

CIDTs in the U.S: Opportunities and Challenges



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CDC, Enteric Diseases Laboratory Branch

CDC Enteric Diseases Laboratory Branch (EDLB)



National Center for Emerging and Zoonotic Infectious Diseases
Division of Foodborne, Waterborne, and Environmental Diseases



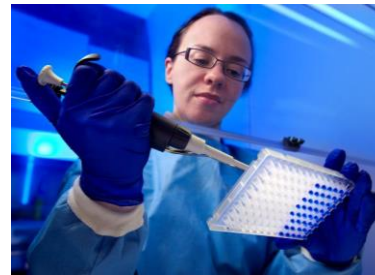
Diagnostic Methods Through Time



1860s:
Culture-based tests



1980s-90s:
Antigen-based tests



2000s:
Polymerase Chain
Reaction (PCR) tests



2010s:
Multiplex Syndrome-
based PCR panels

Culture-independent Diagnostic Tests

Syndromic CIDT Panels: GI Disease

CLEARED



BD Max

CLEARED



BioFire FilmArray



GenMark Dx
eSensor XT-8

In Clearance



Cepheid GeneXpert



Nanosphere's Verigene
Enteric Pathogens (EP)
Test

CLEARED



CLEARED



Luminex xTag GPP



Applied Biocode



CIDT Benefits



- Faster results
- Targeted treatment
- Single test can detect or rule-out multiple pathogens (e.g., viruses, parasites, and bacteria)
- Unified laboratory workflow
- Likely more sensitive than culture
- Faster information for local public health action
- Data on agents not formerly available (e.g. ETEC)

Demise of GC Culture



- Rapid (hours)
- Urine specimen (vs urethral swab)
- Includes *Chlamydia trachomatis*
- High sensitivity/specificity
- No susceptibility data
- No public health strain tracking ability
- Specimen incompatible with culture

Challenges

➤ Patient management

- Interpretation issues
 - ❑ Viable, dead cells not distinguished
 - ❑ Multiple pathogens may be detected
- Empiric treatment only (based on R_x guidelines)
- High specificity

➤ Surveillance & outbreak management

- Interpretation issues
 - ❑ Back-to-school/work
 - ❑ Understanding trends
 - ❑ Case definitions
- No isolates for laboratory-based surveillance
 - ❑ Susceptibility monitoring, informs R_x guidelines
 - ❑ Outbreak detection / investigation (e.g. PulseNet)
 - ❑ Virulence monitoring



SHORT REPORT

The new variant of *Chlamydia trachomatis* was present as early as 2003 in Örebro County, Sweden, but remained undetected until 2006

Margaretha Jurstrand,^{1,2} Hans Fredlund,^{2,3} Magnus Unemo^{2,3}

ABSTRACT

Objectives In 2006, a new variant of *Chlamydia trachomatis* (nvCT) was reported in Sweden. Because of a cryptic plasmid deletion, the nvCT was undetectable by several of the genetic diagnostic systems used worldwide at the time. This study aimed to evaluate whether the nvCT was present in specimens obtained from patients attending the outpatient sexually transmitted infection (STI) clinic at Örebro University Hospital, Örebro, Sweden.

Jurstrand M, Fredlund H, Unemo M. Sex Transm Infect. 2013; Nov;89(7):607-8

INTRODUCTION

In October 2006, a new variant of *Chlamydia trachomatis* (nvCT) was reported in Sweden.¹ The nvCT has a 377 bp deletion on the cryptic plasmid. This cryptic plasmid deletion includes the DNA target sequences for the earlier versions of nucleic acid amplification tests (NAATs) from Roche Diagnostics and Abbott Laboratories, which at the time were widely used internationally.¹ Consequently, during several years, thousands of false-negative results were generated across Sweden. In 2008, both Roche Diagnostics and Abbott Laboratories had Conformité Européenne (CE) mark-certified novel dual-target NAATs capable of detecting nvCT.²

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Accurate Case Counts: Burden, Attribution, Trends

Foodborne Illness Acquired in the United States—Major Pathogens

Elaine Scallan,¹ Robert M. Hoekstra, Frederick J. Angulo, Robert V. Tauxe, Marc-Alain Widdowson, Sharon L. Roy, Jeffery L. Jones, and Patricia M. Griffin

RESEARCH

Foodborne Illness Acquired in the United States—Unspecified Agents

Elaine Scallan,¹ Patricia M. Griffin, Frederick J. Angulo, Robert V. Tauxe, and Robert M. Hoekstra

Estimates of foodborne illness food safety policy and intervention and passive surveillance and that each year 31 major pathogens caused 9.4 million episodes (95% confidence interval [CI] 6.6–13.1 million) (80% CI 36.534–75.065, CI 712–2,266). Most (58%) by *Salmonella*, followed by *Escherichia coli* (11%). *Campylobacter* spp. (15%), *Listeria monocytogenes* (15%), and *Toxoplasma gondii* (14%). These estimates cannot (1990) estimates to assess trends were used. Additional data can improve future estimates.

Estimates of the overall number of foodborne illnesses are helpful for allocating resources for food safety interventions. However, it is challenging because food is consumed by many agents (e.g., a variety of foods, and chemicals), transmission mechanisms (e.g., contact with contaminated water), the properties of food differ by pathogen and (and usually), and only a small are confirmed by laboratory testing health agencies.

Laboratory-based surveillance information for assessing foodborne disease. Author affiliation: Centers for Disease Control and Prevention, Atlanta, Georgia, USA. DOI: 10.3201/1441701.P1101

Emerging

Foodborne diseases are a leading cause of death in the United States. Each year, major illnesses in the United States caused 9.4 million episodes of foodborne illness, resulting in 55,961 deaths (1). (Hereafter, episodes as illnesses.) Although the most common pathogens in foodborne illness are well known, only a subset of the total illnesses are confirmed by laboratory testing health agencies.

An additional proportion of illness caused by a heterogeneous group of agents. First, many agents that cause foodborne illness are not identified by laboratory testing health agencies. Author affiliation: Centers for Disease Control and Prevention, Atlanta, Georgia, USA. DOI: 10.3201/1441701.P1201

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Emerging

COMMENTARY

How Safe Is Our Food?

J. Glenn Morris, Jr.

How safe is our food? Put another way, how much illness in the United States is caused by foodborne pathogens? It sounds like a simple question. Getting a reasonable answer, however, is far from simple. The basic problem lies in the fact that only a small fraction of foodborne disease cases get reported through official (or unofficial) reporting systems. Calculating the "real" rate of foodborne illness requires development of models that use reported cases as a starting point to estimate underlying disease rates. Given the plethora of pathogens that can be transmitted through foodborne routes, this is a complex, and somewhat daunting, process. It is, however, necessary for assessing the safety of foods and developing strategies for disease prevention. The articles by Scallan et al. (1,2) in this issue represent the latest efforts to develop such estimates of the magnitude of foodborne illness in the United States.

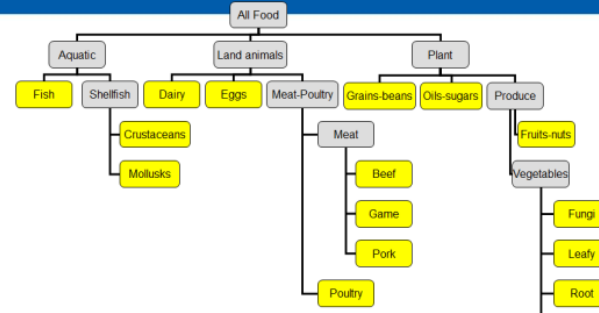
In 1999, Mead et al. (3) published initial estimates of foodborne illnesses in the United States. This landmark undertaking was the first to provide a comprehensive compilation of data from a variety of sources, including the Centers for Disease Control and Prevention (CDC) and the medical literature. It resulted in the often cited estimates that foodborne pathogens cause 76 million episodes of illness, 325,000 hospitalizations, and 5,000 deaths each year in the United States. (Hereafter, episodes of illness are referred to as illnesses.) During the past decade, these numbers have strongly driven ongoing efforts to implement and reform regulatory systems to protect the public from foodborne illness. However, some aspects of the methods have been criticized, particularly the high degree of uncertainty of particular parameters and then of the results themselves (4–6). These concerns have led to requests for CDC to repeat and update the work of Mead et al., using better methods and parameter estimates that more closely reflect current realities.

Now, <11 years later, Scallan et al. have produced "Sense of Mead," which include substantial improvements to the methods used by Mead et al. and to the quality and timeliness of data (1,2). Scallan et al. should be commended for this effort. Author affiliation: University of Florida, Gainesville, Florida, USA. DOI: 10.3201/1441701.C1021

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Emerging Infectious Diseases • www.eid.gov • Vol. 17, No. 1, January 2011

Hierarchical scheme for categorizing foods into commodities



Reliability in diagnostic test performance

Incidence of STEC infections in FoodNet, 2008–2011

2011: 60 (36%) of 184 broths sent public health laboratories could be confirmed as Shiga toxin-positive



Notifiable Disease Case Definitions



Council of State and Territorial Epidemiologists

4. State health departments should create a variable to distinguish CIDT-diagnosed probable *Salmonella* cases from probable cases that are epidemiologically linked to a culture-confirmed or CIDT-diagnosed case. This differentiation of probable cases will facilitate assessment of the impact of CIDT on surveillance.
5. Likewise, CDC should include a variable to distinguish CIDT-diagnosed probable cases from probable cases that are epidemiologically linked in the disease-specific Message Mapping Guide (MMG), to assess the impact of CIDT on surveillance.
6. State health departments should attempt to capture the type(s) of *Salmonella* testing performed for reported salmonellosis cases. This could include surveys of laboratory testing practices, capture of LOINC and SNOMED codes from electronic laboratory reporting, or other methods.

http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/2016PS/16_ID_03.pdf



Challenges

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- High specificity

➤ Surveillance & outbreak management

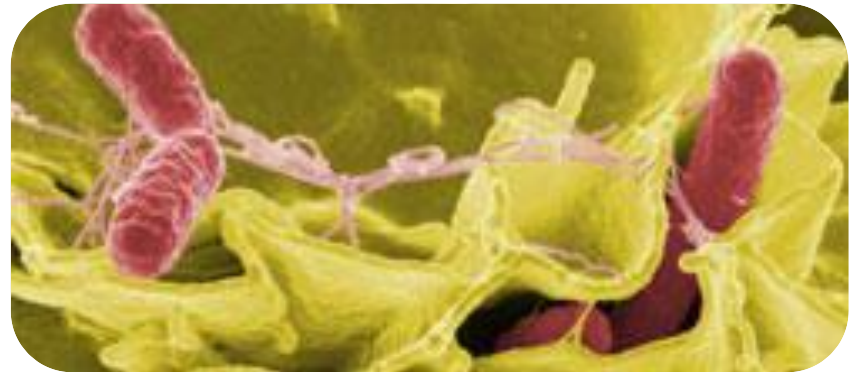
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 - ❑ Virulence monitoring





Foodborne illness in the U.S.

- 48,000,000/yr
- 3,000 deaths

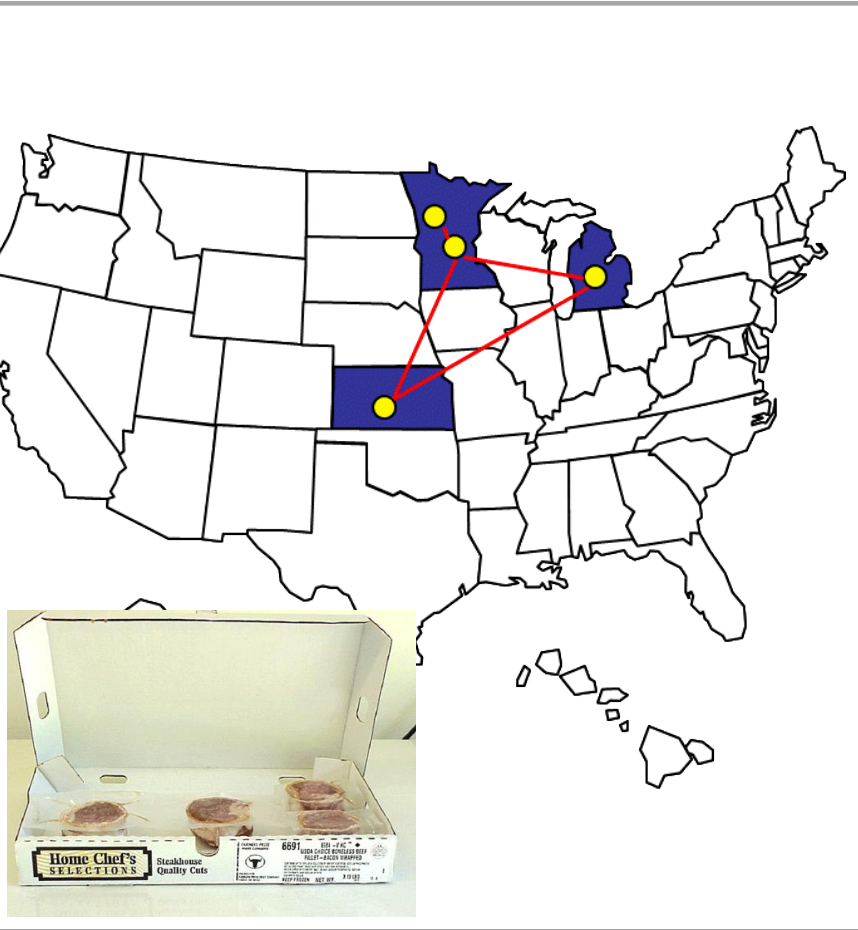


“That's an unacceptable price to pay for contaminations that are mostly preventable.”

– Kathleen Sebelius, Secretary of Health and Human Services

Pathogen-Specific Laboratory-based Surveillance

- Often widely dispersed
- Best way to discover new food production and distribution problems



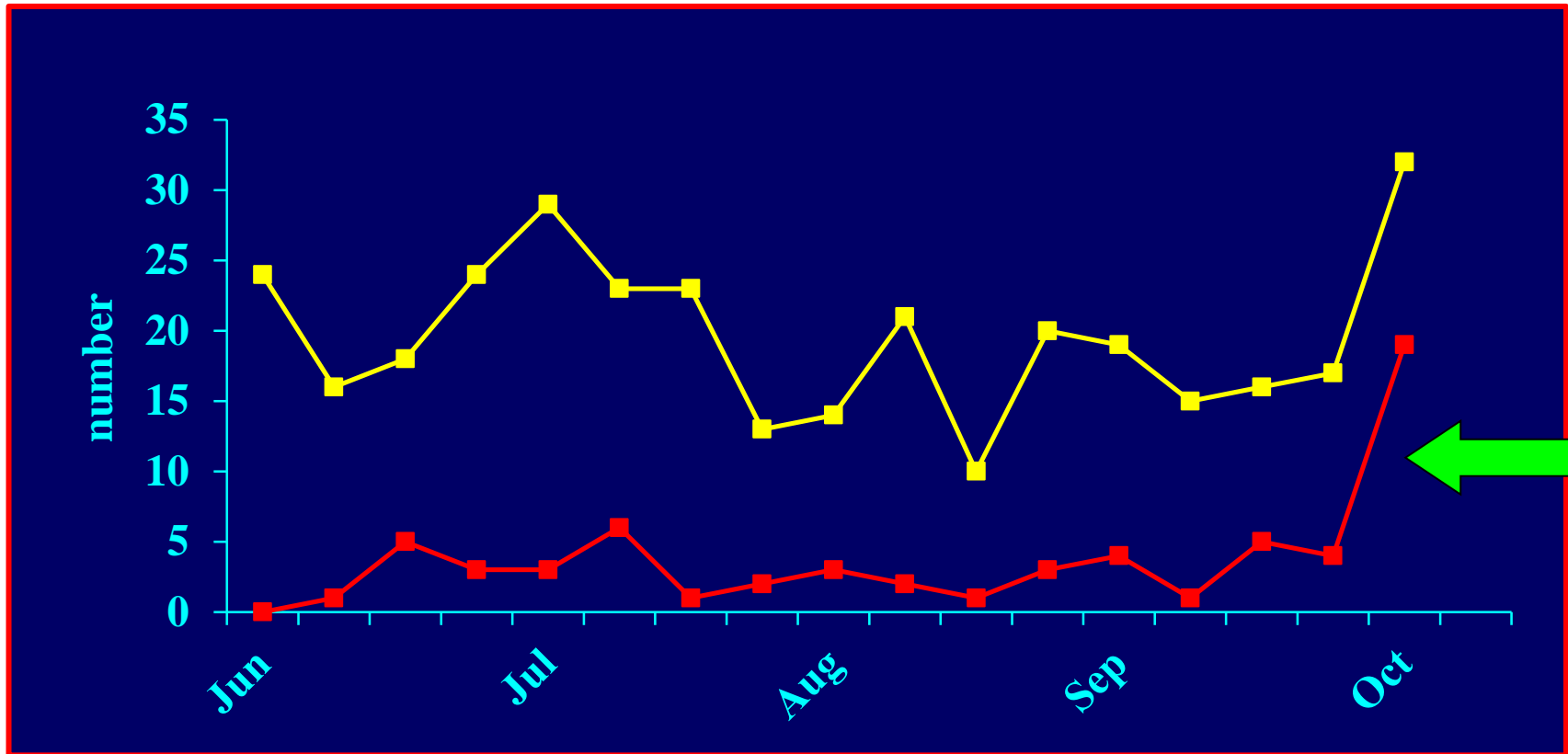
Ice-Cream Associated Outbreak; U.S.A., 1994



>250,000 cases
48 States

Salmonellosis Cases

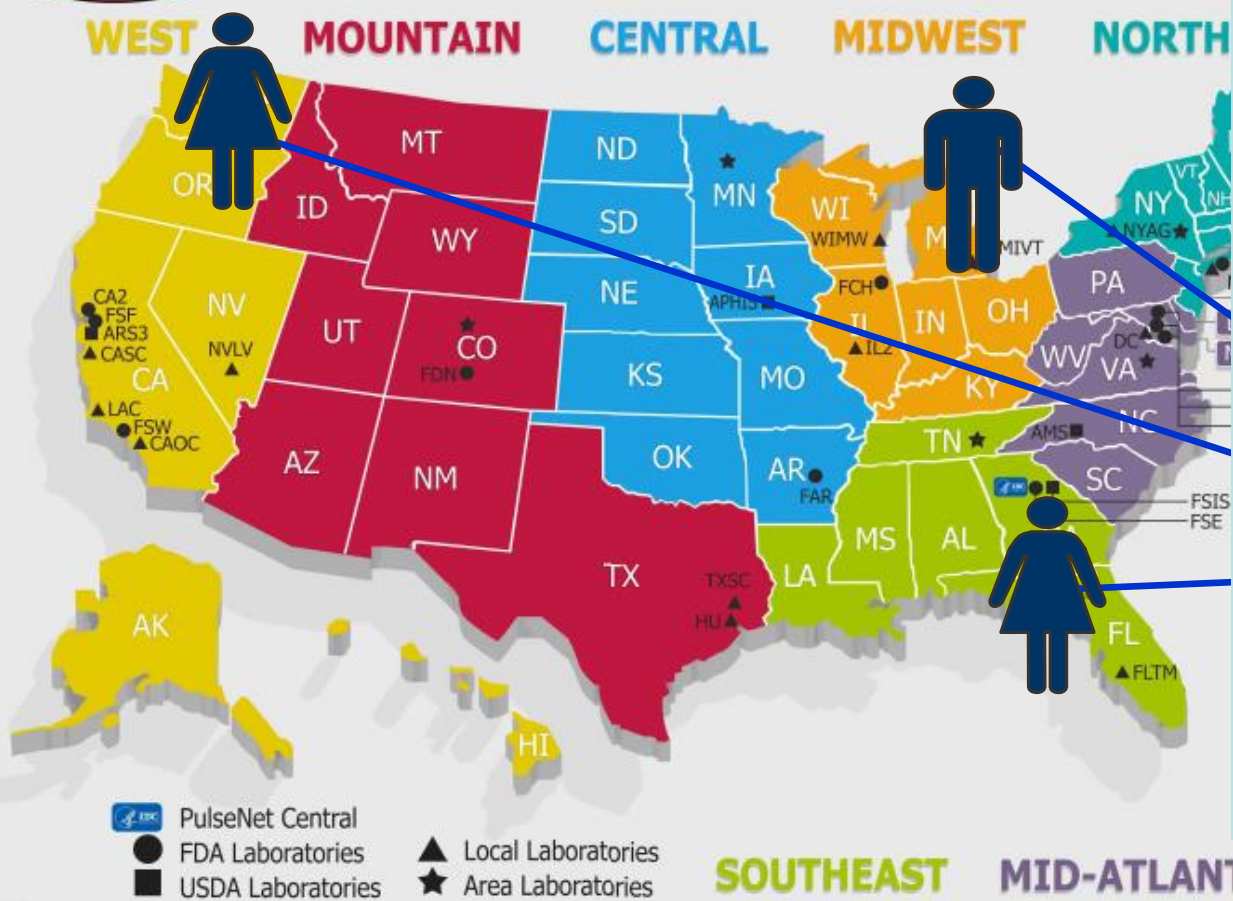
Minnesota; June – October 1995



—■— *Salmonella* spp. —■— *Salmonella* Enteritidis



The National Molecular Subtyping Network for Foodborne Disease Surveillance



Human disease surveillance



Food monitoring



Food animal surveillance

What Is PulseNet?



National Cluster Investigations: 30 – 60 monitored per week

10/1/10	+	10/1/10	10/1/10	10/1/10
10/2/10	+	10/2/10	10/2/10	10/2/10
10/3/10	+	10/3/10	10/3/10	10/3/10
10/4/10	+	10/4/10	10/4/10	10/4/10
10/5/10	+	10/5/10	10/5/10	10/5/10
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10/30/10	+	10/30/10	10/30/10	10/30/10
10/31/10	+	10/31/10	10/31/10	10/31/10

Outbreak Response Team Weekly Unit Meeting

Active Clusters

Monday, August 05, 2013

All data are considered preliminary and subject to change. Document not for distribution.

Outbreak Log	Last wk on RL/HHS	#Wks FU	Isolate dates	Etiologic agent	Total ill	Total new	Last PN LL request	PN cluster # PN pattern	PFGE in top5	Epi contact	Surv Epi	Priority	Comments
PATHOGEN: <i>E. coli</i> (n=2)													
2013-0117	07/10	7	05/29/13 07/12/13	<i>E. coli</i> O157:H7	12	2	07/29	1306MAEXH-1 EXHX01.0530 EXHA26.2371	<input type="checkbox"/>	Nguyen	Nguyen	Hypoth Generati ng	Cluster of KY cases reported at from primary cluster. Requesting (earlier cluster: MA restaurant cl
monitoring													
2013-0149		3	06/09/13 06/30/13	<i>E. coli</i> O111	8	0	08/02	1307MLEXD-1 EXDX01.0938 EXDA26.0692	<input type="checkbox"/>	Heiman	Heiman	Hypoth Testing	8 confirmed cases from resident has petting zoo that campers visit. Sample from goat yielded STEC patient did not travel to MO. Pati with both O111 and O121 - both
petting zoo/camp in MO. probably close soon.													
PATHOGEN: <i>Hepatitis</i> (n=1)													
2013-0096	06/05 07/17	10		<i>Hepatitis</i> A	147			none	<input type="checkbox"/>	Collier		Vehicle Identifie d	6/4/2013: Cluster consists of 49 investigation in seven states: CO and UT (3). Cases are mainly ci (73%) recalled eating and have removed
nothing new.													
PATHOGEN: <i>Listeria</i> (n=4)													
2013-0130	07/17 07/31	5	05/20/13 06/17/13	<i>Listeria</i> monocytogen	7			1307MNGX6-1 GX6A16.0016 GX6A12.0003	<input type="checkbox"/>	Jackson/Sil k	Jackson	Vehicle Identifie d	Seven cases. All five interviewe ate Brand X cheese. Manufactur indistinguishable from the current. Retail samples collected in MN p
was info next Monday. Cheese													
2013-0145		3	04/16/13 07/05/13	<i>Listeria</i> monocytogen	5			POB1307GX6-1 GX6A16.0029 GX6A12.0069	<input type="checkbox"/>	Jackson/Sil k		Monitor	Matching parsley isolate. No exp
now 1308MLGX6-1													

State Cluster
Investigations:
1,500 – 2,000 per year



August 29, 2014



Cantaloupe



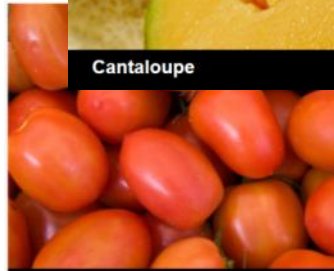
Chicken



celery



Peanut butter



Roma tomatoes



Cantaloupe



Eggs



Ground turkey



Cantaloupe



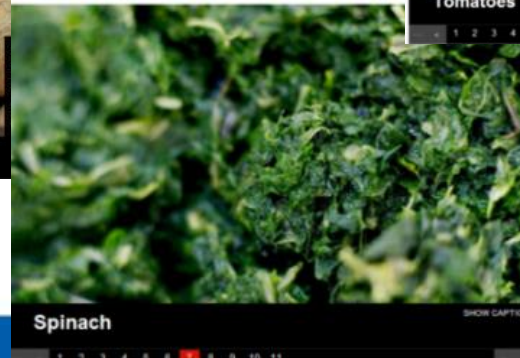
Tomatoes



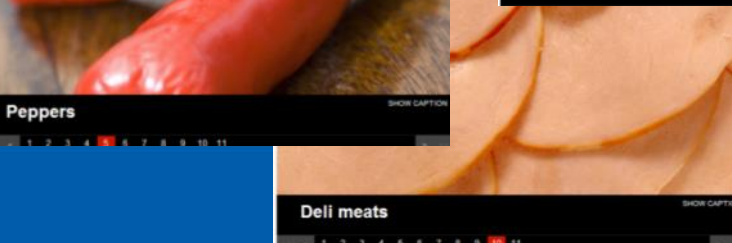
Tuna



Peppers



Spinach



Deli meats



Ricotta cheese

PulseNet Cost Effectiveness (Pre-WGS)

ARTICLE IN PRESS

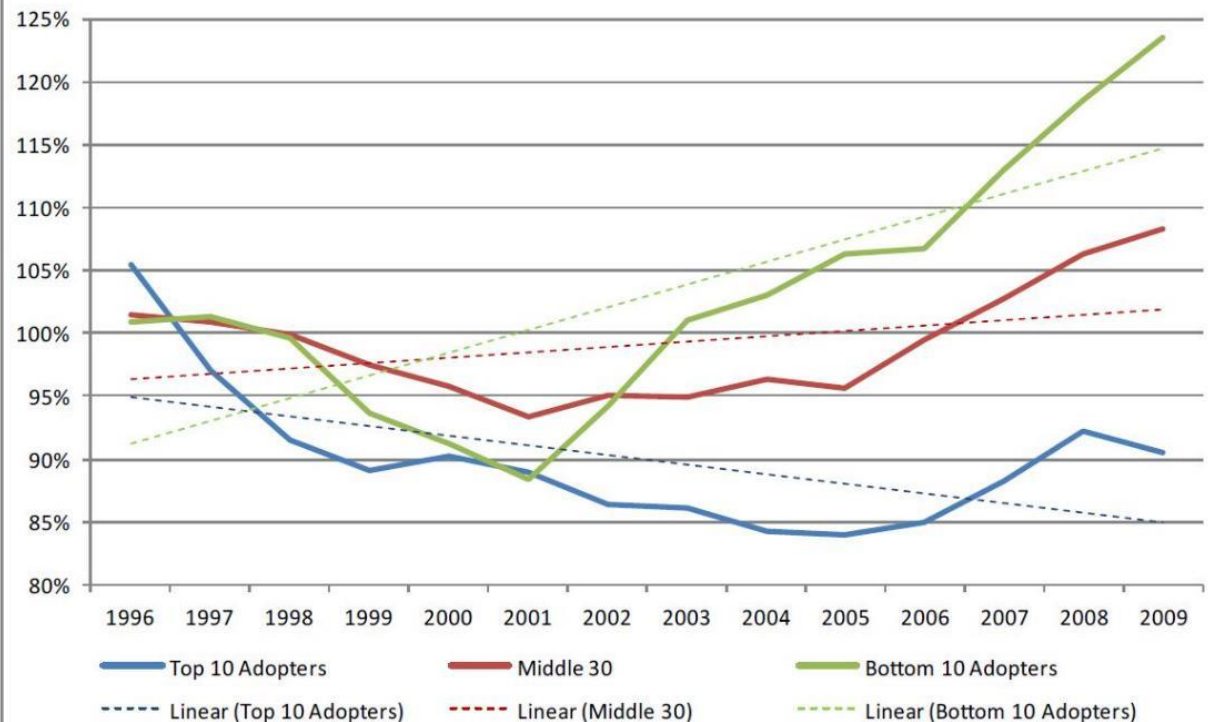
An Economic Evaluation of PulseNet A Network for Foodborne Disease Surveillance

Robert L. Scharff, PhD, JD,¹ John Besser, PhD,² Donald J. Sharp, MD,² Timothy F. Jones, MD,³
Peter Gerner-Smidt DMS, MD,² Craig W. Hedberg, PhD⁴

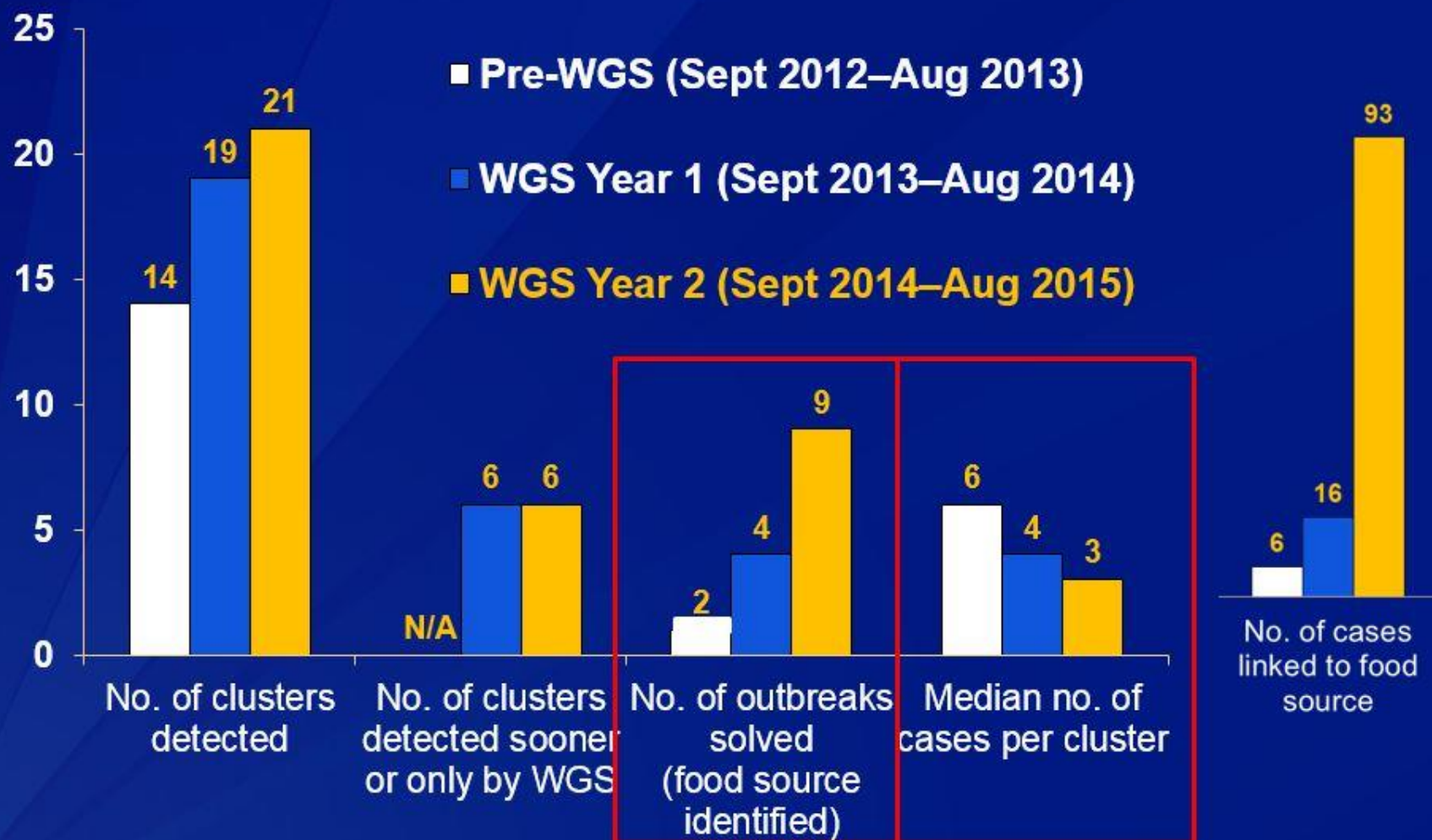
The PulseNet surveillance system is a regulatory agency laboratories designed to detect and control foodborne outbreaks. This study estimates health care costs associated with the staggered adoption of PulseNet across the United States, which is measured as reduced medical costs, enhanced industry accountability, and reduced food waste.

- ❑ >270,000 illness prevented/year
- ❑ >\$507,000,000 saved per year

Reported *Salmonella* Illnesses for PulseNet Adopters
(relative to 1994-96 baseline - 3 year moving average)



Listeria Cluster Metrics Before and After WGS



Food Poisoning Bulletin

Listeria Outbreak Linked to Oasis Cheese Ends

December 11, 2014 by Carla Gillespie



1 dead, 2 hospitalized after listeria outbreak linked to

FDA shuts down Roos Foods cheese plant over listeria outbreak

©CBSNEWS



Stone fruit recall widens on possible Listeria outbreak

Karma Allen | @lam_karma

Monday, 4 Aug 2014 | 4:31 PM ET

CNBC



1 dead, 11 others hospitalized in listeria outbreak linked to Dole salads

Rectangular Salads



Liz Szabo, USA TODAY 6:50 p.m. EST January 22, 2016



35 COMMENT EMAIL

A listeria outbreak linked to Dole packaged salads has hospitalized 12 people in six states in the past six months, including a Michigan resident who died of the illness, the Centers for Disease Control and

Recalled Bean Sprouts Linked to 2 Listeria Deaths, 3 Hospitalizations

NEWS DESK | NOVEMBER 8, 2014

to people have died and three others have been hospitalized after eating Listeria-contaminated bean sprouts produced by wholesome Soy Products of Chicago, according to the U.S. Centers for Disease



Listeria Outbreak Leads to Massive Frozen Food Recall in 50 States

by Whitney Fillion May 4, 2016, 9:34 AM @whitneyfillion

SHARE (0/0) TWITTER



DON'T MISS STORIES. FOLLOW EATER

The Seattle Times
Winner of Nine Pulitzer Prizes

Originally published January 30, 2015 at 1:02 PM | Page modified January 31, 2015 at 12:27 AM

Snoqualmie making ice cream again after listeria problems resolved

Snoqualmie Gourmet Ice Cream Inc., which supplies ice cream, gelato, custard, sorbet and other products to Seattle-area stores and resumed production after listeria at the Snohomish plant sickened two men.

By PAULA COHEN CBS NEWS March 18, 2016, 4:12 PM

Deadly listeria outbreak linked to raw milk



A 2014 listeria outbreak has been traced to raw milk

Comment / Share / Tweet /

Last Updated Mar 22, 2016 10:12

Health officials say a deadly outbreak of listeria linked to an organic farm in Pennsylvania.

Whole Genome Sequencing Pinpoints Single Case and Potential New Listeria Source



Blue Bell Recalls All Products After Listeria Outbreak

By AUSTIN RAMZY APRIL 21, 2015



Blue Bell Creameries faced its first recall in its 108-year history last month.
Orlin Wagner/Associated Press

Blue Bell Creameries, which distributes frozen desserts to about half of the United States, said that it was voluntarily recalling all of its products after the bacteria listeria was found in two cartons of ice cream.

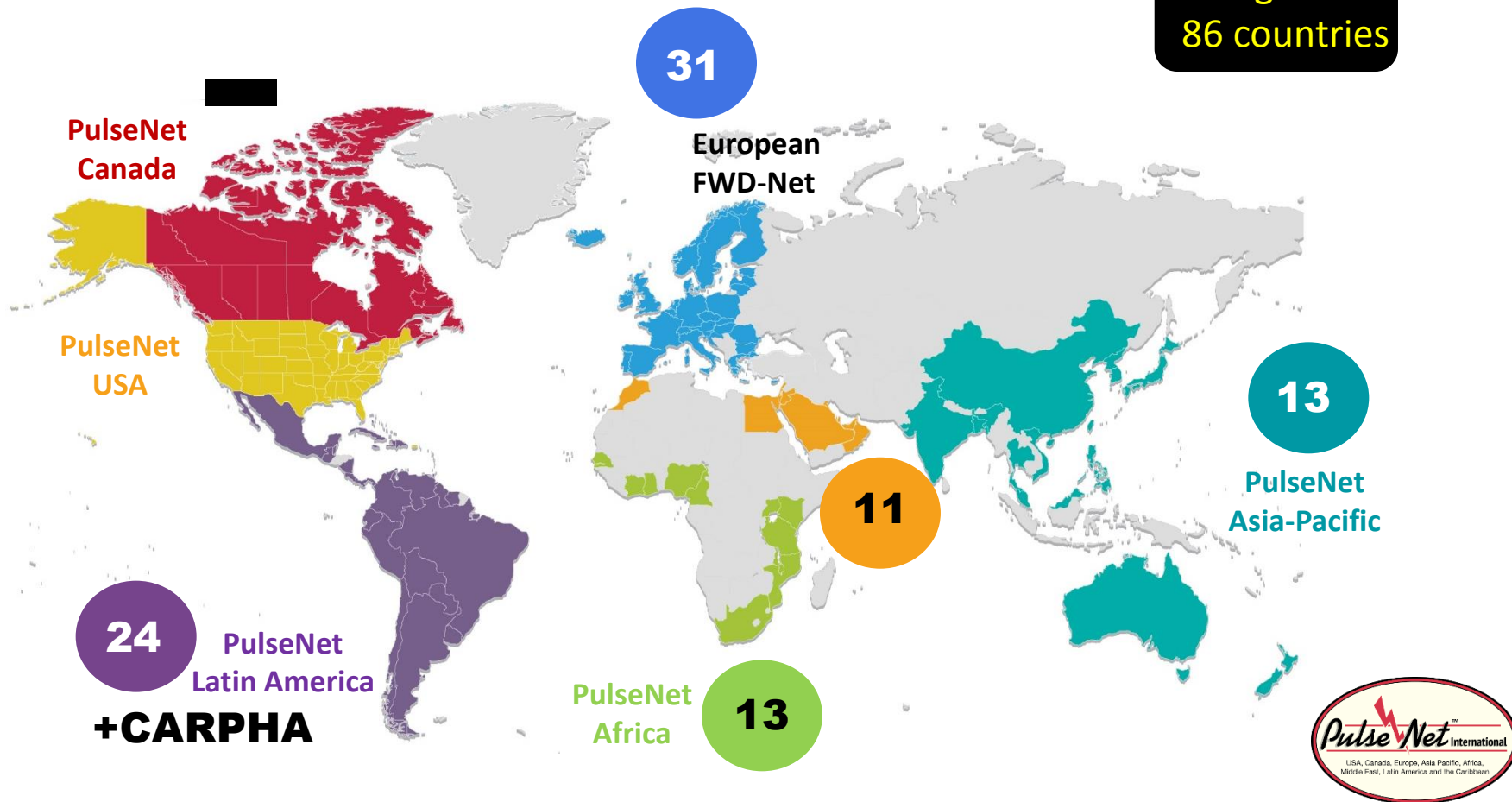
The United States [Centers for Disease Control and Prevention](#) said on Monday that tests indicated Blue Bell products from plants in Texas and Oklahoma were the source of a listeria outbreak that has infected five adults in Kansas, three of whom died, and has sickened another three adults in Texas.

"This is a complex and ongoing, multistate outbreak of listeriosis occurring over an extended period of several years," the C.D.C. said.

Email

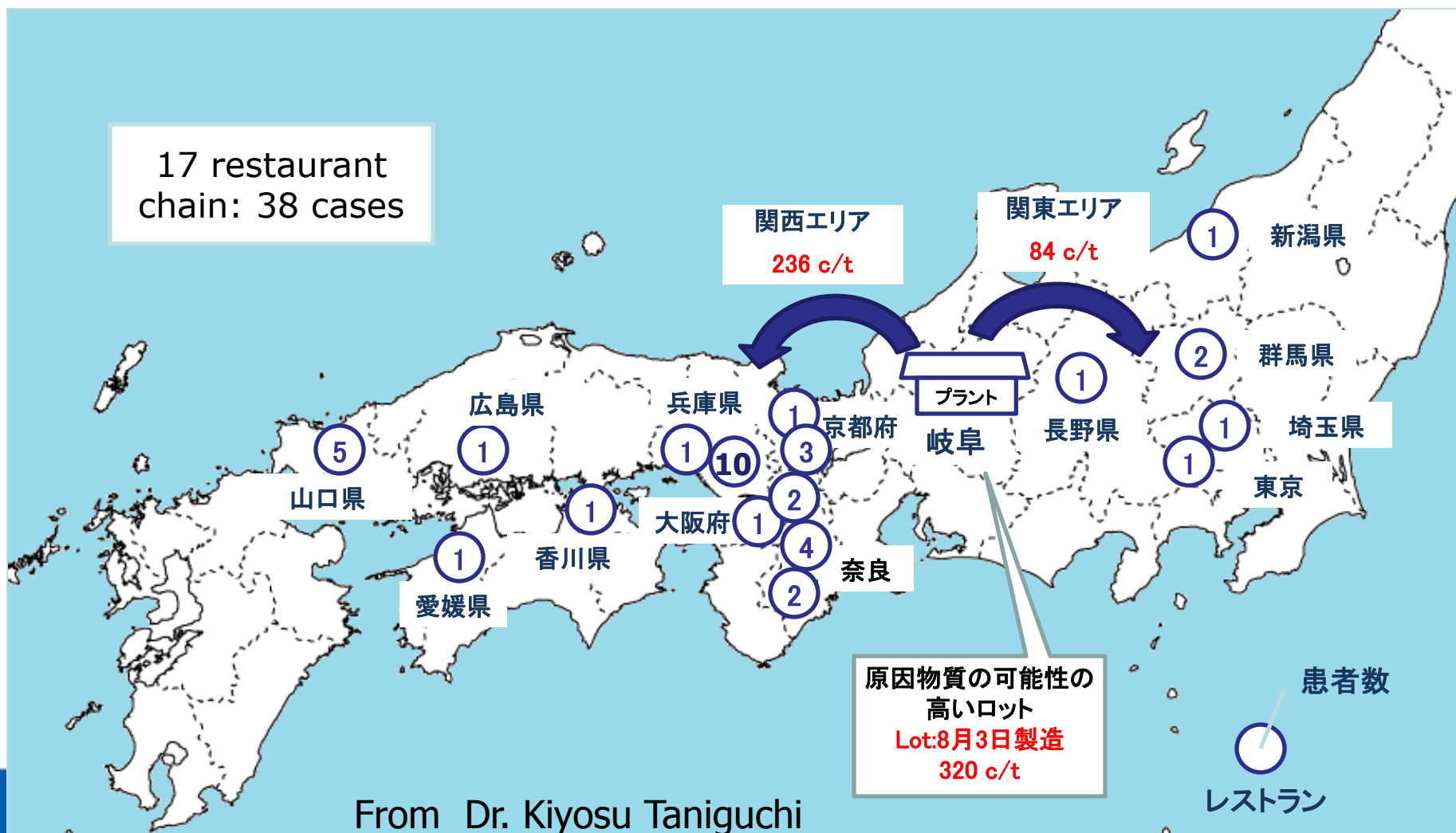
PulseNet International

7 Regions
86 countries



Diffuse outbreak of EHEC caused by molding meat manufactured by one factory

17 restaurant chain: 38 cases



From Dr. Kiyosu Taniguchi

PulseNet: Isolate Dependency



Method	Isolates Required?
PFGE	Yes
MLVA	Yes
WGS	Yes

A Conundrum....



The adoption of new laboratory tests which will likely *improve* patient care, could result in *hundreds of thousands of additional cases per year*....unless we take appropriate action.

CDC Plan to Adapt to CIDTs (Isolate Issue)

1. *Preserve cultures*

**Surveillance by
current methods**
(serotyping, AST,
PFGE, MLVA etc.)

2. *Build a sequence-based infrastructure*

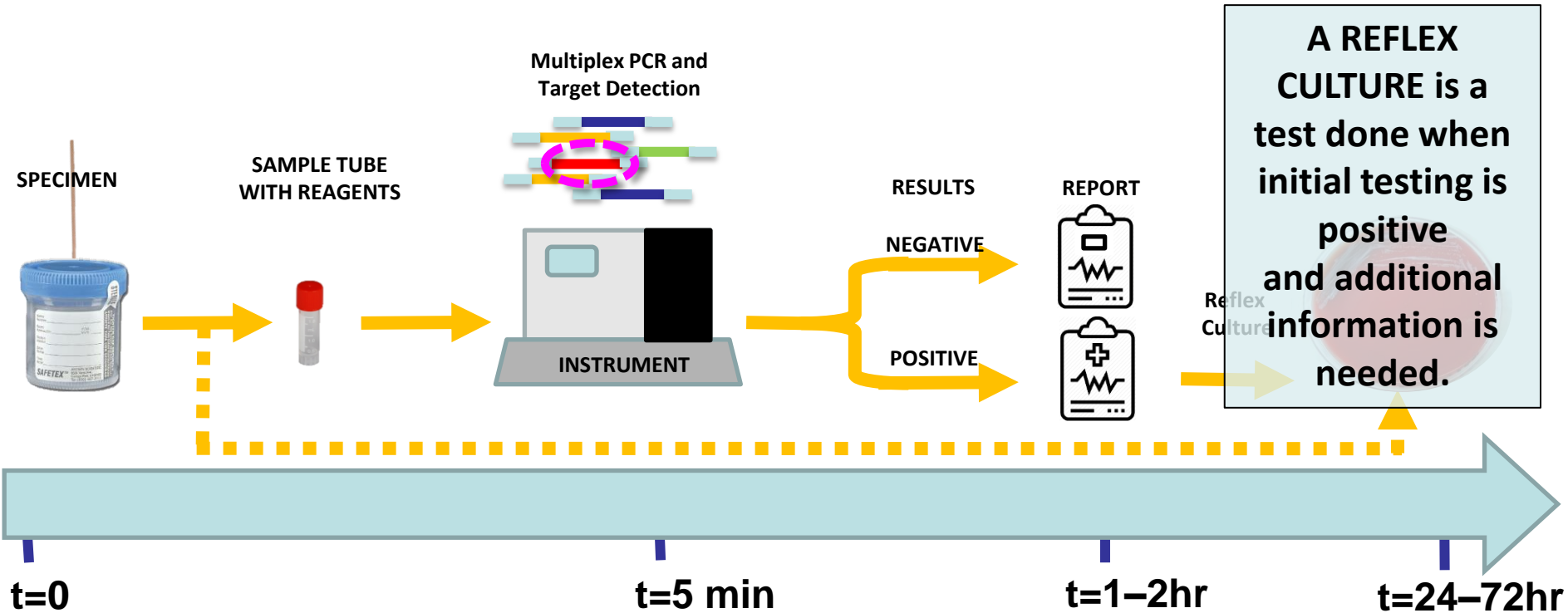
**Surveillance by
whole genome
sequencing
(WGS)**

3. *Culture- independent methods*

**Surveillance by
direct
characterization
in specimens**



Multiplex PCR Panels – Generic Workflow

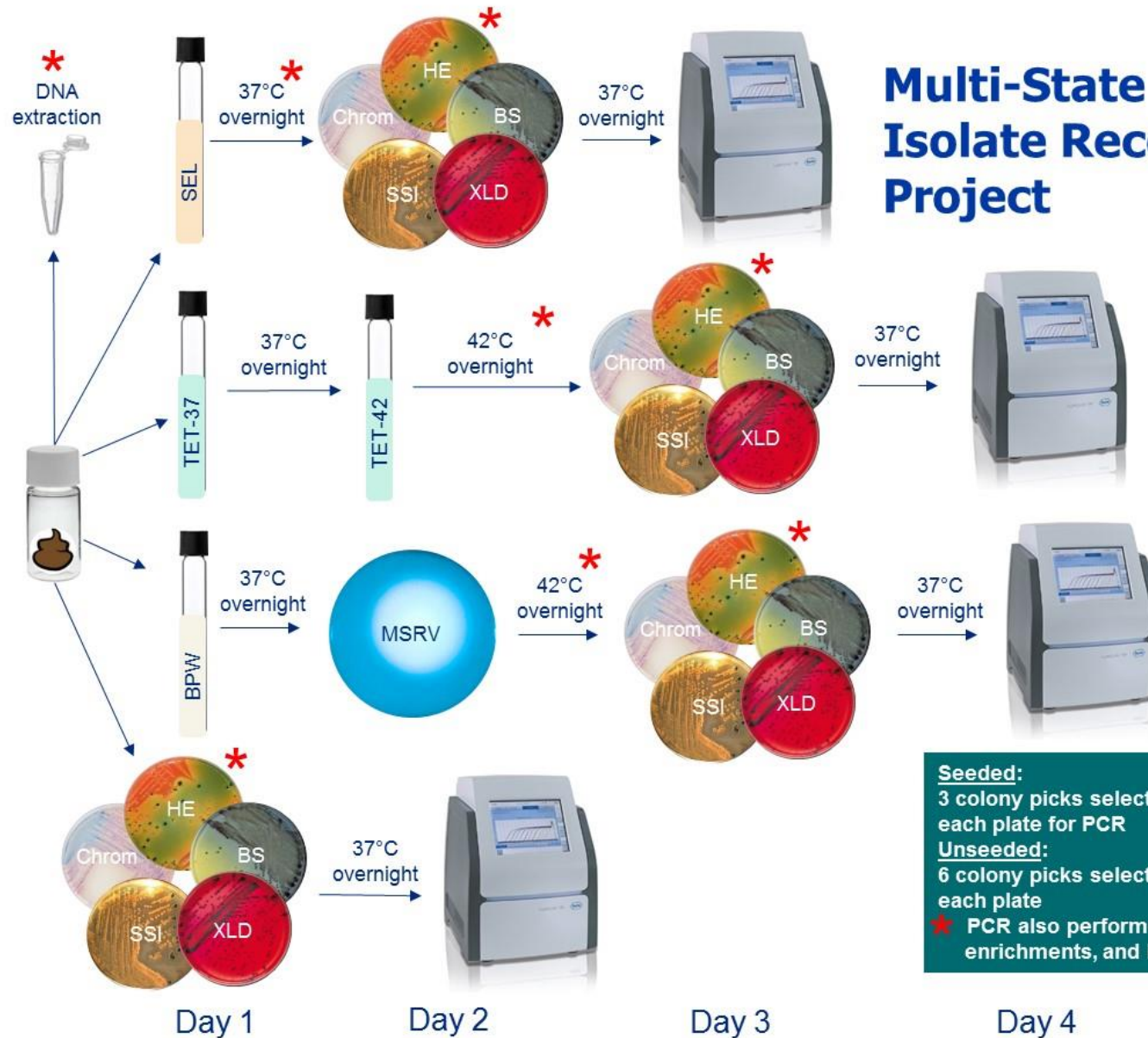


Strategies for Preserving Isolate Availability



- ☐ Development of streamlined pathogen-specific isolate recovery protocols
- ☐ Making sure reflex culture is possible
- ☐ Encouraging reflex culture

Multi-State Isolate Recovery Project



Seeded:
3 colony picks selected from each plate for PCR

Unseeded:
6 colony picks selected from each plate

★ PCR also performed on DNA, enrichments, and HEK

Strategies for Preserving Isolate Availability



- ☐ Development of streamlined pathogen-specific isolate recovery protocols
- ☐ Making sure reflex culture is possible
- ☐ Encouraging reflex culture

Encouraging Reflex Culture



- ☐ Provide public health information in product inserts
- ☐ Seek reimbursement mechanisms for laboratories
- ☐ Guide states in development of disease reporting rules

"Regulatory" Workgroup

Test Regulation	Laboratory Regulation	Test Reimbursement	Reporting Rules, state capacity (culture of +'s)	Test Development
FDA-Device Licensure	CLIA, CAP, Joint Commission	CMS AHIP	State Governments, APHL, CSTE	Medical Device Industry (Advamed)

Also represented: IDSA, CDC/OID/NCHHSTP; CDC/OSELS/LSPPO



Regulatory Workgroup Products

- ❑ Product insert language
- ❑ Information packets for device industry
- ❑ Model language for State Reporting Rules
- ❑ Document exploring laboratory reimbursement for reflex culture

Suggested Public Health Language to be included in the precaution statement of package inserts for newly cleared or approved molecular multi-analyte gastrointestinal disease agent detection panels

Precaution related to Public Health Reporting: Local, state, and federal rules and regulations for notification of reportable diseases are continually updated and include a number of organisms that are important for surveillance and outbreak investigations.¹⁻². Laboratories are responsible for following their state and/or local rules pertaining to reportable pathogens and should consult their local and/or state public health laboratories for isolate and/or clinical sample submission guidelines.

1. Summary of Notifiable Diseases. MMWR

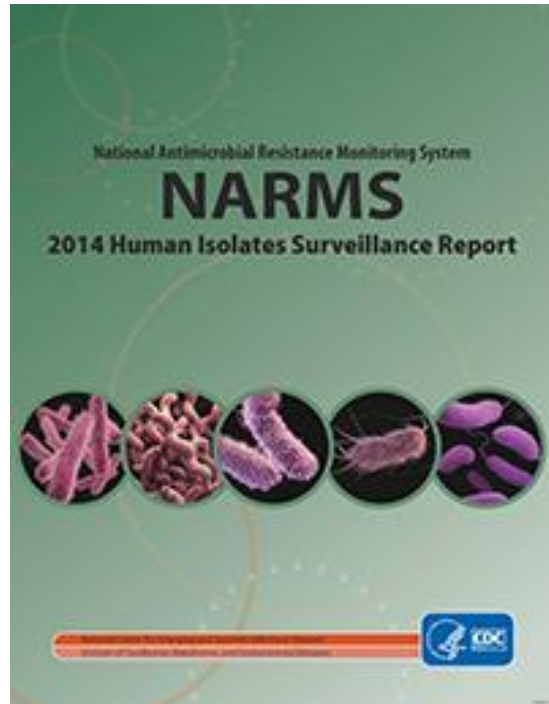
<http://www.cdc.gov/mmwr/PDF/wk/mm6153.pdf>

2. CIFOR Analysis of State Legal Authorities.

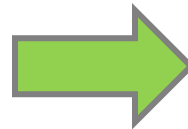
<http://www.cifor.us/documents/CIFORAnalysisStateLegalAuthorities.pdf>



Antibiotic Susceptibility Monitoring



Sentinel isolate-based
surveillance



Treatment Guidelines

CDC Plan to Adapt to CIDTs (Isolate Issue)

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(serotyping, AST,
PFGE, MLVA etc.)

2. *Build a sequence-based infrastructure*

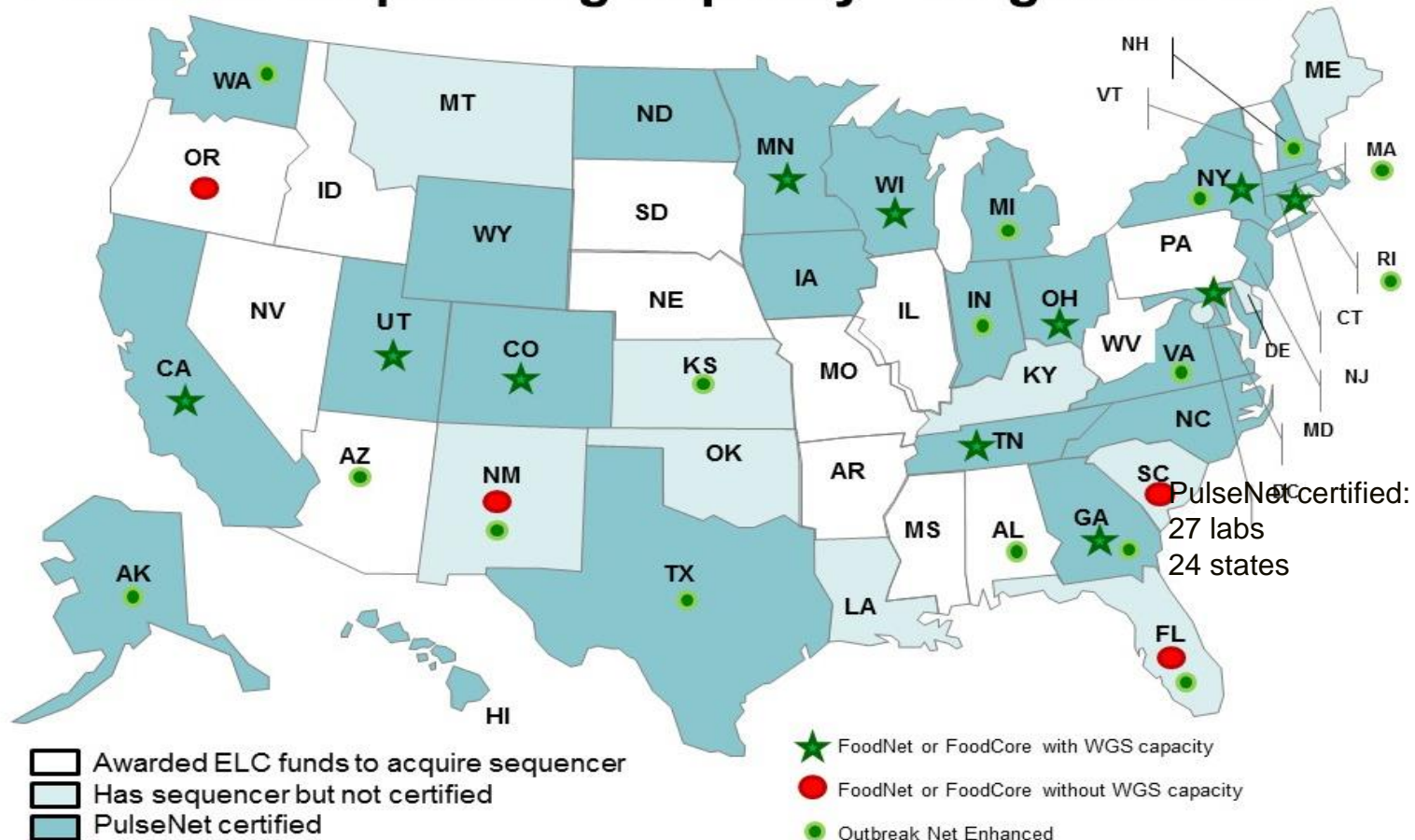
**Surveillance by
whole genome
sequencing
(WGS)**

3. *Culture- independent methods*

**Surveillance by
direct
characterization
in specimens**

Whole Genome Sequencing Capacity In The States

PulseNet Sequencing Capacity – August 2016



Lab Perspective: Current and Future Activities

1. *Preserve cultures*

**Surveillance by
current methods**
(serotyping, AST,
PFGE, MLVA etc.)

2. *Prepare for the future working on pure cultures*

**Surveillance by
whole genome
sequencing
(WGS)**

3. *Culture- independent methods*

**Surveillance by
direct
characterization
in specimens**



Why Develop Direct-from-specimen Tests to Characterize Pathogens?

- **Specimen compatibility with commercial systems**
 - Even if biologically inactivated
- **Reduced time to actionable results**



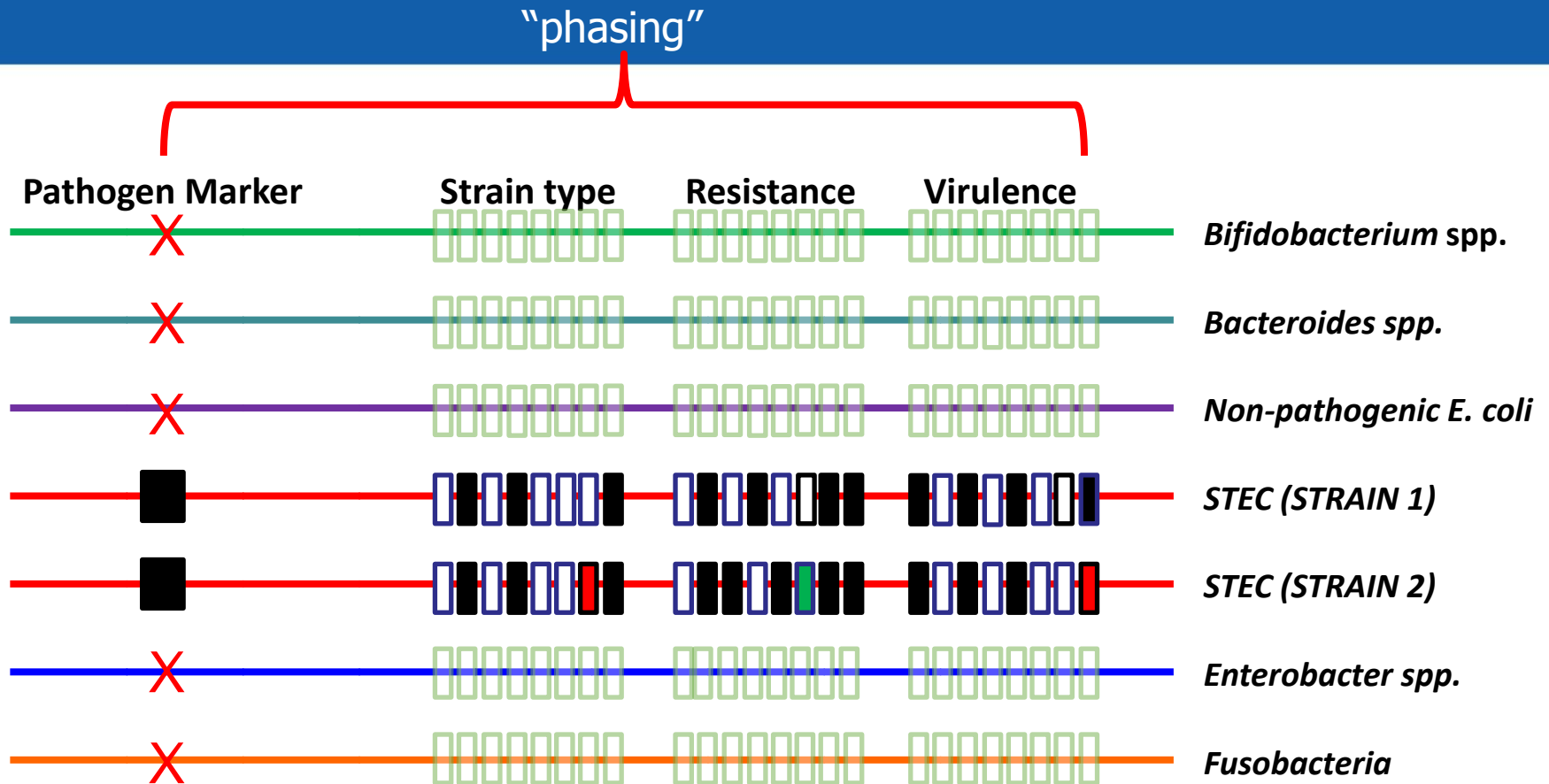
Human Feces



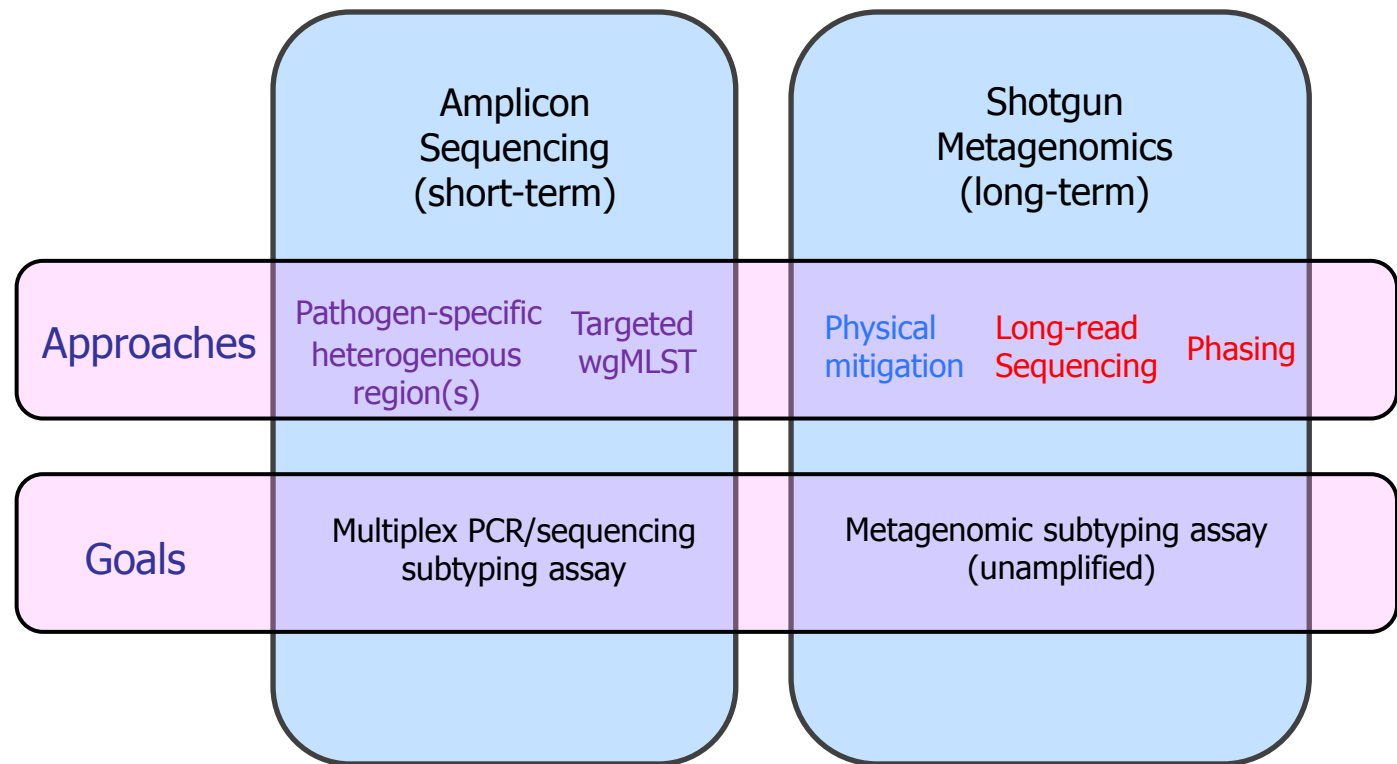
Science. 336:8 1246-1247

- Microbial genomes; ~1,000 species per person, ~100 billion organisms/gram
 - Bacteria
 - Viruses
 - Parasites
 - Fungi
- Other genomes
 - Human
 - Food Animals
 - Plants
- Some pathogens genetically similar to commensal flora

Direct-from-stool Pathogen Characterization



CIDT Challenge: to obtain pathogen subtyping data directly from patient stools given low signal:noise and presence of related commensal bacteria



CIDTs and Public Health: Medical Device Industry

- ❑ During CIDT Design Phase, consider public health implications
 - Specimen collection and storage (to maintain pathogen viability)
 - Product insert language
 - Consider downstream implications of product design....e.g. ability to harvest DNA from device for public health purposes



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The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention

