National Center for Emerging and Zoonotic Infectious Diseases

Meeting the Challenge of Changing Diagnostic Testing Practices and the Impact on Public Health Surveillance

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The Shift from Culture to Culture-Independent Diagnostic Tests (CIDTs)

- **Cx is traditional method; organism causing illness is isolated and available for additional testing**
  - Antimicrobial susceptibility, subtyping
- **CIDTs do not require isolation of the organism**
- **Advantages of CIDT over Cx**
  - Potentially cheaper and easier to use
  - Faster and likely more sensitive
  - Detect multiple pathogens and wider range of pathogens
- **Disadvantages of CIDT over Cx**
  - Variation in test performance from one another and from culture
  - New strains not picked up by CIDT
  - Loss of ability to test for antimicrobial susceptibility
  - Detection of multiple pathogens in a single specimen makes interpretation difficult

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

2017

Antigen-based tests (FDA approved)

- 3 tests for Campylobacter
- 5 tests for Shiga toxin

Laboratory-developed tests (not FDA approved)

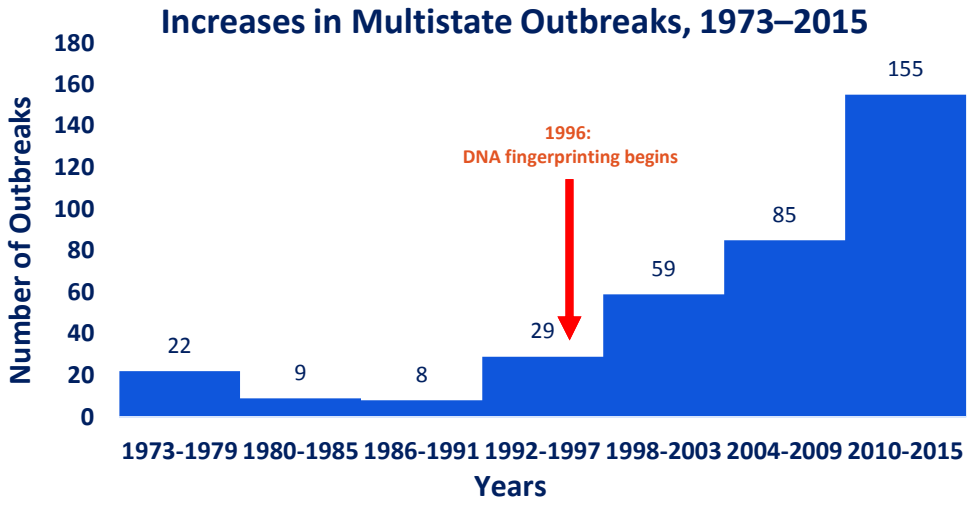
- Molecular detection (PCR) tests for single or multiple pathogens

Syndromic multiplex PCR panels (FDA approved)

- BD Max
- BioFire Gastro
- BioFire ME
- Luminex
- Nanosphere
- ProGastro SSCS
- Verigene BC

What are the drawbacks for outbreak detection if CIDTs are used for enteric infections without doing any cultures?

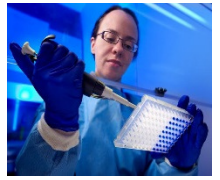
- **Public health will not get the detailed DNA fingerprints it needs to detect and stop outbreaks**
  - Food supply will be less safe
  - Before CDC received detailed DNA fingerprints, it was harder to detect multistate foodborne outbreaks
  - Outbreak detection using whole genome sequencing technology requires cultured isolates
- **Are we currently seeing any effects from CIDTs?**
  - Decreased number of outbreaks reported and clusters identified for *Salmonella*, Shiga toxin-producing *E. coli*, and *Campylobacter* during 2015-16 compared with 2012-13



Source: National Outbreak Reporting System

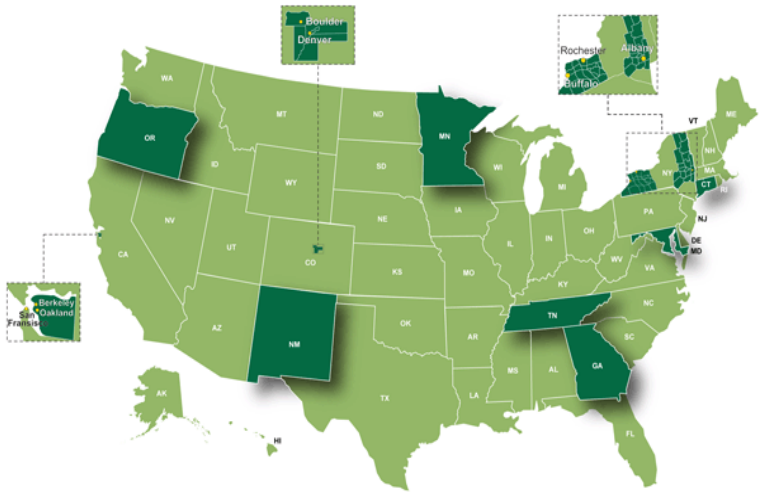
The challenges of changing diagnostics to public health surveillance

- CIDTs are easier and quicker to use than because do not require isolation
  - Reflex culture can be performed after positive CIDT to obtain isolate for determination of species, subtype and antimicrobial susceptibility
  - Will laboratories maintain culture capability and will they perform reflex culture?
- Many types of CIDTs with variable sensitivity and specificity
  - Are all reports real cases?
- Syndromic panel tests can detect or rule out multiple pathogens
  - Might this effect healthcare provider testing practices?
  - Will testing volume of laboratories change?



Foodborne Diseases Active Surveillance Network (FoodNet)

- Collaboration among CDC, 10 state health departments, USDA-FSIS, and FDA
- Tracks important foodborne illnesses
- Generates information that provides a foundation for food safety policy and prevention efforts
- Population-based active surveillance for *Campylobacter*, *Cryptosporidium, Cyclospora, Listeria, Salmonella,* Shiga toxin-producing *E. coli* (STEC), *Shigella, Vibrio*, and *Yersinia*; pediatric hemolytic uremic syndrome

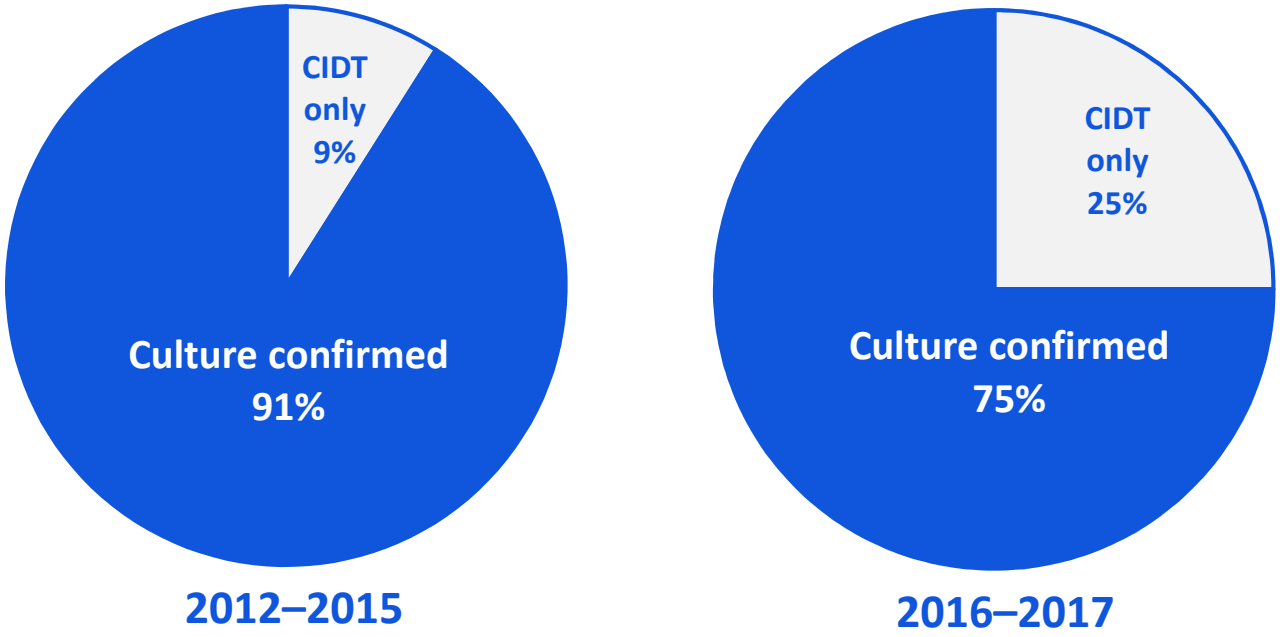


Surveillance Activities

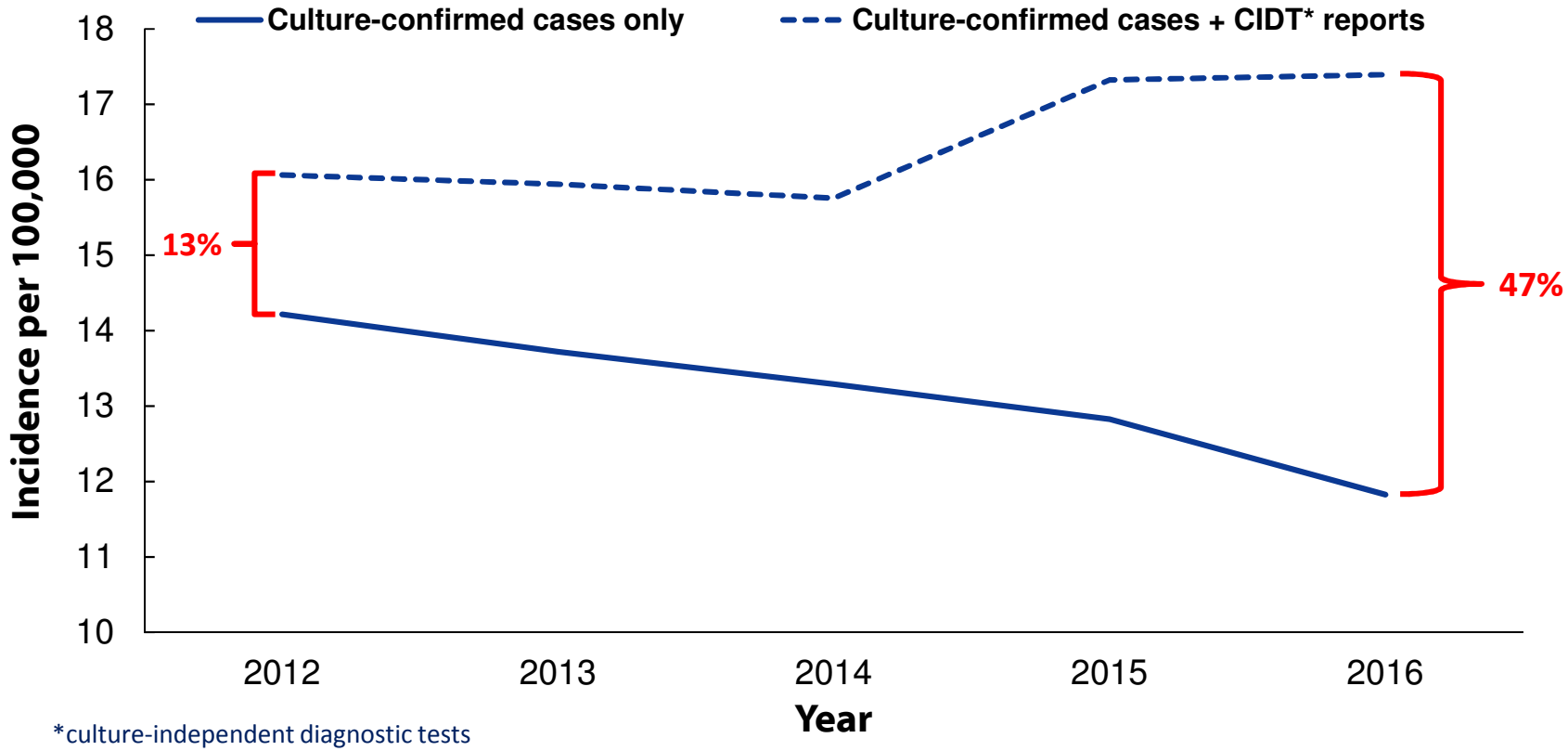
- Active surveillance for laboratory-confirmed infections through a network of ~650 laboratories
  - Confirmed infections since 1996
  - Culture-independent diagnostic test (CIDT)-positive infections since 2012
    - Type, brand, location of test
- Surveys of clinical laboratories in catchment area to assess changes in diagnostic testing practices since 2012

Use of CIDTs Are Increasing — FoodNet, 2012–2017

Annual percentage of bacterial infections diagnosed by CIDTs

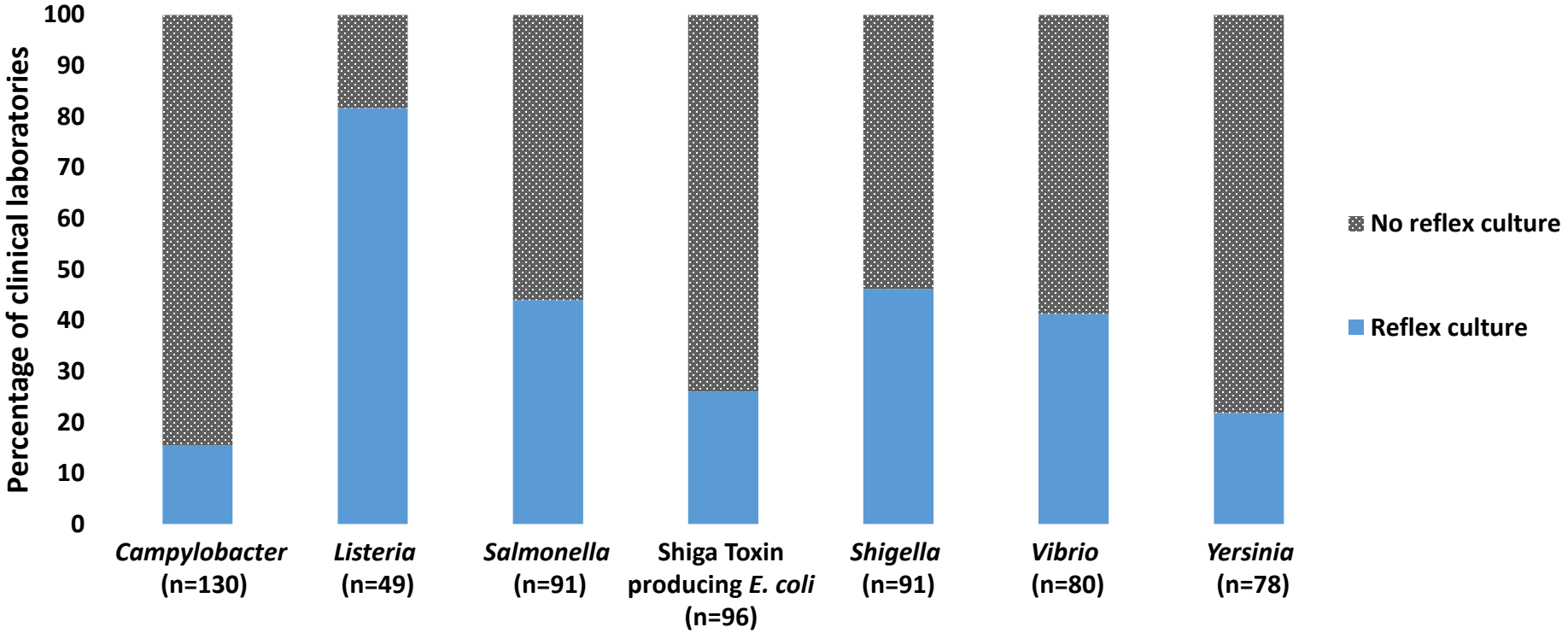


Incidence of *Campylobacter* infection by case type — FoodNet, 2012–2016

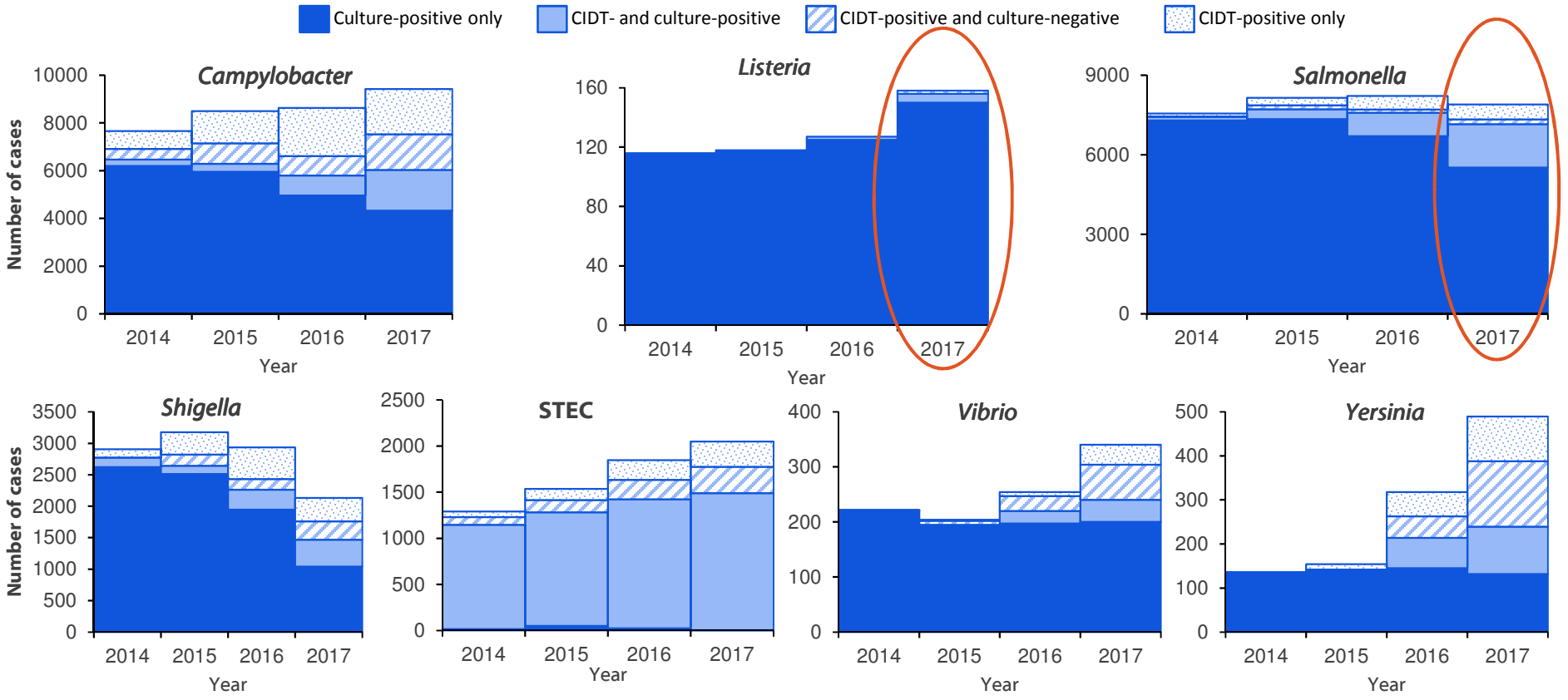


*culture-independent diagnostic tests

Reflex culture practices among clinical laboratories that perform CIDT, by pathogen — FoodNet, Fall 2017



Number of infections diagnosed by culture or culture-independent diagnostic tests, by pathogen, year, and culture status — FoodNet, 2014–2017



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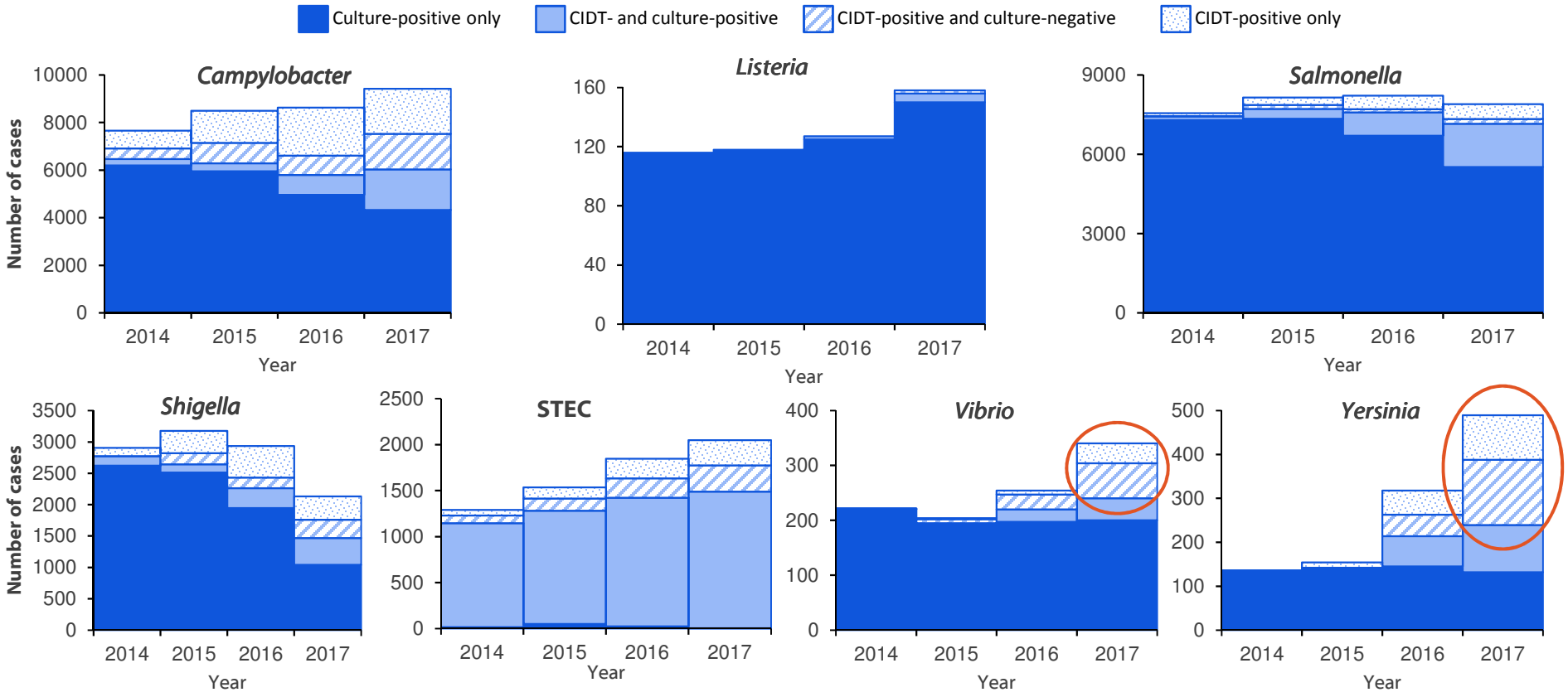

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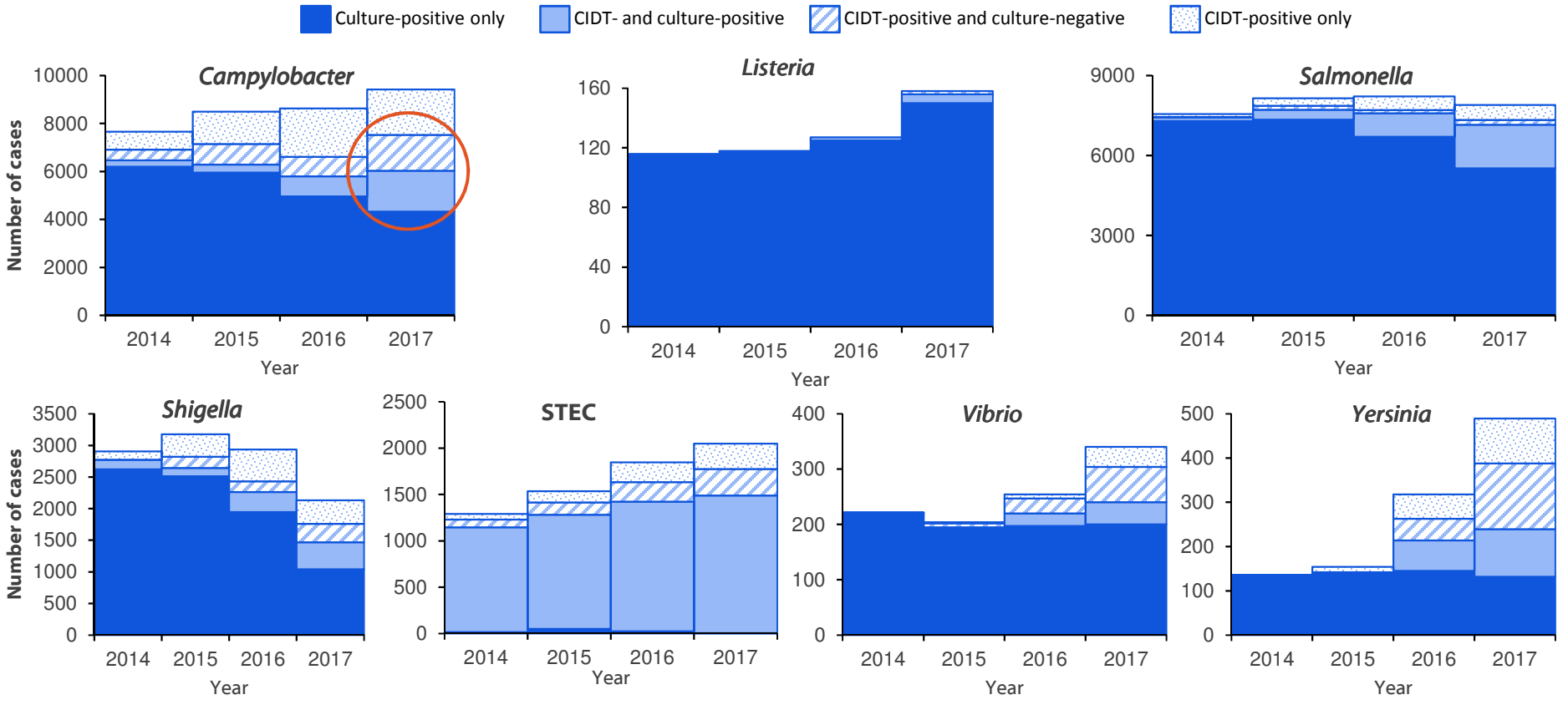

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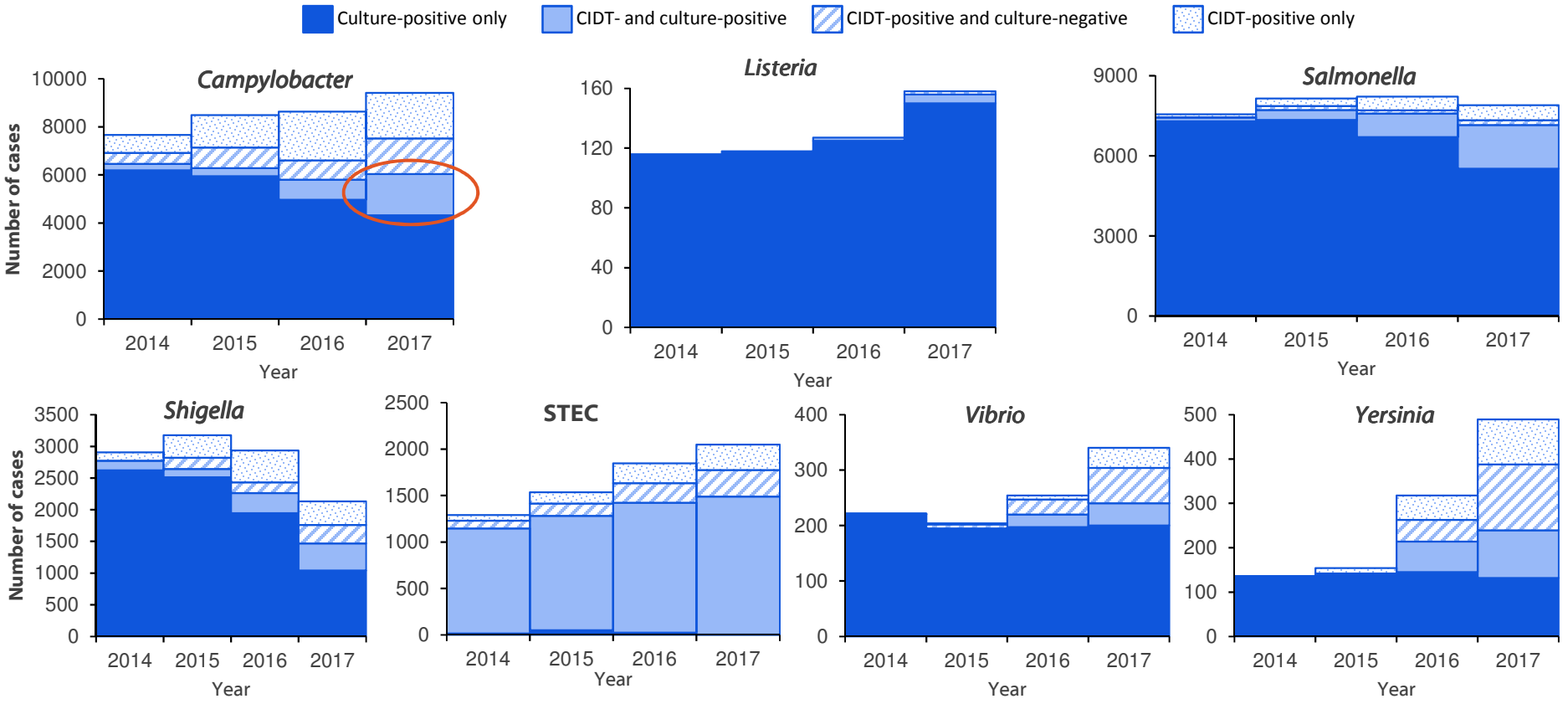

Where do we go from here?

- Not all CIDTs are created equal
  - Variation in performance not only between types of tests, but between brands of tests
  - Additional validation studies needed
- Sentinel sites to perform culture and obtain isolates for species, subtype, and antimicrobial sensitivity characterizations
- To restore interpretability of our incidence measures and comparisons over time FoodNet plans to
  - Estimate provider testing practices and laboratory testing volume by test type
  - Develop models to interpret incidence measures over time
- Ensure surveillance systems are flexible; adapt surveillance to capture changes
  - Update case definitions to capture CIDT (+) cases: Campylobacter 2015; Salmonella, Shigella, and Vibrio 2017; Listeria, Salmonella Typhoid/Paratyphoid, Yersinia 2019
  - Update state reporting rule language and requirements for submission of isolates and clinical specimens and isolates from clinical laboratories

CIDTs and FDA Food Code

What challenges do CIDTs pose to the FDA Food Code?

- FDA Food Code
  - A model regulation that state and local jurisdictions can adopt when excluding high risk transmission cases caused by enteric pathogens
  - Laboratory testing defined in this guide does not include information on CIDTs that might be more sensitive than CX
  - Needed: data on sensitivity of CIDT vs CX and duration of positive results by CIDT and CX

Case Management of High Risk Cases — CIDT versus Culture

CIDT	Initial interpretation (for clearance)	Culture (3 days after CIDT)	Final Interpretation	Case Management Issues
Positive	**Positive**	Positive	**Positive**	• Do you wait for the culture result to clear?
Negative	**Negative**	Positive	**Positive**	• Do you wait for the culture result to clear? • If you use CIDT result you risk having to pull case out of school/work after clearing them 2 days earlier
Positive	**Positive**	Negative	**?**	• Is this detection of non-viable cells/DNA? • Is this due to the expected random variation when a test might be negative or positive due to the small pathogen load near the end of the carriage period? • Should we exclude if either test was positive, which could unnecessarily extend absence from work/school?
Negative	**Negative**	Negative	**Negative**	• Do you wait for the culture result to clear?

Detection and Monitoring of High Risk Cases — CIDTs versus Culture

Case Detection Method	Case Clearance Method	Pros	Cons
Culture	**Culture**	• Straightforward interpretation	• Slow screening of cases • Case detection might be less sensitive • Delayed and less sensitive detection of clearance
CIDT	**CIDT**	• Faster and more sensitive case detection • Faster determination of clearance	• Variable CIDT performance (sensitivity/specificity) • Correlation of CIDT results with clearance is unknown
CIDT	**Culture**	• Faster and more sensitive case detection • Straight forward interpretation of clearance	• Variable CIDT performance • Delayed and less sensitive detection of clearance
Culture	**CIDT**	• Sensitivity of culture is well-described • Fast detection of clearance	• Slow screening and less sensitive case detection • Variable CIDT performance • Correlation of CIDT results with clearance is unknown
CIDT	**CIDT and Culture**	• Faster and more sensitive case detection • Maximum information for determining clearance	• Expensive • Variable CIDT performance • Interpretation/management issues
CIDT and Culture	**CIDT and Culture**	• Faster and more sensitive • Maximum information	• Expensive • Interpretation/management issues

Median annual number of high risk transmission cases and length of time excluded, by pathogen — FoodNet Sites Informal Survey, 2017

- ***Salmonella* Typhi/Paratyphi**
  - 2 cases (range: 1–14)
  - 20 days
- ***Salmonella* (non-typhoidal)**
  - 61 cases (range: 12–1,233)
  - 15 days (range: 1–304)
- **Shiga toxin-producing *E.coli***
  - 21 cases (range: 11–177)
  - 14 days (range: 1–79)
- ***Shigella***
  - 19 cases (range: 12–151)
  - 41 days (range: 1–71)

Challenges to collecting the data needed

- In many cases, local state health departments oversee exclusion procedures
  - Definitions of high risk cases vary by state
  - Negative results and dates of exclusion/testing not routinely and systematically collected in state surveillance systems
- Exclusion procedures differ by state and pathogen
  - Sporadic cases vs outbreaks
- Clearance testing is performed at both clinical and/or state laboratories
  - Testing capabilities (CIDT type) differ by laboratory and state
- Concurrent testing by CIDT and CX are not typically performed for clearance
  - Cost ($$$)

Enhanced laboratory testing and follow-up of high risk transmission cases

Cadillac study version

- All Pathogens (*Salmonella, STEC, Shigella*)
- All FoodNet sites
- Multiple test types
- Testing all specimens during exclusion period
- CIDTs and CXs conducted at the same laboratory

Pinto study version

- Select pathogens, site specific pathogens
- Select FoodNet sites
- Sample of test types
- Testing a sample of specimens during the exclusion period
- CIDTs and CXs conducted at multiple laboratories

FoodNet data presented is all generated through the dedicated work of many

FoodNet Sites

- California Emerging Infections Program
- Connecticut Emerging Infections Program
- Colorado Department of Public Health and Environment
- Georgia Department of Public Health
- Maryland Department of Health and Mental Hygiene
- Minnesota Department of Health
- New Mexico Emerging Infections Program
- New York State Department of Health
- Oregon Health Authority

US Department of Agriculture Food Safety and Inspection Service

US Food and Drug Administration

US Centers for Disease Control and Prevention FoodNet Staff