Exploring Novel Approaches to Shared TB Laboratory Services: California-Wisconsin Shared Services Pilot Study

Julie Tans-Kersten, MS, BS-MT (ASCP)
Tuberculosis Laboratory Program Coordinator
Wisconsin State Laboratory of Hygiene
tanskejl@mail.slh.wisc.edu
(608) 263-5364
Outline

• Background and Objectives of the Shared Services Project
• Logistics of the Project
• Testing involved
• Results
• Conclusions
Background

• Although tuberculosis (TB) remains a significant burden to public and private health care organizations nationwide, the number of TB cases continues to decrease.

• For laboratories in areas that are low-incidence for TB, it may be a struggle to offer a full spectrum of TB laboratory services in the face of ever-decreasing test volumes.

• Ongoing budgetary concerns and retirement of experienced laboratory professionals contribute to this struggle.
Background

• To maintain quality laboratory testing and to control expenses, laboratories may consider a variety of shared service options
  – Referral for specialized testing
  – Laboratory partnerships
• Laboratories are hesitant to explore these opportunities, as many aspects of shared laboratory services have not been fully examined.
Objectives of Shared Services Pilot

- Assess feasibility and consequences of referring smear-positive sediments to a reference laboratory for detection of TB by NAAT.
- Assess utility of universal referral of sediments and cultures for rapid molecular detection of drug resistance for a population at low risk for drug resistance.
- Assess feasibility and consequences of referring MTBC-positive sediments and cultures to a reference laboratory for conventional first- and second-line DST.
Shared Services Project

- Wisconsin State Laboratory of Hygiene (WSLH) referred specimens to the California Department of Public Health Laboratory (CDPHL)
  - Nucleic Acid Amplification Testing (NAAT)
  - Detection of drug resistance by molecular methods (PSQ=pyrosequencing)
  - Conventional TB first- and second-line drug susceptibility testing (DST)
- Wisconsin performed parallel NAAT and conventional TB first-line DST
- Nine-month study period (9/1/12 to 5/31/13)
### Summary of California and Wisconsin Mycobacteriology Services

<table>
<thead>
<tr>
<th></th>
<th>CDPHL</th>
<th>WSLH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleic Acid Amplification Testing (NAAT)</strong> for detection of <em>M. tuberculosis</em> complex</td>
<td>Pyrosequencing, <em>IS6110</em></td>
<td>Laboratory-developed real-time PCR, <em>IS6110</em></td>
</tr>
</tbody>
</table>
| **Detection of Drug Resistance by Molecular Methods** | Pyrosequencing (PSQ)  
INH (*katG, inhA, ahpC*)  
rifampin (*rpoB*)  
fluoroquinolone (*gyrA*)  
infectables (*rrs*) | Referred to CDC for Molecular Detection of Drug Resistance (MDDR) program  
(INH (two concentrations), rifampin, ethambutol, PZA by MGIT) |
| **TB first-line DST, Conventional** | INH (two concentrations), rifampin, ethambutol, PZA by MGIT | INH (two concentrations), rifampin, ethambutol, PZA by MGIT |
| **TB second-line DST, Conventional** | Amikacin, moxifloxacin, ethionamide, and capreomycin by MGIT | Referred to CDC for agar proportion testing |
Number of Specimens Referred to CDPHL and Number of Results Reported by CDPHL

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of specimens shipped</td>
<td>182</td>
</tr>
<tr>
<td>Number of patients with specimens shipped</td>
<td>162</td>
</tr>
<tr>
<td>Total number of shipments</td>
<td>90</td>
</tr>
<tr>
<td>NAAT: detection of <em>M. tuberculosis</em> complex from primary patient sediment</td>
<td>139</td>
</tr>
<tr>
<td>Detection of drug resistance (molecular)</td>
<td>47</td>
</tr>
<tr>
<td>Conventional TB First-line DST</td>
<td>41</td>
</tr>
<tr>
<td>Conventional TB Second-Line DST</td>
<td>13</td>
</tr>
</tbody>
</table>
Results
### Submission and Transport Time

<table>
<thead>
<tr>
<th>Description</th>
<th>Time</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Submission (average number of days from receipt at WSLH until send-out to CDPHL for Testing), smear + sediment</td>
<td>0.877</td>
<td>0-5 days</td>
</tr>
<tr>
<td>Average number of days in transit (FedEx or UPS)</td>
<td>1.13</td>
<td>1-5 days</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.0 days</td>
<td></td>
</tr>
</tbody>
</table>
# Shipping Costs

<table>
<thead>
<tr>
<th>Description</th>
<th>Unit Cost</th>
<th>Number of Packages</th>
<th>Total ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category A Shipment</strong></td>
<td>Infectious shipper $15.10 FedEx* overnight $64.12</td>
<td>30</td>
<td>2,377</td>
</tr>
<tr>
<td><strong>Category B Shipment</strong></td>
<td>Shipper + cold pack $15 UPS** overnight $19.70</td>
<td>60</td>
<td>2,082</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>$4459</strong></td>
</tr>
</tbody>
</table>

(*) Federal Express  
(**) United Parcel Service
Shipping Summary

- Both FedEx and UPS offered rapid and reliable package transport (average 1.13 days for overnight service).
- Shipping costs were substantial ($4459)
- Estimated labor costs for packaging and shipping would be $50 \times 90 = $4500
# Detection of TB: Comparison of In-house and Referral Testing

<table>
<thead>
<tr>
<th>NAAT for detection of <em>M. tuberculosis</em> complex (IS6110) from primary patient sediment</th>
<th>WSLH (real-time PCR)</th>
<th>Referral to CDPHL for detection of TB by PSQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAAT Results Reported</td>
<td>135</td>
<td>139</td>
</tr>
<tr>
<td>Number of culture-confirmed TB patients with positive NAAT from primary sediment</td>
<td>23/29 (79.3%)</td>
<td>27/29 (93.1%)</td>
</tr>
<tr>
<td>Average TAT from date of receipt in Wisconsin Lab (days)</td>
<td>0.31 Range = 0-4 days</td>
<td>3.84 Range = 1-11 days</td>
</tr>
<tr>
<td>Percent of Results meeting Healthy People 2020 Goal (identification of TB within 48 hours of receipt in WI Lab)</td>
<td>22/29 = 75.8%</td>
<td>7/29 = 24%</td>
</tr>
</tbody>
</table>
Summary: Referral for Detection of TB

- Although average time to submission for sediments (0.877 days) and average number of days in transit (1.13 days) were short, these delays had a substantial impact on NAAT TAT, despite excellent TAT (1.83 days) for NAAT at CDPHL.
- Only 24% of referred NAATs met the Healthy People 2020 Goal of detection of MTBC within 48 hours of specimen receipt.
- NAAT may not be as conducive to referral as other mycobacteriology testing due to the very short TATs required.
## Detection of Drug Resistance

<table>
<thead>
<tr>
<th>Description</th>
<th>WSLH</th>
<th>Referral to CDPHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average PSQ TAT from date of receipt in Wisconsin Lab (days)</td>
<td>Not performed</td>
<td>3.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range = 1-11</td>
</tr>
<tr>
<td>Median TAT: Conventional TB First Line DST, from date of receipt in Wisconsin Lab (days)</td>
<td>26</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Range = 14-59</td>
<td>Range = 21-114</td>
</tr>
<tr>
<td>Median TAT: Conventional TB Second-Line DST, from date of receipt in Wisconsin Lab (days)</td>
<td>Not performed</td>
<td>41.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range = 27-115</td>
</tr>
</tbody>
</table>
Drug Resistance Detected

- **Pan-Susceptible**: 34 (72%)
- **INH mono-resistant**: 1
- **INH + rif (MDR)**: 1
- **PZA mono-resistant**: 3
- **INH + PZA resistant**: 8

Total detected: 40
Summary: Detection of Drug Resistance by PSQ

- On average, PSQ results were reported 22 days before in-house conventional TB first-line DST results were complete.

- During the study, three new MDR-TB cases were rapidly identified using molecular testing.

- Based on PSQ results, conventional second-line DST could proactively be set up.

- PSQ results were routinely used by the Wisconsin TB Program to ensure appropriate therapy and patient management.
Use of PSQ results by WI TB Program

• **MDR-TB prediction:**
  - Full panel MDDR testing (including *embB* and *pncA* loci) is necessary for therapy decisions of new MDR-TB patients.
  - Continue any “susceptible” 1st line drugs, add fluoroquinolone and injectable

• **INH resistance prediction:**
  - Continue “susceptible” 1st line drugs, lengthen therapy, add moxifloxacin (?)
Use of PSQ results by WI TB Program

- **Pan-susceptible prediction:**
  - Gives TB program first prediction that the patient can be treated with 1\textsuperscript{st}-line drugs
  - Assures nurses to continue standard therapy, even when the patient isn’t doing well in the beginning
  - Good QA check for when conventional results are available (not necessary to repeat testing for “resistant” conventional result?)
Referral for Conventional DST

- Referral lead to a 16-day (median) delay in reporting conventional first-line DST results; TAT for referral for conventional TB first-line DST was 42 days.

- The CDPHL laboratory-developed MGIT assay for amikacin, moxifloxacin, ethionamide and capreomycin yielded rapid second-line DST results.
  - Additional drug testing (e.g. PAS, cycloserine, rifabutin) may be required for therapy decisions in some jurisdictions.
## Discordant Results

<table>
<thead>
<tr>
<th>Nature of Discordance</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAAT: false negative in submitting lab, reference lab, or both</td>
<td>7</td>
</tr>
<tr>
<td>PSQ results don’t agree with conventional results TB first-line DST</td>
<td>3</td>
</tr>
<tr>
<td>Conventional TB first line DST results don’t agree between submitting lab and reference lab</td>
<td>3</td>
</tr>
</tbody>
</table>
## Costs

<table>
<thead>
<tr>
<th>Description</th>
<th>Unit Cost</th>
<th>Number Performed</th>
<th>Total ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAAT/PSQ</td>
<td>$187</td>
<td>139</td>
<td>25,993</td>
</tr>
<tr>
<td>TB First-Line DST by MGIT</td>
<td>$190</td>
<td>41</td>
<td>7,790</td>
</tr>
<tr>
<td>TB Second-line DST by MGIT</td>
<td>$200</td>
<td>13</td>
<td>2,600</td>
</tr>
<tr>
<td>Packaging and Shipping</td>
<td>See slide 13</td>
<td></td>
<td>8,959</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>$45,342</strong></td>
</tr>
</tbody>
</table>
Submitting Laboratory

Smear and Culture

NAAT or GeneXpert

Reference Laboratory

MTBC positive sediment

MTBC-positive broth

MDDR or PSQ

Conventional DST
Conclusions

- Through the CDC/APHL-funded Shared Services Project, we documented successes and challenges associated with sending specimens to a reference laboratory for mycobacteriology testing.

- Rapid TATs are imperative for NAAT. Achieving the Healthy People 2020 Goal of a 48-hour TAT was not possible in this Shared Services project.

- Sharing services provided rapid detection of drug resistance by PSQ to Wisconsin patients. These results were valuable for timely patient management decisions.
Conclusions (continued)

- Referral led to significant delays in conventional DST; these delays were not as consequential if molecular results were available.
- Laboratories should carefully consider testing options and consult with TB Control partners when making referral testing decisions.
- At a time when mycobacteriology laboratories may be experiencing staffing shortages and funding difficulties, reference laboratories can offer testing that may not otherwise be available. Benefits of referral testing may outweigh associated costs and delays.
Please see poster #6 for more details!
CDPHL Laboratory Team

A Special Thanks to:
Dr. Ed Desmond
Grace Lin
Abby Duque
Abiy Tadesse
Shantelle Lucas
References

(1) Centers for Disease Control and Prevention, TB data and statistics:

(2) Wisconsin TB Program statistics:

(3) Healthy People 2020 Objectives:

(4) CDC MDDR Program: http://www.cdc.gov/tb/topic/laboratory/mddr.htm

