Managing Large Contact Investigations and TB Outbreaks

Tuberculosis Program Manager’s Intensive
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Martin Cilnis, MPH, MS
Epidemiologist, Outbreak & Control Section
TB Control Branch, CA Department of Public Health

Goals of this presentation

• Describe what is a TB outbreak
• Describe the steps involved in a TB outbreak investigation
• Case study to illustrate investigation steps
  ▪ A multi-jurisdictional outbreak that began as an extended contact investigation in a school
  ▪ Describe the use of TB genotyping and whole-genome sequencing (WGS) in an investigation
TB outbreak investigations bring together many of the components discussed in the TB program manager’s course.

- Case management
- Contact or congregate site investigations
- Surveillance
- Planning and organization
- Prioritization, resource management, and coordination
- Communication with internal and external partners (sometimes media)

How are TB Outbreaks Different From Other Diseases?

- Pace is usually slow
  - More time to intervene
  - BUT, need to maintain interventions for longer period
- Airborne transmission
- Often among impoverished, marginalized, and non-U.S.-born communities
- TB remains very stigmatized
- Programmatic context: Occur while other TB control activities must be maintained
A Broad Definition of a Disease Outbreak

“The occurrence of cases of a disease above the expected or baseline level, usually over a given period of time, in a geographic area or facility, or in a specific population group. The number of cases indicating the presence of an outbreak will vary according to the disease agent, size and type of population exposed…”

Ref: California Code of Regulations, Title 17, § 2500

CDPH Surveillance Definition for a Confirmed TB Outbreak

1. ≥ 4 TB cases occurring in California, AND
2. Definite epidemiologic links indicating all 4 cases are part of the same chain of transmission, AND
3. Matching TB genotypes*, AND
4. Case 1 and Case 4 counted within three years of each other

*Exception: a pediatric case less than 5 years of age without genotype results can be included as one of the 4 cases
So, how do you know if you have a TB outbreak?

- Recognition of commonalities among cases
- Genotype cluster analysis
- Drug resistance pattern analysis
- Areas with low TB prevalence
  - Outbreaks easier to detect
  - Each new case might be noteworthy
- Areas with high TB prevalence
  - Outbreaks can be harder to detect
  - Clusters can blend into high background TB rate

Detecting a TB Outbreak: Red Flags

- Highly infectious patient with many contacts
- Patient with lengthy infectious period
- Patients in high-risk settings (e.g., prison, shelters)
- Very susceptible contacts (e.g., immunocompromised)
- TB in young children (≤ 5) with no known source case
- New and/or growing genotype clusters
CDPH TB Outbreak Reporting Trigger

• 4 or more epi-linked patients

  *BUT sometimes the bar is lower:* 

• 2 or 3 linked patients involving:
  • multiple households
  • MDR-TB
  • Congregate settings
  • High-risk persons (children, HIV+, etc.)

What are the key differences between contact investigations and outbreak investigations?

<table>
<thead>
<tr>
<th>Focus</th>
<th>Contact Investigation</th>
<th>Outbreak Investigation</th>
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<tbody>
<tr>
<td>Timeframe</td>
<td>Single TB case: TB case’s infectious period</td>
<td>Multiple TB cases: Cases diagnosed within past 2-3 years</td>
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</table>
| Emphasis | • Identify, evaluate, treat contacts | • Identify, evaluate, treat contacts  
• Determine where, when, by whom TB cases were infected |

What are the goals of an outbreak investigation?

• Stop ongoing TB transmission
• Prevent future cases among infected contacts
• Identify gaps in TB control system
• Prevent future outbreaks

AND

• Maintain other essential services

Outbreak Investigation Steps

1. Confirm cases
2. Develop case definition
3. Look for other cases
4. Describe and count cases—person, place, time
5. Determine if there is an outbreak, if it is continuing, and population affected
6. Institute control measures as early as possible and adjust as needed
7. Continue surveillance; evaluate if control measures are working
8. Communicate findings
Case Study

A multi-jurisdictional outbreak that began as an extended contact investigation in a school

Initial notification from a local TB program

- County A had been conducting a contact investigation in a school around a very infectious TB patient
- Some of the activities done thus far:
  - Determined the index patient’s infectious period
  - Met with the school administration onsite to discuss the investigation plan and tour the facility
  - Obtained electronic copies of the patient’s schedule of classes and extracurricular activities
  - Developed a list of potential contacts among students and school employees
  - Sent out exposure letters to parents and guardians
  - Sent a media press release and organized a parent meeting
  - Initial testing of about 100 students was done
Initial test results were very concerning!

- About 30% TST positivity rate among the students → Higher than expected!
- Two classes had >10 positives, including a teacher
- The decision was made to expand the investigation
- County A contacted the CDPH TB outbreak response team to help with data analysis, planning, and implementation

What to do next?

- Determine who else should be tested
  - Data analysis by classroom and by period to determine hotspots of TST positivity
  - Interviews of index patient and school employees to determine other risk groups (friends at school, extracurricular and after-school activities, etc.)
- Obtain additional electronic copies of classroom rosters
- Enter data into a Excel spreadsheet
  - Updated in real-time at the testing events
Other activities

• Hire an industrial hygienist to assess classroom ventilation
• School helped with 3HP DOT, delivery of meds
• Wrote and sent out a provider alert
• Wrote and sent out letters on restricting registration for students who remained unevaluated
• Sent inter-jurisdictional notifications for follow-up of contacts outside of County A
• Scheduled multiple testing events at the school

Prioritization of contacts for testing based on risk of exposure

**Priority 1**
- Social contacts to the index patient

**Priority 2**
- Contacts who were TST or IGRA converters
- Shared ≥1 classroom or extracurricular activities with the index patient

**Priority 3**
- Were in the classroom in the period immediately after the index patient’s period
- Were in the classroom that shared ventilation with the patient’s classroom

**Priority 4**
- Were in a classroom 2 or more periods after the index case was in the classroom
- Were in a classroom that shared ventilation with a classroom with the index 1 or more periods after the index was in the room
- Were in classrooms before the index case’s period
Results of school investigation

- More than 700 contacts tested (students and school employees)
- 23% were newly TST or IGRA positive
  - 5% were converters (i.e., confirmed to have been newly infected)
- 87% of contacts completed LTBI treatment!
  - The county worked with school medical staff to provide onsite 3HP DOT
- 3 students were diagnosed with active TB
Lessons learned, school investigation

- Realize data needs and identify correct sources for data early in an investigation
  - Rapidly identify point person for IT at the school district level
- Obtain electronic data from the school needed for complete analyses of contact evaluation results
- Enlisted assistance from Emergency Preparedness for testing logistics
- Provided evaluation and LTBI treatment for contacts onsite at the school
- Focused, stepwise approach helped ensure highest risk contacts were evaluated; secondary cases identified to date were found with early disease

Case finding using TB genotyping and whole-genome sequencing (WGS)
Genotyping is Important Tool for Outbreak Investigations...

- Detect outbreaks
- Identify other possible outbreak cases
- Rule-out cases from an outbreak
- Evaluate if transmission is contained

...But Use Caution

- More helpful if genotype is uncommon
- Cases with matching genotypes may not represent transmission
  - Need clinical and epidemiologic data to confirm transmission
- Outbreak cases can have closely related, but not identical genotypes
  - Need to look at raw genotype data to detect this (your state TB control program can help with this)
- Genotyping will miss culture-negative cases and culture-positive cases that have not been genotyped
Is this the end of the outbreak?

The genotype was monitored for new cases matching to the outbreak genotype.

Epidemic curve of TB cases, 2012-2014 (n=12)

- Outbreak case (n=9; 5 were clinically diagnosed)
- Not an outbreak case (n=1)
- Case with outbreak genotype, not investigated (n=2)

1 index case
3 outbreak cases among students
5 cases were relatives of the index case

1 non-US-born patient age >60 diagnosed another county, no reported links to outbreak
Epidemic curve of TB cases, 2012-2019 (n=25)

- Outbreak case (n=16; 6 were clinically diagnosed)
- Not an outbreak case (n=7)
- Case with outbreak genotype, not investigated (n=2)

13 new cases from 8 CA counties with the outbreak genotype between 2015 and 2019

7 cases were linked back to the outbreak

A school contact who moved to County B and completed LTBI Tx, developed active TB in County C

4 cases were relatives of the school contact in Counties A, B, D

2 relatives to index case

6 cases could be ruled out as outbreak case by WGS analysis
Comparison of Molecular Methods for TB

- **Spoligotype** (Low Power to Distinguish Between TB Isolates)
  - Analyze <1% of TB genome
  - Reported as GENType

- **MIRU-24** (Current TB genotyping methods)

- **WGS** (High Power to Distinguish Between TB Isolates)
  - Analyzes >90% of TB genome
  - Will report as MLSType starting in 2021

Using WGS analysis in the outbreak investigation

Phylogenetic analysis was requested for the outbreak genotype cluster
WGS Phylogenetic Tree

Displays genetic relationships between isolates in a genotype cluster

Should be interpreted in the context of epidemiologic and clinical data to assess TB transmission

Components of the WGS Phylogenetic Tree

Numbers on lines: # of nucleotide differences between isolates called Single Nucleotide Polymorphisms (SNPs)

TB isolate

Lines connect the most genetically-related TB isolate

Most Recent Common Ancestor (MRCA)
- Hypothetical genome type (not an actual isolate)
- All isolates on the tree are descended from this hypothetical genome type
- Direction of genetic change starts here and moves outward

TB isolates with the same sequence are displayed in one node
General Rules

Isolates 6 or more SNPs apart are less likely to be due to recent transmission.

Isolates 5 or less SNPs apart are more likely to be due to recent transmission.

Interpretation of the WGS Phylogenetic Tree

Isolates 6 or more SNPs apart = not part of the outbreak!

Clinical and epi data required to confirm or refute transmission!

Isolates from outbreak cases

Recent transmission among 2 cases in another county.
Convened meetings with Counties A, B, C, and D to discuss the outbreak and to address inter-jurisdictional case and contact follow-up issues.

Index pt

School

Family/ Household/
Social

County C

Index pt

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Lessons learned, inter-jurisdictional outbreak

- Meetings with 4 local TB programs helped to
  - Provide background about the outbreak
  - Manage inter-jurisdictional notifications of cases and contacts
  - Intensify follow-up of cases and contacts
- Genotyping helped to monitor the outbreak on a statewide level
- Phylogenetic analysis of WGS data helped to rule out TB patients from the outbreak
- Epidemiologists can help to
  - Collect, manage, and analyze data from extended contact and outbreak investigations
  - Use genotyping data to monitor for new cases with genotypes associated with extended contact investigations and outbreaks

Program Management Issues

- Organization:
  - Outbreak response plans
  - Ensure resources for outbreak response
- Communications: internal, external, media
- Financial considerations such as:
  - Overtime, temp help, additional interpreters
  - Increased need for incentives, enablers
  - Consider funding augmentation options
- Recognize when to seek additional resources
  - Explore surge staffing options to maintain reasonable workload
  - CDPH TB Control Branch is a resource for CA local health departments
CDPH TB Outbreak Response Team

• Please report any outbreaks of TB in CA to the outbreak response team (even if only suspected)

• The outbreak response team can:
  ▪ Assist CA local health departments in outbreak response efforts
  ▪ Be a resource for consultation, tools, and templates

• Contact information:
  TB Control Branch Main Line
  M-F 8am-5pm
  Phone (510) 620-3000

References

CDC TB genotyping website
• [https://www.cdc.gov/tb/programs/genotyping/default.htm](https://www.cdc.gov/tb/programs/genotyping/default.htm)
  ▪ The CDC website includes:
    ➢ Introduction to genotyping and WGS of TB
    ➢ A recorded training module “Using WGS for detection and investigation of recent transmission”

  ▪ Contact investigations (module 8) and outbreak investigations (module 9)

• CDPH TB School CI Toolkit (soon to be available online; available upon request)
Acknowledgements

- Local public health partners
- CDPH TB Control Branch
- CDC partners in the lab and molecular epi team