CHAPTER 12: TUBERCULOSIS GENOTYPING AND CLUSTER INVESTIGATION

INTRODUCTION

Tuberculosis (TB) is an airborne disease that spreads from person to person. As such, TB transmission is an important driver of TB morbidity. Efforts to identify and interrupt transmission are vital to the New York City (NYC) Bureau of TB Control's (BTBC) TB prevention and care activities.

TUBERCULOSIS GENOTYPING

TB genotyping is a set of laboratory-based techniques used to characterize *Mycobacterium tuberculosis* (*M. tuberculosis*) complex strains based on distinct patterns identified in specific regions of the TB genome. Several TB

genotyping methods are commonly used in the United States (U.S.), including spacer oligonucleotide typing (spoligotyping), variable-number tandem repeat of mycobacterial interspersed repetitive unit analysis (MIRU), IS*6110* restriction fragment length polymorphism analysis (RFLP), and whole genome sequencing (WGS).

TB genotyping results, when combined with epidemiologic data, help to identify TB patients who may be involved in the same chain of recent transmission, or to rule out transmission among patients who are otherwise linked but have nonmatching genotypes. These results can also help distinguish between relapse and re-infection in patients with a prior history of TB disease.

BTBC implemented universal TB genotyping in 2001 using spoligotyping and RFLP analysis, following a NYC Health Code change mandating that at least one *M. tuberculosis* complex isolate from all patients with at least one positive culture for TB be sent for genotype analysis. Nationally, universal genotyping was initiated in 2004 through the National TB Genotyping Service, which conducts spoligotyping and MIRU analysis for all culture-positive patients in the U.S.

Whole genome sequencing (WGS) was made available to TB programs selectively through the Centers for Disease Control and Prevention (CDC) in 2013. In 2018, CDC began sequencing all isolates as part of a planned transition to replace spoligotyping and MIRU with WGS in 2022. NYC began universal WGS in 2016 in partnership with the New York State Department of Health Wadsworth Center. Currently, BTBC uses a combination of genotyping methods to characterize strains, assess transmission, link patients, guide epidemiologic investigation, and detect potential outbreaks.

> The NYC Health Code [§ 13.05(a)] mandates that within 24 hours of observing growth of *M. tuberculosis* complex in a culture from any specimen, a portion of the initial culture must be sent for deoxyribonucleic acid (DNA) analysis to the New York City Health Department Public Health Laboratory (NYC PHL). (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.)

TUBERCULOSIS GENOTYPE REVIEW AND CLUSTER DETECTION

TB genotype results are reviewed by epidemiologists as they are received from labs and are considered alongside patient characteristics and other epidemiologic data. BTBC staff review genotyping results for evidence of potential specimen contamination to quickly identify patients with known outbreak strains, and to support or refute transmission among patients with known epidemiologic links. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) Patients whose TB isolates have genotyping results matching at least one other patient with TB disease in NYC are clustered, reviewed, and prioritized for further investigation.

While the genotyping methods used to define clusters have varied over time in NYC, the fundamental components of the cluster detection process and the application of genotyping results to refute/identify potential transmission remain unchanged.

The CDC's National TB Genotyping Service performs universal genotyping for all patients with culture-positive TB in the U.S. using spoligotyping, 24-locus MIRU-VNTR analysis, and whole genome sequencing. The **TB GENOTYPING INFORMATION MANAGEMENT SYSTEM (TB GIMS)** is a secure web-based system that facilitates the linking of genotyping results with patient data reported to the National Tuberculosis Surveillance System, allowing users to review and analyze data related to TB genotype clusters.

CLUSTER PRIORITIZATION

Patients with TB disease having characteristics suggestive of recent infection and/or with a clustered TB strain suggestive of recent transmission in NYC are reviewed and subsequently prioritized for investigation. Although consensus on an exact definition is not well-defined in the literature, recent transmission generally refers to a transmission event within two years prior to the onset of active TB disease. As such, cases are prioritized for further review using the following considerations:

- Patient characteristics suggestive of recent, local transmission (e.g., young age; human immunodeficiency virus [HIV] infection or other immunosuppression; recent test for TB infection conversion; recent history of healthcare work; homelessness or incarceration)

- Strain characteristics (e.g., strains newly identified in NYC; rapid cluster growth)

- Time component among clustered patients (e.g., diagnosis within 24 months of a previous patient with matching strain and pulmonary TB)

- Infection with a multidrug-resistant (MDR) strain

- Other factors (e.g., date of arrival in NYC among foreign-born patients; similar patient characteristics among clustered patients)

The decision to prioritize a genotype cluster for investigation is multifactorial. The following questions help frame key considerations for prioritizing cluster investigations:

- Are there multiple cases with the same strain identified in the previous 12 months?

- Are recent patients in the cluster sputum smear-positive or do patients have cavitary lesions (i.e., suggestive of infectious TB disease)?

- Did any recent patients have prolonged infectious periods before diagnosis?

- Is a homeless shelter, correctional institution, or other congregate setting involved?

- Do patients have risk factors, such as substance use, that can be associated with difficult or incomplete contact investigations?

- Do patients and their contacts have similar risk factors that suggest an increased risk for disease progression, such as HIV or renal failure?

- Do any patients have drug-resistant TB (DR-TB)?

- Were any cases found among contacts missed by previous contact investigations? Could other contacts have also been missed?

- Were any cases among persons previously identified as contacts but not fully evaluated or treated? Could other contacts be at risk?

- Are epidemiologic links among patients unclear or not identified, or is there reason to suspect that contact investigations have not been adequately thorough?

- Is the cluster comprised of cases with a new genotype in the county or state?

- Is it the same genotype as a known outbreak?

- Has the cluster grown rapidly in the past two to three years?

- Does the cluster include children younger than five years of age?

- Do patients in the cluster have evidence of recent infection (e.g., test for TB infection conversions)?

🔗 For additional guidance on TB cluster prioritization, see the CDC document: *Prioritizing Tuberculosis Genotype Clusters for Further Investigation & Public Heath Action* at https://www.cdc.gov/tb/programs/genotyping/Prioritizing_Tuberculosis_Genotype_Clusters_August2017.pdf.

CLUSTER INVESTIGATION

Once reviewed, eligible clusters are assigned to an epidemiologist and investigated systematically to identify links between patients, identify previously unknown exposure sites or contacts, inform transmission hypotheses, and inform potential public health intervention. The extent of investigation varies depending on patient and cluster characteristics and may include the following:

- Review and analysis of patient characteristics (demographic, clinical, social) and other surveillance data

- Medical chart review

- Review of case management, contact investigation, and previous cluster investigation notes

- Consultation with regional and clinic staff

- Patient interview

- Mapping and spatial analysis

- Social network analysis

- External database searches

- Community visits

- Consultation with external stakeholders (e.g., healthcare providers, other city agencies, community organizations)

DATA SOURCES

In addition to review of medical charts, patient characteristics, and other data available in the electronic TB surveillance and case management system, investigators utilize a number of external data sources. These include notes from previous contact and cluster investigations, local social service and medical facilities databases (e.g., shelter history, immunization registry), vital records, social media platforms, and public records databases. Communication with regional and clinic staff are an integral part of cluster investigation and occur throughout the prioritization and investigation process.

PATIENT INTERVIEW

Whenever possible, patients are interviewed in person using a tailored questionnaire. Interviews are semi-structured and open-ended, and consist of questions relating to a patient's current and previous TB history and exposures; current and previous addresses, worksites, and schools; country of birth, travel history and entry into the U.S.; social history; contacts (e.g., family, romantic partners, roommates, friends); leisure sites and activities; history of stay in congregate settings (e.g., shelters, prisons, healthcare facilities); drug and alcohol use; and medical care-seeking history. The time period of focus for cluster investigation is usually longer than for a contact investigation and may include contacts, sites, and activities for the preceding two to five years. Interview guides are adapted to each cluster and are often informed by information gathered through previous patient interviews.

INCLUSION OF NON-GENOTYPED AND OUT-OF-JURISDICTION PATIENTS

The cluster review and investigation process often includes non-genotyped or clinical TB cases and contacts that may be related to the cluster. This includes cases with known epidemiologic links to cluster cases, cases diagnosed in the same time frame and/or within the same geographic area, and/or patients who have similar demographic and clinical characteristics as cases in the cluster of interest. If there is a possibility that related cases have occurred in another jurisdiction, investigators consult the national TB genotyping database and discuss epidemiologic links and possible intervention with local, state, and/or national colleagues.

ASSESSING PATIENT- AND CLUSTER-LEVEL TRANSMISSION

During cluster investigation, transmission assessments are made at both the patient level and the cluster level. (See *Table 12.1: Criteria Used for Patient-Level Tuberculosis Transmission Assessment*.) Patient-level transmission assessment is based on a number of factors, including the following:

- Known TB exposure and/or history of TB disease or test for TB infection results (e.g., prior positive results, test for TB infection conversion)
- Presence and characteristics of epidemiologic links
- Analysis of genotyping results among epidemiologically linked patients
- Presence of a plausible source case in NYC (e.g., a previously diagnosed patient with infectious TB having genotype results that do not refute transmission)

TABLE 12.1: Criteria used for patient-level tuberculosis transmission assessment

ASSESSMENT	CRITERIA

Cases attributable to *recent* transmission	• **Definite:** Patients younger than 2 years of age
	• **Likely:**
	  • Known contact to a potentially infectious TB disease patient within 2 years (genotyping does not refute)
	  • Documented test for TB infection conversion within 2 years

Cases attributable to *local* transmission	• **Likely:** Known contact to a potentially infectious TB disease patient in NYC (genotyping does not refute)
	• **Unlikely:**
	  • Development of TB disease soon after arrival in the United States
	  • Unique genotype in NYC

Cases attributable to *recent, local* transmission	• **Likely:** Known contact to an infectious TB patient in NYC within 2 years (genotyping does not refute)
	• **Unlikely:**
	  • Development of TB disease soon after arrival in the United States
	  • Unique genotype in NYC
	• **Possible:**
	  • Patients with culture-negative TB disease or incomplete genotype results (date of entry does not refute)
	  • Patients with exact- or near-match genotype to a potentially infectious TB disease patient within 2 years

Abbreviations Used: NYC=New York City; TB=tuberculosis

Epidemiologic links between patients are assessed and documented according to strength of the link. Patients with a definite epidemiologic link include those who have named each other as contacts, have a contact in common without naming each other as contacts, or have reported history of spending time during a common time period at the same location. Possible links exist among patients who have a similar social network or have spent time in the same area (no specific location), without naming each other as contacts.

At the cluster-level, multiple elements contribute to an assessment of transmission among patients with active TB disease, including patients' clinical, demographic, and social characteristics; geographic distribution of patients; known relationships and exposure sites among patients; underlying population characteristics (e.g., socio-demographic); and strain characteristics and history in NYC. Transmission within a cluster is dynamic across time and space, and assessment changes as new patients are identified.

TUBERCULOSIS OUTBREAKS

A TB outbreak investigation is initiated when there is indication of ongoing recent TB transmission and disease that is higher than expected given the local TB epidemiology, population demographics, and/or prevalence of a given strain in NYC. The goals of an outbreak investigation are similar to the goals of routine TB control and include:

- Quickly identify outbreak-associated patients
- Identify and interrupt transmission
- Ensure prompt TB evaluation and diagnosis
- Ensure treatment completion
- Ensure thorough and complete contact investigations
- Identify mechanisms to prevent future outbreaks

Though the steps in an outbreak investigation are similar to those involved in a cluster investigation, an outbreak investigation often requires greater urgency and resources, may involve multiple stakeholders, and often places greater demands on BTBC. Key components of outbreak response include establishing roles and communication mechanisms; identifying and addressing chain-of-command issues across local, state, national, and other agencies; creating data management systems; ensuring ongoing communication among internal and external partners; reassessing priorities/activities as new information becomes available; assessing available resources/barriers frequently; documenting and assessing response activities (e.g., cost, timelines, impact); and identifying opportunities to prevent future outbreaks.

INITIATING PUBLIC HEALTH ACTION

Cluster and outbreak investigation findings are communicated through multiple mechanisms; public health interventions are developed accordingly. Newly identified contacts or exposure sites and additional information that might inform ongoing case management or clinical care (e.g., patient locating information, past medical history) is communicated to case managers and clinicians immediately, while opportunities to improve routine TB control policies/protocols and community-level interventions may be developed over time in conjunction with multiple stakeholders.

The decision to initiate public health intervention is multifactorial. The following questions help frame key considerations for initiating and guiding public health action in the context of available resources and other factors:

›› Is there reason to suspect false-positive lab results? (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)

›› Are there newly-identified contacts or exposure sites? (See *Chapter 11: Contact Investigation*.)

›› Was an opportunity to prevent additional TB cases identified?

›› Was an opportunity to improve routine TB control protocols identified?

›› Is there potential for rapid cluster growth?

- Patient clinical characteristics suggestive of infectiousness

- Patient social characteristics suggestive of high-risk settings/contacts

- Contact characteristics suggestive of high risk for infection or progression

- Barriers to care or delayed diagnoses identified among patients

- Incomplete/difficult contact investigations

- Exposure in congregate setting(s) or healthcare facilities

SUMMARY

Assessment of TB transmission is an integral component of NYC's routine TB care and management activities, and informs public health intervention on multiple levels. Along with epidemiologic data, genotyping is an important tool for understanding local transmission dynamics and informing meaningful public health intervention. TB transmission dynamics are complex and multi-factorial; understanding them often requires extensive knowledge of the patients and communities affected.

KEY SOURCES

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