



CDC Update on Culture Independent Diagnostic Test (CIDT) Issues

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CDC/NCEZID/DFWED



CDC Update on Culture Independent Diagnostic Test (CIDT) Issues

- Background
- What has changed since 2012?
- Where is diagnostics/public health headed?
- What are the current needs?

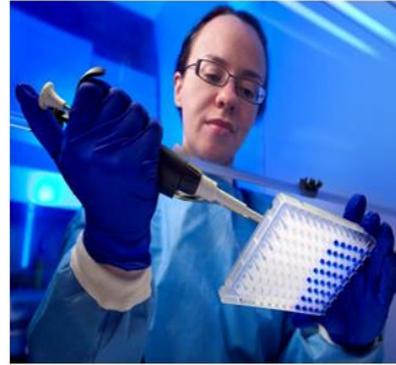
Diagnostic Microbiology Methods



1860s:
Culture-based
tests



1980s-90s:
Antigen-based
tests



2000s:
PCR tests



2010s:
Multiplex PCR panels

Culture-independent diagnostic tests (CIDTs)

Number and Types of Culture-independent Diagnostic Tests Are Increasing

2011

Antigen-based tests (FDA approved)

- 3 tests for Campylobacter
- 2 tests for Shiga toxin

2016

Antigen-based tests (FDA approved)

- 3 tests for Campylobacter
- 5 tests for Shiga toxin

Laboratory-developed tests (not FDA approved)

- Molecular detection (PCR) tests for single or multiple pathogens

Syndromic multiplex PCR panels (FDA approved)

- [Luminex](#)
- [Nanosphere](#)
- [ProGastro](#) SSCS
- [BD Max](#)
- [BioFire](#)
- [Verigene](#) BC

The Benefits of Using CIDTs for Diagnosis



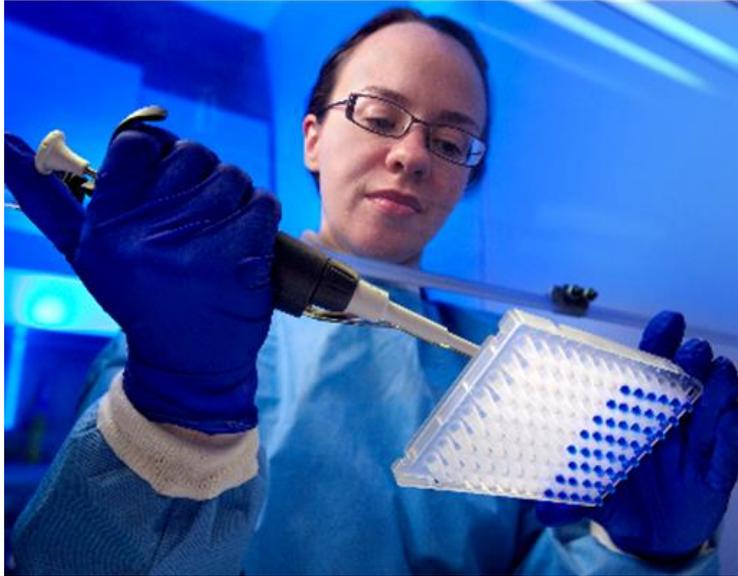
- Faster results
- Targeted treatment
- Single test can detect or rule-out multiple pathogens (e.g., viruses, parasites, and bacteria), including some for which there was previously no practical test (e.g. ETEC, HMPV)
- Likely more sensitive than culture
- Faster information for local public health action

Challenges of Using CIDTs for Diagnosis



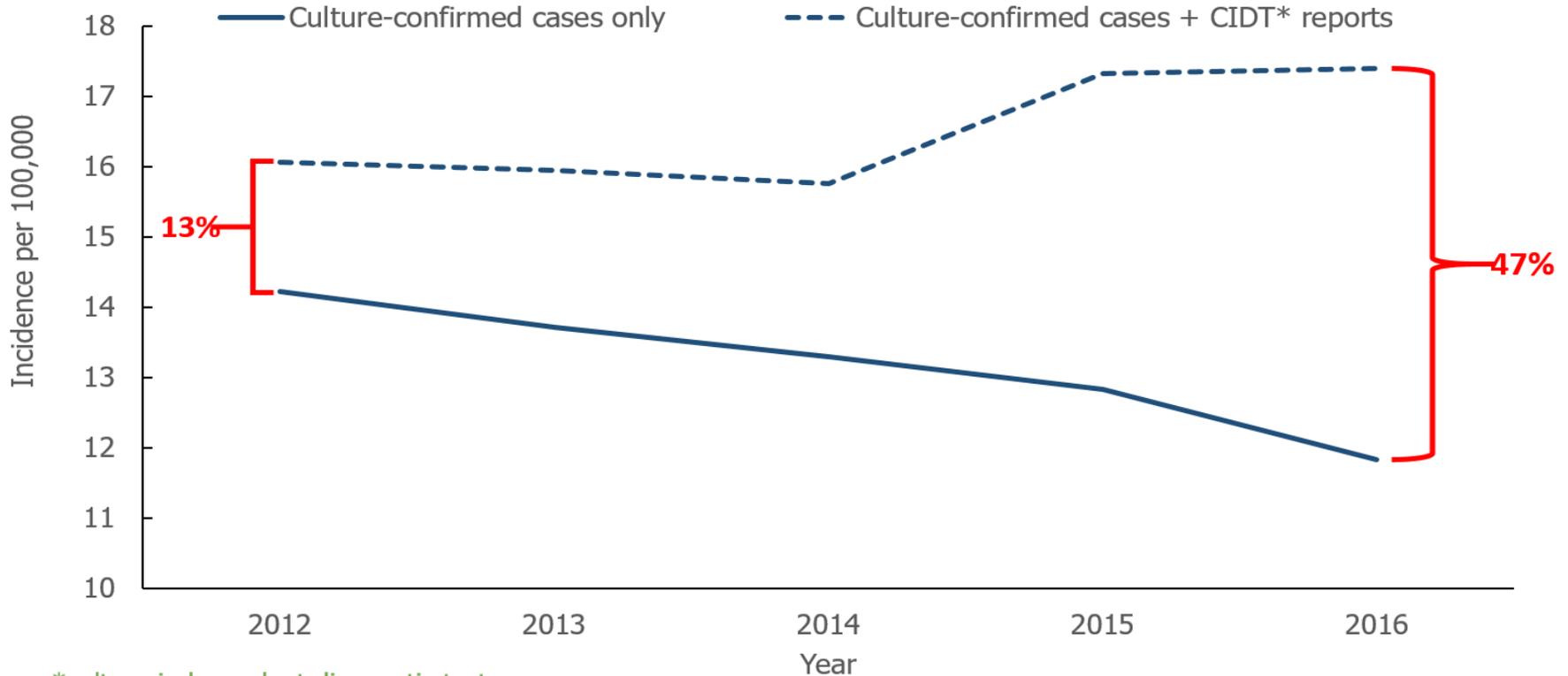
- Interpretation:
 - Uncertain meaning of some targets (e.g. EPEC)
 - Multiple positive analytes in single specimens
 - Does not distinguish between viable/non-viable cells
- No susceptibility information (and specimen may be incompatible with culture-based susceptibility tests)
- Reimbursement issues

CIDT Impacts on Public Health Activities



- Difficulty monitoring trends
 - Variable performance characteristics (different from culture)
 - Use characteristics (e.g. screening vs diagnosis of acute illness, test-of-cure) may be different from culture. Ease-of-use or cost may change testing patterns
 - Potential for agent evolution in response to test (who monitors for this?)
- No isolates produced
 - Surveillance activities (e.g. outbreak detection, susceptibility monitoring) currently depends on isolates

Incidence of *Campylobacter* Infection by Case Type — FoodNet, 2012–2016



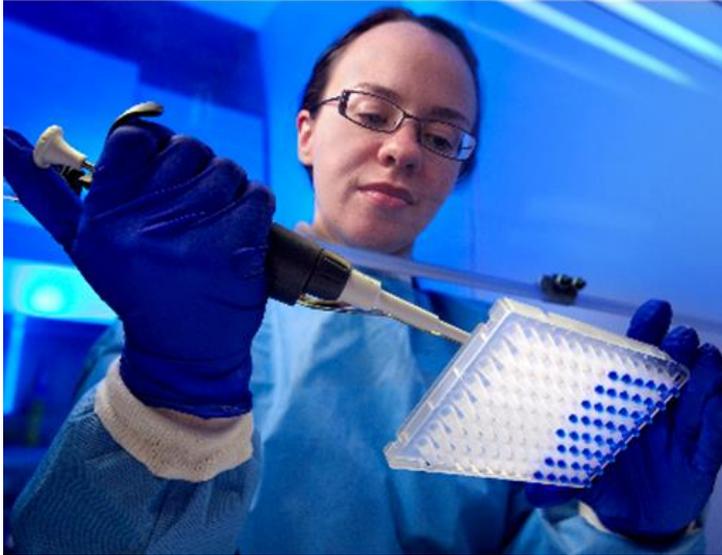
*culture-independent diagnostic tests

“Test-of-cure” testing strategies for exclusion from work/school during outbreaks

Strategy
Detect and monitor cases by culture
Detect and monitor cases by CIDTs
Detect cases by CIDT, monitor with culture
Detect cases with culture, monitor with CIDTs
Detect cases by CIDT, monitor with CIDTs and culture
Detect and monitor cases by culture and CIDTs

- Pros and cons for each strategy
- Multiple interpretation issues
- CLIA issues (e.g. non-intended use)?

CIDT Impacts on Public Health Activities



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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

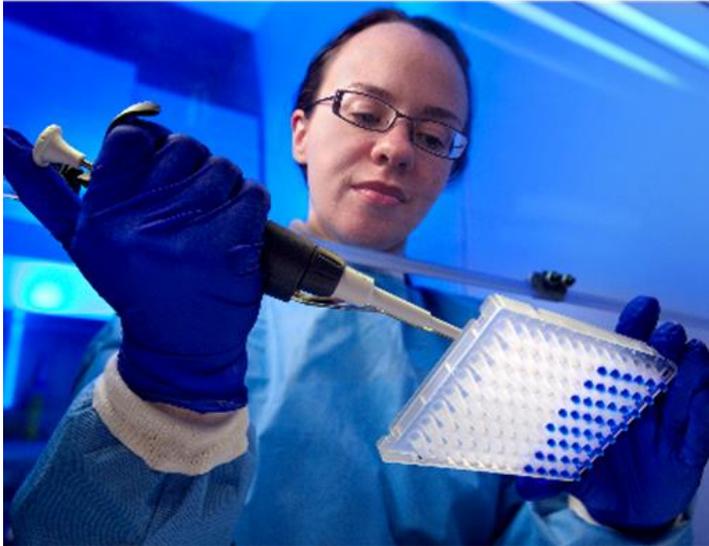
Objectives In 2006, a new variant of *Chlamydia trachomatis* (nvCT) was reported in Sweden. Because of a cryptic plasmid deletion, the nvCT was undetectable in several of the genetic diagnostic systems used worldwide at the time. This study aimed to evaluate whether the nvCT was present in specimens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

diagnosis of CT. Her specimens were diagnosed with Amplicor CT/NG, I (PCR) or a highly optimized culture method (mainly on request from surveillance regression was used in the change in the pro

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

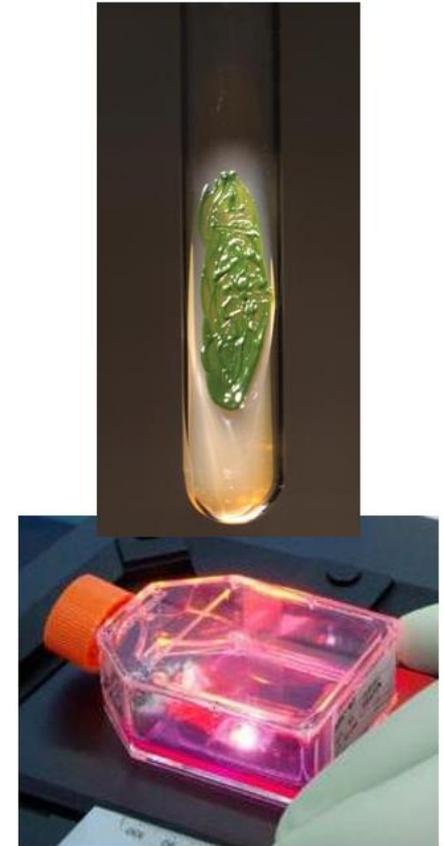
CIDT Impacts on Public Health Activities



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Selected Isolate-Requiring Infectious Disease Surveillance Programs; U.S.

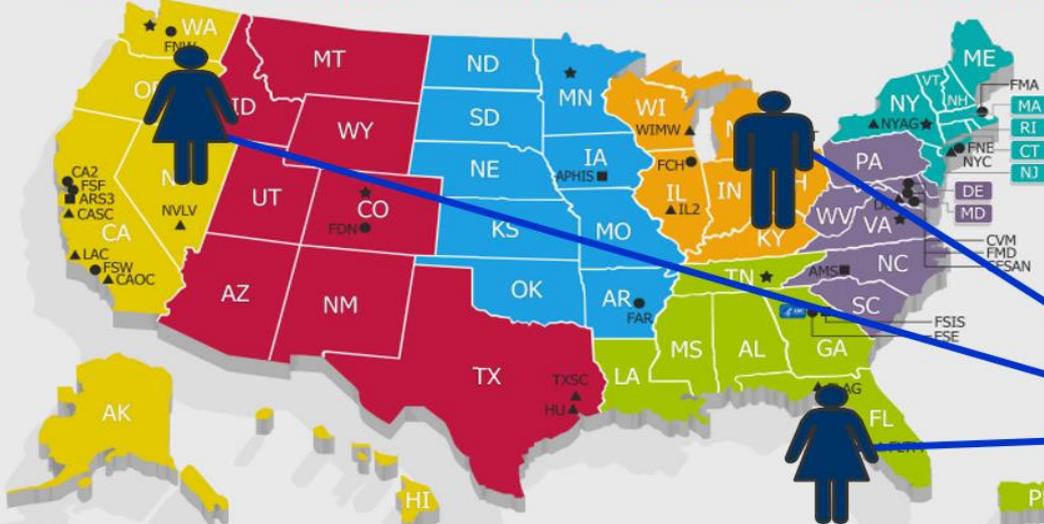
Agent	Public health surveillance
<i>Salmonella spp.</i>	Subtype, AST
Shigatoxin-producing <i>E. coli</i>	Subtype, AST
<i>Listeria monocytogenes</i>	Subtype, AST
<i>Mycobacterium tuberculosis</i>	Genotype, AST
<i>Bordetella pertussis</i>	AST
<i>Neisseria meningitidis</i>	Subtype, AST
<i>Legionella pneumophila</i>	Subtype (outbreaks)
Influenza virus	Serotype, AST
<i>Neisseria gonorrhoea</i>	AST
CRE, MRSA	Subtype (outbreaks), AST
<i>Streptococcus pyogenes</i> , <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i>	Subtype, AST





The National Molecular Subtyping Network for Foodborne Disease Surveillance

WEST MOUNTAIN CENTRAL MIDWEST NORTHEAST



- PulseNet Central
- FDA Laboratories
- Local Laboratories
- USDA Laboratories
- Area Laboratories

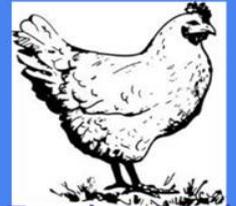
SOUTHEAST MID-ATLANTIC



Human disease surveillance



Food monitoring

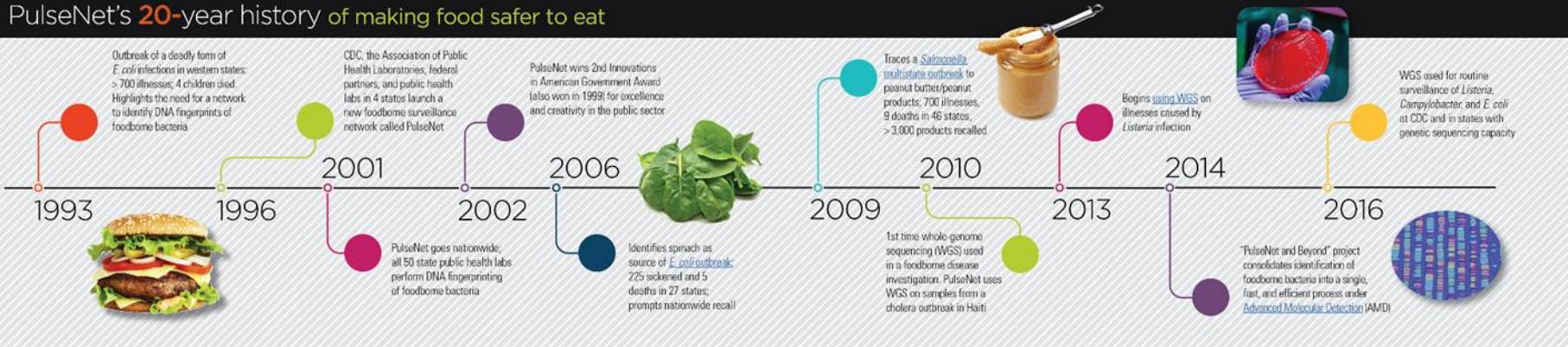


Food animal surveillance



PulseNet's 20th Anniversary

PulseNet's 20-year history of making food safer to eat



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

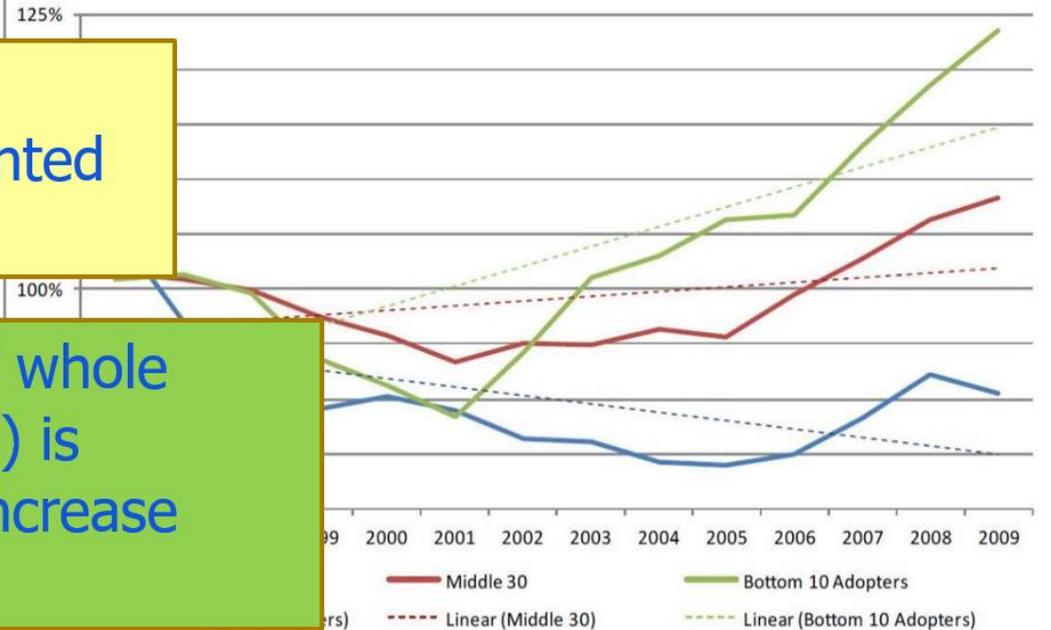
The PulseNet surveillance system is a molecular subtyping network of public health and regulatory agency laboratories designed to identify and facilitate investigation of foodborne outbreaks. This study estimates health and economic impacts associated with PulseNet staggered adoption of PulseNet across the states offers a natural experiment to evaluate effectiveness, which is measured as reduction of reported illnesses due to improved enhanced industry accountability, and more-rapid recalls. Economic impacts attribut

Each year, *at least*....

- 270,000 cases are prevented
- \$507,000,000 saved

The full implementation of whole genome sequencing (WGS) is expected to dramatically increase these benefits

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

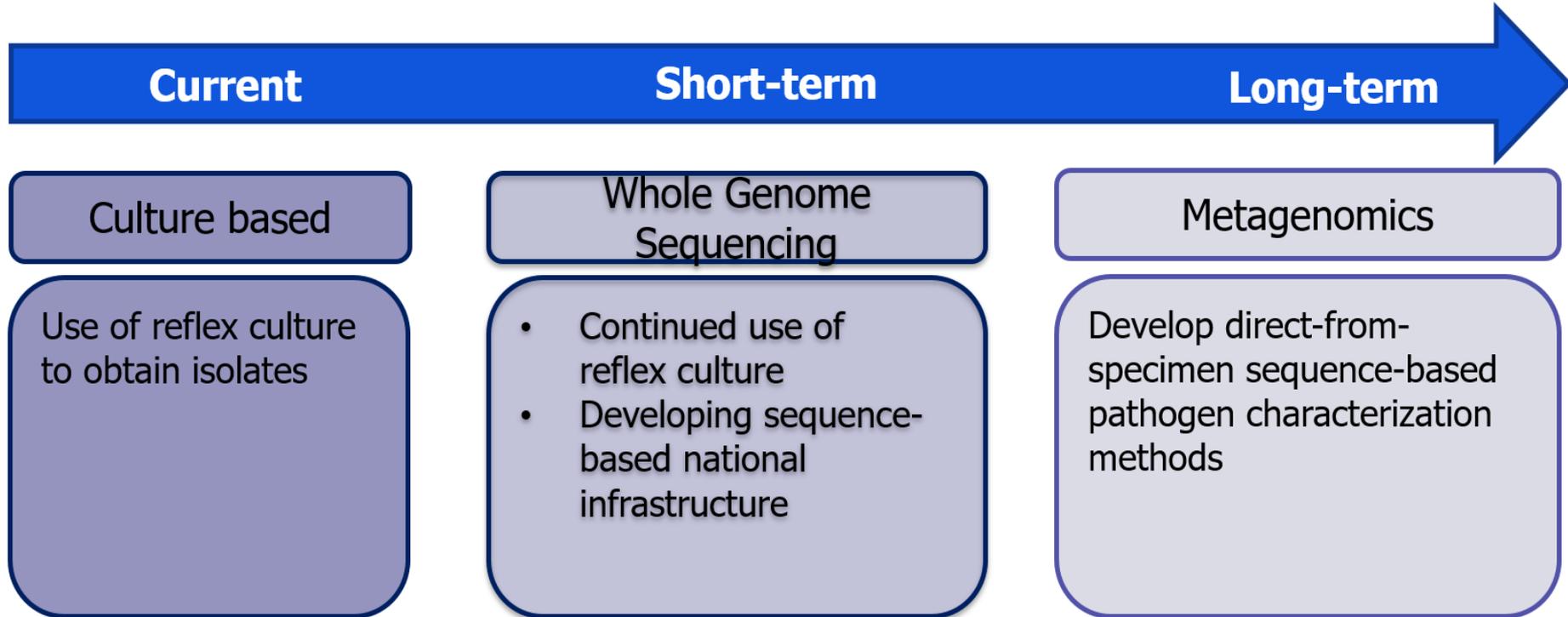


Subtyping Methods: Isolate Dependency



Method	Isolates Required?
PFGE	Yes
MLVA	Yes
WGS	Yes

Strategies to Meet the Surveillance Challenge of CIDT



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2012 Questions for CLIAC Consideration

- How can the public health impact of certain test results be better emphasized as test systems are cleared by FDA
- Are there ways in which the CLIA program can promote public health recommendations (e.g. support CDC guidelines and recommendations)

2012 International Forum

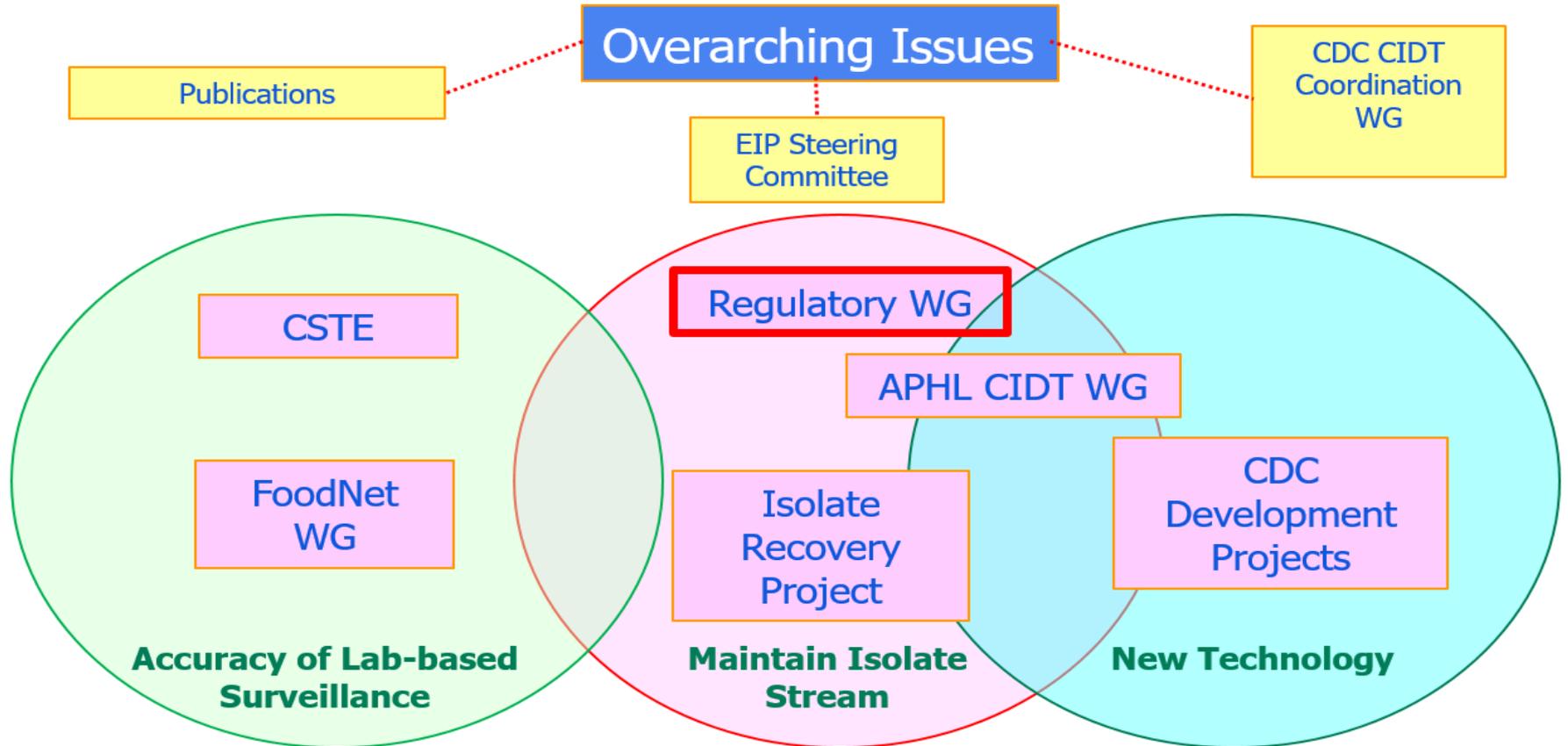


Forum on Culture-Independent Diagnostics: Charting a Path for Public Health

April 25-26, 2012; Atlanta, GA

Sponsored by
CDC, APHL, and CSTE

CIDT: Who Is Doing What?



Activities of the "Regulatory Workgroup" to Assure Continued Flow of Specimens and Isolates to Public Health

Test Regulation	Laboratory Regulation	Test Reimbursement*	Case Reporting Rules, state capacity (culture of +'s)	Test Development
FDA-Device Licensure	CLIA, CAP, Joint Commission	Private or public payers	State Governments, APHL, CSTE	Medical Device Industry (Advamed-Dx)

* Limited CDC involvement

“Regulatory Workgroup” Questions

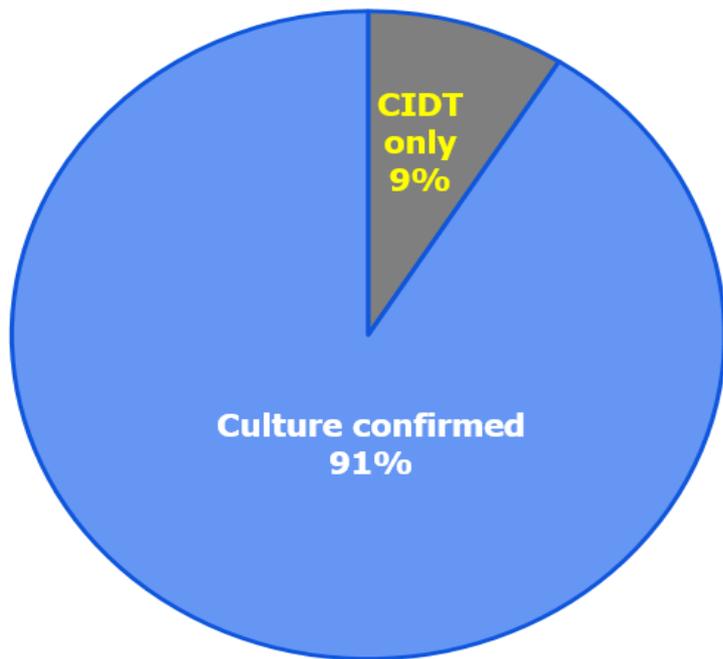
- **Test development (pre-510k process)**
 - What can be done to encourage manufacturers of CIDTs to consider public health needs
- **Licensure, medical devices**
 - To what extent can public health needs be reinforced through the device licensure process, for example by adding language to the product insert?
- **Laboratory regulation**
 - Can laboratory regulatory bodies such as CLIA/ CAP/ JCAHO play a role in enforcing best practices, such as following public health recommendations in the product insert?
- **Reporting rules:**
 - Should states be encouraged to replace language in current “isolate” submission rules to accommodate new culture-independent diagnostics?
- **Reimbursement:**
 - Is there any way that laboratories can be compensated for reflex culture (and other activities that do not directly impact patient care)?

Regulatory Workgroup Products

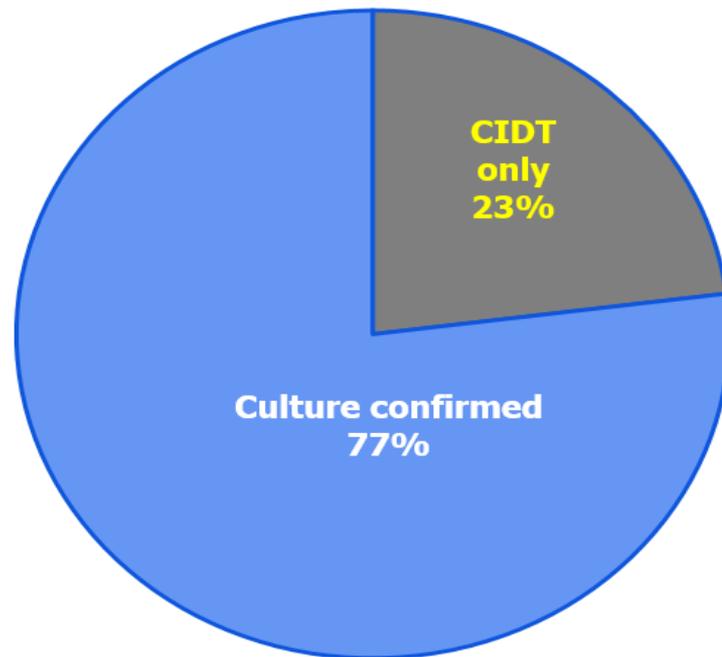
Activity	Status
• ADVAMED	
○ Fact sheet for medical device industry	Distributed
○ CDC presentation to ADVAMED membership	Completed
• Recommended CIDT product insert language	Completed
• State reporting rules (regarding CIDT issues)	
○ Analysis of current rules, recommendations	Published
○ Development of model language, executive summary	In progress
• Reflex culture reimbursement	
○ Fact sheets for private payers	Complete
○ Issues and solutions document	Under review

Use of CIDTs Are Increasing — FoodNet, 2012–2016

Annual percentage of bacterial infections diagnosed by CIDTs



2012–2015



2016

Mycobacterium tuberculosis

Clinical guidances to encourage culture of CIDT-positives



CDC Home Search Health Topics A-Z

CDC

MMWR

Weekly

January 16, 2009 / 58(01):7-10

Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis



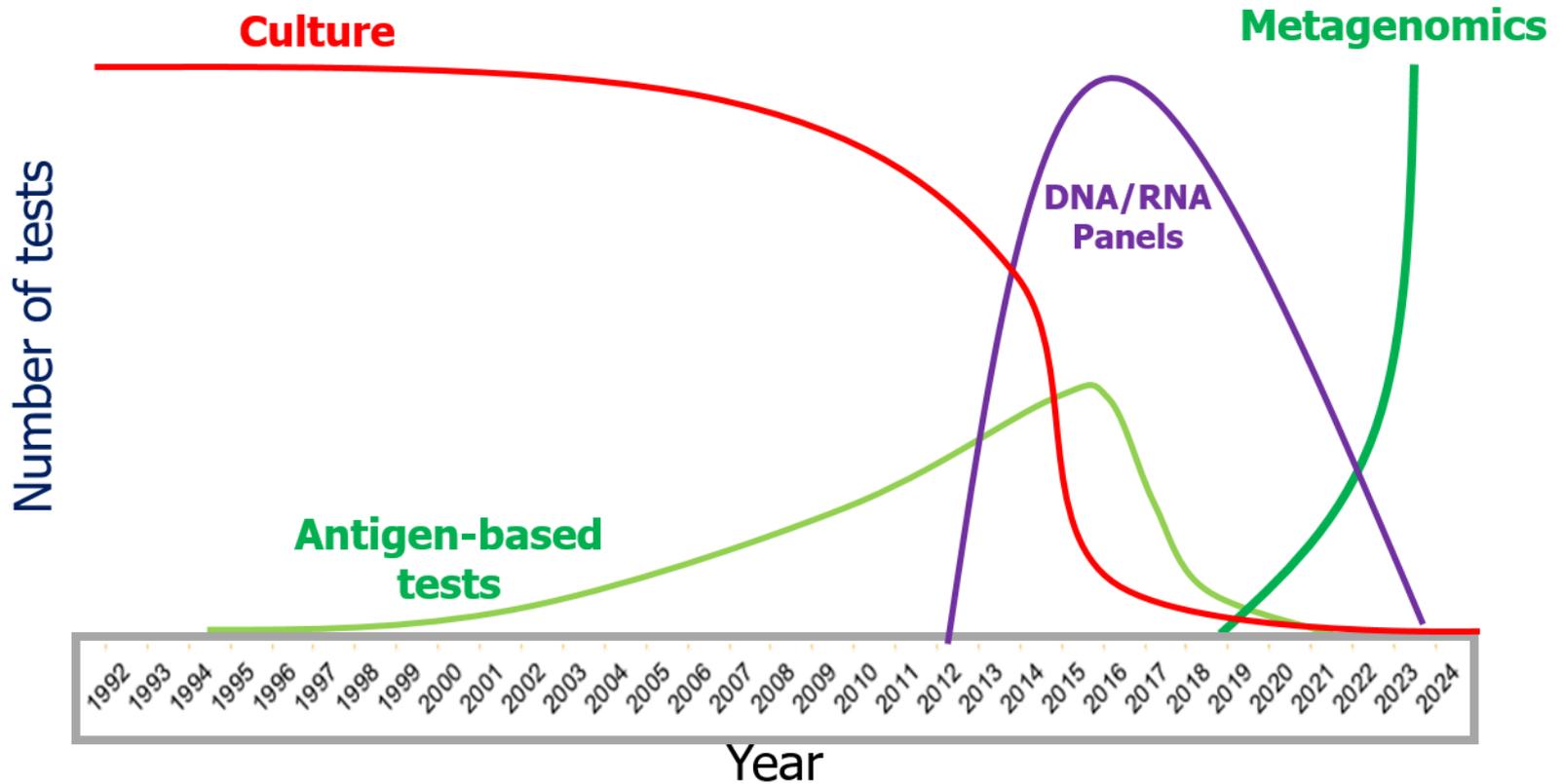
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Major trends

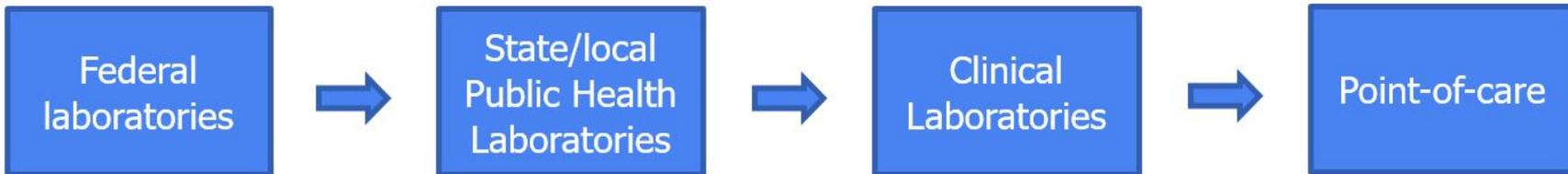
- Point-of-care testing devices (e.g. Gene Xpert Omni)
- Metagenomics (e.g. Karius, inc; currently CLIA/CAP certified for selected normally sterile sites)

Where is Clinical Enteric Microbiology Heading?*



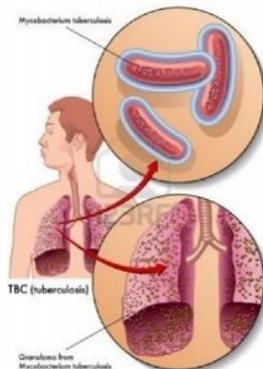
* My opinion only

Clinical Microbiology is Changing



Exotic infections

Rare infections



- TB
- Diphtheria
- Rabies

Salmonella infection

Almost any kind of food or beverage can carry the bacteria that causes salmonella infection, although meat and eggs are the most common sources.

Contaminated food or drink

How salmonella progresses

Bacteria travel to small intestine, adhere to lining, begin to replicate.

In severe cases, bacteria break through intestinal wall to bloodstream; can be deadly if not properly treated.

Symptoms

Within 12-72 hours
Nausea, vomiting, fever, diarrhea, abdominal cramps

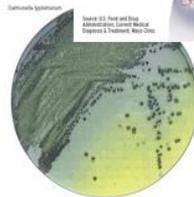
4-7 days
Fever ranges from mild to severe; most people recover without treatment.

Severe cases
More likely with infants, elderly, people with impaired immune systems.

Treatment

Oral or injected antibiotics, usually for 2 weeks.

McClatchy/Tribune



Common infections



Diagnosis by Next-Generation Sequencing



The NEW ENGLAND
JOURNAL of MEDICINE

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ORIGINAL ARTICLE
BRIEF REPORT

Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing

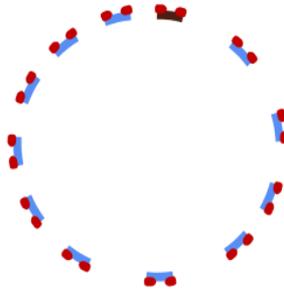
Michael R. Wilson, M.D., Samia N. Naccache, Ph.D., Erik Samayoa, B.S., C.L.S., Mark Biagtan, M.D., Hiba Bashir, M.D., Guixia Yu, B.S., Shahriar M. Salamat, M.D., Ph.D., Sneha Somasekar, B.S., Scot Federman, B.A., Steve Miller, M.D., Ph.D., Robert Sokolic, M.D., Elizabeth Garabedian, R.N., M.S.L.S., Fabio Candotti, M.D., Rebecca H. Buckley, M.D., Kurt D. Reed, M.D., Teresa L. Meyer, R.N., M.S., Christine M. Seroogy, M.D., Renee Galloway, M.P.H., Sheryl L. Henderson, M.D., Ph.D., James E. Gern, M.D., Joseph L. DeRisi, Ph.D., and Charles Y. Chiu, M.D., Ph.D.

N Engl J Med 2014; 370:2408-2417 | June 19, 2014 | DOI: 10.1056/NEJMoa1401268

N Engl J Med. 2014 Jun 19;370(25):2408-17

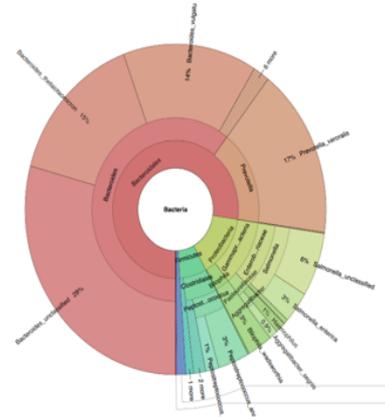
CDC Applied Research: Direct-from-Specimen Pathogen Characterization Development

Amplicon sequencing



1,000's of MLST targets

Shotgun metagenomics



- Enrichment of pathogen targets
- Unbiased sequencing



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Current questions/needs

- What CIDT guidance do clinical laboratories, industry and public health, need to assure continued public health functions.
 - Can reflex culture be mandated?*
 - Are there ways for laboratories to obtain workload credit for conducting reflex culture?
 - What mechanism should be in place for monitoring performance characteristics of CIDTs (recall the situation with Chlamydia testing in Sweden)
- What steps can HHS take to facilitate development of CIDT best practices documents that include public health activities (such as test-of-cure assays for outbreaks and reflex culture)?
- Can information on methodology used by CLIA-regulated labs be provided to public health (to adjust trend models)?

*** This has already occurred in some jurisdictions**



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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