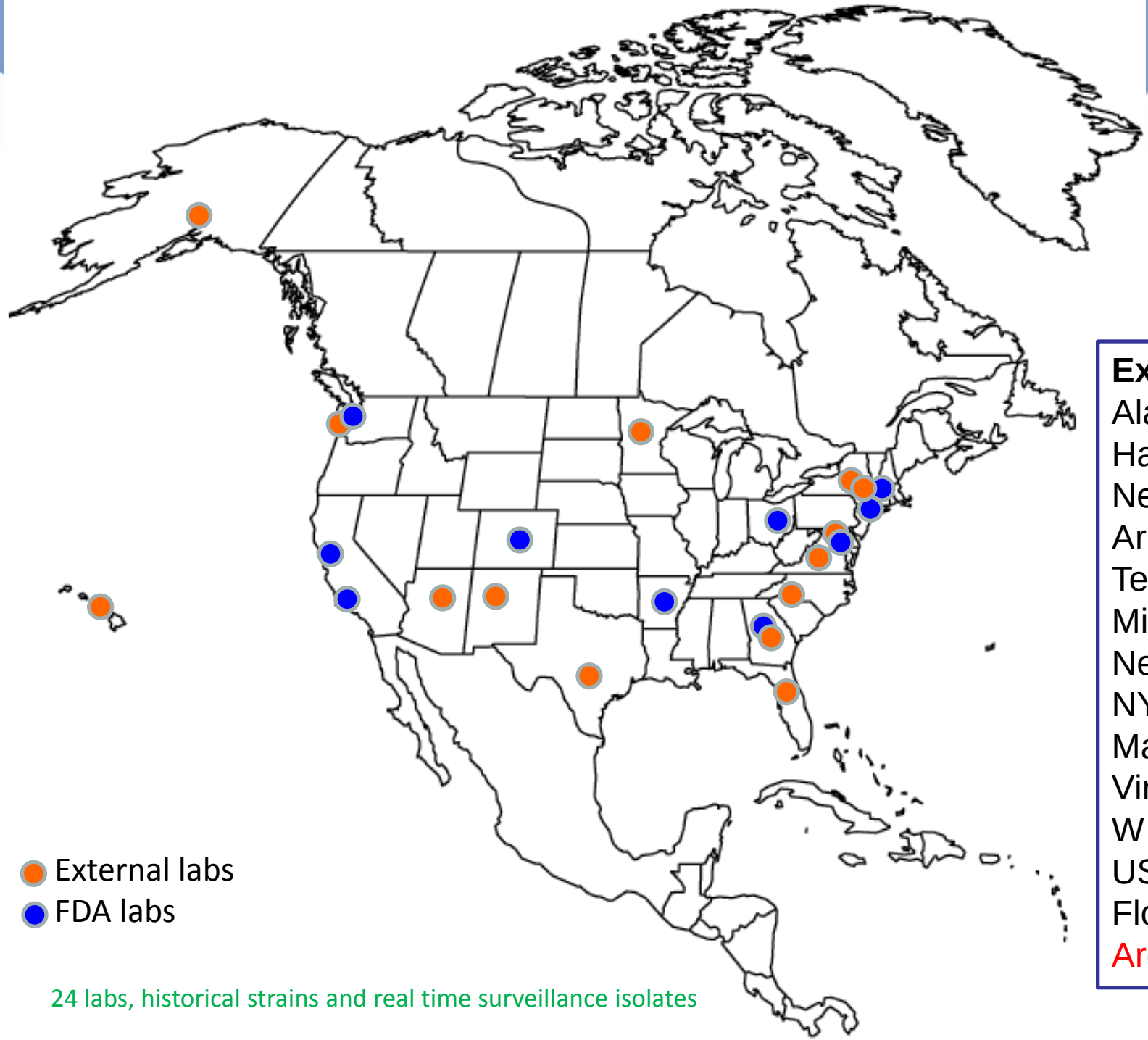
- *NCBI – National Center for Biotechnology Information*
- *EMBL – European Molecular Biology Laboratory*
- *DDBJ – DNA Databank of Japan*



PUBLIC HEALTH APPLICATION AND INTERPRETATION OF DATA

- *Find clinical links*
- *Identify clusters*
- *Conduct traceback*
- *Develop rapid methods*
- *Develop culture independent tests*
- *Develop new analytical software*

11/2014 State, Local, Federal, and Foreign Public Health Agencies Academia/Industry

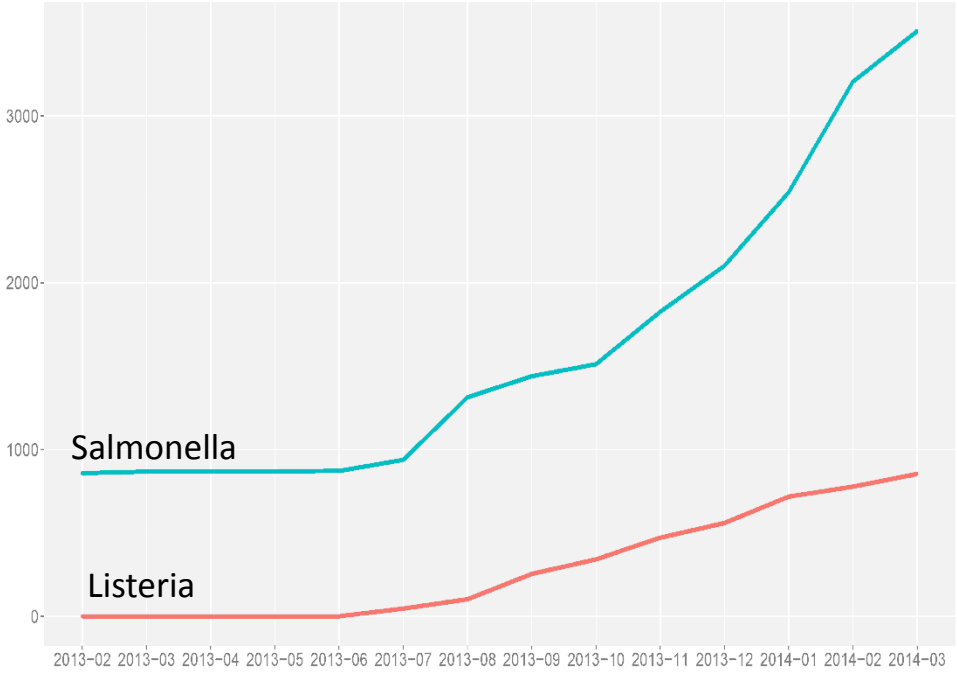


External Labs
Alaska
Hawaii
New Mexico
Arizona
Texas
Minnesota
New York
NY agriculture
Maryland
Virginia
W Carolina U
USDA-FSIS
Florida
Argentina

24 labs, historical strains and real time surveillance isolates

Current status

- WGS clearly defines foodborne outbreaks – more than 15 different examples
- NGS network is reliable, efficient and can provide very good location specificity of outbreaks
- We have sequenced more than 5,500 Salmonella, more than 1,500 Listeria, and closed 100 genomes. Our current rate is about 500 draft sequences a month.
- The need for increased number of well characterized environmental (food, water, facility, etc.) sequences may outweigh need for extensive clinical isolates
- Highly successful partnership with CDC on real-time tracking of Listeria outbreaks



Antimicrobial Resistance

NATIONAL STRATEGY
FOR COMBATING ANTIBIOTIC-
RESISTANT
BACTERIA

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.

September 2014

THE WHITE HOUSE
WASHINGTON

- President directed NSC and OSTP to assess the threat of AMR and develop a multi-sectoral plan to combat resistant bacteria
  - December, 2013
- 5 goals
  - Slow emergence
  - Strengthen One-health surveillance
  - Advance innovative diagnostics
  - Accelerate R&D
  - Improve international collaboration
- Judicious use of antimicrobials in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics

National Antimicrobial Resistance Monitoring System

- A national collaborative network between the FDA, CDC and USDA as well as public health laboratories in all 50 states and local health departments in three major cities

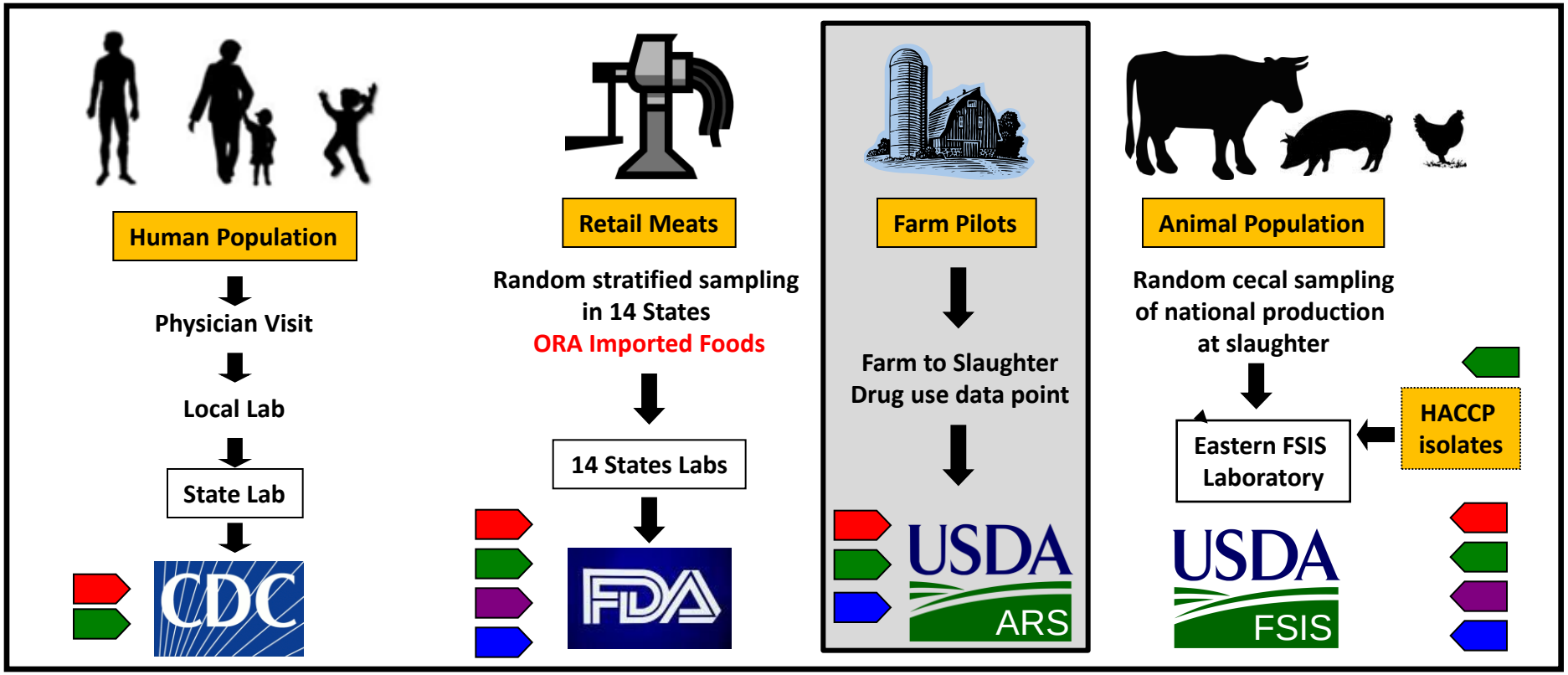
- NARMS was developed to monitor changes in susceptibility of select bacteria from animals, retail meats and humans to antimicrobial agents of human and veterinary importance
  - FDA/CVM (retail meat and poultry)
  - CDC (humans)
  - USDA (animal/slaughter)

NARMS Objectives

Dedicated to the protection of human and animal health
Through integrated monitoring of foodborne AMR

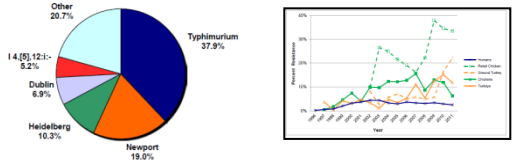
1. Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals
2. Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria
3. Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance
4. Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals

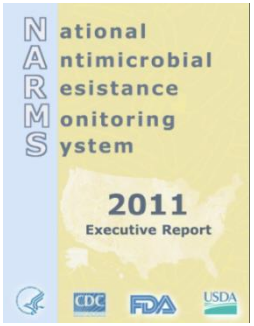
Structure of NARMS in 2015



- Campylobacter
- Salmonella
- Enterococcus
- E. coli

Data Integration





Benefits of a WGS Strategy in NARMS

Methods	Results	Characteristics
Traditional		
Culture → Serotyping	Serotype	Historical continuity Low resolution typing Multiple assays and reagents Limited drug coverage Limited resistance mechanisms Specialized training Labor intensive Costly Slow and piecemeal
Culture → Antibiotic Susceptibility	Resistance pattern	
Culture → PFGE	Genetic relationship	
Culture → Molecular study	Resistance mechanisms	
WGS		
Culture → DNA → WGS	Serotype	Requires new standards Higher resolution typing Single assay/one instrument Extended drug coverage Detect all known mechanisms Details on genetic context Computation intensive Lower costs Rapid and comprehensive
	Resistance pattern	
	Genetic relationship	
	Resistance mechanisms	

MDR plasmid in Gen^R *C. coli* in U.S. Retail Meat

Journal of Antimicrobial Chemotherapy Advance Access published February 1, 2015

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dkv001

Novel gentamicin resistance genes in *Campylobacter* isolated from humans and retail meats in the USA

Shaohua Zhao[1]*, Sampa Mukherjee[1], Yuansha Chen[1], Cong Li[1], Shenia Young[1], Melissa Warren[1], Jason Abbott[1], Sharon Friedman[1], Claudine Kabera[1], Maria Karlsson[2] and Patrick F. McDermott[1]

[1]*Division of Animal and Food Microbiology, Office of Research, Center for Veterinary Medicine, US Food and Drug Administration, Laurel, Maryland, USA;* [2]*Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA*

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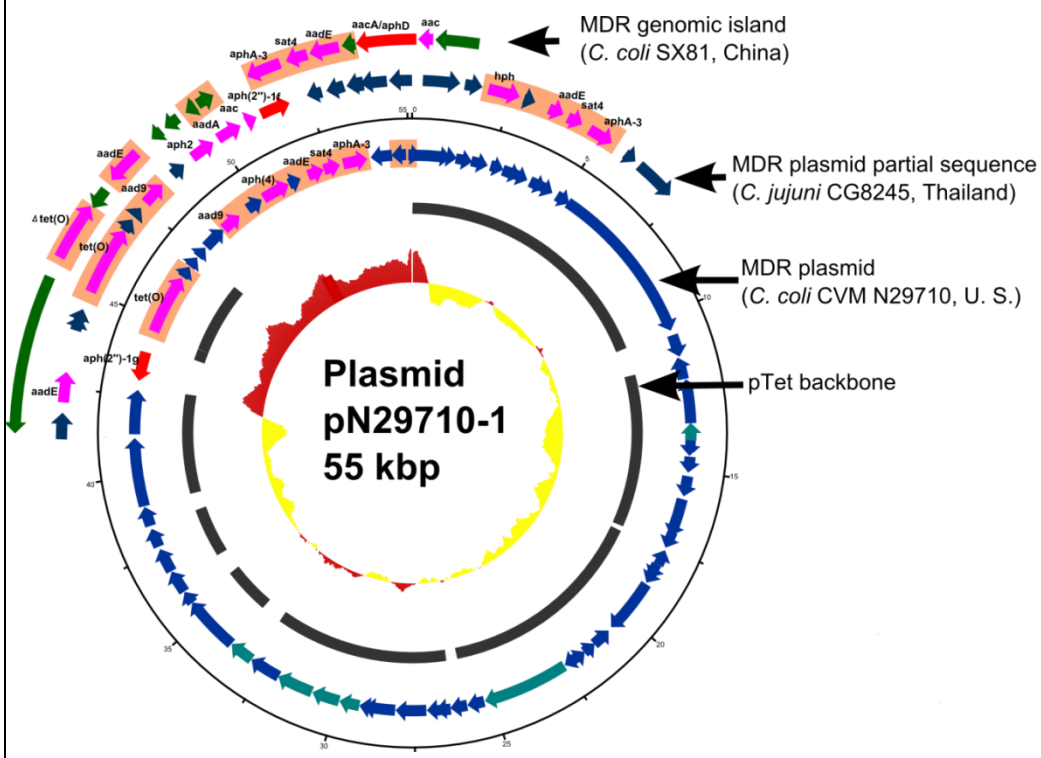
Received 18 September 2014; returned 26 November 2014; revised 9 December 2014; accepted 28 December 2014

Objectives: To understand the molecular epidemiology of gentamicin-resistant *Campylobacter* and investigate aminoglycoside resistance mechanisms.

Methods: One-hundred-and-fifty-one gentamicin-resistant *Campylobacter* isolates from humans ($n=38$ *Campylobacter jejuni*; $n=41$, *Campylobacter coli*) and retail chickens ($n=72$ *C. coli*), were screened for the presence of gentamicin resistance genes by PCR and subtyped using PFGE. A subset of the isolates ($n=41$) was analysed using WGS.

Results: Nine variants of gentamicin resistance genes were identified: *aph(2″)-Ib, Ic, Ig, If, If1, If$_3$, Ih, aac(6′)-Ie/aph(2″)-Ia* and *aac(6′)-Ie/aph(2″)-If$_2$*. The *aph(2″)-Ib, Ic, If1, If$_3$, Ih* and *aac(6′)-Ie/aph(2″)-If$_2$* variants were identified for the first time in *Campylobacter*. Human isolates showed more diverse aminoglycoside resistance genes than did retail chicken isolates, in which only *aph(2″)-Ic* and *-Ig* were identified. The *aph(2″)-Ig* gene was only gene shared by *C. coli* isolates from human ($n=27$) and retail chicken ($n=69$). These isolates displayed the same resistance profile and similar PFGE patterns, suggesting that contaminated retail chicken was probably the source of human *C. coli* infections. Human isolates were genetically diverse and generally more resistant than the retail chicken isolates. The most frequent co-resistance was to tetracycline (78/79, 98.7%), followed by ciprofloxacin/nalidixic acid (46/79, 58.2%), erythromycin and azithromycin (36/79, 45.6%), telithromycin (32/79, 40.5%) and clindamycin (18/79, 22.8%). All human and retail meat isolates were susceptible to florfenicol.

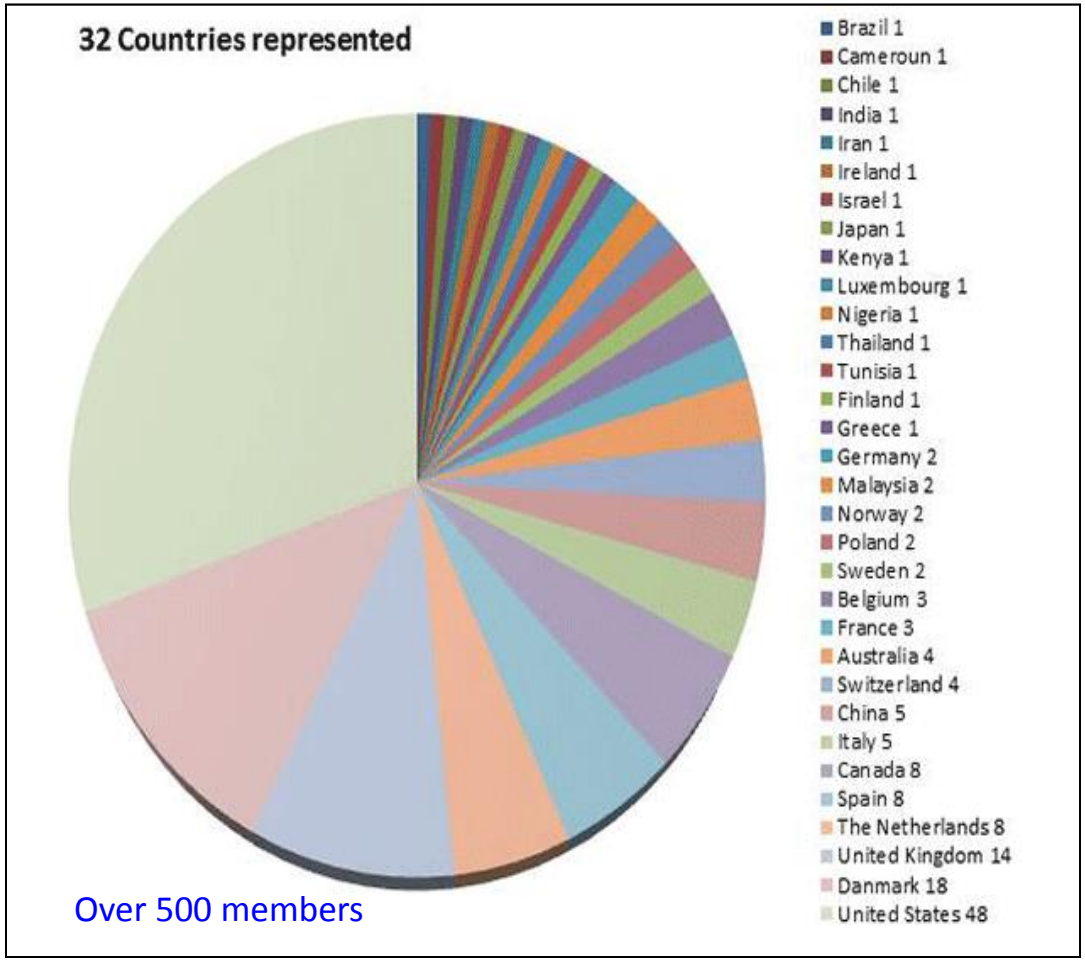


Future NARMS Objectives?

1. Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals
2. Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria
3. Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance
4. Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals

1. Monitor genomes in antimicrobial resistant foodborne bacteria from humans, retail meats, food animals, companion animals, feral animals, the environment etc.
2. Characterize the resistome in complex biological samples using culture-independent metagenomic analyses.
3. Disseminate timely information on precise changes in the resistome to promote interventions that reduce resistance among foodborne bacteria and to prevent rare resistances from becoming common
3. Conduct in vivo metagenomics research to better understand the emergence, persistence, and spread of antimicrobial resistance under different conditions
4. Provide comprehensive genetic data, along with detailed antibiotic use information, to assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals

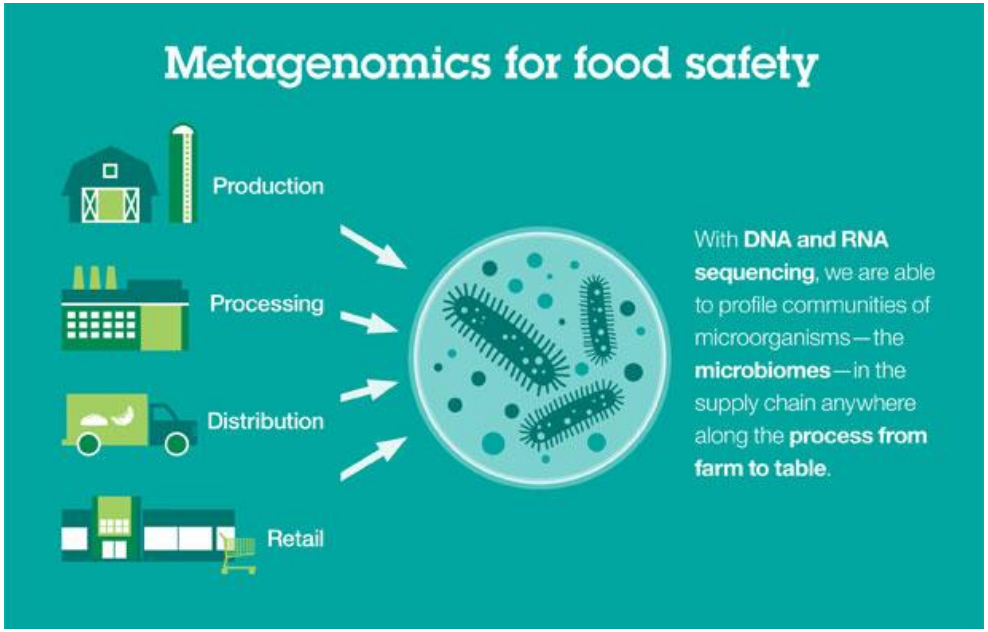
International Efforts



- Global system of DNA genome databases for microbial and infectious disease identification, surveillance and diagnostics
- 5 Work groups
  - Political challenges, outreach and building a global network
  - Repository and storage of sequence and meta-data
  - Analytical approaches
  - Quality assurance
  - Pilot project
- 8th GMI meeting to take place in Beijing, China, May 11-13, 2015

Consortium for Sequencing the Food Supply Chain

- IBM and Mars, Inc will study the microbial ecology of foods and related processing environments
- Sequencing ALL microorganisms
  - Microbiome

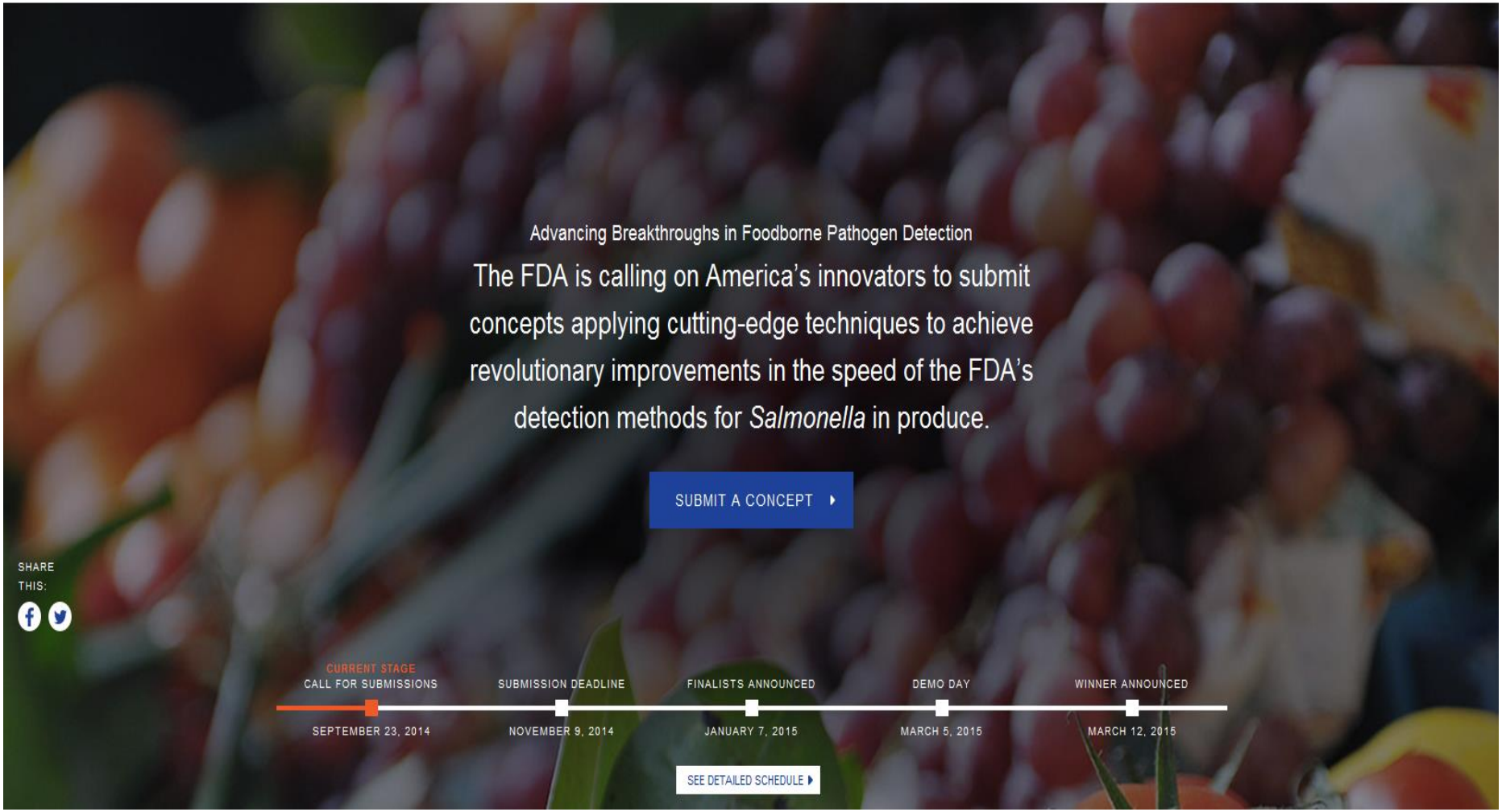


http://www.research.ibm.com/client-programs/foodsafety/index.shtml

Public-Private Partnerships

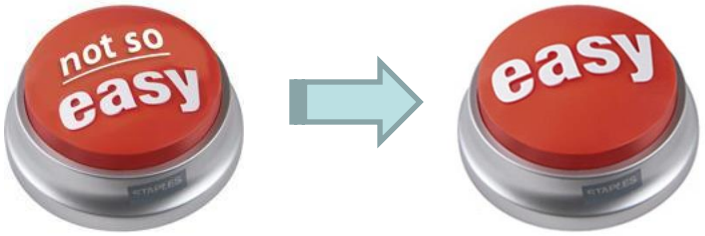
- America COMPETES Act and President Obama's Strategy for American Innovation
  - Granted Agencies authority to offer prize competitions
  - Use Grand challenges as an innovation tool to engage the public
    - Ambitious goals – catalyze breakthroughs
    - Pay only for success
    - Leveraging outside novel approaches
- Open innovation challenge efforts
  - FDA/Federal Partners/Industry co-aligned interests lie in the realm of rapidly detecting foodborne pathogens
    - Largest benefit could be gained by making significant advances in pre-enrichment phase of microbiological testing
      - Rapidly recovering enough target organisms or genetic material for current detection/sensor technology platforms
    - Sept. 23rd, 2014 – Food Safety Challenge Announced
      - Incentive Prize Competition Assistance for Improvement and Validation of Methods for the Detection of Microbial Foodborne Pathogens

2014 Food Safety Challenge



Summing up ….

- WGS is revolutionizing the microbiology laboratory contribution to public health
- WGS can be used to mitigate tracebacks and delimit the scope of food contamination events unlike ever before
- Developing a mutual/shared understanding and vision how to advance real time surveillance for foodborne pathogens using WGS
- Looking to the future
  - Roles, responsibilities and coordination of partners
  - Resources, training, SOPs, QA
  - Metadata
  - Bioinformatics
  - Data presentation



With Additional Thanks….

And a Growing Cast of Colleagues….

FDA

Steven Musser
Marc Allard
Justin Payne
Christine Keys
James Pettengill
Gopal Gopinathrao
David Melka
Maria Hoffman
Tim McGrath
Cong Li
Shaohua Zhao
Patrick McDermott
Peter Evans
Charlie Wang
Errol Strain
Hugh Rand
Chis Grim
Cary Pirone Davies
Eric Stevens
Don Burr
George Kastanis
Ruth Timme
Eric Brown
Rebecca Bell
Yan Luo
Darcy Hanes
Palmer Orlandi
Justin Payne
Andrea Ottesen
Jie Zheng
Tim Muravunda

National Institutes of health (NCBI)

David Lipman
Martin Shumway
Jim Ostell
Richa Agarwala
William Klimke

State Health Labs

Bill Wolfgang (NY)
Elizabeth Driebe (AZ)
Ailyn Perez-Osorio (WA)
Dave Boxrud (MN)
Angela Fritzinger (VA)
More to come…….
Anita Wright (FL)

CDC

Chris Braden
Cheryl Tarr
Marguerite Pappaioanou
Duncan MacCannell
Eija Trees
John Besser
Peter Gerner-Smidt

USDA

David Goldman
Kristin Holt

Illumina

Susan Knowles
Omayma Al-Awar
Kelly Hoon