Benefits of Culture-Independent Diagnostic Testing to Public Health: A State Perspective

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WI State Lab of Hygiene

InFORM Meeting
Nov 21, 2015
Objectives

- Discuss the impact of CIDT in WI
- Describe ongoing PH efforts to address CIDT
- Share WSLH experiences with CIDT and culture preservation
- Generate discussion- what is going on in other states/jurisdictions to address culture preservation and the effects of CIDT?
Advantages to CIDT Use

• Generally faster to result than traditional tests
• Classically-trained microbiologists not needed in many cases
• May be more cost-effective than traditional, conventional tests
• Syndromic-based testing approach possible with multi-target tests
• Ability to detect non-cultureable or fastidious pathogens
Advantages to CIDT Use

• Improved sensitivity and specificity?
  ▪ Compared with culture
  ▪ Need to assess the validity of the developer validation studies; specimens and/or isolates used may not have been optimal or representative of true clinical specimens

• Detection of nonviable organisms*
  ▪ If truly pathogenic or significant cause of GI illness
Disadvantages to CIDT Use

• Price of some CIDT platforms may be cost-prohibitive for laboratories
• Loss of culture isolates
  ▪ To clinical laboratories for AST
  ▪ To public health for surveillance
• Loss of classical microbiology experience; staff unable to determine when results don’t make sense
Disadvantages to CIDT Use

- Detection of nonviable organisms*
  - Are they significant; are they the cause of illness?
  - Ineffective use for test of cure; patient may shed nonviable organism or organism DNA well after the infection has passed

- Interpretation of results
  - In relation to the clinical picture of the patient
  - Significance of multiple pathogens detected?
  - Reportable conditions guidelines blurred (Confirmed, suspect or probable case?)
WSLH Efforts

- Become familiar with CIDT’s on market
- Monitor CIDT performance
- Partner with clinical laboratories
- Communicate with epidemiologists, clinical health professionals and industry
- Effectively utilize existing resources
- Explore new funding sources
Commercially-Available CIDT’s

• Know what CIDT’s are available and on the market for clinical (and public health) laboratories and laboratory systems
  ▪ Visit vendor booths at scientific meetings
  ▪ Ask for in-house demonstrations
  ▪ Communicate with industry representatives

• If resources permit, assess whether your laboratory wants to do in-house methodology assessment and/or validation
Commercially Available CIDT’s-Gastrointestinal Pathogens

- A handful are available and more are in development
- Variances in targeted GI pathogens among the available CIDT’s (Bacteria only vs bacteria, parasites and viruses)
- Common aspects
  - Same day result
  - Organism isolation and identification are not necessary for diagnosis
Which CIDT Platform?????
WSLH- Use of the Luminex xTAG GPP Assay

- Implemented and validated in-house; had existing Luminex platform which was being used for RVP and *Salmonella* molecular serotyping
- Initial screen (run weekly) of stools rec’d as part of an ongoing community-acquired GI illness study at select clinics across Wisconsin
- Occasional screen (as needed) of outbreak patient specimens at the request of the WI Division of Public Health foodborne disease epidemiologists
WSLH- Use of the Luminex xTAG GPP Assay

- Began testing in July, 2014
- Have tested a total of 418 stool specimens thus far:
  - Total of 158 positives (38%)
  - Total of 18 multiple infections detected (4%); 8 of the 18 multiples were *C. difficile* plus another pathogen; most pathogens detected in a specimen has been three
  - 25 (6%) specimens from 5 outbreaks have been tested
  - 38 (9%) specimens were indeterminate*
## WSLH- Luminex xTAG GPP Assay Pathogens Detected

<table>
<thead>
<tr>
<th>Organism detected</th>
<th>Number Detected</th>
<th>Number Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus 40/41</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>C. difficile</td>
<td>35</td>
<td>NT</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>E. coli O157</td>
<td>3</td>
<td>1 (one specimen Stx-)</td>
</tr>
<tr>
<td>ETEC</td>
<td>4</td>
<td>NT</td>
</tr>
<tr>
<td>Non-O157 STEC</td>
<td>9 (all Stx1+)</td>
<td>6</td>
</tr>
<tr>
<td>Giardia</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Norovirus</td>
<td>38 (25 GII/13 GI)</td>
<td>36(2 NT)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Salmonella</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>1</td>
<td>0 (history not suggestive)</td>
</tr>
</tbody>
</table>

*Note: No *V. cholerae* O1 or *Shigella* found as of 3/10/15*
WSLH- Luminex xTAG GPP Assay Pathogens Not Covered

- High percentage of pathogens detected have been able to be confirmed by a second method
- In addition to the detected pathogens, the following pathogens were recovered from specimens negative in the xTAG GPP Assay:
  - *Aeromonas* (7)
  - *Vibrio cholerae* non-O1 (1)
  - *Y. enterocolitica* (1)
  - *Campylobacter upsaliensis/ helveticus* (1)
  - Sapovirus (1), Rotavirus (1), Astrovirus (3)
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WSLH- Use of the Luminex xTAG GPP Assay with Outbreaks

- Outbreak specimen screening results:
  - Three long term care facilities (LTCF)- *C. difficile* only
  - One college student residence hall- Norovirus G1
  - One outbreak linked to raw milk consumption-multiple foodborne disease pathogens detected
    - *Campylobacter*
    - STEC
    - *Giardia*
2014 Raw Milk Outbreak

- High school football team gathering in Fall, 2014 with sharing of food and beverages
- Chocolate milk served by parents; combination of store-bought choc milk and raw milk (supplied by parents of one team player) with choc syrup added after store-bought ran out
- 38 attendees were sickened in total
- One early case seen at a local clinic was diagnosed with *Campylobacter* by RCA
2014 Raw Milk Outbreak-Continued

- *Campylobacter* was suspected but raw milk potentially contains >1 pathogen...
- WDPH epidemiologists requested Luminex xTAG GPP testing on 9 more stool specimens collected by the county health department:
  - 8 *Campylobacter* positives
  - 3 Stx1 (Non-O157 STEC) positives
  - 1 *Giardia* positive
- All pathogens confirmed by a second method
Subsequent specimens from patients implicated in the outbreak were also found positive for *Campylobacter*, STEC and *Giardia* by Luminex xTAG GPP.

In all likelihood, the STEC and *Giardia* pathogens would not have been detected had the investigation focused solely on the early *Campylobacter* RCA result and the multi-target assay not been utilized.
CIDT Performance

- If funding allows, monitor CIDT sensitivity and specificity vs conventional and/or PCR tests performed in-house
- There remain a number of questions as to the sensitivity, specificity and utility of many of the commercially available CIDT’s
- Data collation and sharing can educate public health and clinical health professionals as well as industry
## Current WI Molecular CIDT Laboratories

<table>
<thead>
<tr>
<th># Number of Laboratories in WI</th>
<th>CIDT Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Verigene Enteric Pathogens Test</td>
</tr>
<tr>
<td>2</td>
<td>Luminex xTag Gastrointestinal Pathogen Panel</td>
</tr>
<tr>
<td>3</td>
<td>Biofire FilmArray Gastrointestinal Panel</td>
</tr>
<tr>
<td>3</td>
<td>Prodesse Progastro SSCS Assay</td>
</tr>
</tbody>
</table>
Salmonella Referred Isolates

- 2013: 963 isolates
- 2014: 900 isolates
- 2015*: 745 isolates

* As of 9/30/2015

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Salmonella Primary Stool Specimens

- 2013: 7 total, 0 CIDT
- 2014: 46 total, 38 CIDT
- 2015*: 73 total, 69 CIDT

* As of 9/30/2015

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Salmonella CIDT Recovery

![Graph showing the number of positive cases and percentage positive for Salmonella CIDT recovery in 2014 and 2015.*]

*As of 9/30/2015
Campylobacter Isolates vs Stools for Confirmation

- **Isolates**: Bar graph showing the number of isolates for 2013, 2014, and 2015.
- **1st CIDT Positive**: Bar graph showing the number of 1st CIDT positive cases for 2013, 2014, and 2015.
- **Combined total**: Bar graph showing the combined total for 2013, 2014, and 2015.

**Data**:
- **2013**:
  - Isolates: 914
  - 1st CIDT Positive: 364
  - Combined total: 1278
- **2014**:
  - Isolates: 784
  - 1st CIDT Positive: 449
  - Combined total: 1233
- **2015**:
  - Isolates: 526
  - 1st CIDT Positive: 488
  - Combined total: 1014

*As of 9/30/2015
Campylobacter Isolates vs Stools for Confirmation

<table>
<thead>
<tr>
<th>Year</th>
<th>% Isolates</th>
<th>% 1º CIDT Stools</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>72</td>
<td>28</td>
</tr>
<tr>
<td>2014</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>2015*</td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>

* As of 9/30/2015
Campylobacter CIDT+ Stools for Culture Confirmation

![Bar chart showing number of specimens and positive cases from 2013 to 2015 and Molecular CIDT as of 9/30/2015.]

*As of 9/30/2015*
Campylobacter CIDT+ Stools for Culture Confirmation

<table>
<thead>
<tr>
<th>Year</th>
<th>Total CIDT</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>57</td>
<td>30%</td>
</tr>
<tr>
<td>2014</td>
<td>63</td>
<td>40%</td>
</tr>
<tr>
<td>2015*</td>
<td>58</td>
<td>30%</td>
</tr>
<tr>
<td>Molecular CIDT</td>
<td>79</td>
<td>100%</td>
</tr>
</tbody>
</table>

* As of 9/30/2015
STEC CIDT+ Specimens for Culture Confirmation

<table>
<thead>
<tr>
<th></th>
<th># Specimens</th>
<th># Total Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>198</td>
<td>157</td>
</tr>
<tr>
<td>2014</td>
<td>226</td>
<td>174</td>
</tr>
<tr>
<td>2015</td>
<td>205</td>
<td>144</td>
</tr>
<tr>
<td>Molecular CIDT</td>
<td>22</td>
<td>19</td>
</tr>
</tbody>
</table>

*As of 9/30/2015*
STEC CIDT+ Specimens for Culture Confirmation

- Total Specimens
- % Total STEC

2013: 79
2014: 77
2015*: 70
Molecular CIDT: 86

* As of 9/30/2015

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STEC CIDT/Culture+ Specimens

# Out of 19

- **O145**: 3
- **O157**: 5
- **O26**: 2
- **O45**: 1
- **O111**: 1
- **non-Big 6**: 3
- **PCR+ Only**: 2

*As of 9/30/2015*
Cryptosporidium CIDT+ Stools for DFA Confirmation

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* As of 9/30/2015
Cryptosporidium CIDT+ Stools for DFA Confirmation

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>2015*</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Molecular CIDT</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>

* As of 9/30/2015

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June 2015 Cyclospora

- Cluster of 11 cases of *Cyclospora cayetanensis* linked to a Mexican style restaurant
- First detected by a clinical lab using BioFire.
- Clusters in WI, TX and GA ultimately linked to fresh cilantro from Puebla, Mexico.
- Likely would not have been detected in WI had the clinical laboratory not been using CIDT.
CIDT Performance/ Isolate Recovery

- Reasons for poor recovery
  - Sensitivity
    - CIDT Better than culture?
  - Viability
    - Organisms die in transit or storage
    - Non-culturable organisms
  - False-positive CIDT
    - Studies have been published questioning some of the commercially-available rapid cartridge assays, particularly RCA’s for Cryptosporidium and Campylobacter
Partner With Clinical Laboratories

• Continue to culture and submit isolates to PHL’s for surveillance
• If isolation is not possible, ask to submit positive clinical specimens to PHL’s for surveillance
  ▪ Courier service
  ▪ Shippers
  ▪ Stool kits
  ▪ Do not batch
Partner With Clinical Laboratories

- Provide guidance to clinical laboratories on CIDT issues such as:
  - Proper specimen storage, handling and shipping
  - Specimen submission to PHL
    - Submit as they are detected (avoid batching if at all possible)
- Discuss reporting issues
  - Will they get a report?
  - What if the PHL cannot isolate the suspected pathogen?
# Specimens | TOC to Receipt
---|---
Total Molecular CIDT* | 131 | 3.15
Total Culture Positive | 96 | 3.05
Total Culture Negative | 35 | 3.40

*positive at clinical laboratory for Salmonella, Shigella, Campylobacter, Aeromonas, Plesiomonas, Vibrio, Yersinia, or STEC
Days to Receipt WSLH

%Positive Culture
% Negative Culture

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Partner With Epidemiologists

• Discuss reporting issues
  - Multiple pathogens - what does it mean?
  - Positive CIDT but negative culture or confirmatory test - What to believe? What to count as a case?

• Communicate to epidemiologists what CIDT results mean
  - Incidental/ non-infectious vs infectious
  - Viable vs non-viable organisms
  - Long term carriage post-infection
CIDT Developer Education

- If able, discuss with CIDT developers the impact of CIDT assays on public health
- Encourage them to add public health-friendly language to the package insert
  - Continuation of culture where indicated (O157)
  - Retention and referral of specimens to PHL
- Recommend to sales representatives that they discuss with customers the importance of isolate and/or specimen preservation and the needs of public health surveillance
Utilize Existing Resources

- Available courier systems
  - In-house
  - Clinical system/hospital
  - Contract with private agency
- “Piggy-back” on developed laboratory network(s)- partnerships and communication systems are already in place
- MALDI-TOF
Utilize Existing Resources/Resource strain

- Staffing
  - Number
  - Training
  - Experience
- Priorities
  - NGS implementation/Other
- Funding
  - Limited
  - Shrinking State support
Pursue Funding Opportunities

- Epidemiology and Laboratory Capacity (ELC) grant
  - PulseNet
  - Multiple areas
- Public Health Emergency and Preparedness (PHEP) grant
- Local or state government funding (Basic agreements)
- Don’t ask, don’t receive
Prepare for the “Culture-less” Laboratory

- Address future infrastructure needs
  - Staff (re)training/hiring
  - Data management and storage needs
  - LIMS reporting and documentation needs
  - Equipment purchase, maintenance and space needs
- Development of Whole Genome Sequencing (WGS)
- Development of Metagenomics
Solutions to CIDT Issues

- Issues exist across the national PHL landscape
  - Varying degrees of jurisdictional PHL impact
  - Varying stages of implementation in each jurisdiction
- Partnership among many players is critical
- Utilize existing resources (APHL, ASM, partner laboratories) to gain answers and optimize your jurisdiction CIDT response
APHL/CDC Resources

- APHL CIDT Subcommittee
- CDC CIDT Regulatory WG
- CDC Clinical Isolate Recovery WG
Summary

• WI seeing similar effects of CIDT on foodborne disease surveillance
• CIDT can also be beneficial to PH efforts through detection of both uncommon and non-culturable pathogens and faster time to results
• Must communicate/ reach out to clinical and epi partners in your jurisdiction to keep apprised of the state of CIDT there
• APHL, CDC and ASM are being proactive to address CIDT impact
Discussion

- Have seen similar impacts of CIDT in your jurisdiction?
- What have you done to address CIDT issue?
- Any PHL using CIDT for diagnostic purposes?
- What challenges do you face now? What challenges do you foresee for the future?
Contact Info

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