Module 4: Epidemiology Investigation

Epidemiology Division
Analysis and Reporting Branch

Module Learning Objectives
- Develop a case definition
- Explain an epidemic curve
- Develop an initial hypothesis
- List three types of study design and a method of statistical analysis
- Calculate measures of association
- Interpret significance of data
- Determine if hypotheses are confirmed or rejected

Estimated Annual U.S. Foodborne Disease Burden, 2011
- Foodborne Illnesses
  - 48 million
- Hospitalizations
  - 128,000
- Deaths
  - 3,000

Estimated Percents of Foodborne Illnesses in U.S., 2011

- Norovirus: 58%
- Staph. aureus: 3%
- Campylobacter: 9%
- Clostridium perfringens: 10%
- Salmonella: 11%
- other: 9%

AL 2011 Reported Diseases

Total = 2,260

- Salmonellosis: 56%
- Cryptosporidiosis: 6%
- E. coli (STEC): 3%
- Giardiasis: 8%
- Shigellosis: 14%
- Campylobacteriosis: 12%
- Shigella: 1%

* Includes Hep A, Hep E, Listeriosis, and Vibrio.

Individual nonvirus cases are not reportable to EPI, just if part of an outbreak.

Salmonella Outbreak Timeline

Example

- Patient eats contaminated food
- Incubation time
- Becomes ill
- Seeks medical care
- Visits doctor
- Stool sample collected
- Specimen delivered and growing
- Salmonella identified
- Public health receives sample
- Serotyping and DNA fingerprinting
- Case confirmed as part of outbreak

Source: CDC
AL Foodborne Outbreak (FBO) Definition

When two or more persons (from different households) experience a similar illness resulting from the ingestion of a common food.

Exceptions: botulism and chemical poisoning
(1 case = outbreak)

Make Epidemiologic Associations

- Person, place, time
- Systematically organize key information
- Develop initial hypothesis

Foodborne Illness: Changing Epidemiology

Agent
• Recently recognized pathogens
• New FB modes of transmission

Environment
• Globalization of food supply
• Centralization of food processing, large producers

Host
• Increasing elderly, immunocompromised
• New eating habits
• Increasing immigration, international travel
Develop Initial Case Definition: Counting Apples and Oranges

- Set of criteria for deciding whether an individual should be classified as “a case”
- Objective criteria
- Links person to place and time
- Outbreak-associated vs. normal background
- Value of routine surveillance data
- Primary vs. secondary cases

Revise Case Definitions

- Precise definitions reduce potential for misclassification:
  - Estimated 41% of enteric infections in U.S. are foodborne;
  - Incomplete case history can haunt you;
  - Incorrectly classifying individuals can bias results;
  - Make it harder to detect true associations.

Person: AL Outbreak Examples

| Table 1. General characteristics on individuals involved in a Norovirus outbreak |
|--------------------------|--------------------------|--------------------------|
|                         | III (n=13)               | IV (n=7)                 |
| Age (years)             | Mean (Range)             | Mean (Range)             |
| Male                    | 37 (12-65)               | 47 (30-58)               |
| Female                  | 8 (61%)                  | 5 (71%)                  |
| Incubation Period (days) | Mean (Range)             | Mean (Range)             |
|                         | 44 (23-70)               | N/A                      |
Place: Common Exposure Location

- Case 1 – restaurants A, B, C, D
- Case 2 – restaurants B, C, E, F
- Case 3 – restaurants A, B, G, H, I
- Case 4 – restaurants B, J, K

What is the common exposure location?

Place: Common Exposure Location (cont.)

- Restaurant
  - Single restaurant location
  - Multiple restaurants (chain or same owner)
  - Multiple chains with a common distributor
- Banquets, Birthday Parties, Wedding Receptions, Conferences, Basketball Game, School Field Trip, Summer Camp, etc.

Point-Source Exposure
Hypothesis

“An unproved theory ...tentatively accepted to explain certain facts or to provide a basis for further investigation”

Source: Webster’s New World Dictionary, 3rd Edition
Example of Hypothesis

- Food item consumed at the Smith Wedding reception caused illnesses
- Data needed to test information
  - What kind of food items were eaten?
  - Who ate the food item? Who did not eat?
  - How much did each person eat?
  - Illness onset (date and time)?

Develop Initial Hypothesis

- Multiple hypotheses may be compatible with data initially
- Helps clarify
  - What is known
  - What is missing
  - Actions needed to gather missing information

Case Definition vs. Hypothesis

**Case Definition**
- Classify cases vs. controls
- Includes
  - Person
  - Place
  - Time
  - Symptoms

**Hypothesis**
- Describe exposure to test analytically
- Theory

Do NOT include hypothesis in case definition!
Unknown Causative Agent
- Review what is known about cases
- Symptoms, severity of disease
- Events attended or anything unusual
- Foods consumed and methods of food preparation
- Identify most likely agent(s)
- Review references
- Consultation

### Acute Foodborne Gastroenteritis Reference Table

<table>
<thead>
<tr>
<th>Cause</th>
<th>Average Incubation</th>
<th>Range Incubation</th>
<th>Fever</th>
<th>Vomiting</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy metals</td>
<td>5-15 min</td>
<td>1 min - 8 hrs</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Staph enterotoxin</td>
<td>2-4 hrs</td>
<td>30 min - 6 hrs</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Bacillus cereus emetic syndrome</td>
<td>2 - 4 hrs</td>
<td>30 min - 6 hrs</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>12 hrs</td>
<td>0 - 24 hrs</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>E. coli Invasive</td>
<td>12 hrs</td>
<td>6 - 24 hrs</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus</td>
<td>12 - 24 hrs</td>
<td>6 - 24 hrs</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Bacillus cereus diarrheal syndrome</td>
<td>12 hrs</td>
<td>6 - 24 hrs</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Salmonella</td>
<td>24 hrs</td>
<td>6 - 72 hrs</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
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<td>E. coli enterotoxigenic</td>
<td>24 hrs</td>
<td>8 - 48 hrs</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Shigella</td>
<td>36 hrs</td>
<td>1 - 7 days</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Norovirus</td>
<td>36 hrs</td>
<td>10 - 50 hrs</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>2 - 3 days</td>
<td>few hrs - 5 days</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>2 - 5 days</td>
<td>1 - 20 days</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>E. coli O157:H7</td>
<td>2 - 4 days</td>
<td>2 - 10 days</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>4 days</td>
<td>1 - 14 days</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Cryptosporidium parvum</td>
<td>7 days</td>
<td>2 - 14 days</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Known Causative Agent
- Review what is known about the agent
- Typical signs and symptoms
- Modes of transmission
- Foods in past outbreaks
- Is this situation similar to other previously reported incidents?
- Be aware of recent food recalls
Measures (Calculations)

- Measure of Occurrence
  - Attack Rate
- Measure of Association
  - Relative Risk (RR): Cohort studies
  - Odds Ratio (OR): Case-Control studies

Association Between Exposure and Disease

- Depends on type of study
  - “Relative risk” cohort studies
  - Risk of developing disease given the exposure
  - “Odds ratio” case-control studies
    - Odds of having the exposure given the disease
- Computer programs greatly speed the calculations

Relative Risk - Cohort Studies

- Measurement of the risk of developing disease given a specific exposure (a food item)
- Compares attack rates between exposed and unexposed groups

Relative Risk (RR) = \frac{\text{Attack Rate (AR) among Exposed}}{\text{Attack Rate (AR) among Unexposed}} = \frac{a / (a + b)}{c / (c + d)}
Odds Ratio-Case-Control Studies

- Measurement of the odds of having an exposure (specific food consumption) given the disease
- Estimates the Relative Risk derived from cohort studies

\[
\text{Odds Ratio (OR)} = \frac{\text{Odds of exposure among cases}}{\text{Odds of exposure among controls}} = \frac{a/c}{b/d} = \frac{ad}{bc}
\]

How Valid Are Your Findings?

Is the observed association between exposure and disease (expressed by the RR or OR) due to alternative explanations?

- Bias: systematic error
  - Selection
  - Information (recall, interviewer, misclassification)
- Chance
  - Sampling variability
  - Sampling size

Examples of Bias

- Random misclassification of cases vs. controls or exposed vs. unexposed
  - Biases OR or RR toward “1”
- Recall bias
  - Cases are more likely than controls to remember exposures
  - Problem with retrospective studies
  - May result in inflated OR
Evaluating the Role of Chance

- **p-value**
  - Probability a given association could have occurred by chance alone
  - “Statistically significant” usually set at \( p \leq 0.05 \)
  - Consider all available evidence when interpreting p-values
- **95% Confidence Interval**
  - Range within which the true association lies

The Significance of Significance

- “Not significant” ≠ “no association.”
- Measure of association (relative risk, odds ratio) indicates direction & strength of the association.
- Statistical test (p-value), indicates how likely the observed association occurred by chance alone.
- Larger samples increase the likelihood of recognizing an association.

Problems Interfere with Solution

- Questionnaire design
- Data collection (ex., incomplete data)
- Sample size (ill and not ill)
- No clinical or food sample for testing
- Reporting time

Source: Field Epidemiology, 1996, Michael B. Gregg
Multi-state FBOs

- Not all agents are created equal (e.g. *S. typhimurium*)
- CDC monitors a database (PulseNet) with microbial fingerprints and notifies states
- Periodical conference calls with involved states and regulatory agencies to collaborate
- May request additional information from cases

National 2011 Multi-State Clusters

- [List of various clusters and codes]

How Are Outbreaks Named By ADPH?

**AL{YYMM}xxx-{county ##}(sequence letter)**

**PHA03 Deli:**

- AL1308NV-6th
- 10
- 08
- NV
- June
- Tuscaloosa County
- 2nd

**PHA08 Church Luncheon:**

- AL1003EG-25a
- 10
- 03
- EG
- March
- Elmore County
- 1st