EPI Case Study 3: Cross-Sectional, Case-Control, and Cohort Studies–Identification of TB Risk Groups and TB Risk Factors in Epidemiologic Studies

Learning Objectives
At the completion of this module, participants should be able to:

- Describe recent trends in tuberculosis (TB) incidence rates by race and ethnicity
- Distinguish between cross-sectional, case-control, and cohort study designs
- Describe the advantages and disadvantages of these epidemiologic study designs
- Understand and identify TB risk groups (demographic and occupational)
- Calculate and interpret odds ratios, relative risks, and attributable risks
- Understand the difference between an odds ratio and a relative risk
- Interpret data from a contact investigation

ASPH Epidemiology Competencies Addressed
C. 3. Describe a public health problem in terms of magnitude
C. 6. Apply the basic terminology and definitions of epidemiology
C. 7. Calculate basic epidemiologic measures
C. 9. Draw appropriate inference from epidemiologic data
C. 10. Evaluate the strengths and limitations of epidemiologic reports

ASPH Interdisciplinary/Cross-cutting Competencies Addressed
I.8. [Public Health Biology] Apply biological principles to development and implementation of disease prevention, control, or management programs
L.10. [Systems Thinking] Analyze the impact of global trends and interdependencies on public-health–related problems and systems

Please evaluate this material by clicking here:
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Statistical output provided in this exercise was generated using JMP 7.0, SAS Institute Inc. Some modifications of headings were made to clarify output for this exercise.

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Introduction

In 2007, the number of TB cases reported (13,299) and case rate (4.4 cases per 100,000) both decreased; this represented declines of 3.3% and 4.2%, respectively, compared to 2006. Since the 1992 TB resurgence peak in the United States, the number of TB cases reported annually has decreased by 50%. However, the trend of the declining annual case rate has slowed, from an annual average decline of 7.3% for 1993 through 2000 to an annual average decline of 3.8% for 2000 through 2007.

The proportion of total cases occurring in foreign-born persons has been increasing since 1993. In 2007, 58% of TB cases occurred in foreign-born persons. Foreign-born persons have accounted for the majority of TB cases in the United States every year since 2001. Moreover, the case rate among foreign-born persons in 2007 was nearly 10 times higher than among U.S.-born persons.\(^1\)

The table presented below summarizes data from the national TB surveillance system for 2003 and describes trends during a 5-year period.

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>U.S.-born</th>
<th>Foreign born</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
<td>2003</td>
<td>2003</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1,262</td>
<td>6.6</td>
<td>1,025</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4,968</td>
<td>16.0</td>
<td>3,941</td>
</tr>
<tr>
<td>Asian/Pacific Islander*</td>
<td>213</td>
<td>5.6</td>
<td>201</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific</td>
<td>154</td>
<td>4.4</td>
<td>3255</td>
</tr>
<tr>
<td>White</td>
<td>3,914</td>
<td>2.1</td>
<td>3,328</td>
</tr>
<tr>
<td>American Indian/Semien Indian</td>
<td>248</td>
<td>12.6</td>
<td>169</td>
</tr>
<tr>
<td>Alaska Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10,633</td>
<td>4.3</td>
<td>6,873</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) Per 100,000 population.
\(^1\) Data for 2003 are provisional.
\(^2\) For comparison with 1998, data for 2003 for Asian/Pacific Islanders include Asians plus Native Hawaiians or Other Pacific Islanders.
\(^3\) Includes persons for whom race/ethnicity was unknown; 16 for total, 10 for U.S.-born, and 6 for foreign-born persons in 1998; 291 for total, 99 for U.S.-born, and 60 for foreign-born persons in 2003. In 2000, persons were included who selected multiple races: 38 for total, 10 for U.S.-born, and 26 for foreign-born persons.


**Question 1**

Describe the trends in TB incidence rates over time for US-born and foreign-born populations.
Answer Key
From 1998 to 2003, TB incidence rates declined in both groups overall, but the percent change is less in foreign-born populations. Incidence rates among non-Hispanic blacks who were foreign-born increased during this same time period.

Study Design
There are 3 major types of epidemiologic studies that appear in medical and public health literature:

• Cross-sectional studies
• Case-control studies
• Cohort studies

Cross-Sectional Studies
In a cross-sectional study, data on possible risk factors and disease outcomes are collected at the same time. These studies are sometimes called prevalence studies since the information collected can be used to provide prevalence ratios (the proportion in a population with a particular outcome). The data collected present a picture of what is occurring at a specific time. Cross-sectional studies cannot provide information on causes of diseases because it is unclear in these studies whether the disease or the supposed risk factor occurred first.²

The following abstract provides an example of a cross-sectional or prevalence study.

**Study Design: Cross-Sectional Study**

*Objective:* To determine the prevalence of and risk factors for tuberculin skin test positivity and conversion among New York City Department of Health and Mental Hygiene employees.

*Design:* Point-prevalence survey. Sentinel surveillance was conducted from March 1, 1994 to December 31, 2001.

*Participants:* HCWs in high-risk and low-risk settings for occupational TB exposure.

*Results:* Baseline tuberculin positivity was 36.2% (600 of 1,658), 15.5% (143 of 922) among HCWs born in the United States, and 48.5% (182 of 375) among HCWs not born in the United States.²


**Question 2**
Based on this abstract, describe the relationship between place of birth and tuberculin skin test (TST) results among these health care workers (HCW). Can it be said that
there is a causal relationship between being born outside the United States and TST positivity?

**Answer Key**

The information presented in the abstract suggests that health care workers born outside the United States are more likely to have a positive TST result. However, this does not mean that a causal relationship between place of birth and TST positivity can be proven. In epidemiology, association does not imply causation. A causal relationship cannot be ascertained from the prevalence survey since it contains only information from one time point. Other study designs must be used that can help to explore the relationship between the risk factor (in this example, place of birth) and the outcome (in this example, TST result).²

The following study explores the relationship between a possible risk factor and TB infection. This hypothetical study was inspired by a study conducted by Lobato and Hopewell,³ but the study design and the data presented are hypothetical.

**METHODS**

**Study Population and Design**

In this hypothetical community, all 1000 healthy children entering kindergarten in a particular year were required to receive a TST prior to school entrance. Overall, 80 of these children had a positive TST result, meaning that they were infected with TB. Additional tests were done to rule out active TB disease.

A random sample of 220 children, among all those who had a negative TST result was identified by the study team. Parents of all 300 of these children were contacted and interviewed by a trained public health worker who was unaware of the TST status of the child. Parents were asked to provide information about any travel that the child experienced during the 12 months prior to the TST. Information was gathered on the length and number of trip(s) and the country that was visited. Travel locations were classified as being to a high-burden country (yes or no) according to the designation assigned by the World Health Organization (WHO). The WHO has identified the following 22 countries as high-burden TB countries: Afghanistan, Bangladesh, Brazil, Cambodia, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Myanmar, Mozambique, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Tanzania, Thailand, Uganda, Vietnam, and Zimbabwe because they account for 80% of TB globally.⁴

**Question 3**

What type of study is this? Please explain.
**Answer Key**

This is a case-control study since the study population was assembled based on TST results (children with a positive TST result are the cases and the random sample of children with a negative TST result are the controls). Then information on prior exposure was collected, specifically whether the children had traveled to a country that is designated as a high-burden TB area within the 12 months prior to their TST.

**Results for travel to a high-burden TB country**

Parents of all 300 children consented to be in this study. Of these 300 children, 22 had traveled to a high burden TB country during the 12 months prior to their TST. Twelve of the 80 children with a positive skin test had traveled to a high-burden TB country during the 12 months before their skin test.

**Question 4 A-B**

A. Using the information provided in the above paragraph, create a 2 x 2 table for the group of children who had traveled to a high-burden TB country during the 12 months prior to their TST.

<table>
<thead>
<tr>
<th>Group: All children</th>
<th>TST Results</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Travel to a high-burden country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>300</td>
</tr>
</tbody>
</table>

**Answer Key**

<table>
<thead>
<tr>
<th>Group: All children</th>
<th>TST Results</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>(cases)</td>
<td>(controls)</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (a)</td>
<td>10 (b)</td>
</tr>
<tr>
<td>No</td>
<td>68 (c)</td>
<td>210 (d)</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>220</td>
</tr>
</tbody>
</table>

B. Calculate the odds ratio (OR) and provide an interpretation of the findings.
Answer Key
Group: all children: OR = (12 X 210) / (10 X 68) = 3.7; The interpretation of this OR is: children who are TST-positive have more than 3 times the odds of having visited a high-burden TB country within the 12 months prior to receiving their TST than those who are TST-negative.

Question 5
Can a relative risk (RR) be calculated for this study? Please explain why or why not.

Answer Key
A RR cannot be calculated for this study because the study group is not a cohort of exposed and nonexposed individuals who are followed over time. Therefore, incidence rates are not available. Since RR is calculated as the incidence rate in the exposed group divided by the incidence rate in the unexposed group, a RR for this study cannot be generated.

Question 6
Under what circumstances is an OR a good estimate of RR (Hint: See reference 5)?

Answer Key
According to Gordis (Epidemiology, Second Edition, p. 165), an OR is a good approximation of the RR when the following conditions are met:

“1. When the cases studied are representative with regard to the history of the exposure of all people with the disease in the population from which the cases were drawn.
2. When the controls studied are representative with regard to the history of exposure of all people without the disease in the population from which the cases were drawn.
3. When the disease being studied does not occur frequently.”

Question 7
The public health workers who interviewed the parents of these children did not know the TST status of these children. Why is this important?

Answer Key
This is important because, in a case-control study, it reduces the chance that interviewer bias could be introduced into ascertaining exposure history. The interviewer’s knowledge of the subject’s TB status should not influence the way the questions are asked or the intensity used to probe for information.
**Question 8**
When conducting any study, researchers must be concerned about other possible biases. What is recall bias?

**Answer Key**
Recall bias could occur if parents were informed of their child’s TST result prior to the interview and if parents of children who had a positive TST result were more likely to recall the exposure than parents of children who had a negative TST result. In addition, asking parents to recall events that occurred up to 1 year ago may be difficult, but if the errors in recall are unrelated to outcome (the TST result) then this type of nondifferential recall should not bias the OR.

The next part of the exercise is based on a study published in Morbidity and Mortality Weekly Report. The findings from this study have been paraphrased below.

**Morbidity and Mortality Weekly Report**

**Tuberculosis Outbreak in a Community Hospital — District of Columbia, 2002**

During July 2002, 5 patients at a community hospital in Washington, DC, were diagnosed with active TB disease. An employee at this hospital was also diagnosed with active TB in September 2002. The DC Department of Health contacted the Centers for Disease Control and Prevention (CDC) and requested assistance with an investigation of this unusual occurrence (outbreak) of TB. A team was formed to investigate the occurrence of these cases. The team included individuals from the CDC staff, the local health department, and the infection control department at the hospital. The team reviewed the hospital and health department records of these 6 active TB cases.

One case was a patient who spent 3 weeks on 2 general medical wards at the hospital before being placed in respiratory isolation with a diagnosis of TB on April 2, 2002. DNA fingerprinting was conducted on specimens from all 6 active TB cases and all 6 had matching genotypes. Based on the review of hospital and health department records, this patient was identified as the source (or index case) of the outbreak. The figure presented below shows the amount of time during which the index case and the other (secondary cases) were in contact, along with the dates of diagnosis of TB disease.
Hospital staff members who may have come into contact with this patient were identified by examining the patient’s medical records and comparing that information with the dates and assignments that were found in the hospital’s employment records. A total of 784 members of the hospital staff were categorized into 3 exposure groups: 1) direct-care providers, who had direct contact with the patient; 2) workers on the same ward as the patient, but who were not involved in the patient’s medical care; or 3) other workers who spent time on the ward but were not assigned there while the patient was present.

Overall 495 (or 63%) of these 784 staff members were evaluated using a TST. The Table below provides the TST results for all tested staff at their hospital by assignment, as a measure of the amount of possible exposure to the patient. Those with direct patient care should have had the most exposure; staff members who were ward-based should have some exposure, and other staff should have had the least amount of exposure.
EPIDEMIOLOGY CASE STUDY 3: Cross-Sectional, Case-Control, and Cohort Studies–Identification of TB Risk Groups and TB Risk Factors in Epidemiologic Studies INSTRUCTOR’S GUIDE VERSION 1.0

TABLE. Tuberculin skin test (TST) results among staff at hospital A, by type of work assignment — District of Columbia, April–September 2002

<table>
<thead>
<tr>
<th>Assignment</th>
<th>No. workers</th>
<th>No. evaluated</th>
<th>TST-positive*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct care</td>
<td>105</td>
<td>65</td>
<td>21 (32)</td>
</tr>
<tr>
<td>Ward-based</td>
<td>49</td>
<td>26</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Other</td>
<td>629</td>
<td>404</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>784</td>
<td>495</td>
<td>56 (11)</td>
</tr>
</tbody>
</table>

**Question 9**
What type of epidemiologic study design is this investigation? Please explain.

**Answer Key**
This is a cohort study since it examines a cohort (workers) classified by exposure status and assesses TST results as the outcome.

**Question 10**
Assuming that no staff members who were tested had a prior positive TST result, what type of measures are the TST positive percentages?

**Answer Key**
Assuming that no staff member had prior positive TST results, then these are cumulative incidence rates (no. of cases/population at risk). Incidence density would have person-time exposure in the denominator.

**Question 11**
Using the incidence rate in the other group as the referent group, calculate and interpret the RR for direct care and ward-based workers.
Table for Answer key only:

TABLE. Tuberculin skin test (TST) results among staff at hospital A, by type of work assignment—District of Columbia, April—September 2002

<table>
<thead>
<tr>
<th>Assignment</th>
<th>No. workers</th>
<th>No. evaluated</th>
<th>TST-positive* No. (%)</th>
<th>RR† (95% CI§)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct care</td>
<td>106</td>
<td>65</td>
<td>21 (32)</td>
<td>4.5 (2.7–7.4)</td>
</tr>
<tr>
<td>Ward-based</td>
<td>49</td>
<td>26</td>
<td>6 (23)</td>
<td>3.2 (1.5–7.0)</td>
</tr>
<tr>
<td>Other</td>
<td>629</td>
<td>404</td>
<td>29 (7)</td>
<td>Referent</td>
</tr>
<tr>
<td>Total</td>
<td>784</td>
<td>495</td>
<td>56 (11)</td>
<td></td>
</tr>
</tbody>
</table>

* A TST of ≥5 mm during the investigation in a person with a documented negative TST during the preceding 2 years.
† Relative risk.
§ Confidence interval.

**Incidence TST + direct care** = RR  direct care
**Incidence TST + other**

RR= 32/7=4.5. This means that the direct care employees were 4.5 times more likely to have a positive TST result compared with those described as other employees. Similarly, the RR of 23/7.2 (decimal not in table)=3.2. Exposure appears to be related to the risk of developing new infection.

**Question 12**
How is it possible to determine if these RRs are more than would be expected by chance?

**Answer Key**
Determining the 95% CIs around the RRs would be equivalent to testing the differences in incidence rates at the alpha .05 level.
The authors present the following information:

**TABLE. Tuberculin skin test (TST) results among staff at hospital A, by type of work assignment — District of Columbia, April—September 2002**

<table>
<thead>
<tr>
<th>Assignment</th>
<th>No. workers</th>
<th>No. evaluated</th>
<th>TST-positive*</th>
<th>RR† (95% CI‡)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct care</td>
<td>106</td>
<td>65</td>
<td>21 (32)</td>
<td>4.5 (2.7–7.4)</td>
</tr>
<tr>
<td>Ward-based</td>
<td>49</td>
<td>26</td>
<td>6 (23)</td>
<td>3.2 (1.5–7.0)</td>
</tr>
<tr>
<td>Other</td>
<td>629</td>
<td>404</td>
<td>29 (7)</td>
<td>Referent</td>
</tr>
<tr>
<td>Total</td>
<td>784</td>
<td>495</td>
<td>56 (11)</td>
<td></td>
</tr>
</tbody>
</table>

* A TST of ≥5 mm during the investigation in a person with a documented negative TST during the preceding 2 years.
† Relative risk.
‡ Confidence interval

**Question 13**
Are these RRs statistically significant?

**Answer Key**
Yes, at the alpha .05 level because the 95% CIs on the RRs do not include the number 1.0.

**Question 14 A-B**
A. Can it be determined if there is a significant difference at the .05 significance level between direct care and ward-based employees by looking at the RRs and CIs provided in this table?

**Answer Key**
No, these RRs and CIs only allow comparisons to the reference group “others”.
A new RR (32/23= 1.4) comparing direct care to ward-based employees and a new CI on that RR would need to be calculated. Another way would be to conduct a chi-square or Fisher Exact Test.
B. Interpret the results of the statistical test below.

Table 3. Contingency table
Type of Worker (Direct/Ward-Based Care) by TST Result (Positive/Negative)

<table>
<thead>
<tr>
<th>Count</th>
<th>Positive</th>
<th>Negative</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Col %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Row %</td>
</tr>
<tr>
<td>Direct care</td>
<td>21</td>
<td>44</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>23.08</td>
<td>48.35</td>
<td>77.78</td>
</tr>
<tr>
<td></td>
<td>77.78</td>
<td>68.75</td>
<td>71.43</td>
</tr>
<tr>
<td></td>
<td>32.31</td>
<td>67.69</td>
<td></td>
</tr>
<tr>
<td>Ward-based care</td>
<td>6</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>6.59</td>
<td>21.98</td>
<td>22.22</td>
</tr>
<tr>
<td></td>
<td>22.22</td>
<td>31.25</td>
<td>23.08</td>
</tr>
<tr>
<td></td>
<td>23.08</td>
<td>76.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>64</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>29.67</td>
<td>70.33</td>
<td></td>
</tr>
</tbody>
</table>

Test Chi-square p value
Pearson 0.758 0.3839

Fisher Exact Test
Left 0.8707 Prob(TB test result=negative) is greater for type=direct than ward
Right 0.2722 Prob(TB test result=negative) is greater for type=ward than direct
2-Tail 0.4537 Prob(TB test result=negative) is different across type

Relative Risk
Description RR Lower 95% CI Upper 95% CI
P( positive|direct)/P(positive|ward) 1.4 0.638528 3.069559

Answer Key
The chi-square p value is 0.39, which is greater than the preset significance level of .05. In addition, the 95% CI on the RR ranges from 0.64 to 3.1. Since an RR of 1 means no additional risk in the exposed compared with the nonexposed, a 95% CI that includes the number 1.0 suggests no significant difference in risk between direct and ward-based employees. However, there may not have been enough power to detect a difference.

Question 15
What are the implications of the fact that not all employees received a TST in this study?

Answer Key
It is not possible to determine if the results represent the whole population since this is neither a full accounting nor a probability sample. Those who did not agree to be tested may differ somewhat from those who did.
**Question 16**
What is the amount of risk attributed to direct patient contact compared with contact on the ward?

**Answer Key**
The amount of risk attributed to direct patient contact is called the attributable risk (AR). The AR is calculated as the incidence rate in the exposed (direct patient contact) group minus the incidence rate in the unexposed (on the ward) group. In this case, the AR would be: 32% - 23% = 9%

The following editorial note appeared at the end of the article:

This report describes recent nosocomial transmission of *M. tuberculosis* in a community hospital. The index patient spent 3 weeks hospitalized with unrecognized TB, possibly masked by HIV infection. AIDS patients can have atypical presentations of TB disease resulting in diagnostic delays (6). Because TB was not initially a diagnostic consideration, the patient was not placed immediately in respiratory isolation.

Although the incidence of TB continues to decline (7), heightened awareness and vigilance is required by hospital staff to identify and treat persons with suspected TB promptly. Patients with suspected TB should be placed in respiratory isolation until infectious TB is ruled out. When the patient is transported for medical procedures that cannot be performed in the isolation room, the patient should wear a surgical mask. Hospital infection-control programs are encouraged to develop protocols and implement administrative procedures for HIV-infected patients with pulmonary symptoms suggestive of TB. Finally, local TB-control programs can assist hospital infection-control staff in investigating community contacts of persons hospitalized with TB (2).

This note emphasizes the importance of prompt diagnosis of TB along with a strong infection control program in the prevention of nosocomial (or hospital-based) outbreaks of diseases such as TB.

**References cited in this editorial note**
2. CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. *MMWR. 1994;43(No. RR-13).*


Works Cited

2. New Jersey Medical School National Tuberculosis Center. Basic Epidemiology for Tuberculosis Program Staff. 2005:43.


