Use of Nucleic Acid Amplification Tests in TB patients in California 2010-2012

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August 21, 2013
Objective: To describe, with surveillance data, how NAATs were used in TB patients in CA 2010-2012
• CDC recommendation: Use NAAT for diagnosis of pulmonary TB when the test result would alter case management or TB control activities

• NAAT can reliably detect *Mycobacterium tuberculosis* bacteria in specimens 1 or more weeks earlier than culture

• NAATs: high specificity, but modest and highly variable sensitivity, especially in smear-negative and extrapulmonary TB

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1Updated Guidelines for the use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis, 2009. MMWR vol. 58, No. 1

Questions related to NAAT use

• How many pulmonary TB patients had NAAT?
• Can we determine, with surveillance data only, how NAATs were used to inform treatment decisions?
How many pulmonary TB patients had NAAT: NAAT report dates before or after culture?

- 4543 pulmonary culture-positive TB cases
- 2381 (52%) NAAT reported
- 1632 (69%) NAAT reported before culture
- 1632 (36%) NAAT
- 693 (29%) NAAT reported at/after culture
- 56 (2%) NAAT reported missing dates
- 2162 (48%) no NAAT reported
- 2855 (64%) no NAAT
How many pulmonary TB patients had NAAT?

• 52% of all pulmonary culture-confirmed TB patients had NAAT reported

BUT

• 36% had NAAT reported before culture

Assumptions: 29% of reported NAATs with report dates at/after culture were:

• Not used as rapid diagnostic tests*
• Did not influence treatment decision

* We are not considering use of NAATs for DST in these analyses
CDC recommends that NAAT be performed ...each patient with ...pulmonary TB ...

*and for whom the test result would alter case management or TB control activities*
How were NAATs used to:

*alter case management or TB control?*

• How were patients with NAAT different than those without?
• Did patients with NAAT start treatment earlier than those without?
• How rapidly were NAATs reported?
• Did NAAT turnaround time vary by lab type and jurisdiction?
• Did patients with positive NAATs start treatment earlier than those with negative NAATs?
Methods

• Study population:
  – Pulmonary culture-confirmed TB patients with a known AFB smear, reported to CA TB registry, 2010-2012

• Definitions
  – NAAT = NAAT reported before culture
  – No NAAT = NAAT not reported or NAAT reported at/after culture
  – Unless otherwise noted, time to treatment initiation = number of days between date of earliest specimen collection and date of treatment start, excluding patients who started treatment at or before specimen collection
  – NAAT TAT = time between specimen collection and NAAT report date

• Statistical analysis: frequencies compared across strata with chi-squared or Fisher’s exact tests; median timeframes compared with Wilcoxon rank-sum tests
How were patients with NAAT different than those without NAAT?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NAAT N (%)</th>
<th>No NAAT N (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1632</td>
<td>2855</td>
<td>4487</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>128 (8)</td>
<td>231 (8)</td>
<td>359 (8)</td>
</tr>
<tr>
<td>Black</td>
<td>93 (6)</td>
<td>168 (6)</td>
<td>261 (6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>645 (40)</td>
<td>1003 (35)</td>
<td>1648 (37)</td>
</tr>
<tr>
<td>Asian/PI</td>
<td>762 (47)</td>
<td>1449 (51)</td>
<td>2211 (49)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 65 yrs.</td>
<td>1183 (72)</td>
<td>1984 (69)</td>
<td>3167 (71)</td>
</tr>
<tr>
<td>65+</td>
<td>449 (28)</td>
<td>871 (31)</td>
<td>1320 (29)</td>
</tr>
<tr>
<td><strong>Sputum smear</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1476 (90)</td>
<td>1496 (52)</td>
<td>2972 (66)</td>
</tr>
<tr>
<td>Negative</td>
<td>156 (10)</td>
<td>1359 (48)</td>
<td>1515 (34)</td>
</tr>
<tr>
<td><strong>Chest x-ray findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnl w cavities</td>
<td>480 (31)</td>
<td>538 (20)</td>
<td>1018 (24)</td>
</tr>
<tr>
<td>Abnl no cavities</td>
<td>1091 (69)</td>
<td>2140 (80)</td>
<td>3231 (76)</td>
</tr>
</tbody>
</table>
How were patients with NAAT different than those without NAAT, cont.?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NAAT N (%)</th>
<th>No NAAT N (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1632</td>
<td>2855</td>
<td>4487</td>
</tr>
<tr>
<td><strong>Co-morbidity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>479 (29)</td>
<td>687 (24)</td>
<td>1166 (26)</td>
</tr>
<tr>
<td>End stage renal dz</td>
<td>41 (3)</td>
<td>84 (3)</td>
<td>125 (3)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>108 (7)</td>
<td>177 (6)</td>
<td>285 (6)</td>
</tr>
<tr>
<td>TNF antagonist rx</td>
<td>11 (0.7)</td>
<td>16 (0.6)</td>
<td>27 (1)</td>
</tr>
<tr>
<td>Post organ transplant</td>
<td>5 (0.3)</td>
<td>18 (0.6)</td>
<td>23 (0.5)</td>
</tr>
<tr>
<td><strong>Primary reason evaluated for TB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB symptoms</td>
<td>1197 (73)</td>
<td>1779 (62)</td>
<td>2976 (66)</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>290 (18)</td>
<td>618 (22)</td>
<td>908 (20)</td>
</tr>
<tr>
<td>Contact investigation</td>
<td>44 (3)</td>
<td>69 (2)</td>
<td>113 (3)</td>
</tr>
<tr>
<td>Targeted testing</td>
<td>26 (2)</td>
<td>44 (2)</td>
<td>70 (2)</td>
</tr>
<tr>
<td>Immigration med exam</td>
<td>18 (1)</td>
<td>134 (5)</td>
<td>152 (3)</td>
</tr>
<tr>
<td>Incidental lab result</td>
<td>45 (3)</td>
<td>164 (6)</td>
<td>209 (5)</td>
</tr>
<tr>
<td>HCW/admin/unk</td>
<td>11 (0.7)</td>
<td>46 (2)</td>
<td>57 (1)</td>
</tr>
</tbody>
</table>
Compared to patients without NAAT, patients with NAAT were more likely:

- Younger
- Hispanic
- Not Asian
- Sputum smear-positive

And to have:

- Cavities on chest radiograph
- Diabetes co-morbidity
- TB symptoms as the primary reason for TB evaluation
Did patients with NAAT start treatment earlier than those without NAAT?
Timing of diagnostic tests and treatment initiation

240 (15%) patients with NAAT vs. 320 (11%) patients without NAAT started treatment presumptively (at/before specimens were collected) P-value=0.0019
Timing of diagnostic tests and treatment

**TB considered**
Specimens collected
Smear and/or NAAT reported
Culture growth of Mtb complex reported

**Time**

**Smear-positive patients***
- 98% with NAAT started treatment before culture reported vs.
- 75% without NAAT

**Smear-negative patients***
- 81% with NAAT started treatment before culture reported vs.
- 38% without NAAT

*excluding patients starting treatment at/before specimen collection
P-value <0.0001
Did patients with NAAT start treatment earlier than those without NAAT?

<table>
<thead>
<tr>
<th>Group</th>
<th>NAAT Median time* (N)</th>
<th>No NAAT Median time* (N)</th>
<th>P-value for Wilcoxon rank sums test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All *</td>
<td>3.0 (1357)</td>
<td>13.0 (2410)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smear-positive*</td>
<td>2.0 (1224)</td>
<td>4.0 (1233)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smear-negative*</td>
<td>14.0 (133)</td>
<td>25.0 (1177)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Time (days) between date of earliest specimen collection and treatment initiation
Pulmonary culture-positive TB cases initiating treatment after specimen collection
How rapidly were NAATs reported?

Among 1357 pulmonary culture-confirmed patients starting treatment after specimen collection

Median TAT=4 days
Mean=5.3 days
IQR=2 to 6 days
Did NAAT turnaround time vary by laboratory type?

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>NAAT median TAT¹</th>
<th>P-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public health</td>
<td>2 days</td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>3 days</td>
<td>0.008</td>
</tr>
<tr>
<td>Other</td>
<td>2 days</td>
<td>0.05</td>
</tr>
</tbody>
</table>

¹NAAT turnaround time (working days between date of NAAT specimen collection and NAAT report, median)
²Wilcoxon rank-sum comparison of median NAAT TAT with NAAT TAT for public health lab
Did NAAT turnaround time vary by jurisdiction?

<table>
<thead>
<tr>
<th>Health department</th>
<th>NAAT, N (% total pts with NAAT)</th>
<th>NAAT TAT median days excluding wkend</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12 (0.7)</td>
<td>7.0</td>
</tr>
<tr>
<td>B</td>
<td>37 (2)</td>
<td>1.0</td>
</tr>
<tr>
<td>C</td>
<td>49 (3)</td>
<td>8.0</td>
</tr>
<tr>
<td>D</td>
<td>266 (16)</td>
<td>2.0</td>
</tr>
<tr>
<td>E</td>
<td>519 (32)</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Varying NAAT TATs suggest that

Accessibility to NAAT varied by local health jurisdiction
For patients with NAAT, how did NAAT results inform treatment decisions?

Population
• NAAT reported before culture
• treatment initiated after specimens collected
• treatment initiated after NAAT reported
How many patients started treatment after NAAT report?

- Of 1092 pulmonary culture-confirmed TB cases starting treatment after NAAT specimen collected
  - 531 (49%) started treatment after NAAT report
  - 561 (51%) started treatment before NAAT report
Did NAAT results impact treatment initiation times?

NAAT positive  →  Treatment start

Delay?

NAAT negative  →  Treatment start
Timing of treatment and smear status
NAAT-positives vs. NAAT-negatives

1092 pulmonary culture (+)

531 (49%) start rx post-NAAT report

561 (51%) start rx pre-NAAT report

444 (84%) smear (+)

87 (16%) smear (-)

416 (94%) NAAT (+)

28 (6%) NAAT (-)

63 (72%) NAAT (+)

24 (28%) NAAT (-)

*starting treatment after specimens collected for NAAT
Did patients with positive NAATs start treatment earlier than those with negative NAATs?

<table>
<thead>
<tr>
<th>Group</th>
<th>NAAT positive Median time *(N)</th>
<th>NAAT negative Median time* (N)</th>
<th>P-value for Wilcoxon rank sums test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.0 (479)</td>
<td>8.0 (52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smear-positive</td>
<td>0.0 (416)</td>
<td>5.0 (28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smear-negative</td>
<td>2.0 (63)</td>
<td>15.0 (24)</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

*Time (days) between date NAAT reported and treatment initiation

Pulmonary culture-positive TB cases initiating treatment after NAAT report
Limitations

• Chart review was not performed so not all factors contributing to treatment decision were known
• Type of NAAT was not collected so we could not assess the use of different NAATs
Conclusions

• 36% pulmonary culture (+) TB patients had NAAT used for diagnosis prior to culture
• NAATs reported at/after culture suggest additional training to improve reporting accuracy
• Patients with NAAT were more likely to have clinical indicators of TB than patients without
• Time to treatment initiation was shorter in patients with NAAT compared to patients without NAAT
• NAAT TAT varied by local health jurisdiction, suggesting differential access to NAAT
• Patients with positive NAATs started treatment earlier than those with negative NAATs
Next steps:
The California TB Control Branch is

- Implementing enhanced training on NAAT reporting
- Encouraging the use of NAAT for diagnosis of TB
Acknowledgements

• Pennan Barry
• Carla Cueva
• Alex Golden
• TB Control Branch colleagues
• TB molecular epidemiology group at UCSF Pulmonary Division/San Francisco General Hospital

Contact: lisa.pascopella@cdph.ca.gov
NAAT sensitivity in pulmonary culture-confirmed TB patients in CA 2010-2012

• Smear positives = 94% (95% CI=93-95)
• Smear negatives = 70% (95% CI=63-77)