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:
  o Uncertain meaning of some targets (e.g. EPEC)
  o Multiple positive analytes in single specimens
  o 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

<table>
<thead>
<tr>
<th>Strategy</th>
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<tbody>
<tr>
<td>Detect and monitor cases by culture</td>
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<tr>
<td>Detect and monitor cases by CIDTs</td>
</tr>
<tr>
<td>Detect cases by CIDT, monitor with culture</td>
</tr>
<tr>
<td>Detect cases with culture, monitor with CIDTs</td>
</tr>
<tr>
<td>Detect cases by CIDT, monitor with CIDTs and culture</td>
</tr>
<tr>
<td>Detect and monitor cases by culture and CIDTs</td>
</tr>
</tbody>
</table>

• 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 Unemo²,³

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 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. However, specimens were 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. 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 Since 2008, no patients in Sweden has been infected with the new variant of NVCT.
CIDT Impacts on Public Health Activities

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Public health surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>Subtype, AST</td>
</tr>
<tr>
<td>Shigatoxin-producing <em>E. coli</em></td>
<td>Subtype, AST</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Subtype, AST</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Genotype, AST</td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
<td>AST</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Subtype, AST</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Subtype (outbreaks)</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Serotype, AST</td>
</tr>
<tr>
<td><em>Neisseria gonorrhea</em></td>
<td>AST</td>
</tr>
<tr>
<td>CRE, MRSA</td>
<td>Subtype (outbreaks), AST</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes, S. pneumoniae, Haemophilis influenzae</em></td>
<td>Subtype, AST</td>
</tr>
</tbody>
</table>
The National Molecular Subtyping Network for Foodborne Disease Surveillance
PulseNet’s 20th Anniversary
An Economic Evaluation of PulseNet
A Network for Foodborne Disease Surveillance

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
Subtyping Methods: Isolate Dependency

<table>
<thead>
<tr>
<th>Method</th>
<th>Isolates Required?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFGE</td>
<td>Yes</td>
</tr>
<tr>
<td>MLVA</td>
<td>Yes</td>
</tr>
<tr>
<td>WGS</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Strategies to Meet the Surveillance Challenge of CIDT

Current
- Culture based
  - Use of reflex culture to obtain isolates

Short-term
- Whole Genome Sequencing
  - Continued use of reflex culture
  - Developing sequence-based national infrastructure

Long-term
- Metagenomics
  - Develop direct-from-specimen sequence-based pathogen characterization methods
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- Background

- What has changed since 2012?

- Where is diagnostics/public health headed?

- What are the current needs?
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
### Activities of the “Regulatory Workgroup” to Assure Continued Flow of Specimens and Isolates to Public Health

<table>
<thead>
<tr>
<th>Test Regulation</th>
<th>Laboratory Regulation</th>
<th>Test Reimbursement*</th>
<th>Case Reporting Rules, state capacity (culture of +’s)</th>
<th>Test Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-Device Licensure</td>
<td>CLIA, CAP, Joint Commission</td>
<td>Private or public payers</td>
<td>State Governments, APHL, CSTE</td>
<td>Medical Device Industry (Advamed-Dx)</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ADVAMED</td>
<td></td>
</tr>
<tr>
<td>o Fact sheet for medical device industry</td>
<td>Distributed</td>
</tr>
<tr>
<td>o CDC presentation to ADVAMED membership</td>
<td>Completed</td>
</tr>
<tr>
<td>• Recommended CIDT product insert language</td>
<td>Completed</td>
</tr>
<tr>
<td>• State reporting rules (regarding CIDT issues)</td>
<td></td>
</tr>
<tr>
<td>o Analysis of current rules, recommendations</td>
<td>Published</td>
</tr>
<tr>
<td>o Development of model language, executive summary</td>
<td>In progress</td>
</tr>
<tr>
<td>• Reflex culture reimbursement</td>
<td></td>
</tr>
<tr>
<td>o Fact sheets for private payers</td>
<td>Complete</td>
</tr>
<tr>
<td>o Issues and solutions document</td>
<td>Under review</td>
</tr>
</tbody>
</table>
Use of CIDTs Are Increasing — FoodNet, 2012–2016

Annual percentage of bacterial infections diagnosed by CIDTs

- Culture confirmed 91% in 2012–2015
- Culture confirmed 77% in 2016
- CIDT only 9% in 2012–2015
- CIDT only 23% in 2016
Mycobacterium tuberculosis

Clinical guidances to encourage culture of CIDT-positives
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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

- Federal laboratories
- State/local Public Health Laboratories
- Clinical Laboratories
- Point-of-care

**Exotic infections**

**Rare infections**

- TB
- Diphtheria
- Rabies

**Common infections**
Diagnosis by Next-Generation Sequencing

Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing


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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• Background
• What has changed since 2012?
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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