LEARNING OBJECTIVES
At the completion of this case study, participants should be able to:
- Understand the goals of a tuberculosis (TB) interview in a TB contact investigation
- Be familiar with the criteria used to decide when a TB investigation should be initiated
- Define an outbreak
- Identify the steps you would take in investigating an outbreak
- Create a line list
- Distinguish between a case-control and a cohort study
- Calculate a relative risk and use confidence intervals to identify a statistically significant association between an exposure and an outcome
- Explain the difference between an epidemiologic and molecular link in a TB contact investigation
- Explain how molecular information could be used in an outbreak investigation

ASPH EPIDEMIOLOGY COMPETENCIES ADDRESSED
C.2. Identify the principles and limitations of public health screening programs
C.3. Describe a public health problem in terms of magnitude, person, place, and time
C.6. Apply the basic terminology and definitions of epidemiology
C.7. Calculate basic epidemiologic measures
C.9. Draw appropriate inference from epidemiologic data

ASPH INTERDISCIPLINARY/CROSS-CUTTING COMPETENCIES ADDRESSED
I. Public Health Biology
I.4. Explain the biological and molecular basis of public health
I.8. Apply biological principles to development and implementation of disease prevention, control, or management programs

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This exercise is drawn from an article published in *Chest*, “Mycobacterium tuberculosis Miniepidemic in a Church Gospel Choir” by Mangura and colleagues. Specific aspects of the investigation have been altered, with permission from the authors, to assist in meeting the desired teaching objectives.

Students should be aware that this study describes one particular approach to a TB outbreak investigation. Despite nationally published guidelines and recommendations from the Centers for Disease Control and Prevention for conducting contact investigations, the actual practice implemented during these investigations can vary from program to program.

An epidemiologist investigating a TB outbreak works within the framework of an investigative team that includes persons with expertise in epidemiology, microbiology, TB surveillance, and environmental health. It is through the collaborative efforts of this team, with each member playing a critical role that outbreak investigations can result in a positive outcome.

Suggest Reading can be found on the CDC EXCITE website- Epidemiology in the Classroom- How to Investigate an Outbreak: http://www.cdc.gov/excite/classroom/outbreak/index.htm
PART I. Identifying a Problem

This morning (June 21) the local health department (large town health department) received a telephone call from the infection control practitioner (ICP) from a nearby hospital reporting that 2 patients were seen in the emergency department (ED) late yesterday with complaints of fatigue, fever, night sweats, and cough. As part of their work-up, the ED physician ordered chest x-rays for both patients. The health department was informed that, in both cases, the radiology report indicated abnormal findings consistent with TB. As a result, both patients were admitted to the hospital with a diagnosis of suspected pulmonary TB. Once admitted, sputum samples collected from both patients were read as positive on microscopic smear with final culture identification pending.

You know that tuberculosis (TB) is an infectious disease caused by bacteria called *Mycobacterium tuberculosis*. The bacteria usually affect the lungs (pulmonary TB) but also can affect any part of the body outside the lungs (extrapulmonary TB) with the most common sites being the lymph nodes, bone, kidney, and pleura. While TB disease was once the leading cause of death in the United States, it can now be treated successfully with appropriate antibiotics. However, if not diagnosed early or not treated appropriately, TB disease can be fatal.

You also know that according to the CDC the “presence of acid-fast-bacilli (AFB) on a sputum smear or other specimen often indicates TB disease. Acid-fast microscopy is easy and quick, but it does not confirm a diagnosis of TB because some acid-fast-bacilli are not *M. tuberculosis*. Therefore, a culture is done on all initial samples to confirm the diagnosis. (However, a positive culture is not always necessary to begin or continue treatment for TB.) A positive culture for *M. tuberculosis* confirms the diagnosis of TB disease. Culture examinations should be completed on all specimens, regardless of AFB smear results. Laboratories should report positive results on smears and cultures within 24 hours by telephone or fax to the primary health care provider and to the state or local TB control program, as required by law.” ² While some microbiology laboratories have access to advanced technology and have the ability to identify TB in a specimen in just a few days, your laboratory requires 4 to 8 weeks for growth and final identification. Therefore, you will need to wait for the results on these 2 suspected cases.

Your health department (large town health department) receives calls of suspected TB cases several times a week. At total of 40% of these reports turn out to be negative for TB.

**Question 1:**
What questions should you ask and what information should you collect from the ICP while he/she is on the telephone with you? At this early juncture, should you consider initiating an investigation about these 2 cases?
The CDC classifies TB as a notifiable disease. “A notifiable disease is one for which regular, frequent, and timely information regarding individual cases is considered necessary for the prevention and control of the disease.”3

**Question 2:**
At this point, would you consider this an outbreak?

Please note: the CDC uses the words *outbreak* and *epidemic* interchangeably, although outbreaks are often considered more local occurrences. In TB control in the United States the term most commonly used is *outbreak*.

You decide that the next step you should take is to visit the patients in the hospital, collect information from their medical records, and interview them.

**Question 3:** What should you have as goals in your interviews with these suspected TB cases?
According to the CDC... “The period of infectiousness is the time period during which a person with TB disease is capable of transmitting M. tuberculosis. Determining the period of infectiousness can help focus the contact investigation efforts on those persons who were exposed while the patient was infectious.”

The following guidelines may be used to estimate the beginning of the infectious period.

**TABLE 2. Guidelines for estimating the beginning of the period of infectiousness of persons with tuberculosis (TB), by index case characteristic**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recommended minimum beginning of likely period of infectiousness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 months before symptom onset or first positive finding (e.g., abnormal chest radiograph) consistent with TB disease, whichever is longer</td>
</tr>
<tr>
<td>No</td>
<td>4 weeks before date of suspected diagnosis</td>
</tr>
<tr>
<td><em><em>AFB</em> sputum smear positive</em>*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 months before symptom onset or first positive finding consistent with TB disease, whichever is longer</td>
</tr>
<tr>
<td>No</td>
<td>4 weeks before date of suspected diagnosis</td>
</tr>
<tr>
<td><strong>Cavitary chest radiograph</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 months before symptom onset or first positive finding consistent with TB disease, whichever is longer</td>
</tr>
<tr>
<td>No</td>
<td>4 weeks before date of suspected diagnosis</td>
</tr>
</tbody>
</table>

The CDC guidelines also state that the period of infectiousness ends when **all** the following criteria are met:

- Symptoms have improved
- The patient has been receiving adequate treatment for at least 2 to 3 weeks
- The patient has had 3 consecutive negative sputum smears from sputum collected on different days

From your interview you are able to learn the following:

- **Jack Gold**, a 62-year-old male who lives at 87 Jefferson Street in Large Town, NJ, has not been feeling well for 2 weeks and for the past 7 days he has been feeling weak, has also had some unexpected weight loss, fever, and cough. Mr. Gold has a history of bladder cancer. He works at Large Company X in Large Town, NJ. His home phone number is 973-555-2233, and he could not remember his work number. Mr. Gold also does not know anyone with similar symptoms, including anyone hospitalized with similar symptoms. Mr. Gold lives with his wife and his 85-year-old father. Mr. Gold was born in the United States and he has never traveled outside North America.

- **Marla Smith**, a 47-year-old female who lives at 33 Madison Avenue in Large Town, NJ, and has been sick for 3 weeks. She has been feeling weak, has had some unexpected weight loss, fever, night sweats, and cough. She works at Large Company Y in Large Town, NJ. Her cell phone number is 973-555-1290 and work number is 973-555-1212. Ms. Smith has a history of hypertension, diabetes, and obesity and also indicates that she does not know anyone with similar symptoms, including anyone hospitalized with similar symptoms. Ms. Smith lives with her husband and 2 children 13 and 17 years of age. Ms. Smith was born in...
the United States. Ms. Smith has not traveled outside the United States since her children were born. Previously, she had traveled to South American and Europe.

You decide to test the families of these 2 individuals for TB infection. The families of these suspected cases were given tuberculin skin tests (TST), and results of all were negative (0 mm). After 4 weeks, you receive the culture results from Mr. Gold and Ms. Smith. As was suspected, you learn from the hospital microbiology department that *tuberculosis* was identified on final culture from both patients. You also learn that genotyping, or DNA fingerprinting results will be available within the next 2 weeks. You know that DNA results represent a valuable piece of information that could potentially link, or not link, these cases to other known cases.

Meanwhile a colleague of yours in the TB Control Program happens to tell you about a case that he has been following: a 38-year-old homeless non-US born male who emigrated from Somalia (a high-incidence country) to the United States 1 year ago, named Ali Yusef. Since his arrival, Mr. Yusef has worked as a church custodian. The patient complained of having a productive cough for 1 month prior to his being hospitalized on May 3 and reported a history of pneumonia and malnutrition. A cavitary chest x-ray coupled with a positive sputum smear raised suspicions of TB and, as a result, appropriate TB treatment was prescribed. The diagnosis of TB was confirmed when *tuberculosis* was identified on final culture. Upon discharge from the hospital with 3 negative sputum smears, Mr. Yusef was placed in a homeless shelter and provided directly observed therapy (DOT) by health department staff. Outpatient care is currently being provided by the local health department clinic.

When the DNA results become available, you are informed that not only do the 2 culture isolates (from Mr. Gold and Ms. Smith) possess the same banding pattern (see Figure 1 below), but they also match a third person (Mr. Yusef) who was previously identified in Large Town in early June as a confirmed TB case. In addition, according to a search through a national DNA database, the strain profile of all 3 cases indicates that they are most commonly found in Africa.

The IS6110 RFLP analysis is one technique used to explore the molecular epidemiology of *M tuberculosis* complex. IS6110 RFLP analysis is done by inserting an IS6110 probe into the DNA, which then attaches to a specific enzyme, called a restrictive enzyme, whose location is unique to each strain of TB. The size of each fragment depends on its distance from this site to the next restrictive enzyme and the location of each of these restrictive enzymes can be measured to see if the samples taken from each patient have the same or similar strains.
Figure 1. IS6110 RFLP analysis of cases 1, 2, and 3

Since Mr. Yusef emigrated from Somalia (remember neither Mr. Gold nor Ms. Smith have traveled outside the country recently), the DNA strain that they all share is most commonly found in Africa and Mr. Yusef was diagnosed with TB much earlier than the other 2 cases, we can assume that Mr. Yusef is the index case (the first case of the disease in an outbreak). We will refer to Mr. Yusef as Case 1 for the remainder of this investigation.

This new information provides molecular evidence that Case 1 appears to be the source or index to Cases 2 and 3. With this new information, it has been decided that follow-up interviews with all 3 cases should be initiated to not only review previously collected information but to focus in-depth on establishing a common link (person, place, and time) between the cases that may not only provide an exposure site but could potentially lead to the identity of additional contacts and cases. Follow-up interviews reveal that the common link shared among all 3 cases was that they are all congregants of the same church and that all 3 cases are members of the church choir.

*"the first case or instance of a patient coming to the attention of health authorities"
You now decide to combine and organize into a line list information collected on all three cases starting with the first confirmed case, Mr. Yusef. You organize the information that you have collected into a line list.

**Question 4:** Complete the line list below for the confirmed cases.

<table>
<thead>
<tr>
<th>ID</th>
<th>TB Status</th>
<th>Name</th>
<th>Age/Sex</th>
<th>Smear/Culture</th>
<th>Address</th>
<th>Place of Employment</th>
<th>Symptoms/Chest X-Ray</th>
<th>Date Onset</th>
<th>Med Hx</th>
<th>Social Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confirmed</td>
<td>Ali Yusef</td>
<td>38/M</td>
<td>+/+</td>
<td>None</td>
<td>Homeless/ from Somalia</td>
<td>Church</td>
<td></td>
<td></td>
<td>Church choir</td>
</tr>
<tr>
<td>2</td>
<td>Confirmed</td>
<td>Jack Gold</td>
<td>62/M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Church choir</td>
</tr>
<tr>
<td>3</td>
<td>Confirmed</td>
<td>Marla Smith</td>
<td>47/F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Church choir</td>
</tr>
</tbody>
</table>

**Question 5:**
Is this now an outbreak? Provide your reasons.

**Question 6:**
What are the steps you should take in investigating this outbreak?
Your supervisor suggests that you use a concentric circle analysis in your investigation\(^4\). The concentric circle approach (Figure 2) is a method of testing contacts by their exposure time and risk, with those at highest risk of infection or disease tested first. In this approach, the original TB patient (the index case) is at the center. The circle is divided into 3 concentric rings to represent the 3 levels of risk: high, medium, and low. The circle is also divided, like a pie, into segments that represent the 3 types of environment where the exposure may have taken place: household or residential, work or school, leisure or recreation environments.

**Figure 2 Concentric circle approach\(^4\)**

![Concentric circle approach](image)

**Question 7:**
The purpose of this investigation is to identify any additional cases of TB and individuals who may have been infected by these cases. What is your “case definition” for transmission in this investigation? Remember a complete case definition should include information on person, place, time, and clinical characteristics.
The Tuberculin Skin Test (TST) may be used to determine if a person has TB infection. A TST is available at the health department or at a doctor’s office. A health care worker injects a small amount of testing fluid (called tuberculin or PPD) just under the skin on the underside of the forearm. After 48 to 72 hours, the patient must return to have the skin test read by the health care worker. He/she may have a swelling-called induration-where the tuberculin was injected. The health care worker will measure this induration and explain to the patient whether the results are positive or negative. A positive reaction usually means that the patient has been infected with the TB bacteria. If a person has recently spent time with and been exposed to someone with active TB disease, his/her TST reaction may not yet be positive. He/she may need a second skin test 8 to 10 weeks after the last date of exposure to the TB patient because it can take several weeks after infection for the immune system to react to the TST. If a person’s reaction to the second test is negative, he/she is considered not infected.¹⁰

**Question 8:**
At this point, who needs to be tested for transmission of TB, through a TST?
PART II. Outbreak Investigation

A choir list was matched to the state TB registry and 2 additional confirmed cases of TB within the choir were identified and their information was added to the line listing below:

Table 3. Updated Line List of *M. tuberculosis* Clinical Cases in Large Town Church Choir

<table>
<thead>
<tr>
<th>ID</th>
<th>TB Status</th>
<th>Name</th>
<th>Age/Sex</th>
<th>Smear/Culture</th>
<th>Phone #s</th>
<th>Address</th>
<th>Place of Employment</th>
<th>Symptom/Chest X-ray</th>
<th>Date Onset</th>
<th>Med Hx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confirmed</td>
<td>Ali Yusef</td>
<td>38/M</td>
<td>+/+</td>
<td>None</td>
<td>Homeless/ from Somalia</td>
<td>Church</td>
<td>Cough/+</td>
<td>April ?</td>
<td>Pneumonia, malnutrition</td>
</tr>
<tr>
<td>2</td>
<td>Confirmed</td>
<td>Jack Gold</td>
<td>62/M</td>
<td>+/+</td>
<td>973-555-2233</td>
<td>87 Jefferson St., Large Town, NJ</td>
<td>Large Company X Large Town, NJ</td>
<td>Some unexpected weight loss, fever, cough/+</td>
<td>June 7</td>
<td>Bladder Cancer</td>
</tr>
<tr>
<td>3</td>
<td>Confirmed</td>
<td>Marla Smith</td>
<td>47/F</td>
<td>+/+</td>
<td>973-555-1290 973-555-1212</td>
<td>33 Madison Ave., Large Town, NJ</td>
<td>Large Company Y Large Town, NJ</td>
<td>Unexpected weight loss, fever, night sweats, cough/+</td>
<td>June 1</td>
<td>Hypertension, diabetes, obesity</td>
</tr>
<tr>
<td>4</td>
<td>Confirmed</td>
<td>James Jones</td>
<td>48/M</td>
<td>+/+</td>
<td>973-555-1290 973-555-1212</td>
<td>33 Madison Ave., Large Town, NJ</td>
<td>Large Company Y Large Town, NJ</td>
<td>Unexpected weight loss, cough</td>
<td>June 20</td>
<td>Hypertension</td>
</tr>
<tr>
<td>5</td>
<td>Confirmed</td>
<td>Mark Carlen</td>
<td>52/M</td>
<td>+/+</td>
<td>None</td>
<td>33 Madison Ave., Large Town, NJ</td>
<td>Large Company Y Large Town, NJ</td>
<td>Some unexpected weight loss, fever, cough/+</td>
<td>June 25</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Table 3—continued

<table>
<thead>
<tr>
<th>ID</th>
<th>TB Status</th>
<th>Name</th>
<th>Choir</th>
<th>Vocal Range</th>
<th>DNA testing</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confirmed</td>
<td>Ali Yusef</td>
<td>8 am and 11 am</td>
<td>Tenor</td>
<td>African-continent strain</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Confirmed</td>
<td>Jack Gold</td>
<td>11 am</td>
<td>Tenor</td>
<td>African-continent strain</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Confirmed</td>
<td>Marla Smith</td>
<td>11 am</td>
<td>Alto</td>
<td>African-continent strain</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Confirmed</td>
<td>James Jones</td>
<td>8 am</td>
<td>Tenor</td>
<td>Not done</td>
<td>Commuted to choir practice with Case 1</td>
</tr>
<tr>
<td>5</td>
<td>Confirmed</td>
<td>Mark Carlen</td>
<td>11 am</td>
<td>Tenor</td>
<td>Not done</td>
<td></td>
</tr>
</tbody>
</table>

**Question 9:**
Are Cases 4 and 5 epidemiologically linked to the other cases? (Look at Table 3 above)
The suspected index case (Case 1) is a tenor in the 8 and 11 AM church choirs. In the winter months, he was occasionally driven to church with Case 4, a tenor in the church choir. There were 5 different choir groups totaling approximately 300 to 500 members (per an outdated choir list). Aggregate and separate choir practices were held once a week in the church or in its basement with 3 separate choir groups singing together or in staggered time periods.

Choir groups were labeled as to the time the choir sang in church each Sunday (8 AM choir and 11 AM choir). Choir members’ ages ranged from 5 to 70 years. The adult choirs rehearsed together once a week; on average, rehearsal time was 1 hour. Many choir members lived in other urban or suburban communities away from the church location. Commuting together usually was sporadic and *ad hoc*. The church and choir members were largely working, middle class African-Americans.

**Part III. Analysis**

**Question 10:**
Can you develop a hypothesis regarding this outbreak?

Only 300 of the assumed total of 500 choir members were accessible and available for tuberculin testing. Nonchoir church members were not tested. The entire church building including the stage and basement where all the choirs rehearsed was inspected for contributory factors (such as ventilation outlets) to environmental transmission.

**Question 11:**
What was the response/cooperation rate of the choir members, assuming there were 500 choir members? Why is this important?

It could not be ascertained for certain where transmission occurred, but the main church’s choir loft, where most rehearsals occurred, was considered the most likely location for cases 1, 2, 3, and 5. Transmission to Case 4 could have occurred in the choir loft during joint practice or while commuting with Case 1. The basement, where some transmission could have occurred, had air conditioning units with 8 air outlets from a dropped ceiling. Air was re-circulated.

Of the 300 traced choir members tested, 120 belonged to the 11 AM choir; 25 members of the 120 11 AM choir members were TST reactors; 12 of the 25 reactors were tenors and 12 of 36 tenors were reactors.
Question 12:

Use the data from the 120 11 AM choir members who received TSTs to create a contingency table to look for an association between vocal range (as a proxy for location/exposure to the index case in the choir) and skin test result. Assume that the group has been assembled based on their exposure status and that level of exposure is stratified by vocal range (tenor vs nontenor) because the index case was a tenor. These 120 choir members received TSTs and when the data is available, populate this table.

<table>
<thead>
<tr>
<th>Vocal Range</th>
<th>+ (Reactor)</th>
<th>- (Nonreactor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontenor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>120</td>
</tr>
</tbody>
</table>

Question 13:

Conduct an appropriate statistical test to examine the relationship between the location in the choir and TST result.

Question 14:

What type of study design is this?

Question 15:

A. Assuming all positive TSTs were newly infected, what is the measure of relative risk associated with being a tenor?

B. Was the risk of developing a skin test reaction indicating TB infection statistically significantly higher among tenors compared with nontenors?
Part IV. Control and Prevention of an Epidemic

Question 16:
What preventive measures would you recommend for those who had a positive TST, but did not have any other sign of disease?

Question 17:
Based on the pathogenicity—the ability of an agent to cause disease after infection, measured as the proportion of persons infected by an agent who then experience clinical disease—\(^8\) of TB, do you recommend future TSTs and studies?

Part V. Conclusion
Ten weeks after the initial tuberculin testing, 86 of the 11 AM nonreactor choir members were retested. Two new reactors (both tenors) were found and given treatment for latent TB infection. No additional cases were found. It should also be noted that the sopranos who sat directly in front of the tenors, separated by the floor air outlet-intake vents, did not have TB, and few sopranos had positive TST results.
Works Cited


