Presentation Objectives

- Define genotyping
- Describe genotyping methods
- Describe the isolate submission procedure
- Explain how to interpret genotyping results
- Demonstrate how genotyping can improve TB prevention and control practices
Genetics 101

- Genotyping is based on analysis of DNA
- Mycobacteria reproduce by binary fission—each new bacilli (almost always) has identical DNA
- Mutations in DNA occur spontaneously at a low frequency
- Over time, mutations have accumulated to produce the genetic diversity of M. tuberculosis strains.
- The diversity of strains provides a means to study the patterns and dynamics of TB transmission
What is TB Genotyping?

- **Definition**: a laboratory approach using specific elements of bacterial DNA that serve as markers for *M. tuberculosis* strains.
  - Different strains of *M. tb* have different genotype patterns
  - *M. tuberculosis* organisms isolated from >2 TB patients that are closely enough genetically related to indicate potential recent transmission from one to the other
Why is genotyping important?

- Detect (and interrupt) recent transmission to prevent outbreaks
- Identify unsuspected relationships
- Enhance contact investigations
  - Identify previously unidentified source cases
  - Identify previously unidentified locations (especially difficult to investigate settings)
- Distinguish new TB disease from recurrence or relapse of previously diagnosed disease
- Recognize false positives
- Monitor trends (new and growing clusters)
- Evaluate program performance
What is molecular epidemiology?

- **Molecular epidemiology:** Combines bacterial genotyping (“DNA fingerprinting”) information with traditional epidemiology data.
Genotyping Methods

- CDC’s National TB Genotyping Service (NTGS) uses two genotyping methods to identify and characterize *Mycobacterium tuberculosis* strains:
  - PCR (Polymerase Chain Reaction) methods (*Routine*)
    - Spoligotyping = Spacer oligonucleotide typing
    - MIRU-VNTR = Variable-Number Tandem Repeats of Mycobacterial Interspersed Repetitive Units
  - RFLP = IS6110-based Restriction Fragment Length Polymorphism analysis (*Special request*)
PCR Method: Spoligotyping

- Hybridization assay that detects variability in the direct repeat (DR) of the DNA of M. TB
- The DR region consists of multiple copies of a conserved 36-base pair sequence (direct repeats) separated by multiple unique spacer sequences (spoligotype assay uses 43)
- Spacer sequences form a dark band on the assay membrane
- For each isolate, spoligotyping assay produces a series of bands much like a bar code.
  - Band indicates spacer is present, no band indicates spacer is absent.
PCR Method: Spoligotyping

- Spoligotyping looks at presence or absence of spacers in DNA
- Results are displayed as a 15-digit number

Spoligotype 14 3
PCR Method: Spoligotyping

- Band pattern is converted to a series of 0s (no band) and 1s (band present) that is 43 digits long (“Binary Code”)
- The 43-digit binary code is converted to the 15-digit octal code (using base 8, having the digits 0-7)
  - 43 digit binary code divided into 14 sets of 3 digits (spacers 1-42) with final additional 0 or 1 (spacer 43)
  - Each 3-digit binary set is converted to its octal equivalent with the final additional digit remaining as 1 or 0.
  - Translation: 000=0, 010=2, 011=3, 100=4, 101=5, 110=6, 111=7

### Example 1

<table>
<thead>
<tr>
<th>Spacers</th>
<th>Original banding pattern</th>
<th>Binary code</th>
<th>14 + 1 grouping</th>
<th>Octal designation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>111111111111111111111110111111111111110000111111</td>
<td>111-111-111-111-111-111-100-111-111-111-110-000-111-111-1</td>
<td>7 7 7 7 4 7 7 7 6 0 7 7 1</td>
<td></td>
</tr>
</tbody>
</table>
PCR Method: Spoligotyping

- The report from the laboratory is much simpler - results are automatically converted to the 43-digit binary code, which is converted to the 15 digit octal designation for each isolate.

- If one isolate’s designation is different from another even by a single digit, they have different spoligotypes.
Spoligotype Patterns for Known Strains

Figure 3.2. Graphical representations of spoligotype patterns of certain strains. Strains H37Rv and BCG are used as control strains in the assay and between them contain all 43 spacers. The Beijing spoligotype contains only the final nine spacers (35 through 43). The octal designations for the patterns are H37Rv, 777777477760771; BCG, 676773777777600; Beijing, 000000000003771; S2, 777777777760771; A, 777771777760771; B, 677771777760771; C, 777771437760771; and D, 677771437760771.
PCR Method: MIRU-VNTR (MIRU)

- MIRU-VNTR Assay based on analysis of DNA segments containing “tandem repeated” sequences
- Number of copies of the repeated sequence varies among strains.
- Method relies on PCR amplification and calculated number of repeats on the basis of the size of the amplified product.
PCR Method: MIRU-VNTR (MIRU)

- MIRUs are a class of tandem repeated sequences.
- There are 41 MIRU loci, of which 24 have been selected for genotyping.
  - MIRU1: Initially focused on 12 loci
  - MIRU2: Additional 12 loci with equal weight to the initial 12 loci (started March 2009)
- MIRU are reported as a 12-character designation, with each character corresponding to the number of repeats at one of the 12 MIRU
**PCR Method: MIRU-VNTR (MIRU)**

Table 3.1. Examples of MIRU results. MIRU results are reported as a 12-digit designation, with each digit representing the number of repeats detected at the respective 12 MIRU loci. For loci with more than nine repeats, letters are used (e.g., “a” for 10 repeats, “b” for 11, etc.). See text for details.

<table>
<thead>
<tr>
<th>Example 1</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRU locus name</td>
<td>02</td>
<td>04</td>
<td>10</td>
<td>16</td>
<td>20</td>
<td>23</td>
<td>24</td>
<td>26</td>
<td>27</td>
<td>31</td>
<td>39</td>
</tr>
<tr>
<td>No. of repeats</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>MIRU designation</td>
<td>232234253322</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 2</th>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>MIRU locus name</td>
<td>02</td>
<td>04</td>
<td>10</td>
<td>16</td>
<td>20</td>
<td>23</td>
<td>24</td>
<td>26</td>
<td>27</td>
<td>31</td>
<td>39</td>
</tr>
<tr>
<td>No. of repeats</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>MIRU designation</td>
<td>14322404354b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PCR Methods

- Both Spoligotyping and MIRU are standardized techniques producing digital results
  - Highly reproducible
  - Easily analyzed and interpreted results
  - Allows for quick turn-around time
  - Can analyze non-viable organisms
  - Require only a small amount of isolate sample
What Is a Genotype Cluster? (1)

When an isolate genotype matches at least one other person’s isolate genotype
What Is a Genotype Cluster? (1)

When an isolate genotype matches at least one other person’s isolate genotype

Spoligotyping
0000000000003771

MIRU-VNTR
222325173543
424244223348

Match

Spoligotyping
0000000000003771

MIRU-VNTR
222325173543
424244223348
What is a Genotype Cluster? (2)

- Does the isolate match at least one other isolate in the database?
  - Yes: “Clustered” (Genotype/PCR Cluster)
    - May indicate recent transmission
  - No: “Unique”
    - May indicate reactivation of old infection
    - May indicate “imported” TB
    - May result from missing isolates
# CDC cluster naming conventions

<table>
<thead>
<tr>
<th>Field name</th>
<th>Octal code</th>
<th>Cluster designation w / MIRU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spoligotype</td>
<td>Octal code</td>
<td>0000000000003771</td>
</tr>
<tr>
<td>MIRU</td>
<td>12 loci</td>
<td>223325173533</td>
</tr>
<tr>
<td>MIRU2</td>
<td>12 add’l loci</td>
<td>378451664321</td>
</tr>
<tr>
<td>National cluster designation</td>
<td>Cluster designation</td>
<td>Cluster designation w / MIRU2</td>
</tr>
<tr>
<td></td>
<td>PCR000002</td>
<td>PCR000002 - 0001</td>
</tr>
<tr>
<td>State cluster designation</td>
<td>FL_0042</td>
<td>FL_0042 - 001</td>
</tr>
</tbody>
</table>
RFLP: Southern Blot Method

- **IS6110-based RFLP**: “gold standard” of MTB genotyping; detects variations generated by the insertion element IS6110
- Insertion elements can make copies of themselves and then insert the copy anywhere in the genome (transposition)
- Restriction enzyme cuts DNA at specific sequences into hundreds of different fragments that are separated by size on agarose gel, transferred to membrane, image captured on film
- Probe detects fragments containing IS6110. Each copy produces one band, ≥7 bands increases discrimination between bands.
RFLP for common genotype families (Manila, Haarlem, Beijing)

Example: Manila family cluster discrimination by RFLP

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>County</th>
<th>Country</th>
<th>Spoligotype</th>
<th>MIRU1</th>
<th>MIRU2</th>
<th>RFLP bands</th>
<th>RFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>46</td>
<td>Montgomery</td>
<td>Philippines</td>
<td>6777477413771</td>
<td>254326223432</td>
<td>424244223348</td>
<td>14</td>
<td>09RF2632_14</td>
</tr>
<tr>
<td>C</td>
<td>26</td>
<td>Baltimore</td>
<td>Philippines</td>
<td>6777477413771</td>
<td>254326223432</td>
<td>424244223348</td>
<td>11</td>
<td>09RF1375_11</td>
</tr>
<tr>
<td>F</td>
<td>26</td>
<td>Howard</td>
<td>Philippines</td>
<td>6777477413771</td>
<td>254326223432</td>
<td>424244223348</td>
<td>11</td>
<td>09RF2666_11</td>
</tr>
<tr>
<td>G</td>
<td>29</td>
<td>Prince Georges</td>
<td>Philippines</td>
<td>6777477413771</td>
<td>254326223432</td>
<td>424244223348</td>
<td>15</td>
<td>09RF2649_15</td>
</tr>
<tr>
<td>J</td>
<td>39</td>
<td>Prince Georges</td>
<td>Philippines</td>
<td>6777477413771</td>
<td>254326223432</td>
<td>424244223348</td>
<td>10</td>
<td>10RF1633_10</td>
</tr>
<tr>
<td>K</td>
<td>43</td>
<td>Washington</td>
<td>Philippines</td>
<td>6777477413771</td>
<td>254326223432</td>
<td>424244223348</td>
<td>15</td>
<td>10RF2649_15</td>
</tr>
</tbody>
</table>

**Manila strain** is common among immigrants from Philippines, but country of origin was the only epi link among these 7 patients. Although these patients appeared to be in the same PCR cluster, RFLP was different for each confirming they were not genetically linked.
## Comparison of Methods

<table>
<thead>
<tr>
<th>PCR Methods</th>
<th>IS6110-RFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not require viable cultures</td>
<td>Requires substantial amounts of viable isolate sample</td>
</tr>
<tr>
<td>Amenable to high reproducibility across labs</td>
<td>Inter-lab reproducibility challenges</td>
</tr>
<tr>
<td>PCR-based → rapid turnaround</td>
<td>Slowest method: 3-6 weeks because based on culture growth</td>
</tr>
<tr>
<td>Pattern results are digital, facilitating laboratory comparisons</td>
<td>Difficult to compare large numbers of patterns (assigned by each lab)</td>
</tr>
<tr>
<td>Less discriminating than IS6110 typing</td>
<td>Most discriminating method, but higher failure rate</td>
</tr>
</tbody>
</table>
Request RFLP additional testing

- Conducted only on isolates that have matching PCR genotypes and no known epidemiologic links
- Adds discriminatory power to provide additional information to guide your investigation
  - Some large clusters will be divided into smaller ones, each of which may represent “true clusters”
- May be applied to historical isolates
Remember

- No one method is sufficient to determine genetic similarity related to transmission
National U.S. Genotyping Service (NTGS)
National TB Genotyping Service

- Goal: to genotype at least 1 M. tuberculosis isolate for each new culture-positive case reported in the U.S.
  - “Universal Genotyping”
  - CDC funded 2 laboratories
  - No cost to patients, healthcare providers, health departments
  - 2010, TB Genotyping Information Management System was launched
    - Facilitates systematic data collection of TB genotyping results
    - Integrates genotyping with epidemiologic data collected by the National TB surveillance System
    - Forms a national and centralized database
Specimen Processing

Specimen collected and processed for culture
(sputa, gastric aspirates, bronchial washings, blood, lymphatic fluid, urine)

- M. tuberculosis
  - Culture Positive
  - Culture Isolation ("isolate"): Local or state lab processes raw specimen
  - Genotyped

- M. tuberculosis
  - Culture Negative

Note: CDC contracts are not set up to genotype M. avium or other NTM
National TB Genotyping Service

- TB GIMS allows users to create, submit, track and manage data for *M. TB* isolates in the U.S.
- Link isolate genotype records with patient surveillance records
- Query line-listed isolate genotype and patient surveillance data
- Generate summary reports and maps of genotype clusters, including national genotype distributions, and national, state and county maps
- Monitor and receive notifications on genotype clusters that may represent recent transmission or outbreaks.
National TB Genotyping Service

- National TB genotyping surveillance coverage refers to the proportion of culture-positive TB cases with a genotyped *M. tuberculosis* isolate.
- High levels of coverage in the U.S. can provide a better understanding of the epidemiologic transmission of TB within a specific geographic area, as well as the entire country.
- National objective for TB genotyping surveillance coverage is 94%
  - Coverage increased from 51% of all reported culture positive TB cases in 2004 to 88% in 2010.
  - More than 13,000 different strains and identify new ones daily.
Nomenclature for Tuberculosis Genotyping in the United States

Spoligotype: 0000000000003771
Initial 12-locus MIRU-VNTR: 223325173533

Sequentially assigned for each unique spoligotype and initial 12-locus MIRU-VNTR combination

PCRTypE: PCR00002

Additional 12-locus MIRU-VNTR: 4445344234281

Sequentially assigned for each unique spoligotype and 24-locus MIRU-VNTR combination

GENTypE G00010

1 The complete set of 24 loci is referred to as 24-locus MIRU-VNTR. The additional 12 loci are interpreted with equal weight as the initial 12 loci.
**Genotyping Nomenclature**

**Table 4.1.** Genotyping cluster designations based on results of the three genotyping methods (spoligotyping, MIRU analysis, and IS6110-based RFLP). Only isolates that match by the two PCR methods should be analyzed by IS6110-based RFLP.

<table>
<thead>
<tr>
<th>PCR-based test results</th>
<th>IS6110-based RFLP results</th>
<th>Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not performed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RFLP patterns match</td>
<td>RFLP patterns do not match</td>
</tr>
<tr>
<td>Both spoligotype and MIRU analysis show matching genotypes</td>
<td>PCR cluster</td>
<td>PCR/RFLP cluster</td>
</tr>
<tr>
<td>Either spoligotype or MIRU analysis show a nonmatching genotype</td>
<td>* Nonmatching (or unique) genotypes</td>
<td>* Nonmatching (or unique) genotypes</td>
</tr>
</tbody>
</table>

*RFLP not indicated in this situation*
What are the Applications of Genotyping in TB Prevention and Control?
Using Genotyping in Practice

- Detect (and interrupt) recent transmission to prevent outbreaks
- Identify unsuspected relationships
- Enhance contact investigations
  - Identify previously unidentified source cases
  - Identify previously unidentified locations (especially difficult to investigate settings)
- Distinguish new TB disease from recurrence or relapse of previously diagnosed disease
- Recognize false positives
- Monitor trends (new and growing clusters)
- Evaluate program performance
What Do I Do with a Genotype Cluster?

• If TB cases are clustered genotypically, is there true evidence of ongoing transmission?

• This is only half of the picture...
Also Need Epidemiologic Data

- To determine recent transmission, BOTH genotype and epidemiologic information is needed

“shoe leather epidemiology”
Definition of Epidemiologic link (Epi-link)

- An identified relationship between TB patients can help explain whether recent transmission may have occurred.
- Woman was diagnosed with pulmonary TB and reported her neighbor’s child as a close contact.
- Genotypeting results indicated they were in the same PCR cluster.
Epi-Links

- Epi-links are essential for determining on-going transmission
  - **Person**: similar demographic and risk characteristics
  - **Place**: location where the TB patients spent time together
    - (i.e., bars, jail, homeless shelter, church, geographic location, leisure settings)
  - **Time**: exposure during infectious period
Identifying Epi-links in Genotype Clusters

• Health departments:
  – Case manager interview
  – Medical records
  – Contact investigation logs

• **Patient interviews** where necessary

• **What to look for:**
  – Did one case name another as a contact?
  – Did cases name the same contact?
  – Did cases live, work or spend time in the same place during the infectious period?
  – If foreign-born: What is the country of origin? Time in the United States?
Types of Epi-Links

- Known epidemiologic link
- Possible epidemiologic link
- No identified epidemiologic link
Known Epidemiologic Link

• Patients are said to have a known epi-link if either of following two conditions apply:
  – One of the patients named the other (contact)
  OR
  – Patients were at same place at same time
Possible Epidemiologic Link

Patients spent time at same place around same time, but overlap of timing was not definite enough

- Patients lived in same neighborhood around same time, but dates not clear

OR

- Patients worked in or were at same geographic area around same time and shared social or behavioral traits that increased chances of transmission
No Identified Epidemiologic Link

- Patients should be classified as having no identified epi-link if they do not meet criteria for known or possible epi-link

- Note: you can never be certain there is NO LINK
Contact Investigation: Recent transmission, a search for commonalities indicating Epi-links

Case information
- Demographics – age, race, ethnicity, US-born vs. foreign-born
- Risk factors – HIV status, homeless, drug use, incarcerations

Infectious periods
- Work / School History
- Social History
- Travel History
- History of TB exposures
- Contact lists

Location ... Location ... Location
A tale of 2 investigations...

<table>
<thead>
<tr>
<th></th>
<th>Contact Investigation (CI)</th>
<th>Cluster Investigation (CLI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who?</strong></td>
<td>One TB case/suspect</td>
<td>2+ TB cases in a genotype cluster</td>
</tr>
<tr>
<td><strong>What?</strong></td>
<td>Investigate named contacts</td>
<td>Investigate genetic links between cases to find unknown epi links</td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td>Identification of TB case/suspect</td>
<td>Genotype cluster report</td>
</tr>
<tr>
<td><strong>Where?</strong></td>
<td>Household, Workplace Congregate settings</td>
<td>Often unusual settings like bars, religious gatherings, card games</td>
</tr>
<tr>
<td><strong>How?</strong></td>
<td>Interview case/suspect</td>
<td>Review genotype data CI and case record review Re-interview clustered cases Site visit(s)</td>
</tr>
<tr>
<td></td>
<td>Record review</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Home/work place visit</td>
<td></td>
</tr>
<tr>
<td><strong>Why?</strong></td>
<td>Identify LTBI/new TB</td>
<td>Expand contact investigation? Identify LTBI/new TB Prevent new active TB</td>
</tr>
<tr>
<td></td>
<td>Prevent new active TB</td>
<td></td>
</tr>
</tbody>
</table>
Use Genotyping to Enhance Contact Investigations

Adapted from Etkind 1993
Use Genotyping to Enhance Contact Investigations

| Epi Links Detected by Routine CI | Epi Links Detected after CI by Genotyping and CLI |

*Most of these were in social and leisure settings*  

CI = contact investigation  
CLI = cluster investigation  

Cronin et al *Emerg Infect Dis* 2002
Use Genotyping to Enhance Contact Investigations

<table>
<thead>
<tr>
<th>Epi Links Detected by Routine CI</th>
<th>Epi Links Detected after CI by Genotyping and CLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>63%</td>
<td>37%*</td>
</tr>
</tbody>
</table>

*Most of these were in social and leisure settings

CI = contact investigation
CLI = cluster investigation

Cronin et al. Emerg Infect Dis 2002
Combining Contact Investigations (EPI links) with Cluster investigations

Contact investigation of an adult female case found 2 children infected among her named contacts
Combining Contact Investigations (EPI links) with Cluster investigations

- Unexpected matching genotypes should lead to a cluster investigation, which can demonstrate previously unknown EPI links

Spoligotype: 00000000000003771
MIRU: 223325173533
MIRU2: 378451664321
Combining Contact Investigations (EPI links) with Cluster investigations

- Cluster investigation identified a 4th Patient
- Re-interviews uncovered new EPI link. Patient 4 had been visiting the home where Patient 3 was holding a daycare for young children
- Subsequently, more exposed children were identified, including a new case (5)
Cluster Investigation
Example 2

- Low-incidence state identifies 6 isolates with the same cluster designation
- Review of the CI documentation reveals that the patients were all middle-aged US-born black males who lived close to each other.
  - None named any others as a contact
  - 3 reported excessive alcohol use
  - “possible epi links”
- RFLP was requested to determine if they were truly genetically linked
  - All 6 had matching 9 band pattern
Cluster Investigation Example 2

- New evidence suggested even stronger epi-link, but still not confirmed.
- 5 of 6 cases re-interviewed (1 died) to collect additional details of where they spent time and with whom, going back as far as 5 years.
- New epi links were identified including 5 high risk sites where transmission could have occurred:
  - A single-occupancy hotel, 2 homeless shelters, a crack house, and a bar.
Cluster Investigation
Example 2

- Stronger EPI plus matching genotypes strongly suggested recent transmission (ongoing?)
- CI was re-evaluated and expanded, 3 additional TB cases identified matching the cluster genotyping
- Investigation led to evaluation of practices at shelters and recognition that community providers were not recognizing TB among their patients
- Interventions were implemented
  - New screening and infection control procedures at shelter
  - Education of community health care providers to recognize TB symptoms and signs more quickly
- Community transmission decreased.
False Positive Cultures
False Positive Cultures
## Search for False Positive Cultures

- Cluster: specimens collected ± 7 days of each other

<table>
<thead>
<tr>
<th>Accession Number</th>
<th>Cluster</th>
<th>Specimen Collection Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD1000000R</td>
<td>MD_013</td>
<td>December 3, 2010</td>
</tr>
<tr>
<td>MD1000000U</td>
<td>MD_013</td>
<td>December 5, 2010</td>
</tr>
<tr>
<td>MD1000000A</td>
<td>MD_010</td>
<td>December 1, 2010</td>
</tr>
<tr>
<td>MD1100000D</td>
<td>MD_010</td>
<td>January 3, 2011</td>
</tr>
<tr>
<td>MD1100000J</td>
<td>MD_010</td>
<td>May 23, 2011</td>
</tr>
<tr>
<td>MD1100000X</td>
<td>MD_010</td>
<td>June 14, 2011</td>
</tr>
</tbody>
</table>
False-positive Cultures

Patients with false positive cultures typically:

- Have only one positive culture
- Do not have a clinical presentation consistent with TB
- Are usually processed within a few days of the source culture where the contamination originated
- Evidence suggests that false-positive cultures are about 1-3% of all positive cultures
False Positive Cultures

Causes

- Laboratory cross-contamination
- Clinical device contamination: bronchoscope
- Clerical errors: mislabeling of patient specimens
False Positive Cultures

**Causes**

- Laboratory cross-contamination
- Clinical device contamination: bronchoscope
- Clerical errors: mislabeling of patient specimens

**Consequences**

- Incorrect TB diagnosis!
- Unnecessary anti-TB treatment
- Delays in correct diagnosis and treatment
- Overestimation of the TB case rate
Tracking Recent TB Transmission over Time

- Number of **new** patients in large cluster that represents recent transmission
- Total number of **new** clustered patients
- Total number of **new** clusters
- “New” genotype in your program area
Number of New Patients in a Large Outbreak over Time

No. of TB cases

0
10

2003  2004  2005  2006  2007  2008  2009  2010

Year

Transgender cluster

No new cases since 2008 = ? End of outbreak

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Number of New Clustered Patients Over Time

- **Decline in number of new clustered patients = decreased transmission**
Additional Information

- For more information, please contact tbgenotyping@cdc.gov
- Wendy Cronin PhD  croninw@dhmh.state.md.us

- CDC Resources