Best Practices for Genotyping-Based Tuberculosis Outbreak Detection

This document outlines a set of best practices for using genotyping to detect tuberculosis (TB) outbreaks in the United States (U.S.) in public health programs at the federal, state, local, tribal, and territorial levels. These practices complement, but do not replace, routine TB control activities.

This consensus document is a product of the Outbreak Detection Working Group (ODWG)[1], a multi-agency work group of federal, state, local, and academic partners with expertise in TB control and genotyping. The practices are based on the collective expertise of the members and their knowledge of the peer-reviewed literature on genotyping. Supporting evidence for these activities can be found in TB control recommendations and guidelines, TB training materials, and the 2004 TB Genotyping Guide[2]. These best practices do not represent mandatory activities under any currently established U.S. Centers for Disease Control and Prevention (CDC) cooperative agreements, grants, or contracts.

The best practices are listed in order of importance and are each followed by a list of activities that support that best practice. Ideally, every TB control program in the U.S. would implement Best Practices #1 and #2. This would maximize TB genotyping surveillance coverage[3], which is crucial for effectively applying genotyping to routine TB control activities. The current National TB Indicators Project[4] (NTIP) goal for genotyping surveillance coverage is 94%. In addition, programs should add Best Practices #3-#6 as resources allow.

Programs lacking the resources to implement these best practices can consult their state, tribal, or territorial health department, or CDC to determine what support might be available to implement them.

Practices All Programs Should Implement

Best Practice #1: Ensure Each Patient with a Positive *Mycobacterium tuberculosis* Culture Result has a Genotyped Isolate

Best Practice #2: Link Genotyping Results to Surveillance Data Promptly

Practices Programs Should Implement as Resources Allow

Best Practice #3: Integrate Genotyping Information into Routine Case Management, Contact Investigation, and Cohort Review Activities

Best Practice #4: Examine Concerning Genotype Clusters

Best Practice #5: Communicate With Other Jurisdictions[13] and CDC

Best Practice #6: Develop and Maintain Capacity for Using Genotyping Information in Routine TB Control

Each of these best practices is described in detail on the following pages and followed by a list of activities that support that best practice.

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Practices All Programs Should Implement

Best Practice #1: Ensure Each Patient with a Positive *Mycobacterium tuberculosis* Culture Result has a Genotyped Isolate

The first step to maximize genotyping surveillance coverage is to ensure that all patients with a positive culture result identified as *M. tuberculosis* have isolates submitted for genotyping. Submitting the first available isolate minimizes the amount of time for programs to receive genotyping results. Submitting one isolate from each patient is usually sufficient; in some situations, a TB program may choose to submit additional isolates for genotyping. Programs can consult with their state-level public health laboratory or health department, or CDC to determine if genotyping more than one isolate is indicated. Submitting isolates to the designated public health laboratory from private and hospital laboratories in a timely fashion will minimize delays in genotyping of *M. tuberculosis* isolates.

TB control program and public health laboratory activities

- Promote established diagnostic standards to ensure that adequate clinical specimens are obtained and submitted for mycobacteriology laboratory testing, thereby increasing the proportion of active TB cases that have an isolate for genotyping.
- Coordinate to ensure that the first available isolate from each patient with a positive *M. tuberculosis* culture result is submitted to the appropriate CDC-contracted genotyping laboratory.
- Avoid batching of isolates for shipping to the genotyping laboratory when possible. If batching is necessary due to limited staff resources, shipping should occur at least monthly.
- Expedite submission of isolates that are related to current outbreak investigations. Public health laboratories and TB programs should coordinate submission of these isolates for genotyping.
- Establish processes to minimize delays from initial specimen collection to submission of the isolate for genotyping. Establishing regulations or preexisting agreements with private and hospital laboratories to automatically forward isolates to public health laboratories may help minimize delays caused by failure to submit isolates.

CDC activities

- Maintain laboratory capacity within the National TB Genotyping Service (NTGS) and surveillance tools to support TB control programs in maximizing genotyping surveillance coverage.
- Pay for shipping of isolates to genotyping laboratories and the testing of isolates.
- Ensure that genotype results are available within 10 business days of receipt of isolates. Ideally, isolates that need expedited results should be genotyped within 2 business days.
- Provide, or arrange for, laboratory consultation on the interpretation of genotype results.

Best Practice #2: Link Genotyping Results to Surveillance Data Promptly

Results reported by the genotyping laboratories only contain information about the isolate. For meaningful application to TB control activities, genotyping results must be linked[7] to the demographic, geographic, clinical, and risk factor data collected on the Report of a Verified Case of Tuberculosis (RVCT), which is used to report cases to the National Tuberculosis Surveillance System (NTSS). Regardless of the approach used to link, the RVCT should be promptly submitted to CDC for inclusion in NTSS. Genotyping records that are not linked to NTSS records will not appear in TB Genotyping Information Management System (TB GIMS) reports and are not considered when TB GIMS issues alerts for possible outbreaks. Additionally, local programs cannot access or use genotype results unless they are connected back to a case in some way. Therefore, linking and routinely sharing state case numbers (RVCT item #3) and genotype accession numbers (RVCT item #38) with local programs are required to enable use of genotyping data in routine TB control activities.

TB control program and public health laboratory activities

- Promptly assign a state case number to every culture-confirmed case of TB, and either enter this state case number into TB GIMS or enter the corresponding isolate's accession number into the RVCT within 8 weeks of receiving genotype results.
- Initiate a RVCT promptly for every verified case of TB and submit it to CDC at least quarterly.
- Share genotype accession numbers, assigned state case numbers, or both with local programs at least quarterly.

CDC activities

- Support the NTSS and TB GIMS and explore improvements that facilitate linking genotype results to surveillance records at the state, local, tribal, and territorial levels.
- Perform data management activities necessary for linking at least every 2 weeks.
- Conduct regular quality assurance and quality control activities to ensure that RVCT and TB GIMS data are complete and accurate.

Practices Programs Should Implement as Resources Allow

Best Practice #3: Integrate Genotyping Information into Routine Case Management, Contact Investigation, and Cohort Review Activities

Recent transmission is frequently found through contact investigation and case management activities. Integrating genotyping information into these activities can help clarify when recent transmission is occurring by assisting with identifying false-positive culture results, distinguishing relapse disease from new infection, confirming suspected transmission if two cases with known connections have the same genotype, and refuting suspect transmission if two connected cases have substantially different genotypes. Additionally, previously unidentified connections among TB cases can be identified by through genotyping information. Integrating genotyping into the cohort review process can help ensure that genotyping is occurring and that the information is being used effectively.

TB control program activities

- Identify and implement opportunities to integrate review, analysis, and discussion of genotyping results into case management and contact investigation activities.
- Modify public health records, including case management forms and electronic systems, to include a place to record genotype results.
- Incorporate review and discussion of genotype results into case management conferences[8] and cohort reviews[9].
- Identify a program manager, epidemiologist, supervising public health nurse, or other staff person familiar with the jurisdiction's TB cases who will review TB genotyping information at least monthly. Lower morbidity jurisdictions should review results as they become available.

CDC activities

- Develop guidance and tools on how to best integrate genotyping into case management, contact investigation, cohort review, and other routine TB control activities.

CDC, TB control program, surveillance program, and public health laboratory activities

- Coordinate to develop methods for integrating genotyping information into local- and state-level public health information systems.

Best Practice #4: Examine Concerning Genotype Clusters

By following Best Practices #1 and #2, TB control programs will have a robust database of TB case information including demographic, geographic, clinical, risk factor, and genotype information. This database will permit the identification of genotype clusters[10] that are concerning[11] due to characteristics associated with recent transmission (i.e., clusters that might represent a current outbreak) or a high likelihood of future transmission (i.e., clusters that might become an outbreak). One way to identify, prioritize, or monitor 'clusters of concern' is through the TB GIMS Alert Level which is based on statistical measures of geospatial concentration. Other mechanisms that TB control programs can use to identify clusters of concern include a) routine review of all genotype clusters, b) maintaining a list of genotypes associated with past outbreaks or drug resistant cases, or c) applying a locally developed algorithm.

TB control program activities

- Review concerning genotype clusters in their jurisdictions at least quarterly. Implement a systematic approach to investigating genotype clusters, also referred to as 'cluster investigation,' using a standardized approach, such as the CDC cluster investigation[12] framework. To focus on the time period associated with recent transmission, the date range of inclusion for an investigation should generally only include the previous 2–3 years.
- Document and retain the outcomes of cluster investigations for future retrospective reviews.

CDC activities

- Routinely monitor for the development of new clusters of concern, particularly those that involve multiple jurisdictions.
- Develop guidance and tools on how to perform cluster investigations, and integrate cluster investigation tools into TB GIMS.
- Refine TB GIMS outbreak detection methods to minimize false alerts.
- Provide surge capacity to jurisdictions that request assistance investigating clusters of concern.

Best Practice #5: Communicate With Other Jurisdictions[13] and CDC

Current practice in public health is to share public health data between jurisdictions only as permitted by state and local statutes and by established data sharing and cooperative agreements. Careful stewardship of these data is essential to protect the privacy of individuals. Although TB GIMS allows for limited access to data about genotype clusters in other jurisdictions, open communication among TB control programs is still necessary to ensure effective TB control.

TB control program activities

- Determine the potential of multijurisdictional transmission[14] (across national, state, local, tribal, and territorial borders) when investigating genotype clusters and strongly consider contacting the other jurisdiction(s) to participate in the investigation.
- Contact the other jurisdiction(s), CDC, or both when confirmed multijurisdictional transmission is occurring.
- Collaborate and share data with other jurisdictions on involved cases and associated investigations to the extent permissible by federal, state, local, tribal, and territorial laws and confidentiality principles.
- Share requested information with CDC about these clusters of concern (state-level jurisdictions).

CDC activities

- Inform state-level programs when a genotype cluster in their jurisdiction meets criteria for a cluster of concern. These communications should be done in a manner consistent with the jurisdiction's desired communication method (e.g., quarterly cluster review, email, phone call).
- Request only the minimally needed information about clusters to minimize the burden of reporting. Minimally needed information should be defined and periodically reassessed by the ODWG with input from other partner organizations (e.g., National TB Controllers Association [NTCA], National TB Nursing Coalition [NTNC], and Advisory Council for the Elimination of TB [ACET]).

Best Practice #6: Develop and Maintain Capacity for Using Genotyping Information in Routine TB Control

Methods and recommendations for using genotyping in TB control activities are constantly evolving. In order to effectively use genotyping to improve TB control, all programs need access to genotyping expertise. Genotyping expertise can be provided by a variety of sources, including TB controllers, program managers, genotyping coordinators, public health nurses, epidemiologists, TB physicians, local and state-level TB programs, local and state-level epidemiology staff, NTCA, NTNC, Regional Training and Medical Consultation Centers (RTMCC), academic partners, and CDC.

TB control program activities

- Support the development of capacity in their programs for the applications of TB genotyping, with particular emphasis on 1) integrating genotyping into case management, contact investigation, and cohort review activities, and 2) epidemiologic investigation of genotype clusters.
- Identify partners that can be routinely accessed to provide this support, such as state-level TB programs, CDC, and RTMCCs, if they are unable to maintain genotyping capacity among their staff.

CDC activities

- Provide and update tools, guidance, and training materials for TB control programs on the following topics: 1) genotyping methods; 2) applications of genotyping; 3) interpreting genotyping results; 4) integrating genotyping into routine contact investigation and case management activities; and 5) outbreak detection and cluster investigation. These tools should be made easily available, and kept up to date and consistent with the current scientific evidence on genotyping and outbreak detection.
- Develop internal CDC capacity to interpret and use genotyping data among both headquarters and field staff.

CDC, TB control program, NTCA, NTNC, RTMCC, and academic partner activities

- Collaborate to share evidence on the role of genotyping in TB control through the peer-reviewed literature, presentations at conferences, written reports, and other mechanisms.
- Support development of genotyping capacity at federal, state, local, tribal, and territorial TB programs.

References

[1] The Outbreak Detection Working Group included the following members during the time this document was developed (2010-2012) Tambi Shaw (CA Dept. of Public Health [DPH]), Lynn Sosa (CT DPH), Kateesha McConnell and Richard Doggett (FL Dept. of Health [DOH]), Wendy Cronin (MD Dept. of Health and Mental Hygiene), Sarah Solarz (MN DOH), Erick Cortes (NJ DOH), Benita Cook and Diana Fortune (NM DOH), Cheryl Kearns (NY DOH), Shama Ahuja and Bianca Perri (NYC Dept. of Health and Mental Hygiene), Jason Cummins (TN DOH), Jerry Carlile (UT DOH), Larry Teeter (Methodist Hospital, Houston, TX), and Scott Lindquist (Kitsap County, WADOH). CDC members included: Sandy Althomsons, Lauren Cowan, Divia Forbes, Anne Marie France, Tracie Gardner, Smita Ghosh, Juliana Grant, Maryam Haddad, Bruce Heath, Steve Kammerer, Adam Langer, and Tom Navin.

[2] The 2004 TB Genotyping Guide can be found at http://www.cdc.gov/tb/programs/genotyping/manual.htm.

[3] Genotyping surveillance coverage is defined as the proportion of culture-positive TB cases with a genotype result available in the TB Genotyping Information Management System (TB GIMS).

[4] More information about the National TB Indicators Project can be found at http://www.cdc.gov/tb/publications/factsheets/statistics/NTIP.htm.

[5] Genotype testing currently includes spoligotype and 24-locus MIRU. RFLP is not included in these turn around times.

[6] The current contracted requirement is for genotype results to be available within 15 business days of receipt of isolates; there are no contract requirements for expedited testing. The turnaround times specified in this document are an ideal best practice that should be worked towards; they are not formal requirements.

[7] This linking is generally performed by state TB programs and accomplished by either: 1) using the TB Genotyping Information Management System, an online data management and analysis application hosted by CDC; or 2) entering the genotyping lab accession number in item #38 on the RVCT.

[8] Information about case management conferences can be found at http://www.umdnj.edu/ntbc/products planning&implementing.htm.

[9] Information about cohort reviews can be found at http://www.cdc.gov/tb/education/cohort.htm.

[10] Two or more cases with matching genotypes. A genotype is generally defined as matching spoligotype and 24-locus MIRU, although some jurisdictions use RFLP to define a genotype. More information about genotyping methods is available through CDC by emailing tbgenotyping@cdc.gov or going to http://www.cdc.gov/tb/programs/genotyping/.

[11] Some examples of clusters of concern might include clusters with the following characteristics: genotypes that are new or unusual in a specific area; clusters that are growing in size; high likelihood of recent transmission with additional risk factors (e.g., homelessness, substance abuse, corrections); drug resistance; cases at high risk of poor clinical outcome (e.g., HIV infected, children < 5 years of age, immunocompromised); sustained transmission in a specific population. Additional consultation regarding the definition for a cluster of concern can be obtained by emailing tbgenotyping@cdc.gov.

[12] Cluster investigations do not necessarily include additional field work. They generally start with a review of easily available data, such as TB GIMS records and other electronic surveillance data in state or local systems. Additional steps, such as reviewing contact investigation records and interviewing local program staff, might be needed in certain situations. Occasionally, additional fieldwork such as reinterviewing patients may be appropriate. Additional consultation regarding clusters of concern, the Cluster Investigation Worksheet, and other CDC tools can be obtained through the TB GIMS website or by emailing tbgenotyping@cdc.gov.

[13] A jurisdiction is defined as a national, state, local, tribal, or territorial area with a TB control program or health department.

[14] See CDC cluster investigation materials for guidance on how to identify clusters that may involve multijurisdictional transmission. Cluster investigation materials can be obtained through the TB GIMS website or by emailing tbgenotyping@cdc.gov.