False Positive TB Investigations in New York City: Methods and Results

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Presentation Overview

• False-positive TB investigations methods
• False-positive TB investigation data

Goals of False-positive TB Investigation

• Resolve whether or not a TB specimen or related results belongs to the patient in question
• Single positive culture patients are a high priority
  • If confirmed to be a false-positive specimen, TB treatment may be discontinued
• Identify the most likely source/mechanism for a false-positive event
• Disseminate results of false-positive investigations to participating laboratories
• Maintain accuracy of TB specimen results and cases in local and national surveillance systems
Overview of False-positive TB Investigation in NYC

Initiation of False-positive TB Investigation-1

- Request from BTBC colleagues, non-DOH physicians and other jurisdictions
  - Clinical suspicion
    - Patient with a single positive culture with a low suspicion of TB
    - New positive culture in a patient who previously culture converted
    - Changes in susceptibility pattern
- Laboratory inquiries
  - Suspected lab cross contamination
Initiation of False-positive TB Investigation-2

- Single positive respiratory culture list
  - Physician determine if an investigation is warranted
  - Selective clinical characteristics and laboratory results

Initiation of False-positive TB Investigation-3

- Genotyping results (Spoligotype, RFLP, WGS, MIRU) are reviewed as they are received
  - Unexpected results
    - Discordant genotypes among specimens from the same patient
    - Matching genotypes
    - Rare strains in multiple patients within short time span
    - TB lab strain (H37Rv)

Investigation of False-positive-1

- Notify treating physician and relevant BTBC colleagues
- Lab(s) is contacted to:
  - Provide a list of specimens collected and processed with the suspected contaminated specimen
  - Send specimens culture positive for MTBC for DST and genotyping
Investigation of False-positive-2

- **Initiation**
- **Review**
  - Specimen collection and processing dates
  - Genotypes of specimens and patients involved with the investigation
- **Results**
  - Identify Source of contamination
  - Cross contamination
  - Mislabeled specimens
  - Mislabeled specimens during collection or at laboratory accessioning
  - Contaminated medical devices (bronchoscope)

Example: False-positive Investigation Background

Patient A: False-positive investigation was initiated by the treating physician due to:

- Low clinical suspicion
  - Newly diagnosed single positive culture case
  - Abnormal chest x-ray
  - History of MAC infection and COPD
  - Physician did not start anti-TB meds

Example: False-positive Investigation-1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Strain code</th>
<th>Spoligotype</th>
<th>WGS</th>
<th>RFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7777777012/D77Y</td>
<td>S02118</td>
<td>5 SNP</td>
<td>OR (1)</td>
</tr>
<tr>
<td>B</td>
<td>0000000003/D077Y</td>
<td>S02034</td>
<td>NA</td>
<td>WY45 (2)</td>
</tr>
<tr>
<td>C</td>
<td>7777777012/D77Y</td>
<td>S02118</td>
<td>5 SNP</td>
<td>OR (1)</td>
</tr>
</tbody>
</table>

- Contact laboratory regarding investigation
- Review registry for patients with specimens collected at the lab in question
- Patients A, B and C specimens were all processed in the same laboratory
- Patients A and C have matching genotypes
- Rare strain associated with a known outbreak in NYC
- Patient A demographics and social characteristics do not match patients in this outbreak
- Contamination seems possible
- Patient B genotype does not match patients A or C; contamination is refuted for Patient B
**Example: False-positive Investigation-2**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Octal code</th>
<th>Spoligotype</th>
<th>WGS</th>
<th>RFLP</th>
<th>Date Collected</th>
<th>Date Processed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>177777776787771</td>
<td>S02118</td>
<td>0 SNP</td>
<td>OW (14)</td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>B</td>
<td>00000000000003771</td>
<td>S00034</td>
<td>NA</td>
<td>W1445 (20)</td>
<td>Day 2</td>
<td>Day 2</td>
</tr>
<tr>
<td>C</td>
<td>177777776787771</td>
<td>S02118</td>
<td>0 SNP</td>
<td>OW (71)</td>
<td>Day 2</td>
<td>Day 2</td>
</tr>
</tbody>
</table>

Patients A and C specimens were processed on the same day:
- Patient C is a known TB case with multiple specimens culture positive for MTBC associated with this outbreak.
- Another specimen from Patient C was sent for genotyping to confirm genotype of previous specimen.
- Laboratory confirmed Patient A specimen was mislabeled with a specimen from Patient C.
- Initial broth from Patient A was probe and was negative for MTBC.
- Initial broth from Patient C second specimen was probe and positive for MTBC.

**Results of False-positive Investigations**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>Specimen is contaminated</td>
<td>- Cross contamination</td>
</tr>
<tr>
<td></td>
<td>• Specimen belongs to another patient</td>
<td>• Misidentified specimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TB Lab Strain (H37Rv)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Contaminated medical devices</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Unable to determine if a contamination occurred or source of contamination</td>
<td>- Contamination source could not be identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unable to perform further TB testing (i.e. DST or genotype)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Additional specimen is not available</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Specimen has a true result</td>
<td>- Genotypes do not match</td>
</tr>
<tr>
<td></td>
<td>• Specimen belongs to the patient</td>
<td>• Unique genotype identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Additional specimen confirms previous genotype results</td>
</tr>
</tbody>
</table>

**Determination of Patient TB status**

- Based on the result of the investigation with clinical and diagnostic data; the physician will need to determine if patient should:
  - Continue TB therapy
  - Remain a verified case of TB or not
  - Single positive culture patients are high priority
Communicating results of investigation

- Letters discussing the results are sent to:
  - Treating physicians and Health Department field medical consultants
  - Lab(s) involved
  - NY State Reference TB lab (Wadsworth)
  - If confirmed to be a false-positive specimen
- NYC DOHMH case managers and molecular epidemiology team uses the results to inform:
  - Clinical care
  - Case management
  - Contact and Cluster investigations
  - Update surveillance registries (Local and National)
    - Verified case of TB or not

NYC FALSE-POSITIVE INVESTIGATION DATA

Initiation of False-positive Investigations By Referral, 2006-2016
Results of False-positive Investigations, 2006-2016

Disposition of patients with Confirmed False-positive specimen(s), 2006-2016

Outcomes of Patients with False-positive specimens 2015-2016

- 115 specimens (103 patients) were referred for a false-positive investigation
- 32 specimens (27 patients) were determined to be a false-positive
  - 27 due to cross contamination
  - 3 species misidentification
  - 2 due to mislabeling
- 17 specimens were for single positive culture patients
- 11 patients were considered not to have TB
  - 5 patients started therapy
  - Received a median of 32 days of therapy
  - All five patients discontinued therapy as a result of the investigation
Conclusions

• During 2015 and 2016, 115 specimens (103 patients) were referred for a false-positive investigation
  • 52 specimens (27 patients) were determined to be a false-positive
• Close collaborations with Laboratories and Healthcare providers is a key role
• Genotyping is an essential tool to identify false-positive specimens
• Requests from BTBC colleagues and molecular epidemiology team were the majority source of referrals for investigations
• Although labor intensive, false-positive investigations are important because in confirmed cases:
  • TB treatment may be discontinued
  • Prevents unnecessary use of Health Department resources for further case management and contact investigation

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• Hospitals and Commercial Laboratories