



**Southeastern National  
Tuberculosis Center**  
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**GRAND ROUNDS**

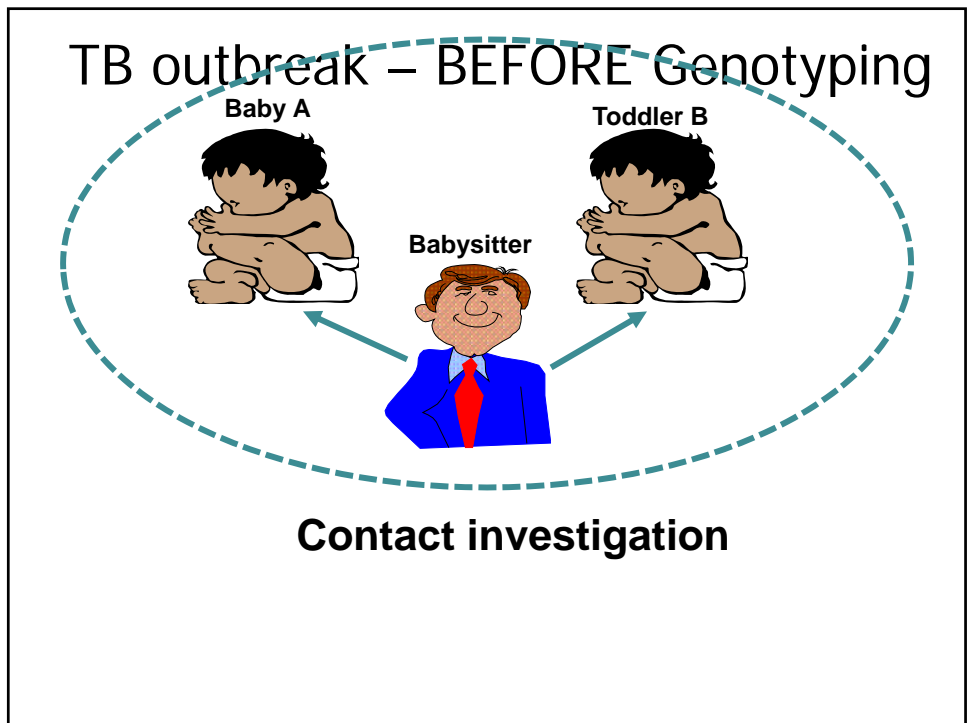
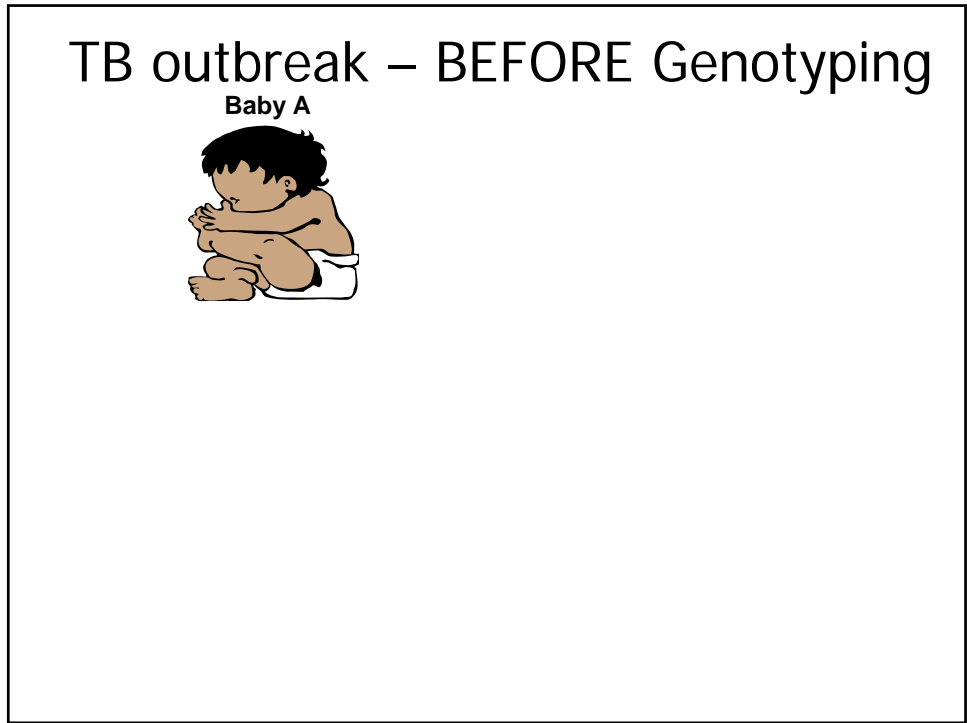
**Applying  
*Mycobacterium tuberculosis*  
Genotyping Results in  
Local Program Activities**

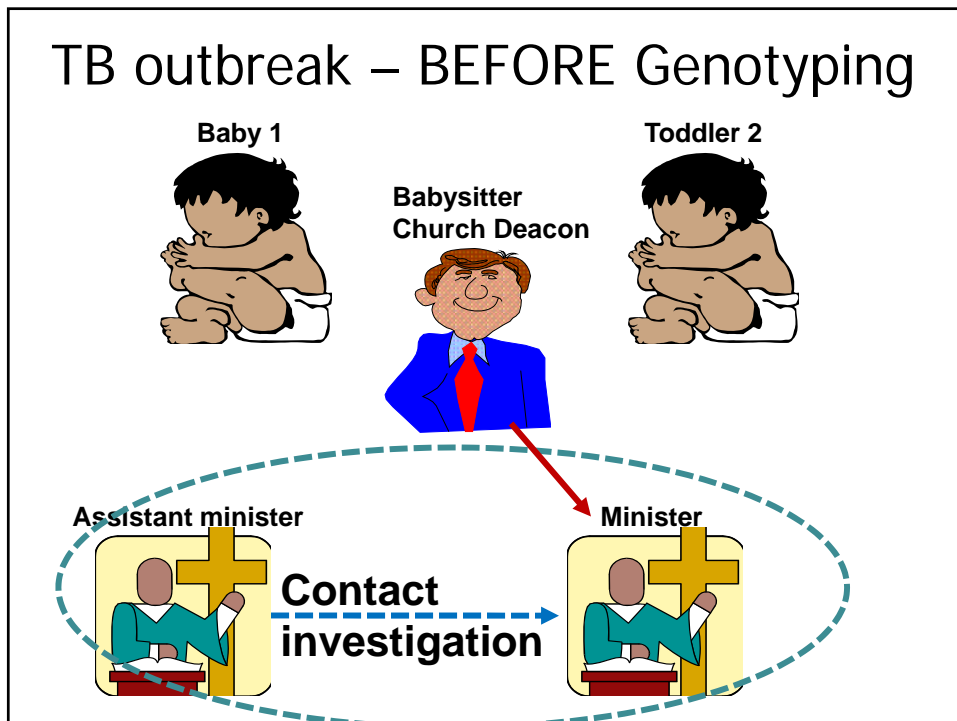
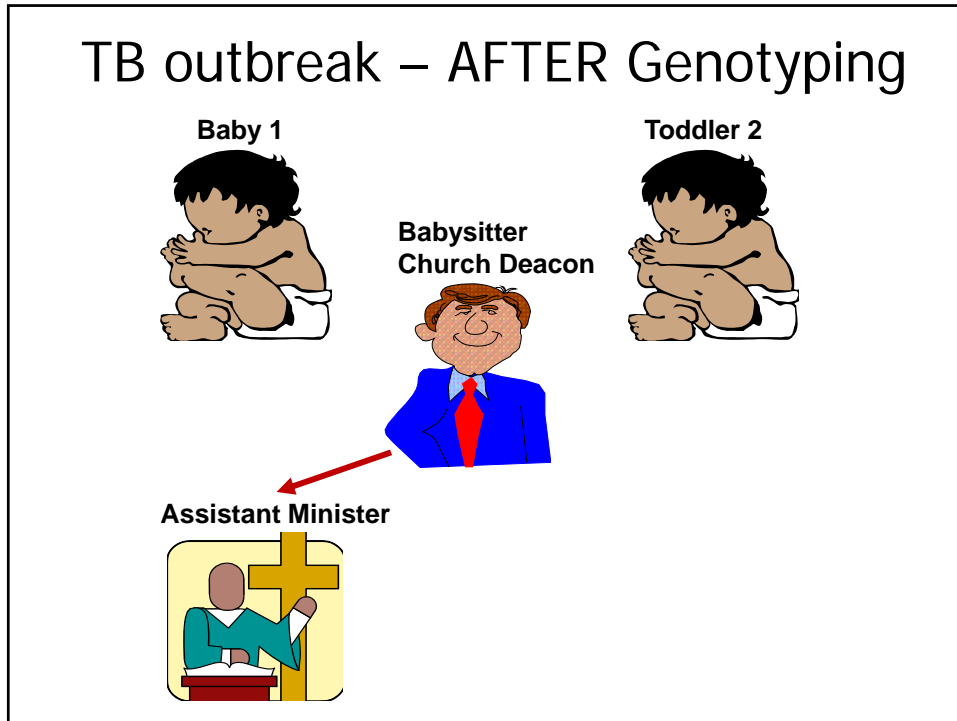


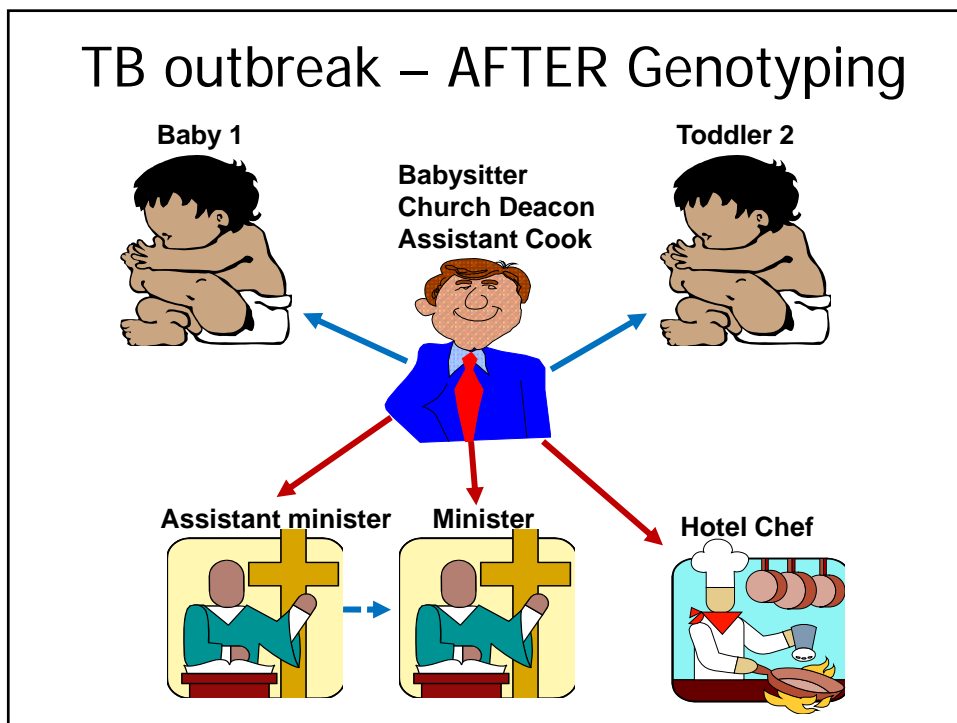
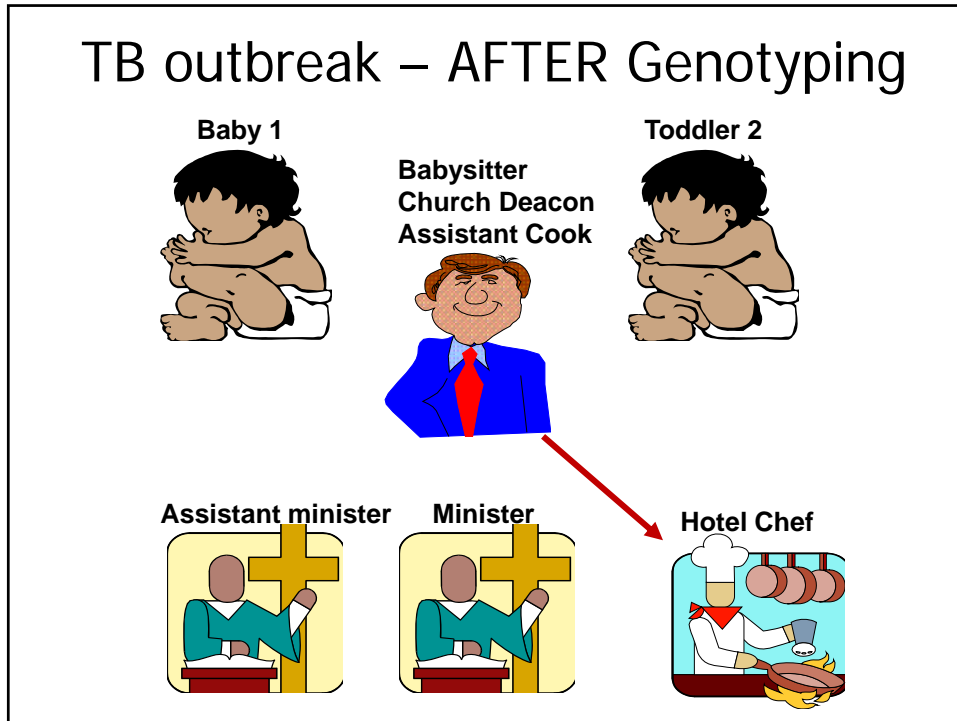
**Wendy Cronin**  
Epidemiologist  
Center for TB Control and Prevention  
Maryland Department of Health and  
Mental Hygiene



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## **What are the Applications of Genotyping in TB Prevention and Control?**

Wendy Cronin, PhD, MT(ASCP)  
Maryland Department of Health  
Center for TB Control and Prevention  
August 24, 2011

## **Presentation Objectives**

- Interpret the meaning of a genotype cluster
- Describe 6 ways that TB genotyping can be applied to local programs
- Describe steps to conduct a cluster investigation
- Describe how genotyping can be used to evaluate and improve local TB control activities

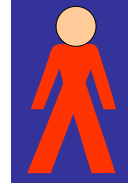
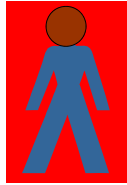
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## **Why is genotyping important?**

- Identify and interrupt recent transmission to prevent outbreaks
- Identify unsuspected relationships
- Enhance contact investigations
  - Identify previously unidentified source cases
  - Identify previously unidentified locations
- Distinguish relapse from new infection
- Recognize false positives
- Monitor trends and evaluate TB Control Program performance

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## What Is a Genotype Cluster?



**When an isolate genotype matches at least one other person's isolate genotype**

Spoligotyping  
00000000003771

MIRU-VNTR  
222325173543  
424244223348

**Match**



Spoligotyping  
00000000003771

MIRU-VNTR  
222325173543  
424244223348

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## What is a Genotype Cluster?

- 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

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## Does a Genotype Cluster mean recent transmission has occurred?

- If TB cases are clustered genotypically, is there true evidence of ongoing transmission?
- This is only half of the picture...

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## Are genotyping reports enough?

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

“shoe leather epidemiology”

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## Definition of Epidemiologic link (Epi-link)

- An identified relationship between TB patients



**Spoligotype**  
**MIRU**  
**MIRU2**



**00000000003771**  
**223325173533**  
**378451664321**

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## Definition of Epidemiologic link (Epi-link)

- An identified relationship between TB patients



**Spoligotype**  
**MIRU**  
**MIRU2**



**00000000003771**  
**223325173533**  
**378451664321**



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## 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

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## A tale of 2 investigations...

	Contact Investigation	Cluster Investigation
Who?	One TB case/suspect	2+ TB cases in a genotype cluster
What?	Named contacts	Epidemiologic links between cases
When?	Infectious case/suspect	Genotype cluster report
Where?	Household, Workplace Congregate settings	Also unusual settings like bars, religious gatherings, card games
How?	Interview case/suspect Record review Site visits	Review genotype data Case manager interview Contact and case record review Re-interview clustered cases Site visit(s)
Why?	Identify LTBI/new TB Prevent new active TB	Expand contact investigation? Identify LTBI/new TB Prevent new active TB

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## Use Genotyping to Enhance Contact Investigations

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Epi Links  
Detected by  
Routine CI

Epi Links  
Detected after CI by  
Genotyping and CLI

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Cronin et al *Emerg Infect Dis* 2002

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## Use Genotyping to Enhance Contact Investigations

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Epi Links  
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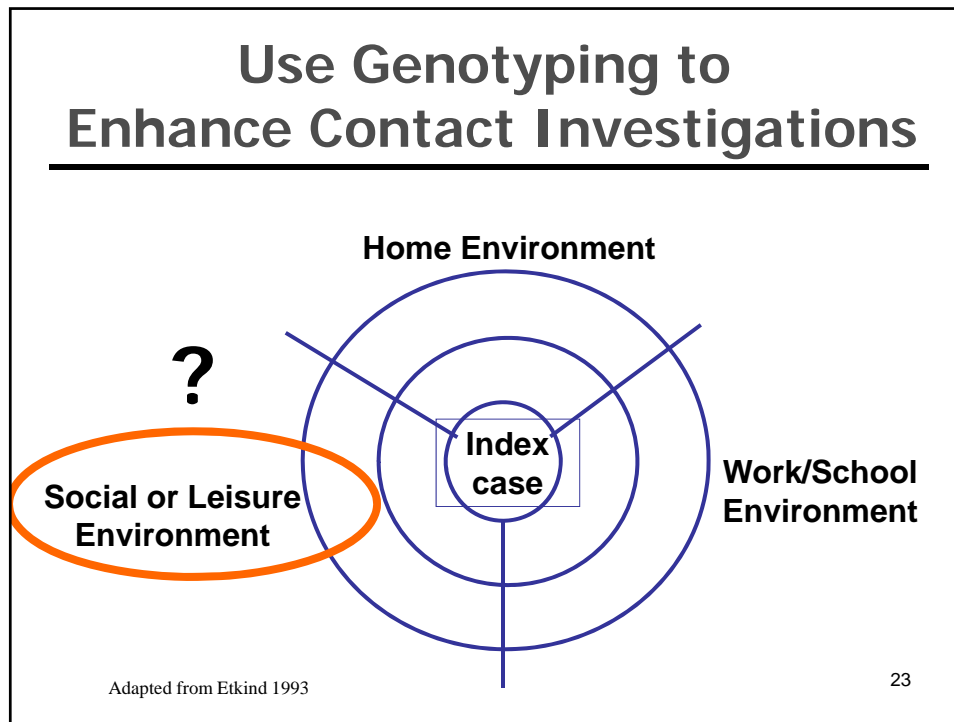
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**63%**

**37%\***

Cronin et al *Emerg Infect Dis* 2002

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- ## Identifying Epi-links
- **Health department:**
    - Case manager
    - Medical records
    - Contact investigation logs
  
  - **Patient interviews** where necessary
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## Identifying Epi-links

- **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? When did the person first arrive in the United States?

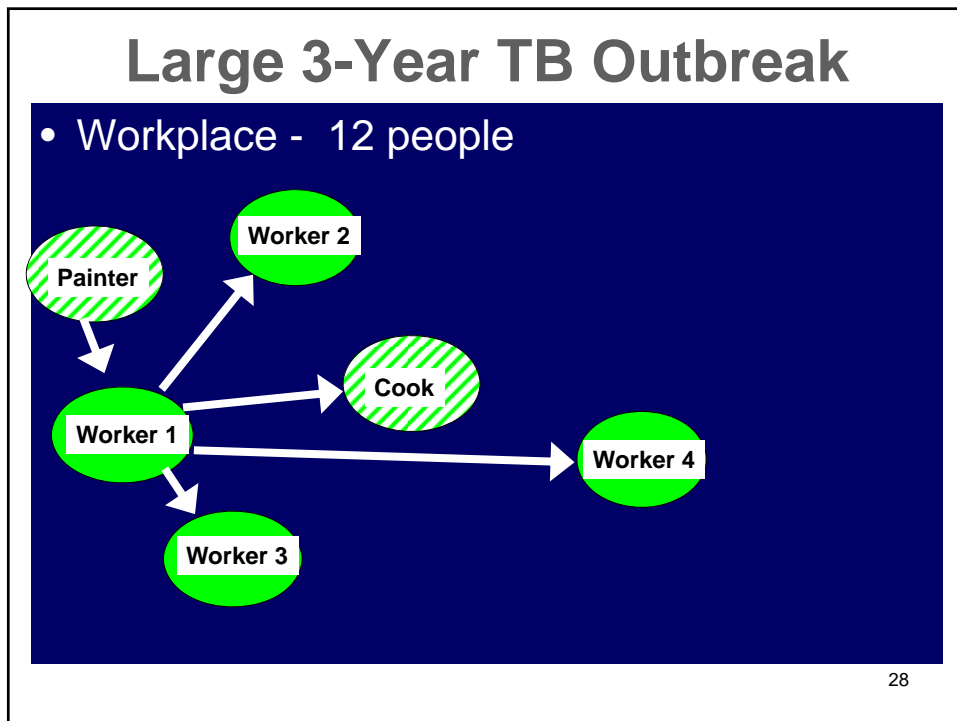
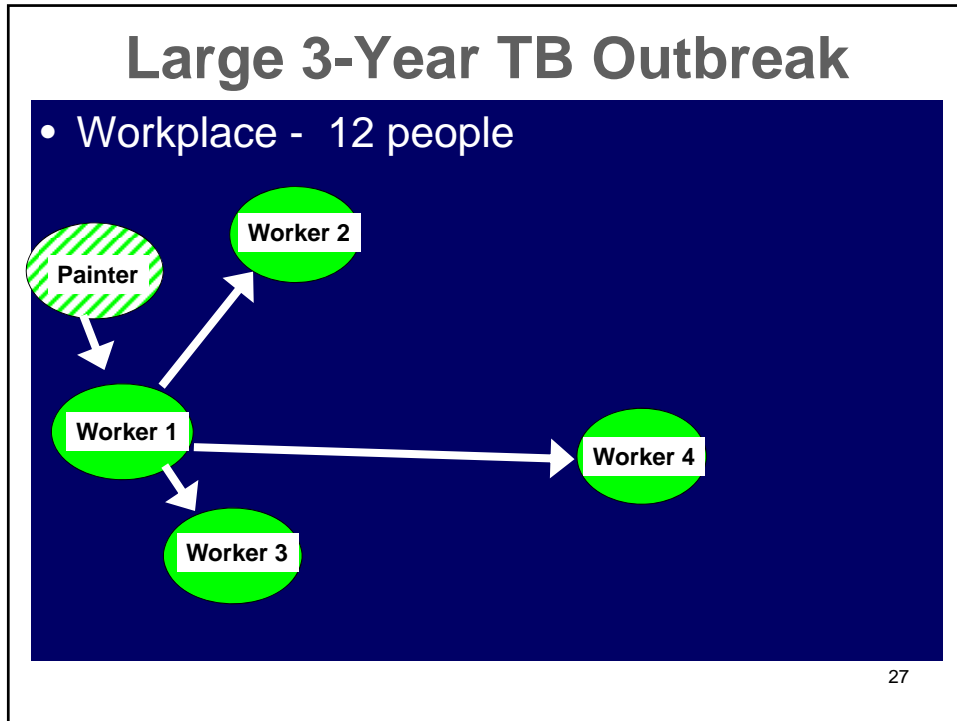
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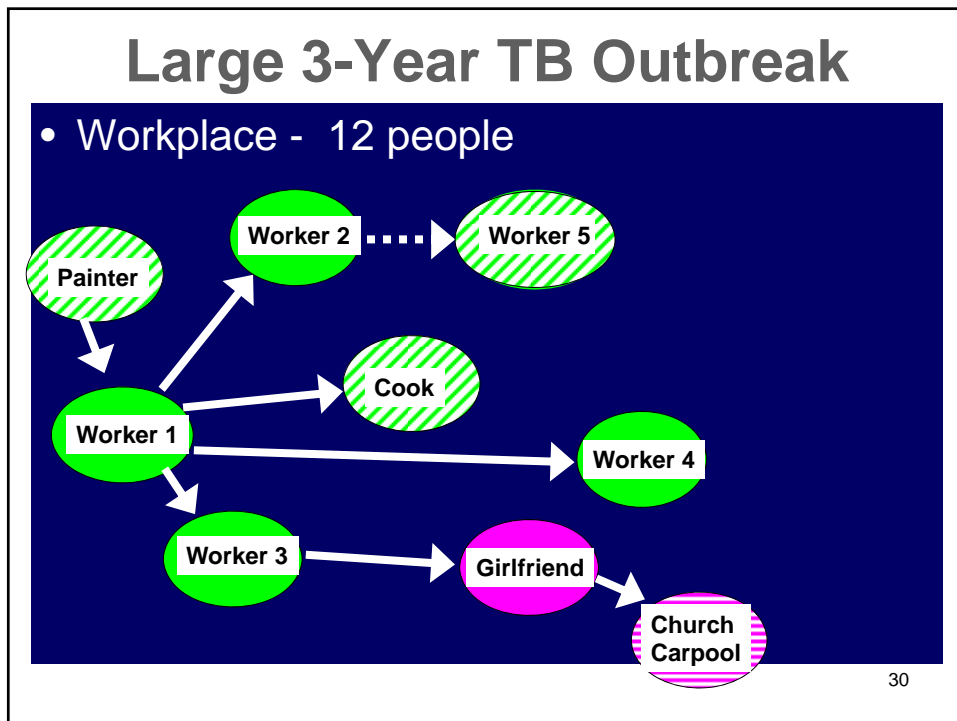
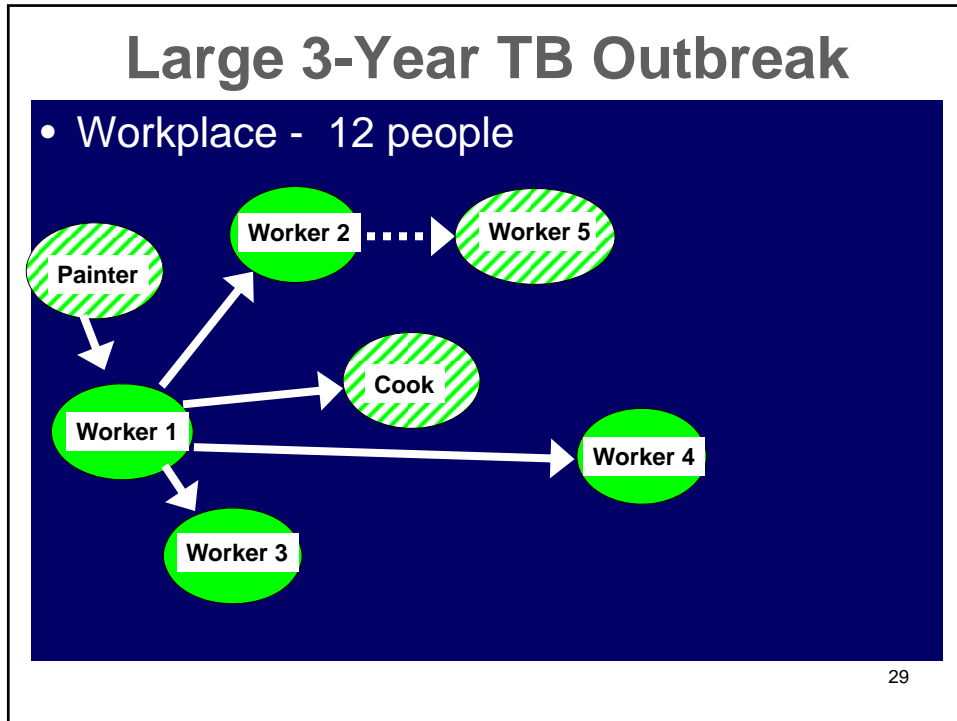
## Large 3-Year TB Outbreak

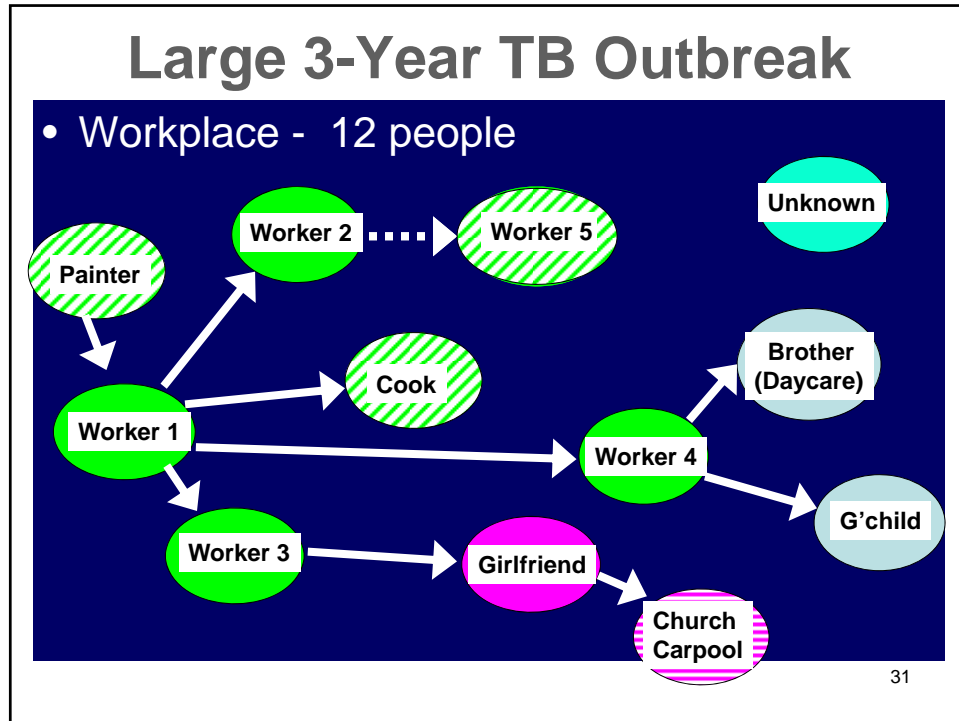
- Workplace - 12 people



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## 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

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## 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

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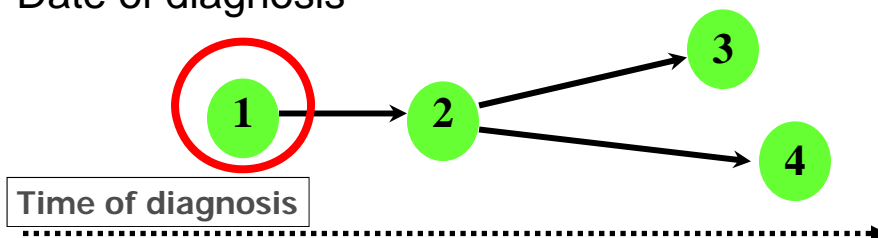
## No Identified Epidemiologic Link

- 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

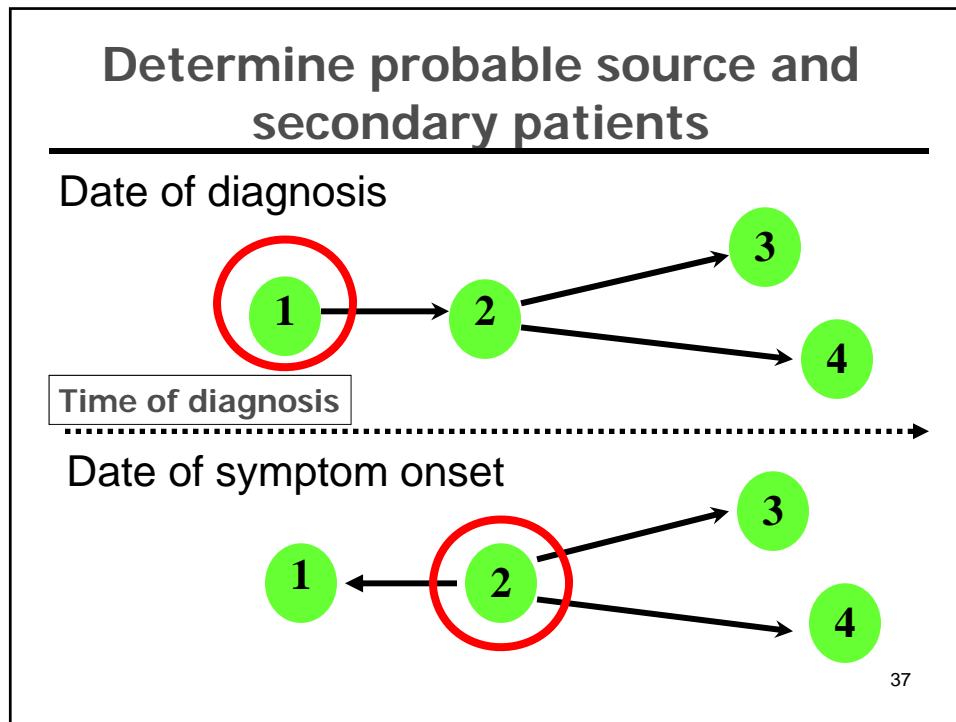
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## Determine probable source and secondary patients

Date of diagnosis



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### Definition of Infectious Period

- Time when a person is capable of transmitting TB to others who share same air space
- Usually estimated by *patient-reported* date of onset of the patient's symptoms (especially coughing)

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### Estimating the Infectious Period

Sputum culture <i>Mtb</i> +	Sputum smear+	Symptoms	Cavitary	Beginning of Infectious Period
YES	YES or NO	YES or NO	YES or NO	<b>3 months before symptom onset or first positive finding consistent with TB</b> - Chest xray - Sputum smear - Sputum culture  <b>(whichever is longer)</b>

Adapted from: CDC. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the NTCA and CDC. MMWR 2005;54(RR-15):p. 7 39

## Summary: Recent transmission, a search for commonalities


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

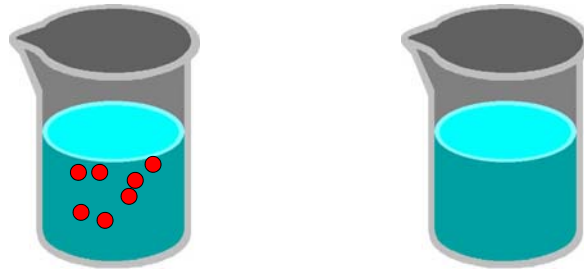
Location ... Location ... Location

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<div style="text-align: center;"> <h2>Relapse or exogenous re-infection?</h2>  </div>						
Genotyping Lab_Accession No.	Submitter_No.	Spoligotype	MIRU	Cluster_name	PCRType	Genotype Report Date
Homeless outbreak strain	Multiple	1777776777760601	223325153322	FL_002	PCR01047	1/3/07 – 8/5/09
08RF2914 Rodney Holmes	JTS08560	677777477413771	254326223432	FL_104	PCR00041	2/4/08

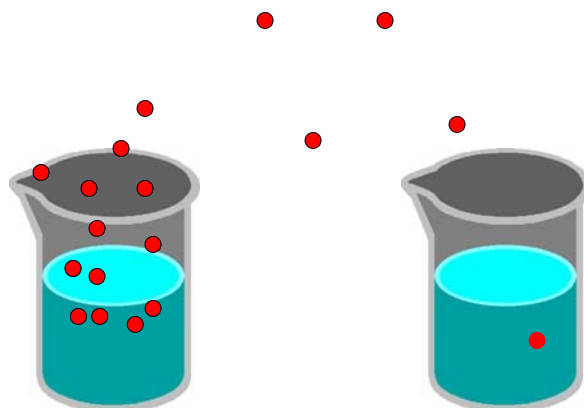
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08RF2914 Rodney Holmes	JTS08560	677777477413771	254326223432	FL_104	PCR00041	2/4/08
04RF3922 Rodney Holmes	JTS04601	677777477413771	254326223432	FL_104	PCR00041	10/14/04

## False Positive Cultures



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## False Positive Cultures



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## Search for False Positive Cultures

- Cluster: specimens collected  $\pm 7$  days of each other

Accession Number	Cluster	Specimen Collection Date
MD20100000R	MD_013	December 3, 2010
MD20100000U	MD_013	December 5, 2010
MD20090000A	MD_010	December 1, 2009
MD20100000D	MD_010	January 3, 2010
MD20100000J	MD_010	May 23, 2010
MD20100000X	MD_010	June 14, 2010

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## False Positive Cultures

### Causes

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

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## 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

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## Program evaluation: Tracking Recent TB Transmission over Time

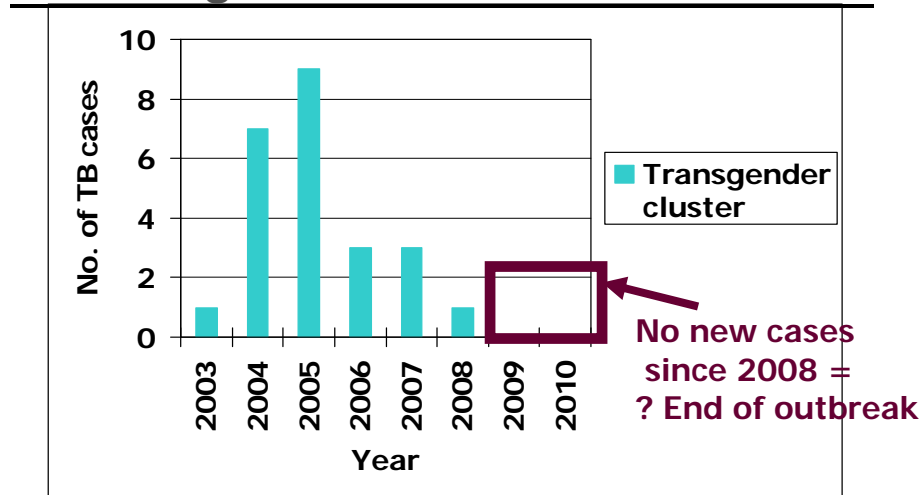
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- Number of **new** patients in large cluster that represents recent transmission
- Total number of **new** clustered patients
- Total number of **new** clusters
- “New” genotype in your program area

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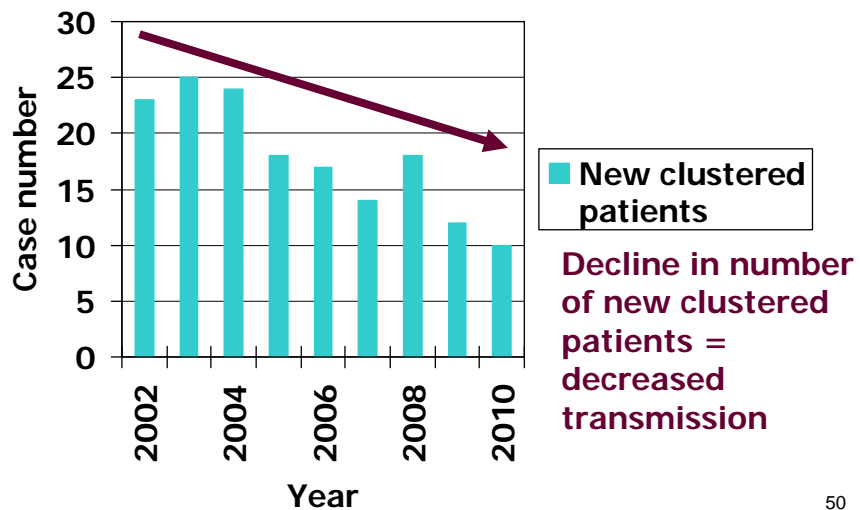


### Example: Number of New Patients in a Large Outbreak over Time



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### Example: Number of New Clustered Patients Over Time



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