

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

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Conference for Food Protection

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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)

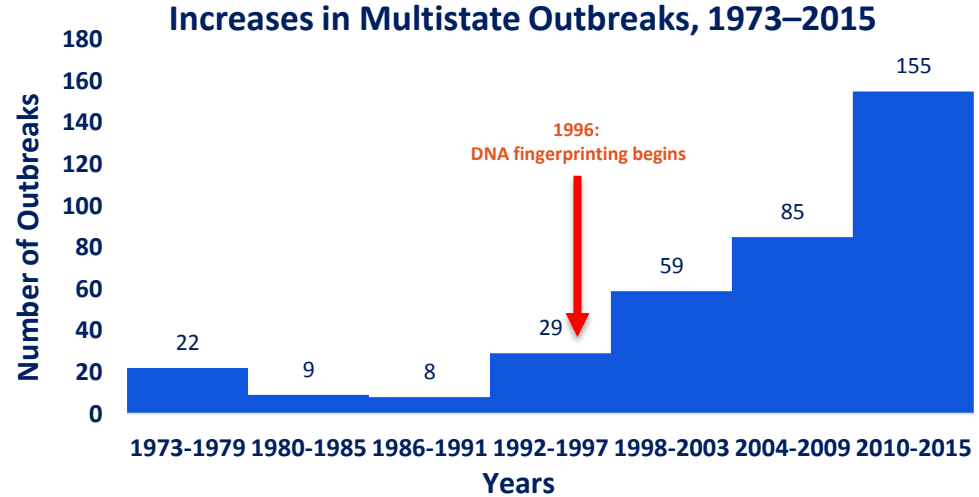
- Molecular detection (PCR) tests for single or multiple pathogens

Syndromic multiplex PCR panels (FDA approved)

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

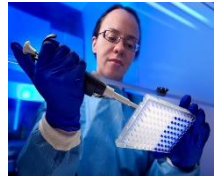
What are the drawbacks for outbreak detection if CIDTs are used for enteric infections without doing any cultures?

- 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



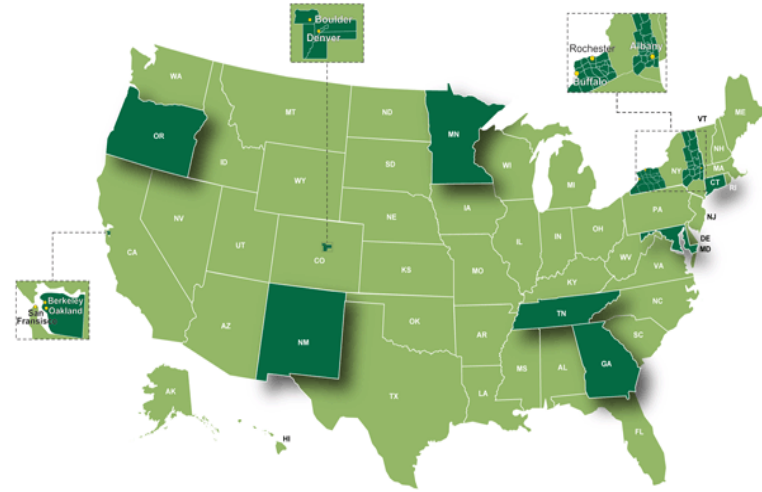
The Challenges of Changing Diagnostics to Public Health Surveillance

- CIDs 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 CIDs 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

FoodNet 

Surveillance Activities

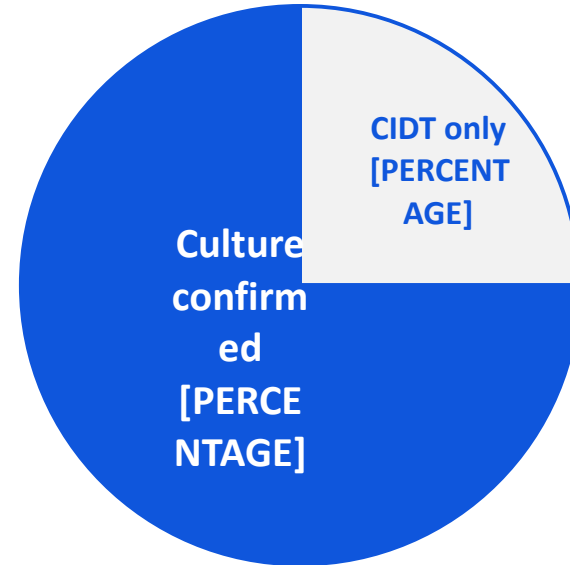
- Active surveillance for laboratory-confirmed infections through a network of ~650 laboratories
 - Confirmed infections since 1996
 - Culture-independent diagnostic test (CIDT)-positive infections since 2012
 - Type, brand, location of test
- Surveys of clinical laboratories in catchment area to assess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

Use of CIDTs Are Increasing — FoodNet, 2012–2017

Annual percentage of bacterial infections diagnosed by CIDTs

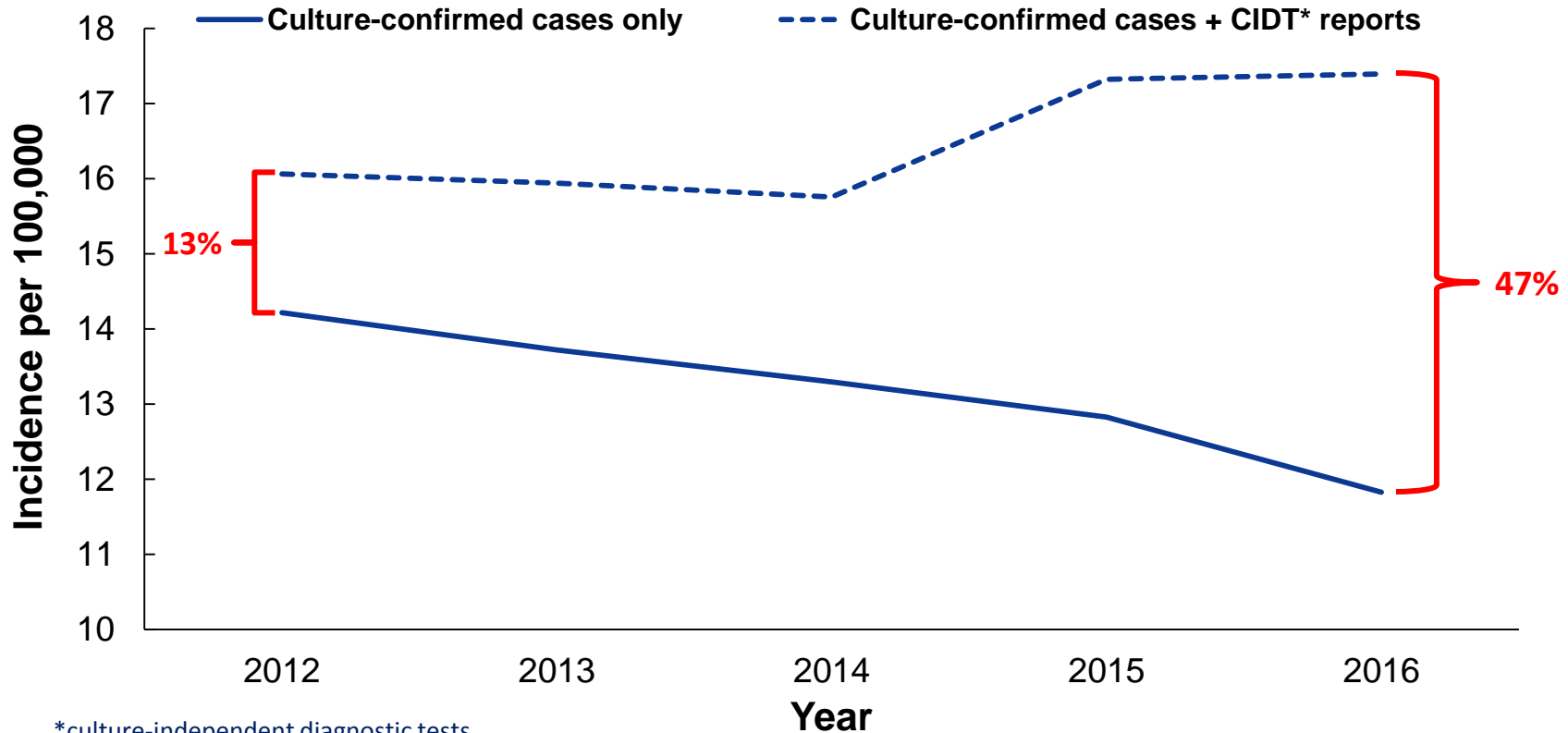


2012–2015

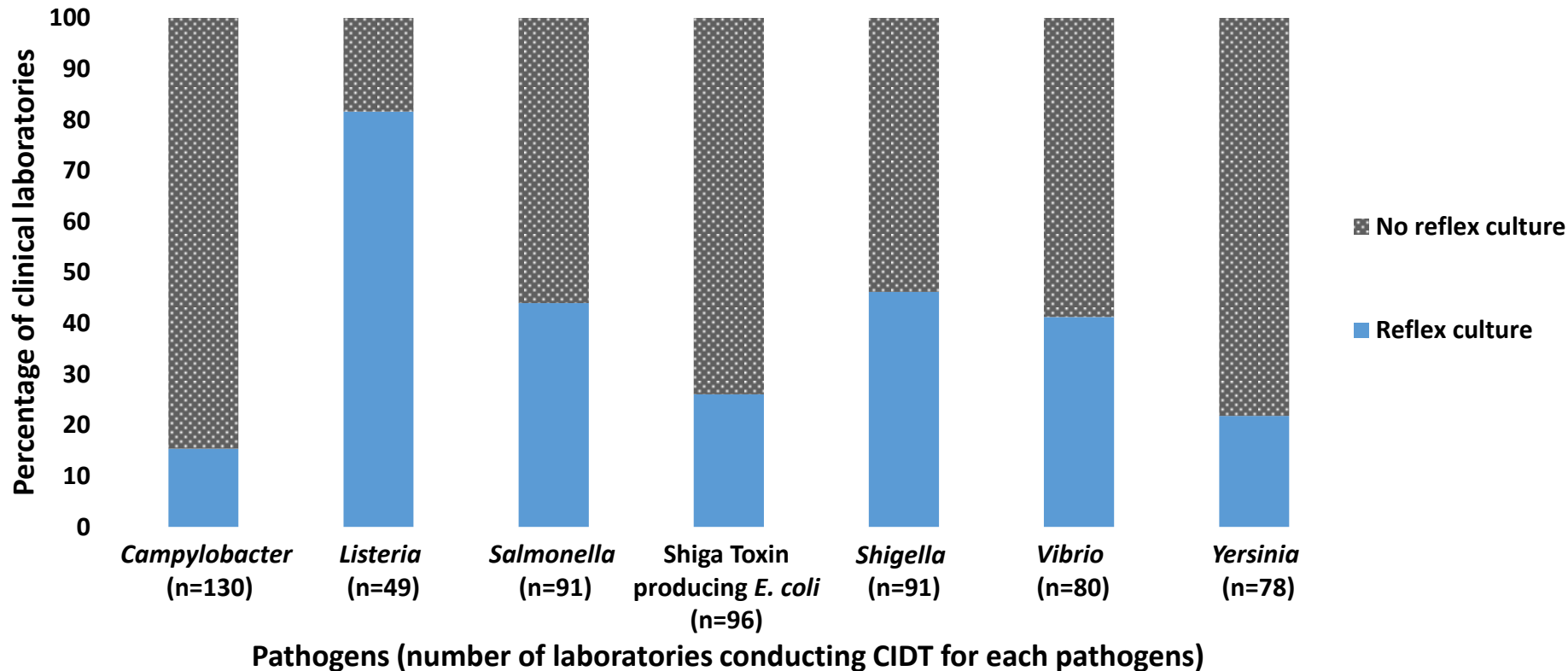


2016–2017

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

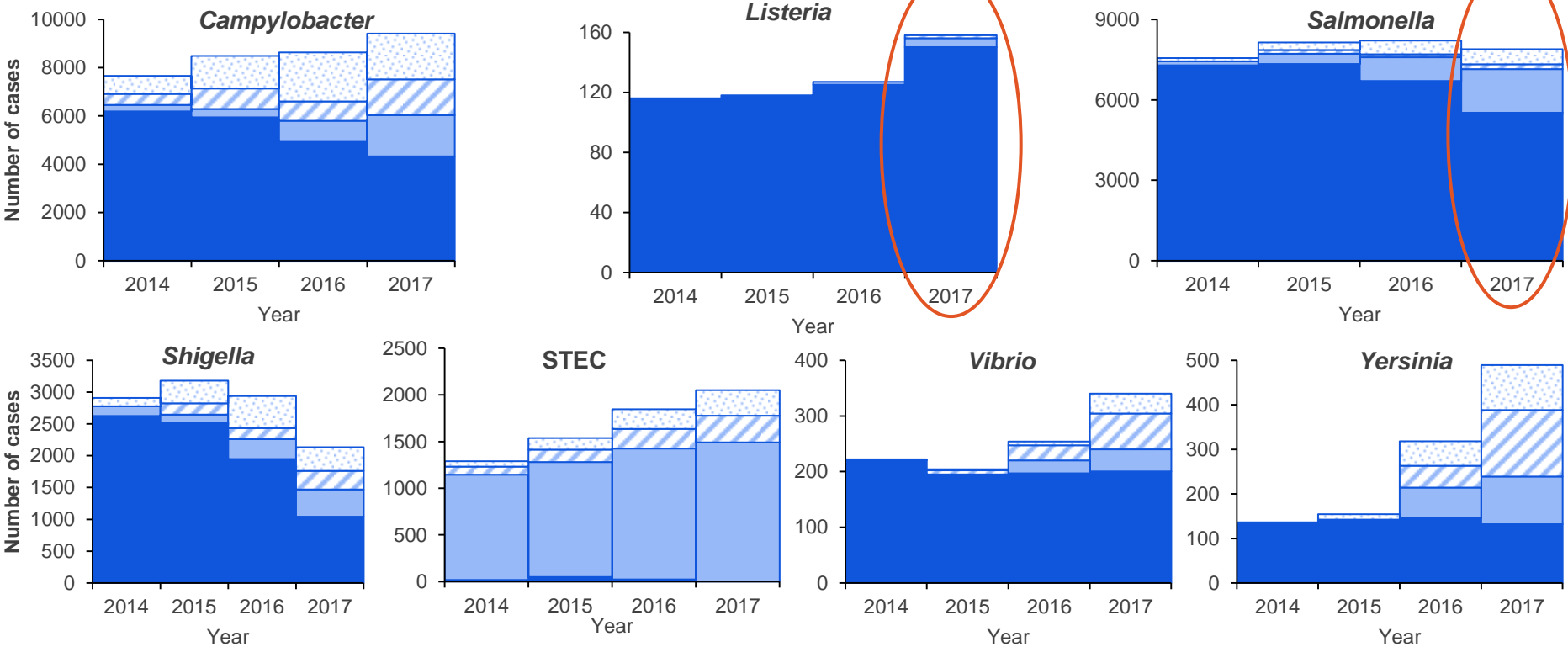


Reflex Culture Practices Among Clinical Laboratories that Perform CIDT, by Pathogen — Fall 2017



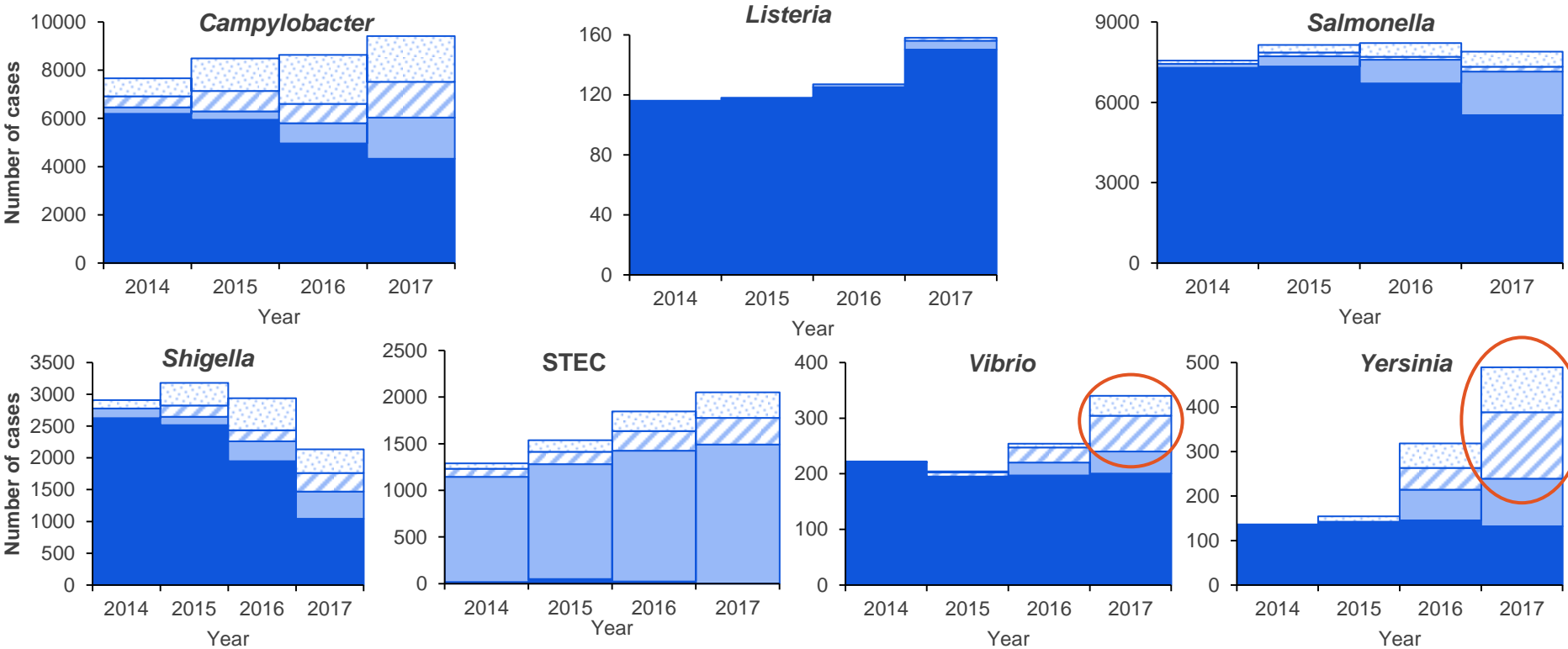
Number of infections diagnosed by culture or culture-independent diagnostic tests, by pathogen, year, and culture status — FoodNet, 2014–2017

■ Culture-positive only ■ CIDT- and culture-positive ■ CIDT-positive and culture-negative ■ CIDT-positive only



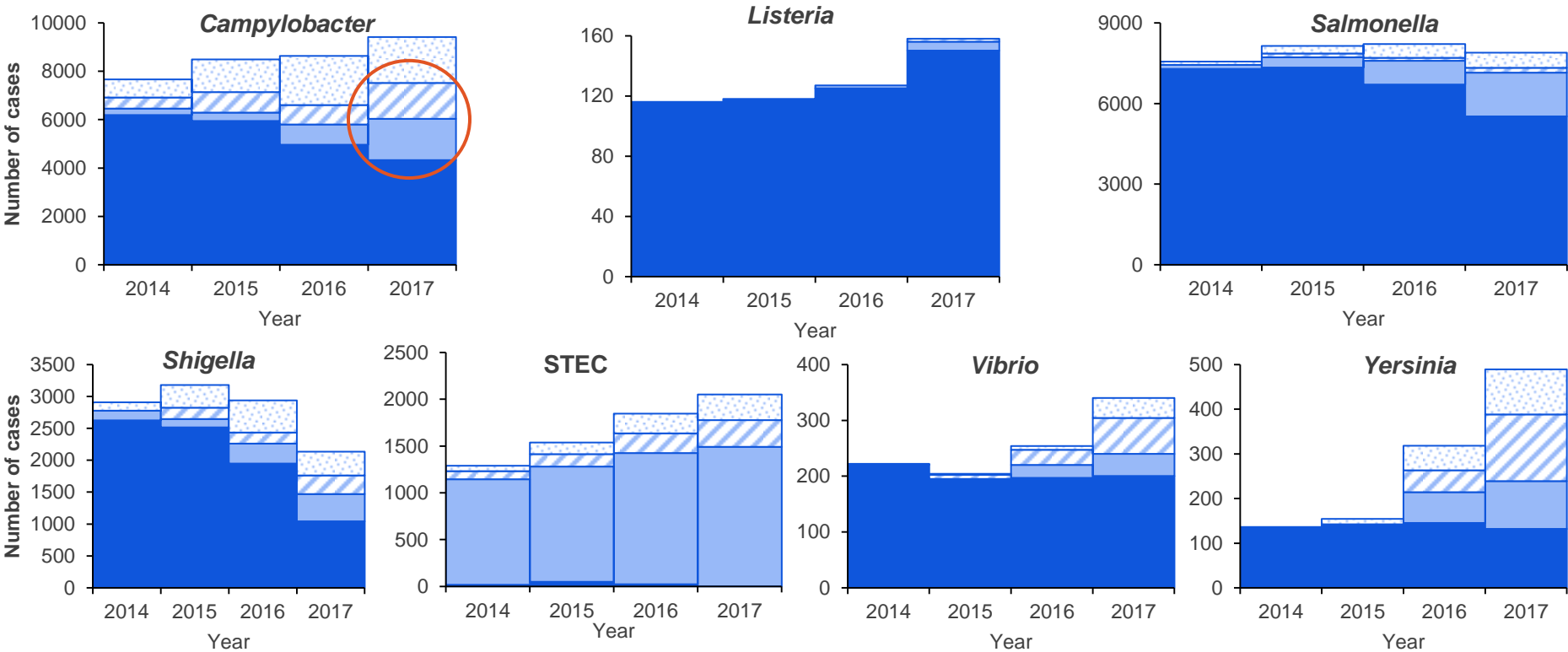
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Culture-positive only CDT- and culture-positive CDT-positive and culture-negative CDT-positive only



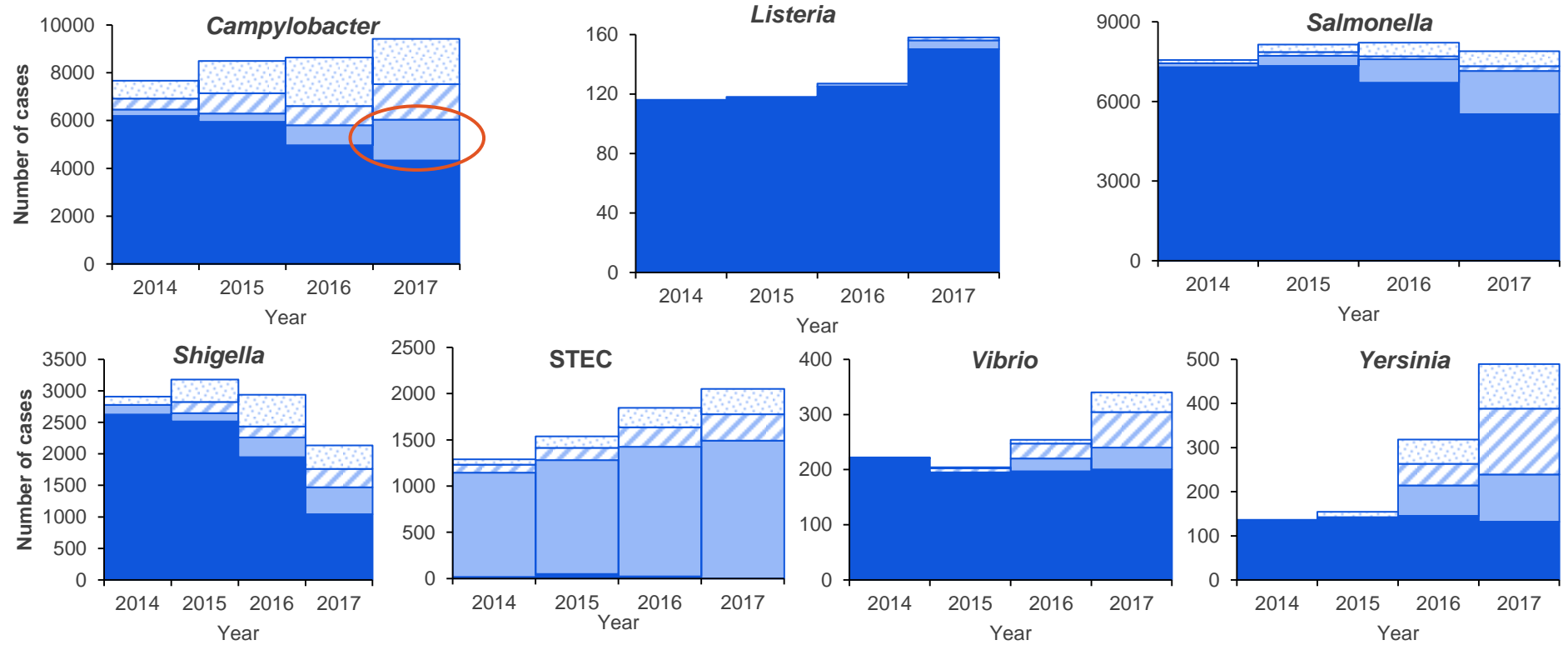
Number of infections diagnosed by culture or culture-independent diagnostic tests, by pathogen, year, and culture status — FoodNet, 2014–2017

Culture-positive only CIDT- and culture-positive CIDT-positive and culture-negative CIDT-positive only



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

Culture-positive only CIDT- and culture-positive CIDT-positive and culture-negative CIDT-positive only



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 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 culture-independent diagnostic tests (CIDTs) that might be more sensitive than culture (CX)
 - Needed: data on sensitivity of CIDT vs CX and duration of positive results by CIDT and CX



Monitoring Exclusion Cases — CIDT versus Culture

CIDT	Initial interpretation (for clearance)	Culture (3 days after CIDT)	Final Interpretation	Case Management Issues
Positive	Positive	Positive	Positive	<ul style="list-style-type: none"> Do you wait for the culture result to clear?
Negative	Negative	Positive	Positive	<ul style="list-style-type: none"> 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	?	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Do you wait for the culture result to clear?

Monitoring High Risk Cases — CIDTs versus Culture

Case Detection Method	Case Clearance Method	Pros	Cons
Culture	Culture	<ul style="list-style-type: none"> • Straightforward interpretation 	<ul style="list-style-type: none"> • Slow screening of cases • Case detection might be less sensitive • Delayed and less sensitive detection of clearance
CIDT	CIDT	<ul style="list-style-type: none"> • Faster and more sensitive case detection • Faster determination of clearance 	<ul style="list-style-type: none"> • Variable CIDT performance (sensitivity/specificity) • Correlation of CIDT results with clearance is unknown
CIDT	Culture	<ul style="list-style-type: none"> • Faster and more sensitive case detection • Straight forward interpretation of clearance 	<ul style="list-style-type: none"> • Variable CIDT performance • Delayed and less sensitive detection of clearance
Culture	CIDT	<ul style="list-style-type: none"> • Sensitivity of culture is well-described • Fast detection of clearance 	<ul style="list-style-type: none"> • Slow screening and less sensitive case detection • Variable CIDT performance • Correlation of CIDT results with clearance is unknown
CIDT	CIDT and Culture	<ul style="list-style-type: none"> • Faster and more sensitive case detection • Maximum information for determining clearance 	<ul style="list-style-type: none"> • Expensive • Variable CIDT performance • Interpretation/management issues
CIDT and Culture	CIDT and Culture	<ul style="list-style-type: none"> • Faster and more sensitive • Maximum information 	<ul style="list-style-type: none"> • Expensive • Interpretation/management issues

Median Annual Number of High Risk Transmission Cases and Length of Time Excluded, by Pathogen – FoodNet Sites, 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

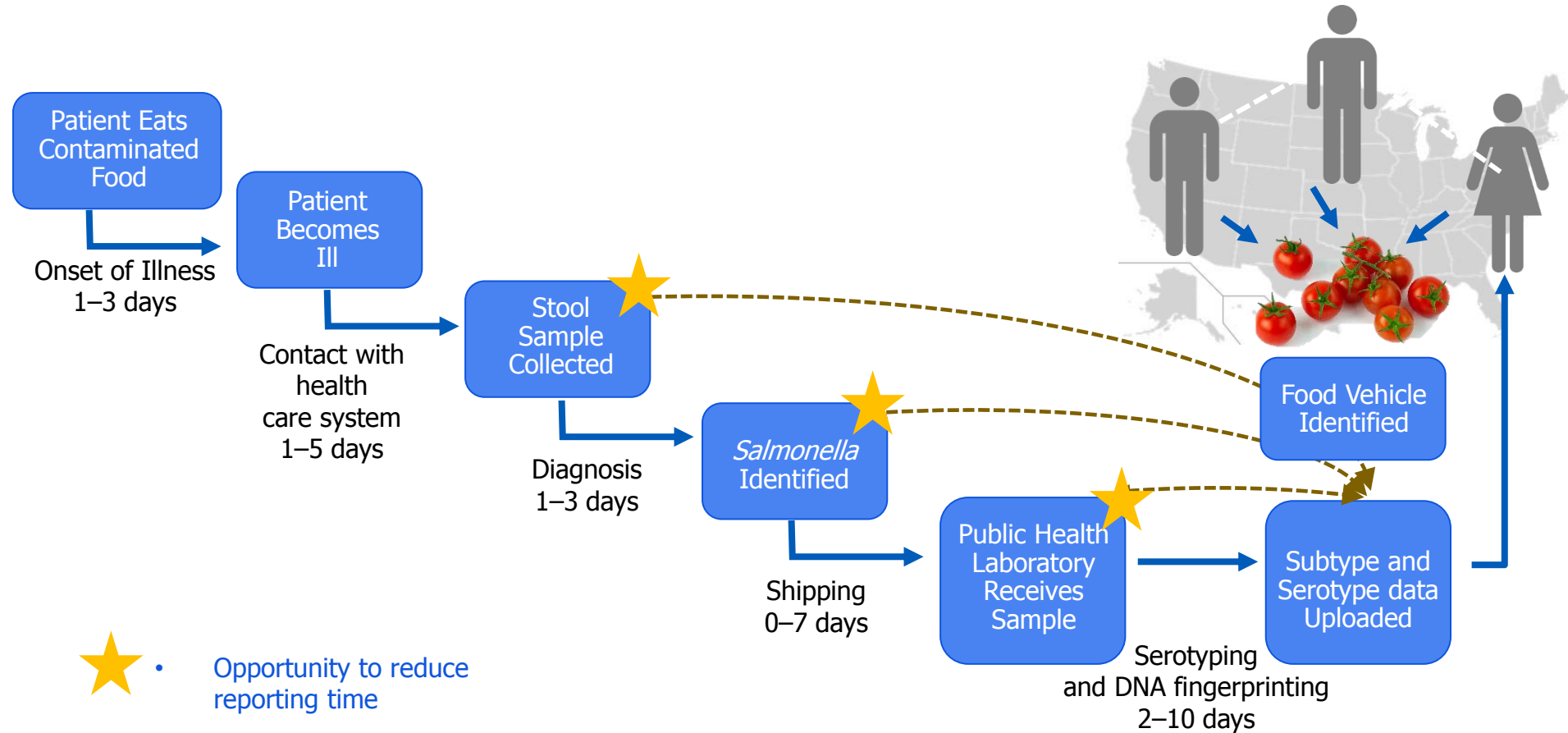
US Food and Drug Administration

US Centers for Disease Control and Prevention FoodNet Staff

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



Direct-from-specimen Tests: Reduce Time to Actionable Results



Changing Diagnostics — The Shift from Culture to CIDTs

- Culture is traditional method; organism is isolated and available for additional testing
 - Antimicrobial resistance
 - Subtyping
- CIDTs are new methods; antigen or specific DNA is detected
 - Conducted more rapidly than culture
 - Subtyping and antimicrobial resistance cannot be obtained
 - “Reflex culture” can be done after positive CIDT to obtain isolate
 - Many types of CIDTs with varying sensitivity and specificity
 - Syndromic panels that test for many organisms simultaneously are becoming more common

CDC and Policies and Partnerships



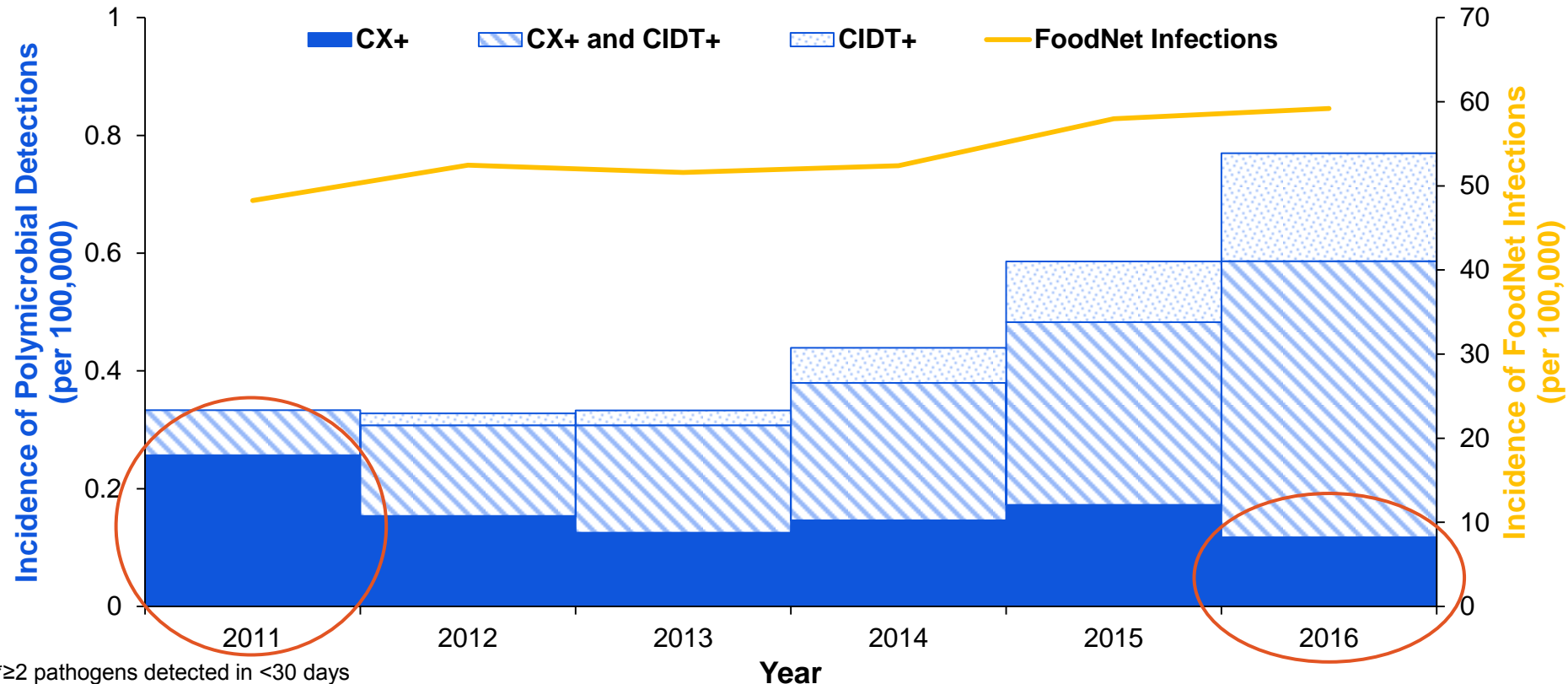
- **Ensure surveillance systems are flexible; adapt surveillance to capture changes**
 - Update case definitions to capture CIDT (+) cases: *Campylobacter* 2015; *Salmonella*, *Shigella*, and *Vibrio* 2017; *Listeria*, *Salmonella* Typhoid/Paratyphoid, *Yersinia* 2019
- **Provide data to inform policy**
 - Exclusion from daycares, food establishments, etc.
 - Insurance reimbursement for CIDT vs Cx
- **Partnerships with consumer groups, state health departments, and industry to identify strategies to meet needs of both public health and diagnostics**
 - Develop and maintain partnerships with Pew, APHL, CSTE, ASTHO, and others
 - Develop and maintain open communication and partnerships with test manufacturers and national reference laboratories to anticipate changes in diagnostic testing
 - Syndromic Panel tests data sharing and technical consult to inform test interpretation
- **Identify surveillance and laboratory needs and gaps**
 - Partnerships with state, federal, academic, and other partners

Summary

- A quarter of clinical laboratories are using CIDs alone for *Campylobacter* and other pathogens are demonstrating similar trends
 - Shift toward use of syndromic PCR-based panels
 - Less than 20% of these perform reflex culture
- Number of cases diagnosed by CIDT is continuing to increase dramatically
- Differential effect on incidence rate by year and subgroup complicates interpretation of our incidence measures over time
 - May reflect difference in populations being tested by CX vs CIDT
 - Healthcare providers might be more likely to order a CIDT because results are obtained more quickly, increasing the number of infections identified
 - Some laboratories may now use CIDs instead of CX, decreasing the number of CX cases, but increasing overall case counts
 - Some CIDT-positive results may be confirmed by CX, increasing number of CX cases
 - CIDs might identify infections that would have been CX-negative or false+ or both
 - Syndromic panel co-detection of pathogens...which one is causing illness?
 - Are CIDs decreasing our ability to detect outbreaks and identify outbreak sources?

Syndromic Multiplex Panels

Incidence of polymicrobial detections*, by year and test result — Select FoodNet Sites†, 2011–2016



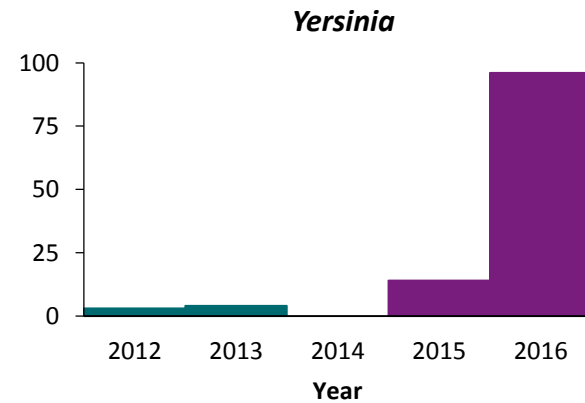
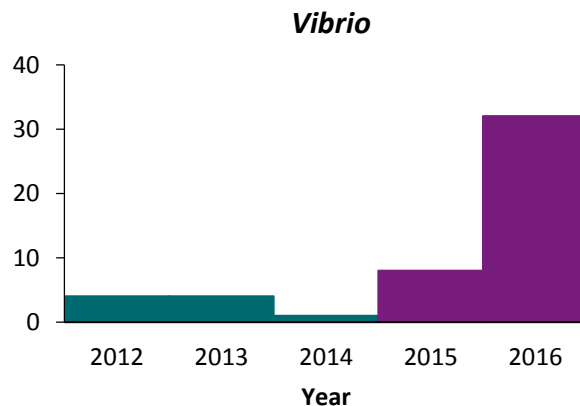
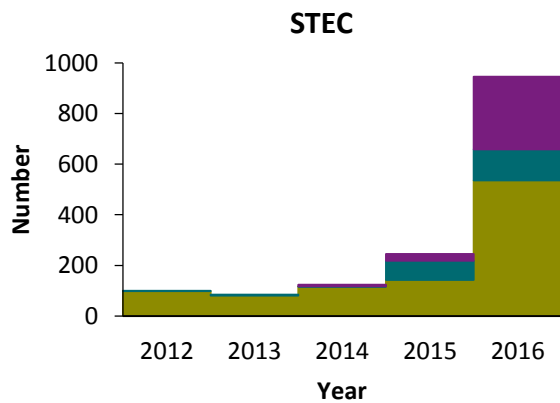
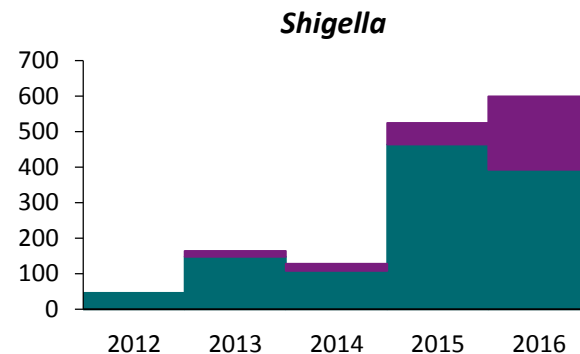
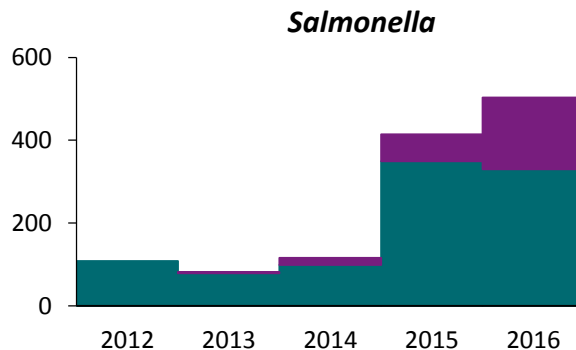
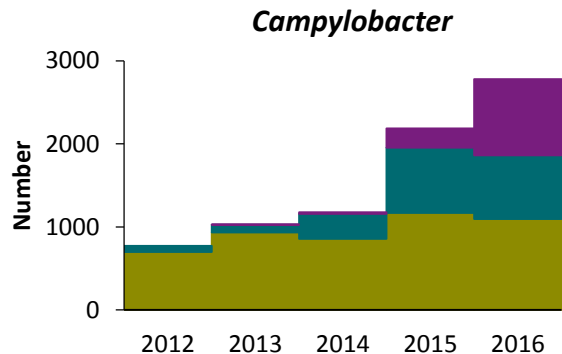
*≥2 pathogens detected in <30 days

†GA, NM, MD, MN, TN and selected counties in CA and CO

Information not for distribution. Data are preliminary and subject to change 9

Number of infections with positive CIDT result, by pathogen, test type, and year — FoodNet, 2012–2016

Antigen-based test Locally-developed PCR test DNA-based syndrome panel test



Demographic and Clinical information of *Campylobacter* infections diagnosed by culture versus CIDT — FoodNet, 2012–2016

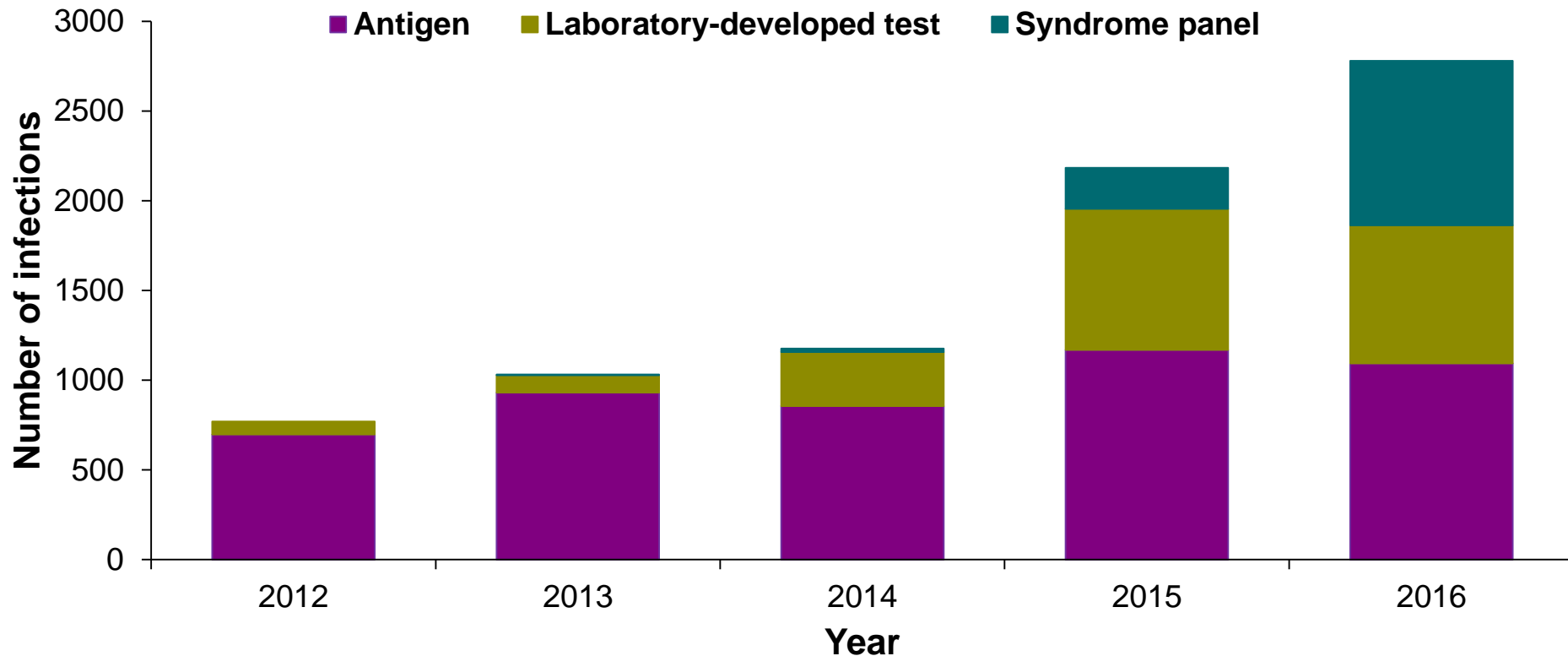
	Culture-diagnosed Infections (n=31,989)	CIDT-diagnosed Infections* (n=8,191)
Median age (range)	39 years	44 years
Female	45%	50%
White	84%	80%
Hispanic	13%	14%
Hospitalized	18%	27%
Symptoms		
Diarrhea	97%	96%
Bloody diarrhea	34%	27%
Fever	66%	46%

*p-value <0.001

Impact of CIDs on *Campylobacter* Surveillance; Early Lessons Learned from FoodNet Data

- Number of cases diagnosed by CIDT increased >2-fold from 2010 to 2016
 - Predominately antigen tests, move toward PCR panels
- Inclusion of CIDs in case counts impacts incidence rates
 - Incidence rates in 2010 would increase by 2%
 - Incidence rates in 2016 would increase by 47%
- Impact on incidence rates differs by subgroup
 - Greatest in persons <5 and >70 years, females, and non-white race
- Patients diagnosed by CIDT are different from CX
 - Could reflect differences in testing practices such as screening in nursing homes, or reflect false positive test results

Number of CDT+ *Campylobacter* infections, by test type — FoodNet, 2012–2016



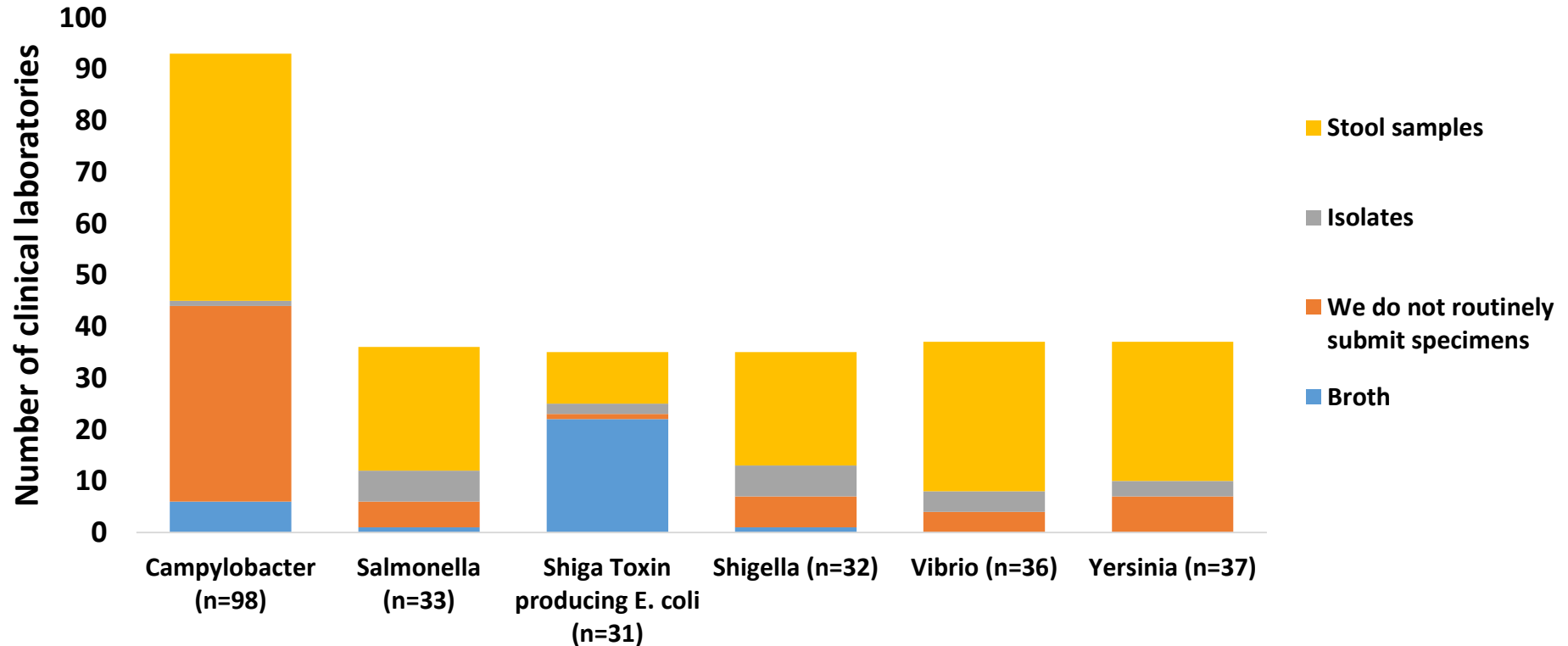
Listeria and Culture Independent Diagnostic Tests (CIDTs)

- Developed and administered laboratory surveys for *Listeria* September 2016
 - New blood culture and meningitis panel with BioFire and Verigene's platform
- March 2017, 11% (29/258) clinical laboratories use CIDTs
 - 65% concurrently run CIDT and culture
 - 24% use CIDTs to screen, the culture positive
 - 10% will only use CIDTs

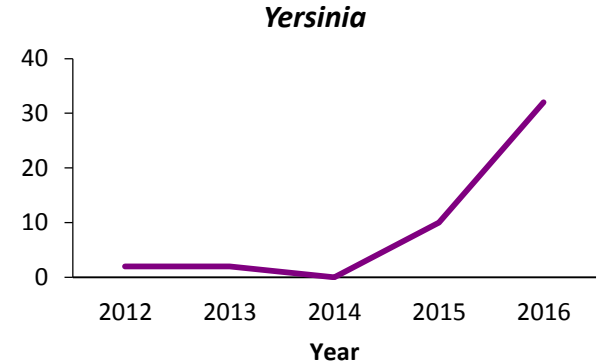
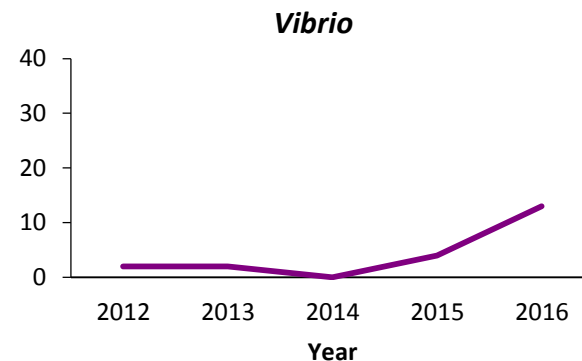
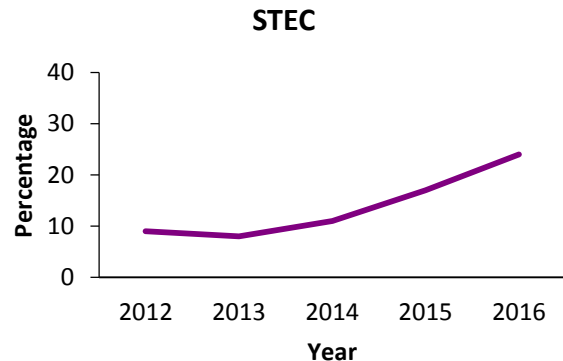
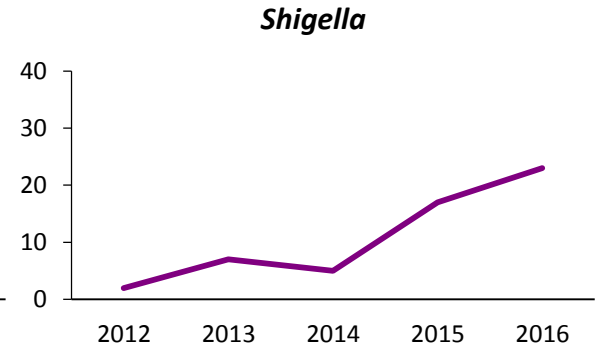
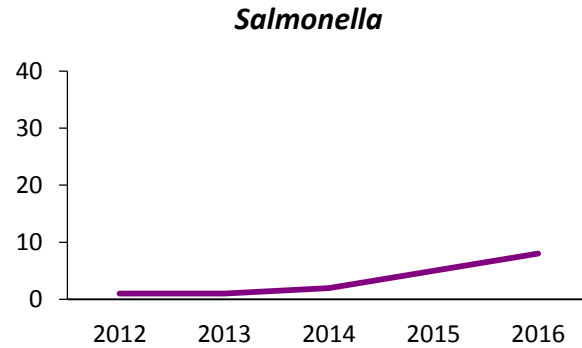
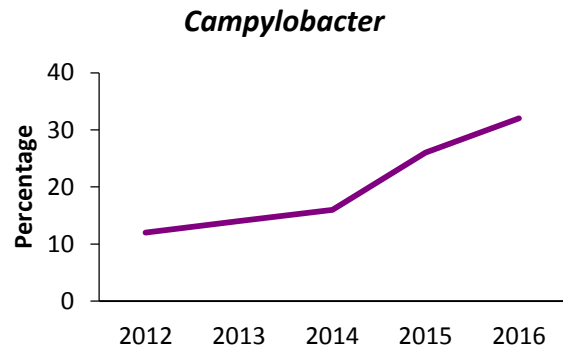
Number of confirmed and CIDI-positive bacterial and confirmed parasitic infections, by pathogen — FoodNet, 2016

		<u>Confirmed</u>		<u>CIDI-Positive</u>		<u>Confirmed or CIDI-Positive</u>
Pathogen		n	(%)	n	(%)	n
Bacteria	<i>Campylobacter</i>	5,782	(68)	2,765	(32)	8,547
	<i>Listeria</i>	127	(100)	0	(0)	127
	<i>Salmonella</i>	7,554	(92)	618	(8)	8,172
	<i>Shigella</i>	2,256	(77)	657	(23)	2,913
	STEC	1,399	(76)	446	(24)	1,845
	<i>Vibrio</i>	218	(87)	34	(13)	252
	<i>Yersinia</i>	205	(68)	97	(32)	302
Parasites	<i>Cryptosporidium</i>	1,816	(100)	0	(0)	1,816
	<i>Cyclospora</i>	55	(100)	0	(0)	55
Total		19,412		4,617		24,029

What are Clinical Laboratories Using CDTs Not reflex culturing Submitting to Public Health Laboratories? FoodNet, March 2017



Proportion of infections detected by only CIDT, by pathogen and year — FoodNet, 2012–2016



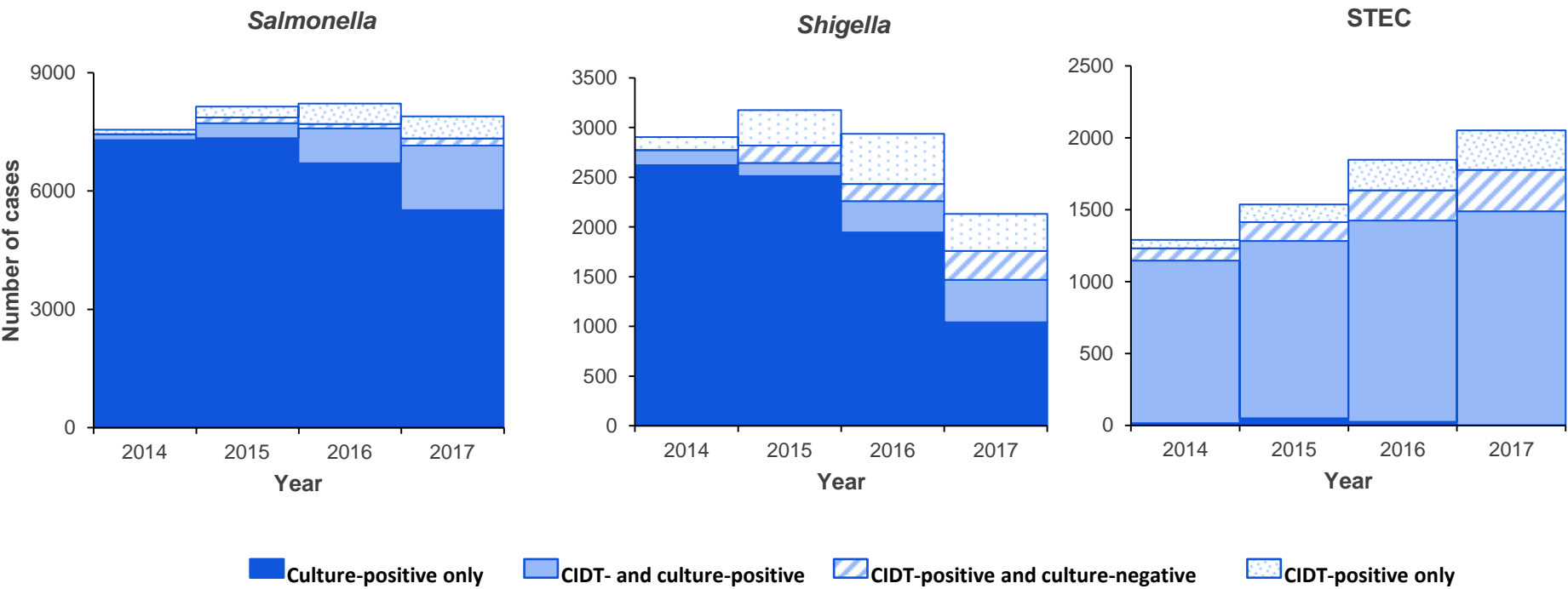
Surveillance Activities

- Tracked culture-confirmed (CX) infections since 1996
 - Patient demographics, hospitalization, outcome, and clinical symptoms
 - Active surveillance of clinical laboratories in FoodNet Catchment ~650 laboratories
- Began to see increase in reports of *Campylobacter* diagnosed by culture-independent tests (CIDT) in 2009
- Case counts, incidence rates, and trends based on CX cases.
- Expanded surveillance was needed to determine what effect the uptake of CIDTs would have on burden and trend estimates.

Expanded Surveillance

- In 2010, began counting CIDT positive reports
 - Patient demographics, hospitalization, outcome, and clinical symptoms
- In 2012, began collecting test type and brand name, location (e.g. clinical and state public health lab), and information on reflex culture
- Conducted biannual clinical laboratory surveys to assess changes in diagnostic testing practices
 - 10 cycles (spring and autumn): 2012–2017

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



Objectives

- Determine burden of foodborne illness in the US
- Monitor trends in burden of specific pathogens over time
- Attribute burden of illness to specific foods or settings
- Disseminate information to improve public health practice and guide development of interventions to reduce burden

How do we interpret changes in incidence?

- A quarter of clinical laboratories are using CIDs alone for enteric pathogens
 - Less than 20% of these perform reflex culture
- Interpretation of incidence measures and trends is complicated
 - Testing and detection may be increasing
 - Syndromic panels
 - Laboratory testing practices
 - Provider testing practices
 - Culture-confirmed cases may be
 - Decreasing as laboratories switch to CIDT
 - Increasing as more CIDT+ cases are reflex cultured
 - Incidence may be increasing because of
 - Increased testing and detection
 - False positives
 - Polymicrobial detections



Cadillac

Pinto

Pathogens

Salmonella Typhi/Paratyphi



Shiga toxin-producing E.coli



Salmonella (non-typhoidal)



Shigella



Frequency of testing

Paired with every culture



Paired with final culture



Location of testing

All sites



Selected sites

