PRIORITIZING TUBERCULOSIS GENOTYPE CLUSTERS FOR FURTHER INVESTIGATION & PUBLIC HEALTH ACTION

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I. Purpose

Routine, systematic review of clusters of tuberculosis (TB) cases with matching genotypes can help determine which clusters to prioritize for public health action. This guidance document can assist state and local TB programs in developing policies and procedures for prioritizing TB genotype clusters for further investigation. Prioritization is especially important for jurisdictions where investigating all TB genotype clusters may be too resource intensive.

This guidance document will present background information on TB genotype cluster investigations and why they are important, describe how a program can establish a cluster prioritization process, and suggest considerations for assessing and prioritizing clusters for public health action. To illustrate how a TB program could employ a cluster prioritization system, hypothetical examples and key concepts have been included. Additional information on the National TB Genotyping Service is included in the Appendix under Key Terms.

II. Overview of TB Genotype Clusters

A. What is a TB genotype cluster?

A TB genotype cluster can be defined as two or more TB cases with matching genotypes. A cluster definition usually includes place and time components, such as "TB cases with a matching genotype diagnosed in County A during the previous 3 years (e.g., in January 2016, cases diagnosed with a matching genotype in County A since January 2013)."

Nationally, a genotype cluster is defined as two or more TB cases diagnosed during a specified 3-year time period with *Mycobacterium tuberculosis (M. tuberculosis)* isolates that match by spacer oligonucleotide typing (spoligotyping) and 24-locus variable-number tandem repeat of mycobacterial interspersed repetitive unit (MIRU-VNTR) analysis results. Based on these results, cluster naming systems called PCRType and GENType were developed (1).

B. What is a genotype cluster investigation?

A TB genotype cluster investigation is a systematic process to:

- Determine whether a group of TB cases with matching genotypes are related by recent transmission;
  and
- Identify epidemiologic links and potential sites of transmission among patients.

In doing so, it may be possible to identify contacts not originally identified during contact investigations, other opportunities for public health intervention, and false-positive TB cultures (2).

Some of the important differences between contact investigations, genotype cluster investigations, and outbreak investigations might be unfamiliar to public health practitioners. For additional information on these types of investigations, see Appendix B.

C. Why prioritize genotype clusters?

A key goal of the prioritization process is to identify clusters of concern due to the

- Presence of patient characteristics associated with recent transmission; or

- Likelihood of ongoing or future transmission.

Cluster prioritization can help a health department focus resources on where interventions can have the greatest impact, benefiting individual patients and the larger community. Considerations for prioritizing cluster investigations will vary, but should always be consistent with local public health priorities and available resources. TB cluster investigations should not take precedence over treating active cases and conducting contact investigations, although cluster investigation results can inform these and other core TB control activities.

Additionally, not all TB clusters require further investigation; a quick review of available data might determine that a cluster is a low-priority for further investigation or public health action. However, cluster prioritization is a dynamic and ongoing process. Assessments of a cluster can change with new information or if additional genotype-matched cases are identified.

III. Establishing a Cluster Prioritization Process

Health departments can improve their ability to respond to genotype clusters by establishing a cluster prioritization process and planning in advance how the program will respond to each priority level. This process should also involve clearly outlining in advance who will be involved in the prioritization process and how they will respond. The cluster review process will vary across programs and depend on multiple factors, including the jurisdiction's TB incidence and epidemiology, staff resources, and program organization. However, collaboration and communication between state and local programs and other stakeholders is a crucial component to successfully assessing TB clusters. The following is an outline of considerations for establishing a process to review and prioritize cluster investigations.

A. Identify key staff and establish roles

- Identify person(s) responsible for routine review of genotyping data and clustered cases.

- Identify key personnel and communication processes for cluster assessment and prioritization, additional decision-making, and related resource allocation and communication.

> In some jurisdictions, the state TB genotyping coordinator might review all new or growing genotype clusters routinely. A larger team may be convened on a reoccurring or as needed basis to discuss clusters of concern, coordinate additional information gathering, and establish related action items.

B. Determine how to identify clusters

- Genotype clusters may be identified in a number of ways, including:

  » Discussions with local health department staff and other partners who suspect new clusters before genotyping results are available.

  » Use of TB Genotyping Information Management System (TB GIMS) to

    - Routinely identify and review all clusters in a jurisdiction;

    - Selectively review those clusters that have generated TB GIMS alerts based on log-likelihood ratio (LLR) calculations; and

    - Create personalized notifications through a TB GIMS watch list.

  » Creation of local or state algorithms to detect clustering of TB cases geographically and in a given time frame.

  » Discussions with CDC about clusters of concern identified through other means, such as SaTScan or LOTUS detection.

C. Establish key criteria for cluster review, prioritization, and public health action

- Determine which clusters will be reviewed.

  » Some jurisdictions may review all genotype clusters, whereas others may choose to focus on new or growing clusters or on TB GIMS alerted clusters only.

  » All jurisdictions should consider reviewing previously identified clusters as new cases are added.

- Determine how often clusters will be reviewed. Clusters may be reviewed:

  » At regular intervals (e.g., weekly or monthly),

  » Whenever a new cluster alerts,

  » Whenever new genotyping results are available, or

  » Upon request from federal, state, or local programs.

- Define a tiered system that clearly defines cluster priority levels and corresponding action steps.

  » One example is a 3-tiered priority system, as described in Table 1.

  » Alternatively, some programs might prefer a simpler 2-tiered approach (i.e., investigation warranted, investigation not warranted at this time).

Table 1: Example Cluster Prioritization System

Priority Level	Description	Action
Priority 1	• Clusters with *multiple* characteristics indicating possible recent transmission[1] • *Multiple* characteristics associated with poor patient outcomes • Cases are recent enough that public health intervention is possible	Convene meetings to review available data with stakeholders and *actively* seek additional information.
Priority 2	• Clusters with *some* characteristics indicating possible recent transmission • *Some* characteristics associated with poor patient outcomes • Cases are recent enough that public health intervention is possible	Monitor for additional cases with a matching genotype, or clinical cases that may share characteristics with other cases in the cluster.[2]
Priority 3	• Clusters with *minimal or no* characteristics indicating possible recent transmission • *Minimal or no* characteristics associated with poor patient outcomes • Cases are *not* recent enough that public health intervention is possible	No additional public health action indicated at this time.

IV. Considerations for Prioritizing Cluster Investigations

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

A. Determine if the cluster likely represents recent transmission

- 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 2–3 years?

- Does the cluster include children under 5 years of age?

- Do patients in the cluster have evidence of recent infection (e.g., tuberculin skin test conversions[3])?

- Is the genotype rare nationally?

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1. See Section IV A and B of this document for additional information on characteristics indicative of recent transmission.
2. Consider monitoring for additional cases matching the genotype of interest by using a "watch list" feature and periodically reviewing the TB GIMS National Distribution Report.
3. For more information, consult the following references: *Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis* and *Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection* (8,11).

For example, in reviewing the line list of a concerning cluster in Figure 1A, there is evidence of recent transmission. Note the recent increase in the number of cases and the diagnosis of TB in an infant.

Figure 1A: Line list of patient characteristics and TB risk factors from TB GIMS, GENType G28538, County A, 2013–2016

Case	Count Date	Gender	Race/ Ethnicity	Age Group	Origin of Birth	GENType	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless
Case 6	11/20/2015	Male	Black	45–64	U.S.-born	G28538	Positive	Yes	None	Negative	Yes	No	Yes
Case 5	11/10/2015	Female	Black	00–04	U.S.-born	G28538	Not Done	No	None	Negative	No	No	No
Case 4	09/16/2015	Male	Black	25–44	U.S.-born	G28538	Positive	Yes	None	Positive	Yes	No	Yes
Case 3	05/15/2014	Female	Asian	25–44	U.S.-born	G28538	Negative	No	None	Negative	No	No	No
Case 2	01/20/2014	Male	Asian	25–44	U.S.-born	G28538	Positive	No	None	Negative	Yes	No	No
Case 1	02/08/2013	Male	Asian	25–44	U.S.-born	G28538	Positive	Yes	None	Negative	No	No	No

Upon review of the national distribution of the GENType in TB GIMS, TB program staff determined it to be unique to their jurisdiction (i.e., not seen anywhere else in the United States), further increasing their suspicion of recent transmission in County A.

B. Identify concerning characteristics in a cluster

- Is there evidence to suggest that transmission is ongoing? For example, are there multiple cases 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)?

- 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 human immunodeficiency virus (HIV) or renal failure?

- Do any patients have drug-resistant 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?

Review again the line list of a concerning cluster in Figure 1B, with markers of infectious TB (i.e., positive sputum smears and/or cavitary lesions) and clinical and social TB risk factors (i.e., HIV, substance use, homelessness) among patients noted (3).

Figure 1B: Line list of patient characteristics and TB risk factors from TB GIMS, GENType G28538, County A, 2013–2016

Case	Count Date	Gender	Race/ Ethnicity	Age Group	Origin of Birth	GENType	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless
Case 6	11/20/2015	Male	Black	45–64	U.S.-born	G28538	Positive	Yes	None	Negative	Yes	No	Yes
Case 5	11/10/2015	Female	Black	00–04	U.S.-born	G28538	Not Done	No	None	Negative	No	No	No
Case 4	09/16/2015	Male	Black	25–44	U.S.-born	G28538	Positive	Yes	None	Positive	Yes	No	Yes
Case 3	05/15/2014	Female	Asian	25–44	U.S.-born	G28538	Negative	No	None	Negative	No	No	No
Case 2	01/20/2014	Male	Asian	25–44	U.S.-born	G28538	Positive	No	None	Negative	Yes	No	No
Case 1	02/08/2013	Male	Asian	25–44	U.S.-born	G28538	Positive	Yes	None	Negative	No	No	No

C. Additional considerations

- The cluster review process should also consider non-genotyped or clinical TB cases that may be related to the cluster. Consult TB GIMS or other local surveillance databases for non-genotyped cases in the same time frame and geographic area that have similar demographic and clinical characteristics as cases in the cluster of interest.

- Consider consulting the National Distribution Report in TB GIMS if there is concern that additional related cases with the genotype of interest have occurred in other jurisdictions. Discuss the possibility of epidemiologic linkages with the state TB program or CDC as appropriate, especially if the genotype is rare (i.e., not commonly seen nationally).

- The cluster review process might also include an assessment of cases with closely related GENTypes, especially those that have a single locus variant (i.e., a difference for only one of the 24-locus MIRU-VNTR results) or have a mixed and missing loci (i.e., designated in MIRU-VNTR results as a "%" and "-", respectively) that otherwise matches the GENType of interest. Investigation of recent transmission among single locus variants (SLV) or mixed and missing loci (MML) cases might be warranted if they are epidemiologically linked or share similar characteristics to case(s) with the primary GENType of interest. The extent to which TB programs chose to investigate cases with closely related GENTypes will depend on an assessment of available resources and an understanding of local TB epidemiology. Additional tools are available in TB GIMS to assist local jurisdictions in identifying cases with an SLV or an MML in relation to a primary cluster of interest.[4]

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4. Programs can review cases with a single locus variant or a mixed or missing loci report in TB GIMS by selecting "Single Locus Variant (GENType)" or "Mixed and Missing Loci (GENType)" under the report field on the "Generate Reports" page.

- About two-thirds (65%) of all GENType clusters are made up of only two cases. State and local TB programs may choose to prioritize two-case clusters under specific circumstances such as:
  - » At least one of the patients has multidrug-resistant TB;
  - » At least one of the patients is less than 5 years old;
  - » The GENType is rare and both patients reside in the same local area; **or**
  - » One or more patients has locally identified characteristics of concern such as a shared setting where transmission is suspected

> False-positive culture results can occur due to cross contamination or mislabeling during specimen collection or during processing in the laboratory. Laboratory cross-contamination has been reported to occur in up to 3% of *M. tuberculosis* isolates (4). To detect false-positive TB culture results, some jurisdictions will routinely review specimen collection and laboratory processing dates for all patients in new genotype clusters. Cross-contamination should be considered when *M. tuberculosis* is cultured from a patient specimen that is collected on the same date or processed in the same batch as another specimen (especially when a patient does not have symptoms consistent with pulmonary TB). If there is a suspicion that laboratory results may be the result of an error, discuss with laboratory partners and other appropriate stakeholders. Detecting and identifying false-positive culture results can avoid unnecessary TB treatment and unwarranted cluster investigations. Additional information on investigating false-positive culture results has been described elsewhere (5).

V. Suggested Steps and Outcomes of the Prioritization Process

The following steps are intended as a guide for reviewing and prioritizing TB genotype clusters. The sequence of steps and extent to which the steps are conducted may differ depending on each genotype cluster and should be based on available resources.

Step 1: Identify *readily available* data sources for genotype cluster review

TB GIMS provides patient-level information (e.g., demographic, clinical, and social characteristics) from the National TB Surveillance System, as well as the local, state, and national distribution of the cluster's genotype.

Additional data sources that may be readily available include:

- State and local surveillance data and/or case management databases;
- Existing interview notes and contact investigation records for cases;
- Case managers, directly observed therapy workers, clinicians, laboratorians, or other health department staff who interact most closely with the patients; **and**
- Any other relevant records, such as past investigations of the cluster.

Step 2: Establish the current priority level of the cluster

After review and discussion with stakeholders, assign a priority level for the cluster as described in Section III C above. This determination should be based on the likelihood for recent transmission in the jurisdiction and the level of concern for future growth.

Step 3: Establish action items and next steps

Decide whether public health intervention is indicated (i.e., actively seeking additional information that is not readily available). If intervention is not indicated, it may be possible to progress to Step 6 below (i.e., skip Steps 4 and 5).

If intervention is indicated:

- Assign responsibilities for next steps based on the locally established cluster prioritization system, including roles, expectations, and timeline for reconvening to discuss further; and

- Consider whether additional communication with stakeholders would be helpful, such as frontline staff who may be aware of potential epidemiologic links between seemingly unrelated patients. If warranted, identify who should lead the communication efforts.

Step 4: Obtain additional information that is *not readily available*

To actively seek additional information, consider the following approaches:

- Discuss with frontline TB staff;

- Conduct patient re-interviews;

- Re-review medical records; **and**

- Conduct other record searches as appropriate (i.e., social media[5], fee-based online record searches[6], and other social service databases[7]).

> In some jurisdictions, the state TB genotyping coordinator might examine all the genotyping, surveillance, and contact investigation data available at the state level, and then determine whether additional investigation is warranted.

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5. Social media searches should focus on websites that are most popular in the demographic group of interest; dating websites and named-based queries using search engines can also be considered.

6. Fee-based online record search services are available that can provide additional information that may be useful in identifying epidemiologic links among patients.

7. Social service databases to consider include: jail/prison databases, homeless shelter databases such as the Homeless Management Information System (HMIS), and healthcare facility databases.

Due to the concerning factors identified in the G28538 cluster, County A TB program staff convened a case review meeting with frontline staff, clinic staff, epidemiologists, and the program manager. During the case review, staff were able to identify a previously unrecognized epidemiologic link between Cases 2 and 6. They also communicated known epidemiologic links between the three 2015 cases—Cases 4, 5, and 6. Based on this information, the County A TB program initiated an investigation to review the contact investigations of all the cases in this cluster and possible sites of transmission, including local homeless shelters where two patients in the cluster may have stayed.

Figure 1C: Social Network Diagram of G28538 in County A, 2013–2016
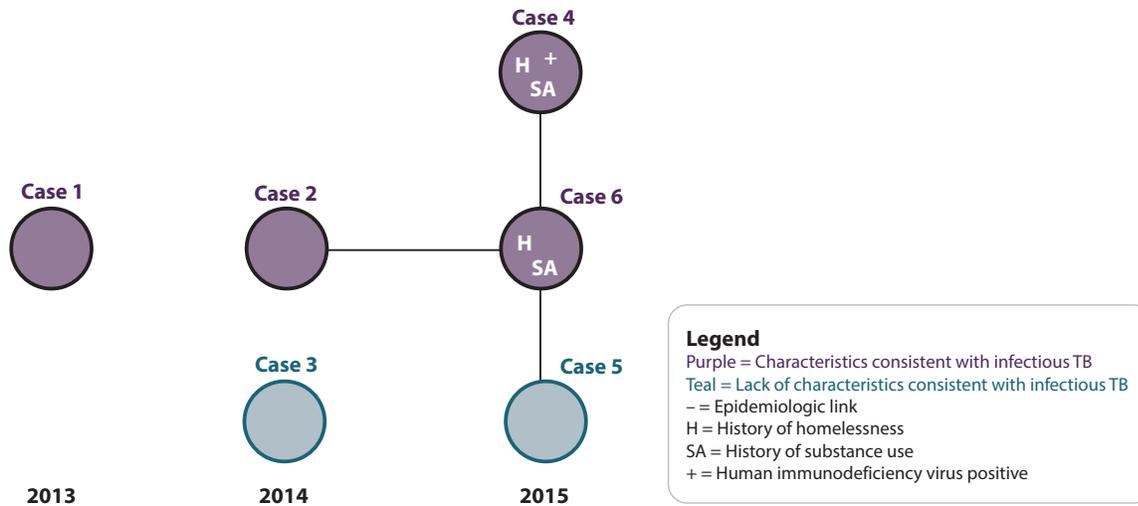
Note: Although TB programs define an epidemiologic link between two patients differently, the process of identifying epidemiologic links may help TB program staff better understand how, where, and when transmission may have occurred. By understanding how patients are epidemiologically linked, transmission patterns can be identified and public health interventions can be implemented. Additional information on epidemiologic links, transmission links, and how they relate to TB outbreak investigations can be found in the Centers for Disease Control's Self-Study Module 9: Tuberculosis Outbreak Detection and Response (6).

Step 5: Identify resource needs and key partners

- What level and types of resources will the health department need to investigate the cluster? To intervene?

- If the cluster involves a challenging or difficult-to-access population, consider identifying key stakeholders and community resources that could be of assistance. These could include homeless shelters, community representatives, and advocacy organizations.

Step 6: Document review and decisions

Develop a systematic method for documenting cluster assessments and actions taken. This could be accomplished by maintaining a simple cluster tracking tool in a spreadsheet or word processing document. Consider capturing the following information:

- GENType/PCRType,

- Jurisdiction(s),

- Identification method (e.g., notification from local health jurisdiction, TB GIMS LLR alert, TB GIMS watch list notification for previously identified cluster),

- Date of first identification,

- TB GIMS alert level (if applicable),

- Most recent date of team assessment,

- Most recent team assessment of the cluster (i.e., priority level)

- Justification/reason for assessment, and

- Public health action taken, if warranted.

> A sample tool for tracking TB cluster assessments is shown in Figure 2. TB program staff developed a spreadsheet to track known clusters in their jurisdiction. In the spreadsheet, staff document when and how the cluster was identified, the team's assessment, and any associated action steps based on the cluster prioritization.

Figure 2: Cluster Tracking Tool, County A

GENType/ PCRType	Jurisdiction	Identification Method	Date of First TB GIMS Alert	TB GIMS Alert Level	Most Recent Date of Team Assessment	Team Priority Assessment	Action Taken
G28538	County A	TB GIMS LLR alert	12/2/2015	Medium	12/3/2015	Priority 1	Initiate cluster investigation

Step 7: Follow up and reconsider cluster prioritization as applicable

Follow up on action items and review new cases or additional information as it becomes available.

For example, reconsider the cluster priority when

- Additional GENType-matched cases are diagnosed, especially when there are more recent cases than expected,

- Common demographic characteristics or shared settings are identified or when the demographic characteristics of cases in the cluster change (e.g., shift from non-U.S.–born persons to U.S.-born persons), or

- Cases with resistance to additional TB medications are detected.

- Based on the availability of resources, determine which cluster priority levels warrant re-review.

Considerations for when whole-genome sequencing might help focus public health action

Although conventional genotyping results help identify clusters that may represent recent TB transmission, these methods have limitations. Genotype clustering can occur among cases that are not related by recent transmission, especially for genotypes that are longstanding or common in a particular population or geographic area. Whole-genome sequencing (WGS) and phylogenetic analysis use a much larger (~90%) portion of the *M. tuberculosis* genome, increasing the molecular resolution for determining the relatedness of cases.

WGS may provide additional information that can inform public health action by:

- Providing increased molecular resolution for a cluster of cases with a genotype that is common in the population or area;

- Identifying a subset of cases where recent transmission is more likely to be occurring during an outbreak investigation; **and**

- Providing additional information that can distinguish cases attributable to recent transmission from cases that are due to reactivation of latent TB infection.

As of 2016, CDC's Division of Tuberculosis Elimination began working with state and local partners to implement the use of WGS nationally, particularly for genotype-matched clusters of concern. Prospective WGS on all TB isolates in the United States will begin in the spring of 2018. Clusters identified through TB GIMS alerts are analyzed using whole-genome single nucleotide polymorphism (wgSNP) analysis. Additionally, wgSNP analysis on older isolates can be performed upon request. If a cluster investigation would benefit from wgSNP analysis, consult with appropriate TB program officials in your jurisdiction. Importantly, data collected during epidemiologic investigations are always needed to accurately interpret WGS results and identify likely transmission among patients. An optional WGS request form is available to assist programs in summarizing information useful for assessing WGS requests.

To consult about a TB GIMS cluster alert, other TB clusters of concern, or to request whole-genome sequencing, e-mail tbgenotyping@cdc.gov.

VI. Examples of Prioritizing Genotype Clusters

Example 1: Assessment of a Priority 3 cluster in County B, a jurisdiction with TB incidence higher than the national average

County B has a population of approximately 600,000 people primarily living in one city in the county, and typically reports about 40 TB cases per year. In 2014, the county reported 43 TB cases, corresponding to 7.2 cases per 100,000 persons, which was higher than the national average (3.0 cases per 100,000 persons).

On September 23, 2015, County B received a TB GIMS alert for G17645 due to an increase in alert level from none to medium (Figure 3).

Figure 3: Sample email for a TB GIMS cluster alert for GENType G17645 in County B

Subject: TB GIMS (CDC)
Sent: Wednesday, September 23, 2015 at 7:01 AM
From: TB GIMS -- TB Genotype Cluster Alert -- County B, State B, G17645

This message is to notify you that the genotype cluster **G17645** in County B, State B, has increased Alert Level from None to Medium as **09/23/2015**. To review data on this genotype cluster, log into TB GIMS application.

An increase in alert level indicates increased geographical clustering of a genotype in a specified county as compared to the rest of the United States, and might be an indicator of recent transmission of TB.

If you have questions about this message, please contact your state TB control program. If you have any questions about TB GIMS, please email the TB GIMS help desk at DTBESupport@cdc.gov

Please note that this e-mail is generated by **TBGIMS** application. For technical issues, please send e-mail to DTBESupport@cdc.gov.

During the regularly scheduled cluster review meeting, TB staff in County B determined this alert was generated based on two cases—one in 2013 and one in 2015. Both were non-U.S.–born patients who were epidemiologically linked to each other as members of the same household. To assist in the review of genotype clusters, staff routinely develop line lists of known clinical and epidemiologic information (Figure 4).

Figure 4. Line list of patient characteristics and TB risk factors from TB GIMS, GENType G17645, County B

Case	Count Date	Gender	Race/ Ethnicity	Origin of Birth	Years in U.S.	Age Group	GENType	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless
Case 2	9/13/2015	Male	Asian	non-U.S.–born	32	45–64	G17645	Negative	No	None	Negative	No	No	No
Case 1	10/23/2013	Male	Asian	non-U.S.–born	8	25–44	G17645	Negative	No	None	Negative	No	No	No

Because an epidemiologic link between these two patients was known and there was a lack of clinical characteristics consistent with infectious TB (e.g., sputum smear-positive or cavitary lesions) or other TB risk factors for cluster growth, staff suspected this cluster was unlikely to be due to recent transmission in the United States. Utilizing their pre-defined prioritization system, TB program staff designated this cluster as a Priority 3, indicating that no further public health action was indicated at this time.

Key concepts from Example 1

- Conduct an assessment of a TB GIMS alert during recurring cluster meetings,

- Use readily available data (e.g., patient clinical and demographic characteristics, contact investigation records) for genotype cluster review

- Identify known epidemiologic links between cases (e.g., cases within a household),

- Utilize a pre-defined cluster prioritization system during the review process (e.g., Priority 1, Priority 2, and Priority 3), and

- Identify as a Priority 3 cluster and close to public health follow up at this time based on known epidemiologic links and a low suspicion for ongoing transmission.

Example 2: Assessment of a Priority 2 cluster in County B

On February 22, 2015, County B received a TB GIMS e-mail alert message for GENType G56349 due to an increase in alert level from none to medium. During the regularly scheduled cluster review meeting, TB staff determined the alert was generated based on 2 cases: one in 2013 and one in 2015. Upon review of their developed line list, staff identified that both cases were U.S.-born Hispanic males that had no reported social risk factors (Figure 5).

Figure 5: Line list of patient characteristics and TB risk factors from TB GIMS, GENType G56349, County B

Case	Count Date	Gender	Age Group	Race/ Ethnicity	Origin of Birth	GENType	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless
Case 2	7/20/2015	Male	25–44	Hispanic	U.S.-born	G56349	Positive	No	None	Negative	No	No	No
Case 1	2/8/2013	Male	65+	Hispanic	U.S.-born	G56349	Negative	No	Isoniazid	Negative	No	No	No

Based on the national distribution report in TB GIMS, staff recognized G56349 to be unique to County B. To assess for epidemiologic links among cases, TB program staff reviewed case data and readily available contact rosters for both patients and conducted social media searches to look for possible shared contacts. After review, no epidemiologic links were identified. Based on the available information and more than 12 months between diagnoses of these patients, the review team determined this cluster should be assigned a Priority 2, indicating no additional public health action is warranted at this time but that they should monitor for additional cases in the future. Given that both patients are U.S.-born, that this GENType is unique

in this jurisdiction,the cluster includes one patient with drug-resistant TB, and at least one patient has characteristics consistent with infectious TB, staff recognized that there may be unrecognized epidemiologic links among the patients; there could also be other potentially related cases with infectious TB that have yet to be diagnosed. Therefore, the TB program determined this cluster warrants monitoring for the diagnosis of additional cases.

To assist with monitoring this cluster, a staff member was assigned the task of creating a TB GIMS watch list for G56349 in County B (Figure 6).

Figure 6: Creating a watch list in TB GIMS to monitor activity related to GENType G56349 in County B

The TB GIMS view shown may differ based on user role and jurisdiction.

In the future, the TB GIMS user who created the watch list item will receive a notification (through TB GIMS or via email) if a new case has a matching GENType in County B. This notification will help prompt the TB program staff to reassess the prioritization of this cluster.

TB program staff also wanted to monitor for clinical or non-genotyped cases with similar characteristics that may be related to this cluster. To review these cases, staff can view clinical or non-genotyped cases using local databases or through TB GIMS (Figure 7).

> To assist in monitoring for cases with a matching GENType outside of their jurisdiction, the staff member created a national-level watch list. Given this is a unique GENType in their jurisdiction, this national-level watch list will alert staff to cases that may be diagnosed outside of their jurisdiction, but that may be related to their cluster.

Figure 7: Querying clinical or non-genotyped TB cases in TB GIMS

"FBORN" is equivalent to "non-U.S.–born"

The TB GIMS view shown may differ based on user role and jurisdiction.

To view cases without genotype results in TB GIMS, users can select "not genotyped" under "Advanced Options" in patient results. TB programs may also consult local TB surveillance databases to review clinical and non-genotyped cases that may be related to a genotype cluster of concern.

Key concepts from Example 2

- Assess a cluster based on available information,

- Utilize a national distribution report to review genotype matched cases diagnosed outside of the jurisdiction,

- Develop action items during review meeting (e.g., staff member tasked to generate watch list item, review national distribution report quarterly), and

- Create a TB GIMS watch list to monitor a cluster for future activity.

Example 3: Reprioritization of a cluster to Priority 1 in County B

On June 7, 2015, County B TB program staff received a TB GIMS watch list notification for GENType G56349 (Figure 8) that had been previously determined to warrant monitoring for additional cases (see Example 2 above).

Figure 8: Sample TB GIMS watch list notification of additional cases of GENType G56349 in County B

From: TBGIMS (CDC)
Sent: Sunday, October 21, 2015 at 6:46 AM
To: TB GIMS user
Subject: TB GIMS Watch List | Genotype | G56349: Watch for additional cases
Importance: High

This message is to notify you that one or more recent changes have occurred in watch list item **G56349: Watch for additional cases** as of October 21, 2015.

To review data on this watch list item and your other watch list items, log in to TB GIMS.

If you have any questions about this message or TBGIMS in general, please contact your state TB GIMS Super User or. e-mail DTBESupport@cdc.gov

TB program staff reviewed cluster information in TB GIMS and determined that two additional cases with G56349 had been identified. Now, there are four cases with a GENType that is unique to County B in the past three years. TB program staff updated their previous cases to include the two new cases, and re-assessed the cluster during their weekly cluster review meeting (Figure 9).

Figure 9: Updated line list of patient characteristics and TB risk factors from TB GIMS, GENType G56349, County B

Case	Count Date	Gender	Age Group	Race/ Ethnicity	Origin of Birth	GENType	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless
Case 4	09/01/2015	Female	45–64	Black	U.S.-born	G56349	Positive	Yes	None	Negative	No	No	No
Case 3	08/16/2015	Female	25–44	Asian	U.S.-born	G56349	Negative	No	None	Negative	No	No	No
Case 2	7/20/2015	Male	25–44	Hispanic	U.S.-born	G56349	Positive	No	None	Negative	No	No	No
Case 1	2/8/2013	Male	65+	Hispanic	U.S.-born	G56349	Negative	No	Isoniazid	Negative	No	No	No

Upon re-review of the cluster, staff noted a lack of social risk factors. However, two new cases have been diagnosed in a month, of which, one new case had potentially infectious TB. The increase in the number of cases in G56349 in a 2 month period, indicate there has likely been recent transmission associated with this GENType. As a result, the team reprioritized the cluster from a Priority 2 to a Priority 1. A Priority 1 classification had been previously determined to indicate active investigation of the cluster. Staff members were assigned responsibility for initiating a cluster investigation of all four patients involving 1) medical chart data abstractions, 2) social media searches, and 3) re-interviewing each patient with a specific cluster investigation questionnaire.

Through active investigation, program staff were able to identify additional contacts not previously screened during the initial contact investigations, possible sites of TB transmission at a church and a single-family home, and epidemiologic links between cases through shared contacts and locations. By identifying and prioritizing genotype clusters, the local TB staff were able to focus valuable resources on interrupting TB transmission in their county.

Key concepts from Example 3

- Review a watch list item that generates a notification for recent activity related to a previously reviewed cluster,

- Identify patient characteristics consistent with recent transmission,

- Identify patient characteristics that increase the level of concern for potential cluster growth (e.g., infectiousness, homelessness, substance use, HIV), and

- Illustrate how TB GIMS alerts can identify clusters that may represent recent transmission, reassess and prioritize a cluster based on new cases, and describe potential public health actions when recent transmission is suspected.

Example 4: Assessment of a genotype cluster in County C, a jurisdiction with TB incidence lower than the national average

County C has a population of approximately 225,000 people and typically reports about four TB cases per year. In 2014, the county reported five TB cases, corresponding to 2.2 cases per 100,000 persons, which was lower than the national average.

On January 13, 2016, County C received a TB GIMS message for G96482 due to an increase in alert level from none to medium. During the regularly scheduled cluster review meeting, staff determined this alert was generated based on two cases—one in 2014 and one in 2016. Program staff have elected to review and develop line lists of all genotype clusters in their jurisdiction (Figure 10).

Figure 10. Line list of patient characteristics and TB risk factors from TB GIMS, GENType G96482, County C

Case	Count Date	Gender	Age Group	Race/ Ethnicity	Origin of Birth	GENType	Sputum Smear	Cavitary	Drug Resistance	HIV	Substance Use	Corrections	Homeless
Case 2	1/16/2016	Male	25–44	White	U.S.-born	G96482	Positive	Yes	None	Negative	Yes	No	No
Case 1	11/17/2014	Male	25–44	White	U.S.-born	G96482	Negative	No	None	Negative	Yes	No	No

Both cases were in patients who were U.S.-born white males in the same age group with a history of substance use. One of the cases had clinical characteristics consistent with infectious TB (i.e., sputum smear positive and cavitary lesions). Due to the low incidence of TB in County C, staff previously determined that any genotype cluster warranted further investigation for possible recent transmission. Based on this prioritization scheme, a public health staff member was assigned responsibility for 1) reviewing the contact investigations of each case for completeness and possible epidemiologic links, and 2) re-interviewing each patient with a specific cluster investigation questionnaire.

Key concepts from Example 4

- Identify how a low incidence jurisdiction may choose to assess and investigate a genotype cluster, and

- Utilize a pre-defined cluster prioritization system during the review process (e.g. investigation warranted, investigation not warranted).

VII. Appendix

A. Key Terms

Clinical TB Cases

A clinical TB case is defined by meeting all of the following criteria:

- A positive tuberculin skin test result or positive interferon gamma release assay for *M. tuberculosis*;

- Other signs and symptoms compatible with TB (e.g., abnormal chest radiograph, abnormal chest computerized tomography scan or other chest imaging study, or clinical evidence of current disease);

- Treatment with two or more anti-TB medications; and

- A completed diagnostic evaluation.

False-positive TB Culture (sometimes called "false-positive laboratory results")

Persons can be misdiagnosed with TB as a result of specimen mislabeling or cross contamination during specimen collection or during processing in the laboratory. Alternatively, a patient may in fact have TB, but cross contamination from another TB isolate results in an incorrect genotyping result.

GENType

The sequential designation of codes for each nationally unique combination of spacer oligonucleotide typing (spoligotype) and 24-locus mycobacterial interspersed repetitive unit-variable number tandem repeat typing (MIRU-VNTR) results.

Log Likelihood Ratio (LLR)

In TB GIMS, a measure of the geographic concentration over time of a local genotype cluster compared with the national average. The local area for the LLR calculation is defined by county boundaries and the time period is defined as the preceding 3 years.

Large Outbreaks of Tuberculosis in the United States (LOTUS)

Routine surveillance for LOTUS was initiated by CDC in April 2014. Large outbreaks are defined as ≥10 genotype-matched cases within a 3-year period that are related by recent transmission. CDC identifies suspected large outbreaks quarterly and notifies programs. Programs are also encouraged to report outbreaks of ≥10 cases with a 3-year period to CDC.

National TB Genotyping Service

TB genotyping is a laboratory-based approach used to characterize *M. tuberculosis* strains based on a distinct pattern (genotype) identified in specific regions of the TB genome. There are several genotyping methods that are used, including spacer oligonucleotide typing (spoligotyping), variable number tandem repeat of mycobacterial interspersed repetitive unit analysis (MIRU-VNTR), IS6110 restriction fragment length polymorphism (RFLP) analysis, and whole genome sequencing (WGS). The National TB Genotyping Service performs universal genotyping for all culture-positive TB cases in the United States using spoligotyping and 24-locus MIRU-VNTR analysis.

PCRType

The sequential designation of codes for each nationally unique combination of spoligotype and 12-locus MIRU-VNTR results. The National TB Genotyping Service began routinely using these two PCR-based methodologies in 2004. In 2009, MIRU-VNTR expanded the number of loci to 24 (see **GENType** above).

SaTScan

This software program analyzes spatial (and/or temporal) data using a scan statistic to detect geographically defined disease clusters and evaluate the statistical significance of each cluster. Significant localized concentrations of cases are detected by zip code location rather than by county or state borders.

Spacer Oligonucleotide Typing (spoligotyping)

Spoligotyping is a hybridization assay that detects variability in the direct repeat (DR) region in the DNA of *M. tuberculosis*. The DR region consists of multiple copies of a conserved 36-base-pair sequence (the direct repeats) separated by multiple unique spacer sequences (the standard spoligotyping assay uses 43). Different *M. tuberculosis* strains have various complements of the 43 spacers, and these different complements form the basis of the assay (7). Like MIRU-VNTR, this typing method yields results in a standardized code that can be easily analyzed and communicated between laboratories and TB programs.

Tuberculosis Genotyping Management System (TB GIMS)

The TB Genotyping Information Management System (TB GIMS) is a secure Web-based system which 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. For questions about access to TB GIMS, contact TB GIMS staff by email at DTBESupport@cdc.gov.

TB GIMS LLR Alert

Cluster detection alerts in TB GIMS are based on a county-level log-likelihood ratio (LLR) statistic (see LLR above). Categories for the alert level:

- "High" (LLR ≥10)
- "Medium" (LLR=5.0–9.99)
- "None" (LLR=0–4.99)

LLR calculations are performed each week and county-level clusters with an increase in alert level and case count (e.g., "None" to "Medium," and 2 to 3 cases) are sent automatically by email to registered TB GIMS users who have requested these alerts.

TB GIMS Watch List

A watch list is a user-defined search established in TB GIMS for a specific genotype and jurisdiction that will flag and notify the user of recent activity when an additional isolate or linked patient record is added for the defined genotype.

24-locus variable-number tandem repeat of mycobacterial interspersed repetitive units (MIRU-VNTR)

MIRU-VNTR distinguishes *M. tuberculosis* strains by the difference in the number of copies of tandem repeats at specific regions, or loci, of the *M. tuberculosis* genome. Like spoligotyping, this typing method yields results in a standardized code that can be easily analyzed and communicated among laboratories and TB programs. A total of 41 MIRU loci have been reported. The National Tuberculosis Genotyping Service include 24 loci, which results in a 24-digit code (e.g., 223225163324561333245623).

B. How do TB contact investigations differ from genotype cluster investigations and outbreak investigations?
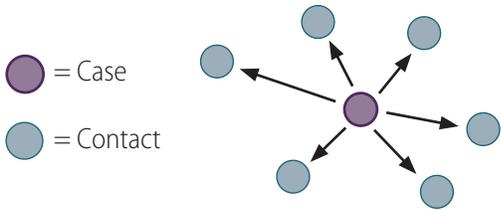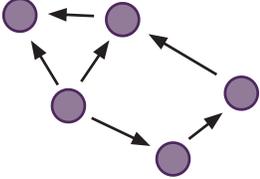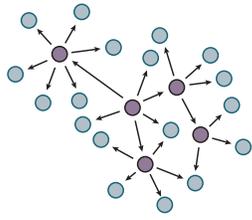
Contact investigations, genotype cluster investigations, and outbreak investigations are important activities in TB control. The ultimate goals of these investigations are similar—to identify, evaluate, and treat active TB cases and their contacts in order to interrupt transmission and prevent additional TB cases. In each investigation, understanding infectious periods for active TB cases is critical for determining where and when transmission may have occurred. Table 2 describes some key differences between each type of investigation.

Because outbreak investigations assess the overall potential for ongoing transmission of *M. tuberculosis*, outbreak investigations encompass contact and cluster investigation activities that may already be in progress. Findings from contact investigations and cluster investigations are often the earliest indications of an outbreak. For example, a contact investigation may identify ongoing transmission when numerous contacts have active TB disease. Similarly, a cluster investigation may identify new epidemiologic links between cases, leading to the identification of more recent transmission than had been previously noted.

It is important to note that not all matching genotype results represent recent transmission. Successful investigation of cases and contacts, however, allows state and local TB programs to promptly identify recent transmission and implement appropriate interventions.

Additional information on contact investigations (8,9), cluster investigations (10), and outbreak investigations (6) are available from the Centers for Disease Control and Prevention.

Table 2: Key Differences between TB Contact Investigations, Clusters Investigations, and Outbreak Investigations

	TB Contact Investigation	Genotype Cluster Investigation	Outbreak Investigation
⬤ = Case ⬤ = Contact			
Focus	Identify and treat TB infection and active disease among contacts of the single patient recently diagnosed with TB.	Identify recent transmission by considering possible relationships among TB cases that are genotypically-matched in a defined geographic area and time frame.	Identify and prioritize the contacts of the outbreak patients so that they can be promptly and appropriately evaluated and treated.
Emphasis	Use information about a single TB case to identify, evaluate, and treat contacts of that case who may have been exposed during the patient's infectious period; this is a routine part of TB control.	Identify epidemiologic links to help determine where, when, and by whom recent TB cases may have been infected.	Implement interventions that interrupt ongoing transmission.
Time frame of interest	Contacts are defined based on the patient's infectious period.	While genotype clusters in some jurisdictions can extend back over many years, cluster investigations typically focus on cases diagnosed in the last 2–3 years in a defined geographic area.	Outbreak investigations typically focuses on cases diagnosed in the last 2–3 years in a defined geographic area and an indistinguishable outbreak genotype.
Personnel involved	Local public health staff, including the TB program manager, nurse case managers, and field-based staff.	In addition to staff who routinely conduct contact investigations, cluster investigations may also include local staff such as epidemiologists, or other TB professionals such as TB controllers, TB genotype coordinators, laboratorians, and other state TB programs.	Because an outbreak indicates that there is potential for extensive recent transmission, an outbreak investigation should always be considered a public health emergency and involve combined efforts from multiple individuals and organizations, both within and outside the health department.

C. Additional resources

1. Centers for Disease Control and Prevention (U.S.). *GENType: New Genotyping Terminology to Integrate 24-locus MIRU-VNTR.* 2012. Available from: http://www.cdc.gov/tb/publications/factsheets/statistics/genotypingterminology.pdf

2. Centers for Disease Control and Prevention (U.S.). *Best Practices for Genotyping-Based Tuberculosis Outbreak Detection.* 2012. Available from: http://www.cdc.gov/tb/publications/factsheets/statistics/Genotyping_BestPractices.pdf

3. Althomsons SP, Kammerer JS, Shang N, Navin TR. *Using routinely reported tuberculosis genotyping and surveillance data to predict tuberculosis outbreaks.* PLoS One 2012; 7(11).

4. Djelouadji Z, Orehek J, Drancourt M. *Rapid detection of laboratory cross-contamination with Mycobacterium tuberculosis using multispacer sequence typing.* BMC Microbiol. 2009; 9:47.

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6. Centers for Disease Control and Prevention (U.S.). *Self-Study Modules 9: Tuberculosis Outbreak Detection and Response.* 2014. Available from: http://www.cdc.gov/tb/education/ssmodules/pdfs/module9.pdf

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8. Centers for Disease Control and Prevention (U.S.). *Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis.* Morb Mortal Wkly Rep. 2005; 54 (RR-15):1–54.

9. Centers for Disease Control and Prevention (U.S.). *Self-Study Modules 8: Contact Investigations for Tuberculosis.* 2014. Available from: http://www.cdc.gov/tb/education/ssmodules/pdfs/module8.pdf

10. Cronin WA, Golub JE, Lathan MJ, Mukasa LN, Hooper N, Razeq JH, et al. *Molecular epidemiology of tuberculosis in a low- to moderate-incidence state: are contact investigations enough?* Emerg Infect Dis. 2002; 8(11):1271–9.

11. Centers for Disease Control and Prevention (U.S.). *Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection.* Morb Mortal Wkly Rep. 2000; 49(RR-6):1–54.

Additional information on genotyping is available at http://www.cdc.gov/tb/programs/genotyping/default.htm *or by contacting* tbgenotyping@cdc.gov.